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Fecal Microbiota Transplantation for *Clostridium Difficile* Infection: A Systematic Review of the Evidence

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Prepared by:
Evidence-based Synthesis Program (ESP) Center
Minneapolis VA Medical Center
Minneapolis, MN
Timothy J. Wilt, M.D., M.P.H., Director

Investigators:
Principal Investigator:
Dimitri Drekonja, M.D., M.S.

Co-Investigators:
Jon Reich, M.D.
Selome Gezahegn, M.D.
Nancy Greer, Ph.D.
Aasma Shaukat, M.D., M.P.H.
Timothy Wilt, M.D., M.P.H.

Research Associates:
Roderick MacDonald, M.S.
Indy Rutks, B.S.

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PREFACE

Quality Enhancement Research Initiative's (QUERI) Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to Veterans Affairs (VA) clinicians, managers and policymakers as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout the VA, and some evidence syntheses inform the clinical guidelines of large professional organizations.

QUERI provides funding for four ESP Centers and each Center has an active university affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help:

- develop clinical policies informed by evidence;
- guide the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- set the direction for future research to address gaps in clinical knowledge.

In 2009, the ESP Coordinating Center was created to expand the capacity of HSR&D Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of QUERI field-based investigators, VA Patient Care Services, Office of Quality and Performance, and Veterans Integrated Service Networks (VISN) Clinical Management Officers. The Steering Committee provides program oversight, guides strategic planning, coordinates dissemination activities, and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP Coordinating Center Program Manager, at Nicole.Floyd@va.gov.

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This report is based on research conducted by the Evidence-based Synthesis Program (ESP) Center located at Minneapolis VA Medical Center, Minneapolis, MN, funded by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. Drs. Drekonja and Shaukat are principal proponents of the following randomized controlled trial currently under review for planning and conduct through the VA Cooperative Studies Program: "The Veterans Affairs Fecal Microbiota Therapy Trial for Recurrent Clostridium difficile Infection: A Planning Request for a VA Cooperative Study". No other investigators have any affiliations or financial involvement (eg, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

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INTRODUCTION

Since its discovery as the cause of pseudomembranous colitis in 1978, *Clostridium difficile (C. difficile)* has become an increasingly important pathogen. Initially, *C. difficile* infection (CDI) was largely confined to patients with healthcare exposure; however, it is now also affecting those with no or limited contact with the healthcare system. In 2013, the U.S. Centers for Disease Control and Prevention placed *C. difficile* into its top threat category of "urgent" in its first threat report on antimicrobial resistance.

A major challenge in treating CDI is the high rate of recurrent disease. Recurrence occurs in 15-30% of patients, and among those with a single episode of recurrence, the risk of further recurrence increases after each episode. Multiple treatment/recurrence episodes can result in repeated hospitalizations, clinic visits, deconditioning, malnourishment, and fecal continence issues. These effects are debilitating, contribute to decreased quality of life and prolonged courses of antimicrobial treatment and rarely can be fatal. Antimicrobial treatment for these episodes of recurrent disease yields reported success rates between 30% and 80%, depending on the number of recurrences, and on the agent and duration of treatment selected. These sub-optimal response rates have helped spur the investigation of additional therapeutic options including fecal microbiota transplantation (FMT) for the treatment of CDI.

CDI is characterized by severe alterations in the colonic microbiome (normal colonic bacteria). Restoring the normal microbiome has been proposed as a method for preventing recurrence. The most widely utilized intervention has been probiotics yet these products provide only a limited number and diversity of microorganisms. Fecal microbiota transplantation is increasingly utilized as a treatment for patients with recurrent CDI; based on the idea that to restore all the organisms that comprise the normal colonic flora, simply import the colonic microbiome of a healthy person. FMT has been performed in hundreds of patients, with outcomes from more than 500 cases reported in the medical literature - most in non-controlled case series. Reported success rates of up to 100% and the recent publication of a randomized controlled trial (RCT) comparing FMT to antimicrobial treatment have increased interest in the procedure.

Purpose of Review

The Minneapolis VA Evidence-based Synthesis Program was asked to conduct a systematic evidence review regarding the effectiveness of FMT for treatment of CDI, in part to help guide policy makers within the Veterans Health Administration determine if the evidence supporting FMT was sufficient to implement FMT programs in their facilities. The topic was nominated by Jason Dominitz, MD, MHS on behalf of the VA Gastroenterology Field Advisory Committee.

The key questions for the review were:

KQ1. What is the effectiveness of fecal microbiota transplantation for recurrent CDI compared to standard therapy? Does effectiveness vary by method of transplantation?

KQ2. What is the effectiveness of fecal microbiota transplantation for refractory CDI compared to standard therapy? Does effectiveness vary by method of transplantation?

KQ3. What is the effectiveness of fecal microbiota transplantation as initial therapy for CDI compared to standard therapy? Does effectiveness vary by method of transplantation?

KQ4. What are the harms of fecal microbiota transplantation therapy compared to standard therapy for initial, recurrent, or refractory CDI? Do the harms vary by method of transplantation?

KQ5. Is the procedure acceptable to patients? Does patient acceptability vary by method of transplantation?

METHODS

Data Sources and Searches

We searched MEDLINE (OVID) for articles published from 1980 through May 2014 (Appendix A). Our search was designed to identify studies of any design although we excluded case reports except for those that reported harms. We limited the search to studies involving human subjects published in the English language. Additional articles were identified from hand-searching reference lists of existing systematic reviews and included studies.

Study Selection

Two investigators independently reviewed full text of articles identified as potentially eligible.

Data Abstraction and Quality Assessment

Study characteristics, patient characteristics, and outcomes data were abstracted from articles eligible for inclusion. Since all but 2 of the included studies were case series or case reports, we did not formally assess study quality, but rather note that conventional methods for rating strength of evidence would classify even well-conducted and reported case series as high risk of bias. Therefore, strength of evidence would typically be considered insufficient or low. Our key outcomes included: resolution of symptoms (primary outcome), time to resolution of symptoms, recurrence, all-cause mortality, and adverse events. In many cases, it was difficult to ascertain whether the resolution of symptoms was due to the pre-FMT antimicrobials for CDI, the FMT procedure, or a combination of the two. Similarly, the outcomes of resolution and recurrence were often combined as "resolution of diarrhea without relapse," or "durable resolution."

Data Synthesis and Analysis

Most findings are summarized narratively. We calculated weighted resolution rates and 95% confidence intervals for the studies of FMT for recurrent CDI stratified by FMT method. There were insufficient studies of refractory CDI or FMT as initial therapy for CDI for numerical synthesis.

RESULTS

Results of Literature Search

Our literature search yielded 161 abstracts or titles. We excluded 100 after abstract review and performed full text review of 61 articles. We excluded 51 leaving 10 included articles. From

hand-searching of reference lists of systematic reviews and included studies and suggestions from reviewers, we identified another 21 articles for a total of 31 included studies – 2 RCTs, 25 case series, and 4 case reports.

Summary of Results for Key Questions

KQ1. FMT for Recurrent CDI

Two small moderate risk of bias RCTs and 19 case series (range 2 to 74 participants; total n=480 receiving FMT) reported use of FMT for patients with *recurrent CDI* (Executive Summary Figure). Patients were older age, the majority female, and all had multiple (3 to 12) CDI recurrences prior to undergoing FMT. FMT was performed 3 to 27 months from the time of the patients' initial episode of CDI. Mean follow-up after FMT ranged from 1 to 30 months. We identified few qualitative differences in baseline characteristics according to treatment approach. Donor screening and selection criteria as well as patient selection, pre-transplant preparation and FMT preparation and delivery varied. A high proportion of patients treated with FMT had resolution of symptoms. However, authors commonly reported that antimicrobials for CDI were given prior to FMT to ensure that patients were asymptomatic or had a "reduction in symptoms" at the time of FMT. Thus, in most cases FMT was administered when patients were asymptomatic or symptoms were resolving, with the FMT possibly contributing to further symptom resolution, prevention, or both. In the RCT comparing FMT via nasoduodenal tube to 2 control groups (n=43), 81% of patients in the FMT group achieved resolution of symptoms within the first 3 months and the results were significantly different from the vancomycin (31%) or vancomycin plus bowel lavage (23%) control groups. In the RCT comparing 2 FMT treatment approaches (n=20), a high proportion of patients in each group had resolution of symptoms; the difference between treatment approaches was not significant (60% in the nasogastric tube group and 80% in the colonoscopy group, P=.63). Across all studies of patients with recurrent CDI, including FMT via an upper gastrointestinal (GI) (k=6), colonoscopy (k=10, including the RCT with both upper GI and colonoscopy groups), enema (k=5), or combination approach (k=1), resolution of symptoms was observed in 83% (95%CI 77%, 87%). Although comparisons across studies should be interpreted with considerable caution, FMT involving colonoscopy resulted in the highest overall symptom resolution rates, followed by upper GI tract and enema. Eleven case series assessed time to resolution of symptoms; 3 reported resolution within 24 hours and the others reported means or medians of one to 7 days. Two reports of FMT focused on immunocompromised patients; one included patients already reported in other case series. Resolution after an initial FMT (methods varied) was reported in 50% of a small series (n=2) and 78% of a larger series (n=80).

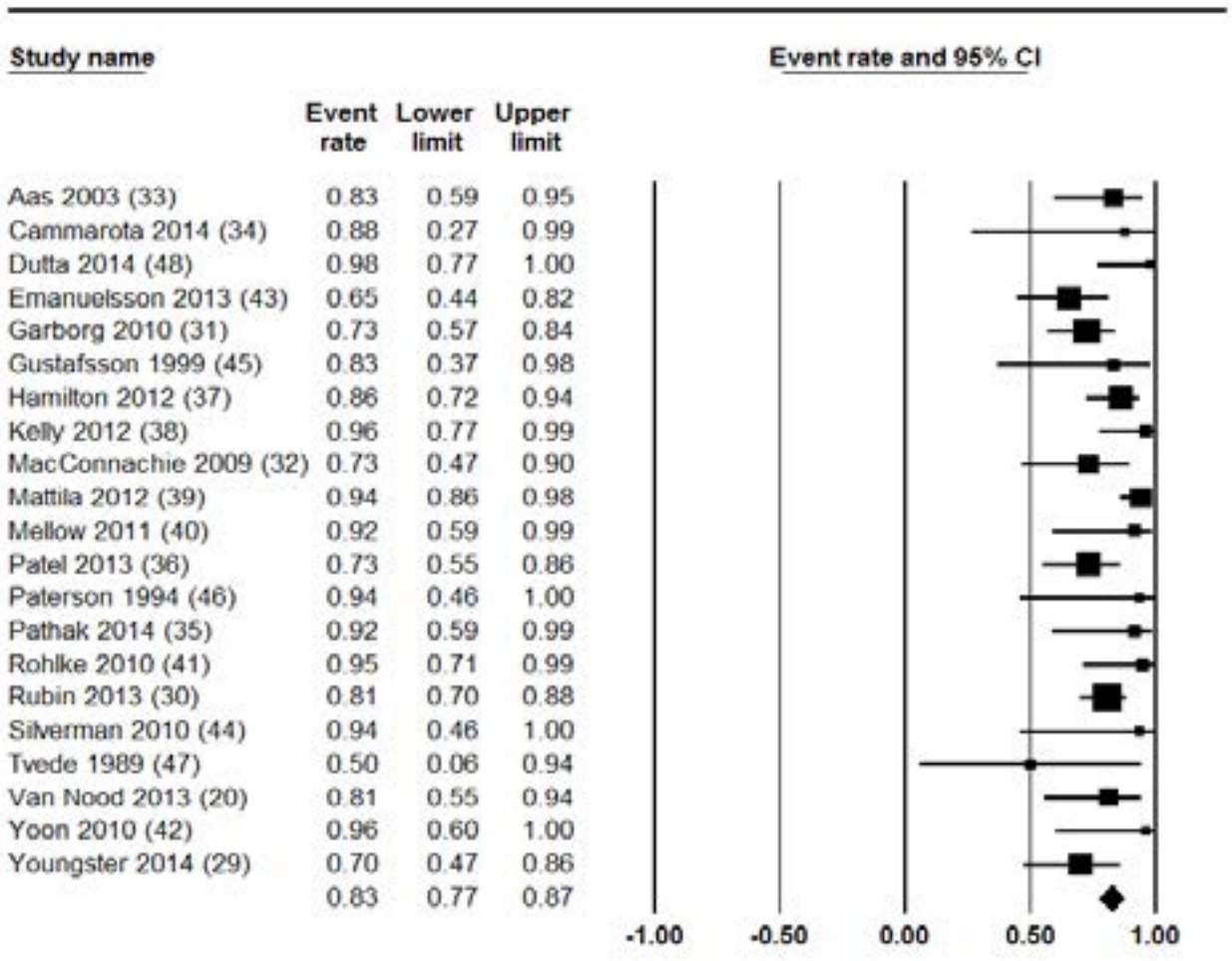
KQ2. FMT for Refractory CDI

We identified 5 case series among patients with refractory CD (117 participants; 112 treated via enema and 5 via colonoscopy). Mean age ranged from 52 to 73 years and between 25% and 67% were male. Reported resolution of symptoms ranged widely (0% to 100%, mean=53%).

KQ3. FMT for Initial CDI

We identified only one patient treated with FMT for *initial CDI*. The patient's symptoms resolved following FMT via enema.

Executive Summary Figure. Reported Resolution of Symptoms after Initial FMT for Recurrent CDI, All Routes for Infusion of Donor Feces*



*Due to small sample sizes in 5 studies that reported 100% success (Cammarota 2014,[34] Yoon 2010,[42]Silverman 2010,[44] Paterson 1994,[46] and Dutta 2014[48]) the software used to generate this figure lowered the estimates for these studies from 100% to 88%, 96%, 94%, 94%, and 98%, respectively, to allow the upper limit of the 95%CI to be 1.0. Actual reported resolution of symptoms is 84%.

KQ4. FMT Adverse Events

Few serious *adverse events* were reported and no clear link between FMT and serious adverse events could be established. In one series of immunocompromised patients, serious adverse events and adverse events were each observed in 15% of patients with approximately one-third considered related to FMT. Long-term safety data regarding FMT are lacking.

KQ5. FMT Acceptability

No study systematically assessed *acceptability* to patients with prior or current episodes of CDI. Anecdotal findings suggest that the procedure was an acceptable alternative for patients with recurrent CDI.

DISCUSSION

Key Findings and Strength of Evidence

Based on results from 2 moderate-quality (moderate risk of bias) RCTs and 23 case series enrolling patients with recurrent, refractory, or an initial episode of CDI, we found low strength evidence (recurrent CDI) or insufficient evidence (refractory CDI or initial episode of CDI) that treatment with FMT led to a large proportion of patients experiencing short-term resolution of symptoms. The pooled reported success rates (*ie*, resolution of symptoms or resolution of symptoms without recurrence at 3 months or less) were 83% for patients with recurrent CDI and 53% for patients with refractory CDI which are substantially better than success rates reported for various medical therapies for recurrent or refractory CDI. Furthermore, in the RCT that directly compared FMT with vancomycin, FMT resulted in a higher percentage of resolution (13 of 16 patients, 81%) compared to either vancomycin (4/13, 31%) or vancomycin plus bowel lavage (3/13, 23%). One death was reported in the vancomycin group. A second small (n=20) RCT found no statistically significant difference in resolution between groups treated via nasogastric tube (6/10, 60%) or colonoscopy (8/10, 80%).

Applicability

Several limitations in the evidence threaten broader applicability. Treatment protocols varied widely with few reports following identical protocol. Patient demographic and disease characteristics as well as donor selection and FMT preparation and delivery methods varied. Only one small non-US RCT directly compared FMT to antibiotic therapy. Most enrollees had 4 or more episodes of CDI prior to enrollment. In contrast, trials of antimicrobial therapy for CDI enrolled those with at most a single recurrence, and had higher antimicrobial success rates. Thus the effectiveness and comparative effectiveness in individuals with fewer recurrences is not known. The high response rates in case series likely represent optimal outcomes. Publication bias may exist whereby lower response rates are not reported. Additionally, several studies reported "symptom resolution" following FMT infusion among patients who were without symptoms at time of infusion-presumably believing that without FMT symptoms would have reoccurred. None of the reported studies were conducted at VA medical centers; many were conducted outside the US, derived from selected samples of subjects with CDI, and did not account for all treated patients. Most study participants were older adults and FMT was initiated after a wide range of CDI recurrences. Most studies used fresh fecal material however, donor screening and selection, fecal material preparation, and FMT dose and delivery varied widely. Nonetheless, CDI in Veterans is common and results in considerable morbidity and health care utilization and costs. Additional, safe, acceptable and effective treatment options are needed especially for individuals with recurrent CDI. The incidence of CDI in VA is approximately 1% of all hospitalized patients; recurrence rates are 22% to 30%. In 2012, 6,046 cases of CDI and 1,517 cases of recurrent CDI were identified using VA inpatient data sources and 8,878 cases when outpatient CDI diagnoses were included.

Research Gaps/Future Research

While a large percentage of patients had resolution after FMT, the current evidence is of low methodological quality and limited applicability. Our findings are based on small case series and 2

very small RCTs of selected individuals. Thus we have low certainty about the efficacy, widespread effectiveness and comparative effectiveness (especially related to alternative antimicrobial-based regimens) of FMT for patients with recurrent or refractory CDI. Almost no data exist on FMT for initial treatment of CDI. Furthermore, many studies attributed "resolution of symptoms" to FMT even among patients who were without symptoms at the time of FMT. Whether resolution was due to the pre-FMT antimicrobials, the FMT procedure, or a combination of the two, was difficult to ascertain. Therefore, any reported effect estimate is likely greater than would be observed in broader clinical settings especially among individuals with ongoing symptoms. Additional data from RCTs, nonrandomized controlled studies or higher quality cohort studies would be of value, in particular to more adequately address the comparative effectiveness of FMT vs. optimal medical management. Because recurrent CDI is defined by stool frequency plus a confirmatory microbiological test (which frequently can remain positive in the absence of symptoms), using standardized stool frequency assessment is of key importance. This is because exceeding a specific threshold typically initiates the evaluation for recurrent disease and can alter definitions of "disease recurrence" and estimates of treatment effectiveness. Additionally, multiple factors can influence stool frequency including knowledge of treatment received. Therefore, future trials should be evaluated with blinding of both patients and providers. Numerous examples exist from uncontrolled studies or small controlled studies showing large symptomatic improvements in conditions that are attributed to interventions which are later not confirmed or markedly attenuated when randomly compared to placebo, sham or blinded interventions (*eg,* knee arthroplasty for knee pain, acupuncture for numerous conditions, medications for restless legs syndrome or chronic insomnia). Future research is also needed to clarify important elements of FMT including: the number of CDI episodes after which FMT provides the greatest benefit (should it exist), optimal medical management (antibiotic type, dose, delivery and duration), and the preferred methods for fecal material and patient preparation, preferred donor selection, and optimal delivery and timing of FMT.

Conclusions

We found low strength evidence from small RCTs and case series that FMT may have a substantial effect and few short-term adverse events for adults with recurrent CDI. One small moderate quality RCT study found that FMT reduced symptom recurrence compared to standard CDI therapy that included vancomycin and one very small moderate quality RCT found FMT resulted in high symptom resolution rate that did not differ by delivery routes (nasogastric tube vs. colonoscopy). There is insufficient evidence on FMT for patients with refractory CDI and only a single case report for initial treatment of CDI. Evidence is insufficient whether treatment effects vary by FMT donor, preparation or delivery method.

ABBREVIATIONS TABLE

CDI	*Clostridium difficile* infection
C. difficile	*Clostridium difficile*
FMT	Fecal microbiota transplantation
FY	Fiscal year
GI	Gastrointestinal
RCT	Randomized, controlled trial
VA	Department of Veterans Affairs

EVIDENCE REPORT

INTRODUCTION

Since its discovery as the cause of pseudomembranous colitis in 1978,[1,2] *Clostridium difficile* (*C. difficile)* has become an increasingly important pathogen, now rivaling *Staphylococcus aureus* as a cause of nosocomial infections. Initially, *C. difficile* infection (CDI) was largely confined to patients with healthcare exposure; however, it is now also affecting those with no or limited contact with the healthcare system.[3] In the early 2000s an increase in the incidence and severity of CDI was observed, with a corresponding increase in mortality.[4] These increases were attributed to the emergence of an epidemic strain of CDI, associated with resistance to fluoroquinolones and increased toxin production. In part due to the effects of this epidemic strain, the US Centers for Disease Control and Prevention placed *C. difficile* into its top threat category of "urgent" in its first threat report on antimicrobial resistance,[5] a distinction shared only by carbapenem-resistant Enterobacteriaceae and drug-resistant *gonorrheae*.

Regardless of strain type, a major challenge in treating CDI is the high rate of recurrent disease. Recurrence (defined here as 3 or more unformed stools daily, plus a positive stool test for the presence of *C. difficile*, after resolution of the initial CDI episode) occurs in 15% to 30% of patients, and among those with a single episode of recurrence, the risk of subsequent episodes increases to 40% to 50%, with the risk of further recurrence increasing after each episode.[6,7] Patients in this cycle of multiple treatment/recurrence episodes can experience repeated hospitalizations, clinic visits, deconditioning, malnourishment, and continence issues. These effects are debilitating, and contribute to decreased quality of life and prolonged courses of antimicrobial treatment.[7] Antimicrobial treatment for these episodes of recurrent disease yields reported success rates between 30% and 80%, depending on the agent and duration of treatment selected.[6-10] Unfortunately, the optimal antimicrobial agent for recurrent CDI, and especially in cases of multiple recurrences, is unknown. The most robust data (*ie*, randomized trails) for the treatment of recurrent CDI is largely derived from studies including only those with a single recurrence,[6] or with a mean of 2.5 prior episodes.[8] Other studies of multiple recurrence episodes are of lesser quality, such as a series of 8 patients (with 4 to 8 prior CDI episodes) treated with vancomycin followed by rifaximin.[11] This regimen resulted in only a single episode of recurrence (88% success rate); a follow-up publication of 6 further cases from the same group resulted in a 66% success rate.[12] Another case series reported 100% success with the use of a prolonged vancomycin taper in 22 subjects with multiple relapses of CDI;[13] however, neither of these regimens has been studied prospectively.

Multiple other antimicrobials have been studied as treatments for CDI, including the commonly used metronidazole, and more rarely used agents such as nitazoxanide, bacitracin, and fidaxomicin, a novel agent recently approved by the U.S. Food and Drug Administration (FDA).[14] No agent has been shown to be superior to another for initial cure of CDI; however, fidaxomicin use results in a 10% decrease in recurrence compared to oral vancomycin (15% vs. 25%; P=.005).[6] Stated as the number-needed-to-treat, treating 10 patients with fidaxomicin will prevent one episode of recurrence. Whether fidaxomicin has a similar favorable effect when used for recurrent CDI is poorly understood.

Central to the pathogenesis of CDI is the alteration of the normal colonic bacteria, also termed the "colonic microbiome." The initial event that precedes most episodes of CDI is some insult to the colonic microbiome, typically via the administration of systemic antimicrobials, but also occurring after the administration of anti-neoplastic drugs. The normal colonic microbiome provides some degree of protection against pathogenic organisms. The mechanism of this protection is incompletely understood, but has been described as "colonization resistance," with a healthy microbiome theoretically making it more difficult for pathogens such as *C. difficil*e to colonize the colon.[15] Disruption of the microbial diversity of the normal colonic microbiome decreases this level of protection, and if viable *C. difficile* organisms or spores are ingested, the patient is at high risk of CDI. Unfortunately, most antimicrobial treatments for CDI are not specific to *C. difficile*, with the result that after successful treatment of a CDI episode, the colonic microbiome remains severely altered, and the patient is at high risk of recurrent CDI—especially since *C. difficile* spores and organisms are widely dispersed in the environment of patients with CDI, and are difficult to remove or destroy with usual household cleaning.[16]

Because CDI is characterized by severe alterations in the colonic microbiome, restoring the normal microbiome has been proposed as a method for preventing recurrence. The most widely utilized intervention has been the administration of probiotics, via a variety of delivery methods, including capsules, yogurt, kefir, and other nutritional products. These products provide only a limited number of microorganisms, whereas molecular techniques have demonstrated that the normal colonic microbiome includes thousands of different microorganisms, most of which do not grow on standard culture media, and are poorly characterized.[17] Accordingly, fecal microbiota transplantation (FMT) has been increasingly utilized as a treatment for patients with recurrent CDI, utilizing the rationale that to most effectively restore all the organisms that comprise the normal colonic flora, simply import the colonic microbiome of a healthy person. First reported in 1958 (prior to the discovery that *C. difficile* was the causative agent of pseudomembranous colitis),[18] FMT has now been performed in many patients, including more than 500 reported in the medical literature.[19] Despite the fact that the majority of cases are from non-controlled case series, the reported success rates of up to 100% have fueled interest in FMT. The recent publication of a randomized controlled trial (RCT) comparing FMT to antimicrobial treatment has further increased interest,[20] as has survey data demonstrating both patient and physician acceptance of the procedure.[21] Mechanistic studies of stool pre- and post-FMT using genetic sequencing have shown that FMT restores the microbial diversity of the colonic microbiome, possibly restoring the colonization resistance thought to be conferred by this complex mix of microbes.[22,23]

Several routes of delivery of FMT have been developed, including instillation of donor feces into the upper gastrointestinal (GI) tract via nasogastric or nasojejunal tubes, instillation of feces into the distal colon via retention enema, and instillation of feces into the entire colon via colonoscopy.[19] Whether one approach is superior to the others is unknown; similarly, the optimal amount of donor stool, the optimal pre-transplant regimen for the recipient, the necessary donor testing, and the long-term efficacy of FMT are also unknown. Additionally, the regulatory status of FMT is in limbo. In May of 2013 the FDA announced that it considered FMT the administration of a biologic agent to treat disease, thus making it an unapproved drug for which an investigational new drug (IND) application was required. However, in July 2013 the FDA announced that it would exercise "enforcement discretion" regarding the IND requirement for the

use of FMT to treat *C. difficile* infection not responding to standard therapies. The announcement specified that written informed consent should be obtained, and that patients receive counseling regarding both the experimental nature of FMT, and the potential risks.[24]

The status quo is that FMT appears to be a highly promising, yet unproven, treatment for a disease that is a leading cause of nosocomial infection, and spreading into the community. However, the evidence base supporting FMT is comprised largely of uncontrolled case series, and 2 recent randomized controlled trials. Additionally, the uncertain regulatory climate leaves clinicians facing significant uncertainty. Providers and health systems who currently do not provide FMT may find themselves struggling to balance the desire to provide the best available care versus the concern of adopting an unproven and unlicensed treatment.

PURPOSE OF REVIEW

The Minneapolis VA Evidence-based Synthesis Program was asked to conduct a systematic review of the evidence regarding the effectiveness of FMT for the treatment of CDI, in part to help guide policy makers within the Veterans Health Administration determine if the evidence supporting FMT was sufficient to implement FMT programs in their facilities. The topic was nominated by Jason Dominitz, MD, MHS on behalf of the VA Gastroenterology Field Advisory Committee. We address the following key questions:

KQ1. What is the effectiveness of fecal microbiota transplantation for recurrent CDI compared to standard therapy? Does effectiveness vary by method of transplantation?

KQ2. What is the effectiveness of fecal microbiota transplantation for refractory CDI compared to standard therapy? Does effectiveness vary by method of transplantation?

KQ3. What is the effectiveness of fecal microbiota transplantation as initial therapy for CDI compared to standard therapy? Does effectiveness vary by method of transplantation?

KQ4. What are the harms of fecal microbiota transplantation therapy compared to standard therapy for initial, recurrent, or refractory CDI? Do the harms vary by method of transplantation?

KQ5. Is the procedure acceptable to patients? Does patient acceptability vary by method of transplantation?

METHODS

TOPIC DEVELOPMENT

We developed the key questions and population, intervention, comparator, outcomes, timing, and setting (PICOTS) parameters for the review with input from operational partners and technical expert panel members representing gastroenterology and infectious diseases.

Population: Adults with initial, recurrent, or refractory CDI; we considered initial CDI to be the first occurrence of CDI in a particular subject, recurrent CDI was considered to be an episode of CDI occurring after previous treatment and favorable response for at least one prior episode of CDI, and refractory CDI was considered to be an episode of CDI that was not exhibiting a response to antimicrobial treatment

Intervention: Fecal microbiota transplantation

Comparator(s): No fecal microbiota transplantation or standard antibiotic therapy; comparative fecal microbiota transplantation methods (*eg,* duodenum vs. colonoscopy, different donor types)

Outcome(s): Resolution of symptoms (primary outcome), time to resolution of symptoms, recurrence, mortality, adverse events, readmission, hospitalization, duration of hospitalization

Timing: Short term cure defined as 3 months or less, long term cure defined as greater than 3 months

Setting: Any

SEARCH STRATEGY

We searched MEDLINE (OVID) for articles published from 1980 through May 2014. Our search was designed to identify studies of any design. We limited the search to studies involving human subjects published in the English language. Search terms included the following Medical Subject Headings (MeSH): *Clostridium* Infections; *Clostridium difficile*; Enterocolitis, Pseudomembranous; Feces; and Transplants. The full search strategy is presented in Appendix A. We also searched reference lists of existing systematic reviews and included studies.

STUDY SELECTION

Abstracts of citations identified from the literature search were assessed for relevance by 2 investigators. We included clinical trials, case series, and case reports of FMT for treatment of recurrent, refractory, or newly diagnosed CDI. We excluded the following:

1. Studies that were not about FMT for CDI or pseudomembranous colitis,
2. Studies that did not report outcomes of interest,
3. Studies that were not case series or were case reports that did not report adverse events, and
4. Studies done in a pediatric/adolescent population.

Full text reports of studies identified as potentially eligible (or indeterminate, *eg,* title only) were obtained for further review using the inclusion and exclusion criteria described above. Each

article was independently reviewed by 2 investigators. Reasons for excluding a study at full text review were noted.

DATA ABSTRACTION

Eligible studies were reviewed for outcomes of interest by investigators. Study characteristics (including inclusion/exclusion criteria and intervention characteristics), patient characteristics, donor characteristics, and outcomes data were abstracted onto tables by one investigator and verified by a second. In many cases, it was difficult to ascertain whether our primary outcome, resolution of symptoms, was due to the pre-FMT antimicrobials for CDI, the FMT procedure, or a combination of the two. Similarly, the outcomes of resolution and recurrence were often combined as "resolution of diarrhea without relapse," or "durable resolution."

QUALITY ASSESSMENT

We assessed the quality of RCTs based the following criteria: allocation concealment, blinding, analysis approach, and description of withdrawals – a modification of the Cochrane approach to determining risk of bias.[25] We did not assess quality of the case series; the value of assessing quality of case series has not been established.[26]

DATA SYNTHESIS

We described and qualitatively compared the patient characteristics, study characteristics, interventions, and findings of included studies. Due to limited reporting we summarized most outcomes narratively. We calculated weighted resolution rates and 95% confidence intervals for the studies of FMT for recurrent CDI stratified by FMT method. We used Comprehensive Meta-analysis Version 2.2 for these calculations.[27] There were insufficient studies of refractory CDI or FMT as initial therapy for CDI for numerical synthesis.

RATING THE BODY OF EVIDENCE

We did not formally rate the overall strength of the body of evidence. Conventional methods for rating strength of evidence, as reported by Owens et al.,[28] would classify case series as high risk of bias. Therefore, strength of evidence would typically be considered insufficient or low at best.

PEER REVIEW

A draft version of this report was reviewed by clinical content experts as well as clinical leadership. Their comments and our responses are presented in Appendix B. The report was modified as needed.

RESULTS

LITERATURE FLOW

Our literature search yielded 161 abstracts or titles (Figure 1). After reviewing the abstracts we excluded 100 and performed full text review of 61 articles. We excluded 51 articles and included 10. A hand-search of reference lists of systematic reviews and included studies and suggestions from technical expert panel members and peer reviewers yielded another 21 articles for a total of 31 included studies (2 RCTs, 25 case series, and 4 case reports).

OVERVIEW

Study, patient, and donor characteristics for each of the included studies[18,20,29-51] are presented in Appendix C, Table 1. Outcomes following initial FMT are presented in Appendix C, Table 2; outcomes following repeat FMT are presented in Appendix C, Table 3. Table 1 provides an overview of outcomes reported in each study organized by CDI status and method of FMT.

Figure 1. Literature Flow Chart

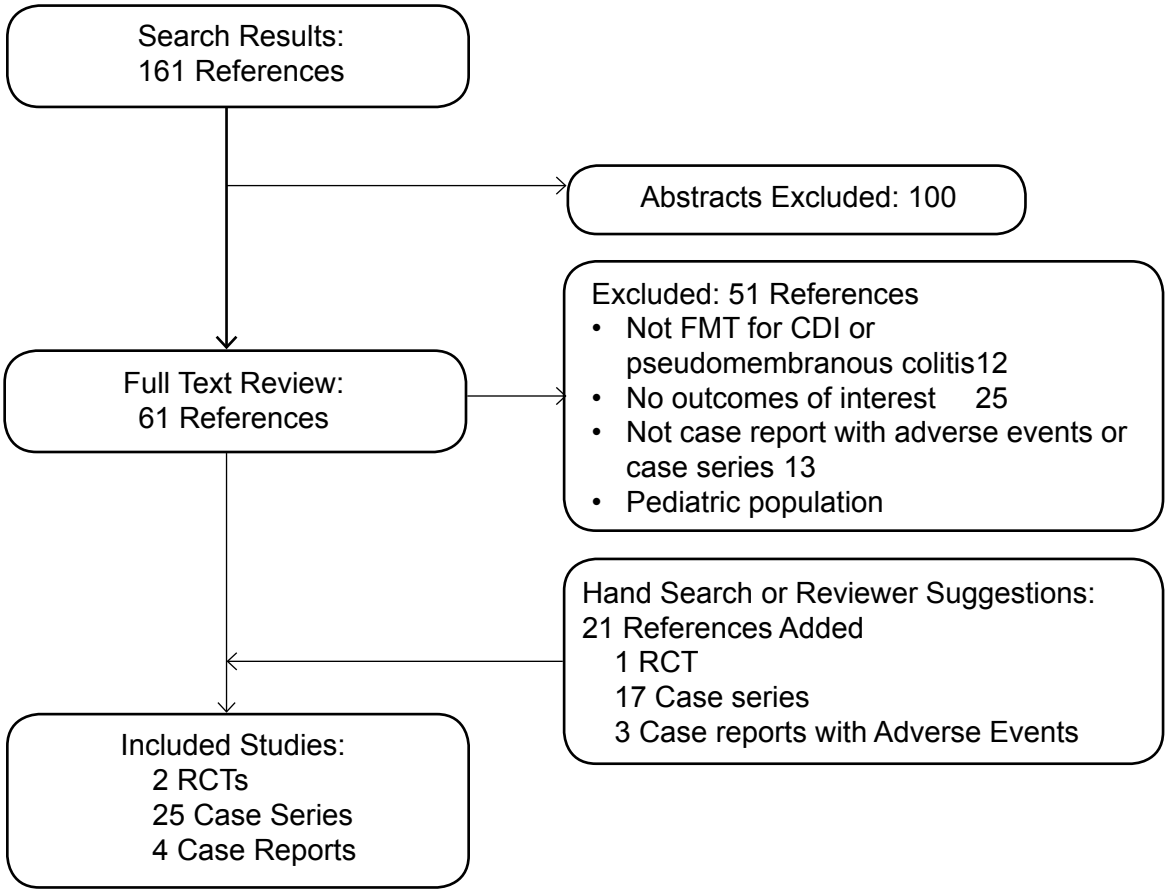


Table 1. Outcomes Reported by CDI Status and Method of Transplantation

Author, Year Design, N	Reported Resolution of Symptoms	Time to Resolution of Symptoms	Recurrence	All-Cause Mortality	Adverse Events
RECURRENT CDI – UPPER GASTROINTESTINAL TRACT (6 studies; n = 198 [171 receiving FMT])					
Youngster, 2014[29] RCT, N = 10 (upper GI)	✓		✓	✓	✓
Van Nood, 2013[20] RCT, N = 43[a]	✓		✓	✓	✓
Rubin, 2013[30] RCS, N = 74 (72 adults)	✓			✓	✓
Garborg, 2010[31] RCS, N = 40	✓	✓		✓	
MacConnachie, 2009[32] RCS, N = 15	✓		✓	✓	✓
Aas, 2003[33] RCS, N = 18	✓	✓	✓	✓	✓
RECURRENT CDI – COLONOSCOPY (10 studies; n = 237)					
Youngster, 2014[29] RCT, N = 10 (colonoscopy)	✓		✓	✓	✓
Cammarota, 2014[34] RCS, N = 3	✓	✓ **(for 1/3 patients)**		✓	✓
Pathak, 2014[35] RCS, N = 12	✓	✓	✓	✓	✓
Patel, 2013[36] RCS, N = 31[b]	✓	✓	✓	✓	✓
Hamilton, 2012[37] RCS, N = 43	✓		✓	✓	✓
Kelly, 2012[38] RCS, N = 26	✓	✓	✓		
Mattila, 2012[39] RCS, N = 70	✓		✓	✓	✓
Mellow, 2011[40] RCS, N = 13 (12 recurrent)	✓	✓	✓	✓	
Rohlke, 2010[41] RCS, N = 19	✓		✓		
Yoon, 2010[42] RCS, N = 12	✓	✓ **by definition**			✓

Author, Year Design, N	Reported Resolution of Symptoms	Time to Resolution of Symptoms	Recurrence	All-Cause Mortality	Adverse Events
RECURRENT CDI –ENEMA (5 studies; n = 45)					
Emanuelsson, 2013[43] RCS, N = 23	✓	✓ by definition	✓		✓
Silverman, 2010[44] RCS, N = 7	✓		✓		✓
Gustafsson, 1999[45] PCS, N = 6	✓	✓	✓		
Paterson,1994[46] RCS, N = 7	✓				
Tvede, 1989[47] RCS, N = 2	✓		✓	✓	
RECURRENT CDI –UPPER GASTROINTESTINAL TRACT AND COLONOSCOPY (1 study; n = 27)					
Dutta, 2014[48] PCS, N = 27	✓	✓	✓		✓
REFRACTORY CDI – COLONOSCOPY (2 studies; n = 5)					
Weingarden, 2013[49] RCS, N = 4	✓	✓	✓	✓	
Mellow, 2011[40] RCS, N = 1 (from series)	✓		✓	✓	
REFRACTORY CDI –ENEMA (3 studies; n = 112)					
Lee, 2014[50] RCS, N = 94	✓		✓	✓	✓
Bowden, 1981[51] RCS, N = 16 (15 adults)	✓	✓		✓	✓
Eiseman, 1958[18] RCS,N = 3 (Patients 1, 2, 4)	✓	✓		✓	
INITIAL THERAPY FOR CDI – ENEMA (1 study; n=1)					
Eiseman, 1958[18] RCS, N = 1 (Patient 3)	✓	✓		✓	

CDI = *Clostridium difficile* infection; FMT = fecal microbiota transplant; PCS = Prospective Case Series; RCT = Randomized Control Trial

[a]Outcomes reported for n=42 (16 of whom received FMT)

[b]Outcomes reported for n=30

KEY QUESTION #1: What is the effectiveness of fecal microbiota transplantation for recurrent CDI compared to standard therapy? Does effectiveness vary by method of transplantation?

Key Findings

- The vast majority of information about FMT effectiveness for recurrent CDI is derived from case series thus severely limiting effectiveness assessment and precluding comparative effectiveness either to standard therapy or to alternative methods of FMT.
- One small moderate quality RCT (n=43, 16 receiving FMT) reported that significantly more patients achieved resolution following FMT (81%) than either a course of vancomycin (31%) or a course of vancomycin plus bowel lavage (23%). Resolution rates in patients treated with vancomycin were low.
- One small (n=20) RCT found no statistically significant difference in resolution between groups treated via nasogastric tube (6/10, 60%) or colonoscopy (8/10, 80%).
- For patients with recurrent CDI (n=480), the pooled response rate was 83% (95%CI 77%, 87%).
- Serious adverse events or adverse events related to FMT were rare except in a series of immunocompromised patients where 15% experienced serious adverse events.

Effectiveness of FMT Compared to Standard Therapy

We identified only one small trial that compared FMT for recurrent CDI to standard therapy.[20] This moderate quality RCT compared FMT, delivered via nasoduodenal tube, to either a course of vancomycin or a course of vancomycin plus bowel lavage. The trial was terminated early because of a significant difference in recurrence between the FMT group and the 2 control groups, driven in part by lower-than-expected response rates in the 2 control groups, resulting in a total enrollment of 42 patients (16 of whom received FMT). Resolution of symptoms without relapse within 10 weeks after FMT was reported in a significantly higher percentage of patients receiving FMT (81%) compared to vancomycin (31%) or vancomycin plus bowel lavage (23%).

The low success rate in the control groups was highlighted in subsequent letters-to-the-editor.[52,53] The authors responded[54] that most enrollees had 4 episodes of CDI prior to enrollment, making them a different population than other trials which enrolled those with at most a single recurrence, and reporting higher vancomycin success rates.[6,10] The study protocol assumed a 60% success rate for the control groups, which dictated the original power calculations of the trial.

Additional details of the study are reported below under "Recurrent CDI – Upper Gastrointestinal Tract."

Effectiveness by Method of Transplantation

Patient Characteristics and Selection

One feasibility study addressed whether effectiveness varied by method of transplantation. The RCT compared FMT via colonoscopy to FMT via nasogastric tube.[29] The study was conducted in the United States and enrolled 20 patients between 7 and 90 years of age (mean 55 years), Forty-five percent were male and 25 percent were hospitalized at the time of FMT. Included

patients had either 3 or more episodes of mild to moderate CDI (and failed vancomycin taper) or 2 or more episodes of severe CDI (requiring hospitalization and associated with significant morbidity). Diagnosis was by positive toxin. Prior treatment included vancomycin taper (95%) and fidaxomicin (60%).

Donor Selection

Five unrelated, volunteer donors were identified. Donors had no significant past medical history, were taking no medications (including no antibiotics in the past 6 months), were of normal BMI, and underwent a physical examination and general laboratory screening tests. Donor feces were screened within 2 weeks of donation and prepared inocula were frozen and stored for 4 weeks to allow donors to be tested again for HIV and hepatitis B and C just prior to administration of the frozen material. Donors were asked to avoid eating common allergens (tree nuts, eggs, peanuts, and shellfish) within 5 days of stool donation.

Patient Preparation

For patients in the nasogastric tube group, oral omeprazole was taken for 48 hours prior to the procedure. Patients in the colonoscopy group underwent standard bowel preparation.

Fecal Material Preparation and Delivery

Fecal material was combined with normal saline and 10% glycerol. The material was frozen for up to 156 days. It was estimated that each sieved inoculum was derived from 41 grams of feces. In the nasogastric tube group, placement of the tube was confirmed with radiography and 90 cc of material was administered. The tube was removed and patients were asked to drink a glass of water. In the colonoscopy group, 90 cc of fecal material was administered to the right colon. The material was then diluted to 250 cc for adults and 160 cc for children. Loperamide was given at the time of the procedure. If the procedure was unsuccessful, patients who wanted a second procedure could choose the route of administration. Inoculum from the same donor was used. Additional study information is presented in Appendix C, Table 1.

Outcomes

After initial FMT, 14 of 20 patients experienced clinical resolution without antibiotics for CDI and without relapse within 8 weeks of FMT, 8 of 10 (80%) in the colonoscopy group and 6 of 10 (60%) in the nasogastric tube group. The difference between groups was not statistically significant (P=.63) (Figures 2 and 3, Appendix C, Tables 2 and 3). One patient in the nasogastric tube group refused a second FMT. All 5 patients who agreed to a second FMT chose nasogastric administration. The second procedure was successful in the 2 patients initially treated via colonoscopy and in 2 of the 3 patients initially treated via nasogastric tube. The overall rate of clinical resolution was 100% for the colonoscopy group and 80% for the nasogastric tube group, a non-statistically significant difference (P=.53). No relapses were observed during the 8 week follow-up.

Mild abdominal discomfort and bloating, likely related to the FMT procedure, was reported in 4 patients (20%). One of the pediatric patients experienced a transient fever on the day after colonoscopy. None of the serious adverse events was considered related to FMT. Serious adverse

events included 2 deaths (one at week 12 and one at week 21 post-FMT), one patient with adenocarcinoma of the esophagus, and one patient with Fournier's gangrene.

The authors noted that an additional 11 patients had a FMT via nasogastric tube using frozen inocula from unrelated donors. The success rate in that group was 91% but it is unclear if that was after one or multiple procedures.

Results by Method of Transplantation

We describe below findings from the RCTs and case series of patients receiving FMT for recurrent CDI via upper GI tract, colonoscopy, enema, or a combination of upper GI and colonoscopy routes. We pooled results for the primary outcome of resolution of symptoms after initial FMT (Table 2). Results for resolution of symptoms after the administration of multiple FMTs are provided when reported by the authors. A combined FMT via the upper GI tract and colonoscopy had the highest overall success rate, followed by colonoscopy alone, upper GI tract, and enema. However, the only direct comparison between 2 methods was the comparative effectiveness trial of Youngster et al., which (although limited by a small sample size) demonstrated no significant difference.[29] Thus, we recommend against comparing success rates across trials.

Table 2. Pooled Results for Reported Resolution of Symptoms after Initial FMT for Recurrent CDI

FMT Method	Pooled Resolution Rate (95% Confidence Interval	Number of Studies (Total N Analyzed)
Upper GI Tract	0.77 (0.70, 0.83)	6 (171)[a]
Colonoscopy	0.89 (0.82, 0.93)	10 (237)[a]
Enema	0.74 (0.56, 0.96)	5 (45)
Upper GI Tract and Colonoscopy	0.98 (0.77, 1.00)	1 (27)
All Methods	0.83 (0.77, 0.87)	21 (480)[a]

[a]10 patients from Youngster 2014[29] included in Upper GI Tract and Colonoscopy rows; total number of studies is one less than sum of individual rows

Recurrent CDI – Upper Gastrointestinal Tract

Key Findings

- Information about FMT for recurrent CDI via the upper GI tract is largely derived from case series (n=26 patients in 2 RCTs, n=145 patients in 4 case series).
- Resolution of symptoms at 3 months or less occurred in the large majority of patients with recurrent CDI treated with FMT via the upper GI tract (77% [range 60% to 83%]). All but one study reported "resolution without recurrence" over follow-up periods of 8 to 13 weeks.
- One small moderate quality RCT (n=43, 16 receiving FMT) reported that significantly more patients achieved resolution following FMT (81%) than either a course of vancomycin (31%) or a course of vancomycin plus bowel lavage (23%). Resolution rates in patients treated with vancomycin were low.
- Time to resolution of symptoms was typically within 24 hours (2 series).

- Adverse events were transient in the RCT comparing FMT to standard care. In the upper GI arm of the comparative effectiveness RCT, one patient was hospitalized with Fournier's gangrene. One case series reported upper GI bleeding in one patient. Another series reported one patient with possible peritonitis 3 days after FMT.

Overview of Studies (Tables 3 and 4; Appendix C, Table 1)

Two RCTs[20,29] and 4 case series[30-33] reported results of FMT administered to patients with recurrent CDI via the upper GI tract. Three studies were done in the United States[29,30,33] including 2 by the same group but at different time periods,[30,33] 2 studies were conducted in Europe,[20,31] and one was done in the United Kingdom.[32] In 4 studies, patients were treated in either hospital or outpatient settings.[20,29,31,33] One study treated all patients in a hospital setting[32] while the one study did not report treatment location.[30]

Table 3. Summary of Patient Baseline Characteristics – Studies of Upper GI Tract Infusion of Donor Feces

Patient Characteristic	Mean (range) Unless Otherwise Noted	Number of Trials Reporting
Number of patients	Total = 199 (range 15-74)[a]	6
Age (years)	73 (59-82)	5[b]
Gender, male (%)	40 (7-58)	6
Time from diagnosis to FMT (months)	7 (3-12)	3
Recurrences prior to FMT	3 (3-5)	4
Treatment location (% inpatient)	48% inpatient 52% outpatient	4[c]
Follow-up (months)	2 (2-4)	6

[a]Includes pediatric patients from Youngster 2014[29] and Rubin 2013[30] and all patients (n=43) in the van Nood 2013[20] RCT because baseline characteristics were not reported separately
[b]One additional study reported median age = 63 years
[c]One additional study reported inpatient and outpatient procedures but did not report numbers of patients

Patient Characteristics and Selection

There were 43 patients in the RCT comparing FMT to standard therapy, 16 of whom were treated with FMT.[20] There were 10 patients (including 1 or 2 pediatric patients) in the upper GI tract arm of the RCT comparing 2 approaches to FMT.[29] The 4 case series enrolled 145 adult patients. One series included 2 pediatric patients[28] and another series enrolled the same patient twice for CDI episodes 2 years apart.[31] We report patient baseline characteristics for all 74 patients in the series with 2 pediatric patients but outcomes for the 72 adults.[30] In that series, median age, including the pediatric patients) was 63 years and 35% of the patients were male. In the other studies, mean ages ranged from 59 years[29] to 82 years[32] and 7%[32] to 58%[20] were male. None of the studies reported race or ethnicity or the participants.

One RCT and 2 of the case series[20,31,32] required that patients have at least one recurrence of CDI. The second RCT and the other 2 case series[29,30,33] required at least 2 recurrences. The method of diagnosis was diarrhea with positive *C. diff*icile toxin by PCR or EIA in all studies. Few patient exclusion criteria were reported. Patients with prolonged or significantly compromised immunity and patients who were pregnant were excluded from the RCTs.[20,29] Patients with anatomic

contraindications to FMT via either upper GI tract or colonoscopy approaches, delayed gastric emptying syndrome, recurrent aspirations, or significant allergy to foods not excluded from the donor diet were excluded from the comparative effectiveness RCT.[29] Patients with a surgically shortened GI tract were excluded from one of the case series.[30] All patients had been treated with vancomycin and/or metronidazole prior to FMT. One RCT and one case series also reported that some patients had received fidaxomicin. One study reported giving patients antibiotics before FMT to reduce the frequency of diarrhea and to "lower the infectious burden of vegetative *C. difficile*.[30] Another reported treating patients with antibiotics until symptoms were reduced.[31] A third reported that antibiotics were given to reduce the *C. difficile* load and the effect was "reduced or eliminated diarrhea in most patients."[33] In all studies, antibiotics were discontinued between 12 hours[32] and 48 hours[29] before FMT.

Donor Selection

In the RCT comparing FMT approaches, donors were volunteers unrelated to the patients.[29] Additional donor characteristics are described above in the section Effectiveness by Method of Transplantation. In the RCT comparing FMT to standard therapy, donors were 15 volunteers (including relatives), under age 60 years, who were screened for HIV, hepatitis, and other transmissible diseases.[20] If CDI did not resolve and the patient underwent a second FMT, stool from a different donor was infused.

Among the case series, one reported that donors for 15 of the 18 participants were family members.[33] Donors were screened for HIV, hepatitis, and other viruses and pathogens. In the remaining series, donors were either "related," close relatives or close household members although the exact number of donors was not reported.[30-32] Two series reported screening for HIV, hepatitis, and other conditions[30,31] while the third reported screening for blood borne viruses, syphilis, and enteropathogens.[32] None of the studies screened donors for auto-immune disease or cancer. Two of the studies included only donors with no antimicrobial use either within the past 3 months[30] or the past 6 months.[33]

Patient Preparation

Patient preparation for FMT varied. In the comparative effectiveness RCT, patients in the upper GI tract group were given oral omeprazole for 48 hours prior to the procedure.[29] In the RCT comparing FMT to standard therapy, patients were given oral vancomycin (500 mg, 4 times per day for 4 to 5 days). On the last day of vancomycin (which was the day before FMT) bowel lavage was performed using 4 liters of macrogel solution.[20] In the 4 case series, patients also received oral vancomycin, discontinuing treatment the day prior to FMT. One series required patients who were undergoing FMT via gastroscope to fast from midnight through the time of the procedure.[31] Three series administered a proton pump inhibitor prior to FMT.[30,32,33]

Fecal Material Preparation and Delivery

The amount of fecal material used and the method of delivery are shown in Table 4. All of the studies used fresh material except for the comparative effectiveness RCT which froze the fecal material.[29]

Table 4. Amount of Fecal Material and FMT Procedure – Recurrent CDI, Studies of Upper GI Tract Infusion of Donor Feces

	Youngster 2014[29]	Van Nood 2013[20]	Rubin 2013[30]	Garborg 2010[31]	MacConnachie 2009[32]	Aas 2003[33]
Fecal Material	NR	50 grams or more	30 grams	50-100 grams	30 grams	30 grams
Liquid	NR	500 cc saline	50-70 ml saline	250 ml saline	150 ml saline	50-70 ml saline
Amount and method of delivery	90 cc via nasogastric tube	500 cc via nasoduodenal tube	25 ml via nasogastric tube (85% of patients), PEG (5%), or gastroscope (9%)	200 ml via gastroscope (95%) or colonoscope (5%)	30 ml via nasogastric tube	25 ml via nasogastric tube

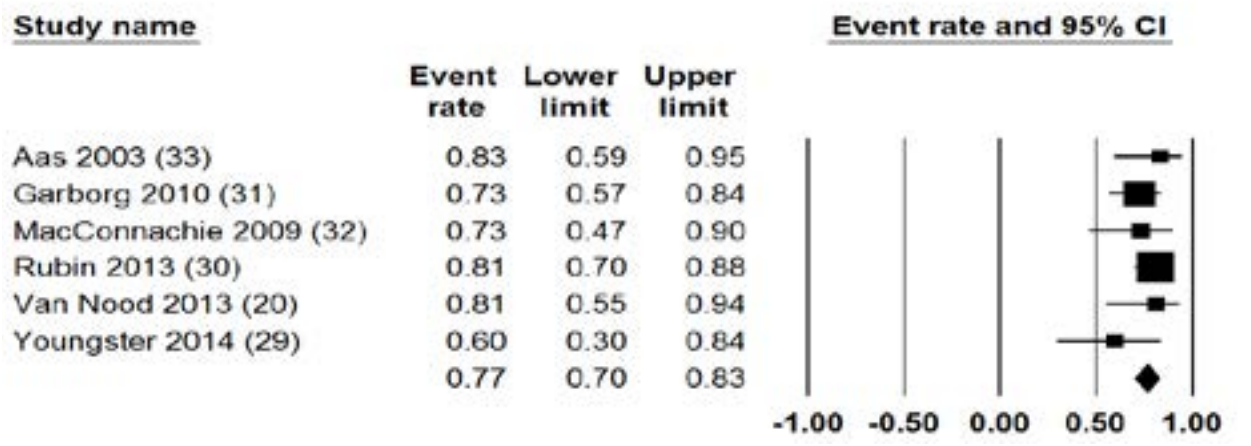
PEG = percutaneous endoscopic gastrostomy

Outcomes (Figure 2, Table 5, and Appendix C, Tables 2 and 3)

As noted above, in the RCT comparing FMT to standard care, 13 of 16 patients (81%) randomized to FMT experienced cure without relapse within 10 weeks after initiation of FMT.[20] The percentage of patients with a positive response in the FMT group was significantly higher (P<.01) than in either the vancomycin group (4/13, 31%) or the vancomycin plus bowel lavage group (3/13, 23%).

In the upper GI tract arm of the comparative effectiveness RCT, the percentage of patients with clinical resolution without antibiotics for CDI and without relapse within 8 weeks of FMT was 60%.[29] Among the case series, one reported a durable clinical resolution (within 60 days of FMT) in 81% of patients.[30] Another reported resolution in 83% based on medical record documentation of clinical resolution during 90 days after FMT or no documentation of *C. difficile* colitis, treatment for *C. difficile* colitis, or repeated hospitalizations related to diarrhea.[33] Pre-FMT antibiotics were noted to have reduced or eliminated diarrhea in most patients prior to FMT. Another series that treated patients with antibiotics prior to FMT until symptoms were reduced and monitored contacts with the clinic for CDI symptoms within 80 days after FMT reported that 73% had no further contact.[31] Another series reported that 73% were symptom free at follow-up of 4 to 24 weeks.[32]The weighted resolution rate was 77% (Figure 2, Table 5). Neither the RCTs nor the case series reported follow-up beyond 3 months.

Figure 2. Reported Resolution of Symptoms after Initial FMT for Recurrent CDI, Upper GI Tract Infusion of Donor Feces



Two case series commented on time to resolution of symptoms. In both series, resolution usually occurred within 24 hours of FMT.[31,33]

Four studies reported recurrence. In the RCT comparing FMT to standard therapy, 3 of 16 patients (19%) in the FMT group underwent a second procedure at 14, 50, and 53 days after initial randomization.[20] In 2 case series, recurrence was observed in 27%[32] and 6%[33] with the lower value in a series that reported diarrhea had been reduced or eliminated prior to FMT. No recurrences were reported in the comparative effectiveness RCT.[29]

Table 5. Outcomes – Recurrent CDI, Studies of Upper GI Tract Infusion of Donor Feces

Outcome	Mean (Range) Unless Noted	Number of Trials Reporting
Number of patients (n)	Total = 171	6
Resolution without recurrence:		
≤3 months with first FMT (%)	77 (60-83)	6
>3 months after first FMT (%)	NR	
Recurrence (%)	14 (0-27)	4
All-Cause mortality (%)	4 (0-13)	5[a]

[a]One additional study reported 2 deaths in 20 patients (10%) including 10 patients treated via upper GI tract and 10 patients treated via colonoscopy[29]

All-cause mortality, reported in all 6 studies, ranged from 0%[30,32] to 13%.[31] The 5 deaths among 40 patients in the series with the highest mortality rate occurred at 3 weeks to 2 months following FMT. The patients were non-responders to FMT and all had serious comorbidities. In the RCT comparing FMT to standard care, there were no deaths in the FMT group or the vancomycin plus bowel lavage group.[20] There was one death in the vancomycin group. In the RCT comparing an upper GI tract approach to colonoscopy, there were 2 deaths among the 20 patients randomized.[29] Results were not reported by treatment group. This study also reported mild abdominal discomfort and bloating in 4 patients (20% of the total group randomized), transient fever in one patient (5%), and serious adverse events in 4 patient (20%). None of the serious adverse events were considered related to FMT. One patient treated via upper GI was hospitalized for Fournier's gangrene. The group assignment of other patients with adverse events was not reported. Adverse events were generally transient in the RCT comparing FMT to standard care (resolving within 3 hours in most cases) but included diarrhea (94%), cramps (31%), belching (19%), and nausea (6).[20] Other reported events included upper GI bleeding (1/15, 7%),[32] and possible peritonitis and pneumonia (1/18, 6%),[33] although the relatedness of these events to the FMT procedures are difficult to ascertain based on the level of detail provided.

In the RCT comparing FMT to standard therapy, FMT was repeated in 3 patients who failed initial treatment.[20] Two of the 3 (67%) patients had symptom resolution. In the RCT comparing FMT approaches, FMT was repeated in 3 of 4 patients in the upper GI tract group who failed initial therapy.[29] Two had symptom resolution following the second procedure. Two of the case series reported repeat FMT. In one series, 6 of 11 patients who failed initial treatment underwent a second procedure with 4 of 6 (67%) experiencing resolution.[31] In the other series, one of 4 (25%) patients eligible for repeat FMT was treated and achieved resolution.[32] Overall, 13 of 39 patients (33%) who underwent a second procedure had symptom resolution.

Few data were reported for hospitalization. One patient in the RCT comparing FMT to standard therapy was hospitalized 56 days after FMT with symptomatic choledocholithiasis.[20] It was unclear whether this patient was hospitalized at the time of FMT. In the RCT comparing methods of FMT, 2 patients were reported hospitalized with serious adverse events unrelated to FMT but it was unclear if they were hospitalized at the time of FMT. One was the patient noted above. In one series, some patients (exact numbers not reported) were hospitalized and some were ambulatory at the time of FMT.[31] It was reported that patients treated while hospitalized were "usually discharged within a few days." In another series, all patients were hospitalized.[32] Ten of the 15 patients (67%) were discharged on the day after FMT.

Recurrent CDI – Colonoscopy

Key Findings

- Mean resolution without CDI recurrence at less than 3 months occurred in 90% (range 73% to 100%) of patients with recurrent CDI treated with FMT via colonoscopic infusion of donor feces based on one arm of an RCT and 9 case series (total n=237). In the RCT, resolution after initial FMT was observed in 80% of the colonoscopy group compared to 60% of the nasogastric tube group (P=.63).
- Time to resolution of symptoms was typically within a few days (range "hours" to 7 days) (6 case series).
- All-cause mortality ranged from 0% to 25% (mean=11%) over follow up periods of one week to 29 months (6 case series). None of the deaths were attributed to FMT.
- Among immunocompromised patients, one case series (n=90), reported resolution after initial FMT in 62 (78%). Twelve (15%) serious adverse events (including deaths and hospitalizations) and 12 (15%) other adverse events were reported.

Overview of Studies (Tables 6 and 7; Appendix C, Table 1)

One arm of an RCT (n=10)[29] and 9 case series (7 retrospective, 2 prospective, n=227)[34-42] using colonoscopic infusion of donor feces were eligible for inclusion. One additional report of FMT via colonoscopic infusion was not included in this analysis because results for many of the patients in the series had already been reported.[55] The RCT and 7 of the case series were conducted in the United States.[29,35-38,40-42] The remaining 2 case series were conducted in Italy[34] and Finland.[39]

Patient Characteristics and Selection

Inclusion criteria were somewhat heterogeneous. All patients had recurrent CDI. Three studies required 3 recurrences[29,38,40] and one study required 2 recurrences.[37] The method of diagnosis in most studies was diarrhea with positive *C. difficile* toxin by PCR or EIA.[29,34,36,37,40-42] Both toxin and culture were used in one study[39] and method was not reported in 2 studies.[35,38] Exclusion criteria included gastrointestinal tract not suitable for FMT,[29,35] recurrent aspirations,[29] significantly compromised immunity,[29] history of significant allergy to foods not excluded from donor diet,[29] less than one year life expectancy,[37] terminal illness,[40] and inflammatory bowel disease or Crohn's disease.[42]

Baseline characteristics of enrolled patients are presented in Table 6. The mean age was 65 years with 32% male. The mean time from diagnosis to FMT was 9.6 months (range 4.4 to 12.6 months).

Table 6. Summary of Patient Baseline Characteristics – Studies Using Colonoscopic Infusion of Donor Feces

Patient Characteristic	Mean (range) Unless Otherwise Noted	Number of Trials Reporting
Number of Patients	Total = 237[a] (range 12-70)	10
Age (years)	64 (49-73)	10
Gender, male (%)	33 (8-66)	10
Time from diagnosis to FMT (months)	9 (4-13)	7
Recurrences prior to FMT	4 (3-6)	6
Treatment location (% inpatient)	13 (0-100)	9
Follow up (months)	10 (2-27)	6

[a]One additional patient lost to follow up (Patel 2013[36]) and one additional patient with refractory disease reported under KQ2 (Mellow 2011[40])

Immune status was explicitly reported in 2 studies. In one study, there were 3 patients on chronic prednisone, 2 with hypogammaglobulinemia, one with liver transplant, one with renal transplant, and one on methotrexate.[36] Another study reported no comorbid conditions reflective of immunosuprression.[42]

Donor Selection

One study used exclusively non-related donors.[29] Two studies used exclusively family members[35,42] while 2 studies used volunteer donors as well as family members and household contacts[39] or family members and friends.[37] Three studies allowed family members and friends or housemates.[36,38,41] One study reported only that donors were chosen by patients,[40] and one study reported that 2 of 3 donors were family members with no information about the third donor.[34] In studies specifying relationship to patient, spouses or partners were donors in 17% to 74% of cases, children or grandchildren in 27% to 67% of cases, other family members in 4% to 21%, and friends or housemates in 3% to 17%.

Nine studies required that donors had no recent antibiotic use;[29,34-41] some specified no use within 3 months of FMT,[35-38] 2 studies required 6 months,[29,39] and one required 2 months.[40] All studies screened donors for HIV, *C. difficile*, hepatitis B, hepatitis C, and stool ova and parasites. Two studies screened for autoimmune disease based on questionnaire,[37,40] one excluded donors taking immunosuppressive medications,[34] while one excluded donors with any significant past medical history.[29] Three studies screened for cryptosporidium,[34,36,37] 6 for hepatitis A,[29,34-36,38,40] 7 for syphilis,[29,34-36,38-40] 7 for enteric pathogens via stool culture, [29,34-36,38-40] and one for microspora and HTLV I/II.[36] One recent study required donors to avoid common food allergens (tree nuts, eggs, peanuts, and shellfish) for 5 days prior to stool donation.[29] This study also escrowed stool donations for 5 weeks so donors could be retested for HIV, hepatitis B, and hepatitis C. In 2 older studies, screening of donors was at the discretion of the recipient[41] or treating physician.[42]

Patient Preparation

All of the studies reported that patients received conventional treatment for CDI prior to FMT. Commonly reported antimicrobials were vancomycin and metronidazole. Other agents included

fidaxomicin, rifaximin, probiotics), intravenous immune globulin, and nitazoxanide. In one study, vancomycin or metronidazole were given until a reduction of symptoms occurred.[39] Conversely, another series reported that 12 of 13 patients were hospitalized or homebound due to diarrhea or weakness at the time of FMT.[40]

Where reported, studies required that patients stop their antimicrobials, if taking, at various intervals prior to FMT. One study stopped treatment 4 hours prior to FMT,[36] one at 24 hours prior to FMT,[35] one at 36 hours prior to FMT,[39] 2 at 48 hours prior to FMT,[37,40] and 2 at least 48 hours prior to FMT.[29,38,42]

In addition, all but one of the studies[42] reported that the patients received bowel preparation (standard, split dose, or low volume) prior to FMT.

Fecal Material Preparation and Delivery

Most studies reported using fresh (within 6 hours of collection) donor stool specimens, the exceptions being one using thawed inoculum[29] and one using both fresh and frozen stool.[37] Preparation and delivery of the FMT material is reported in Table 7.

Table 7. Amount of Fecal Material and Liquid Used in FMT – Recurrent CDI, Studies Using Colonoscopic Infusion of Donor Feces

	Youngster 2014[29]	Cammarota 2014[34]	Pathak 2014[35]	Patel 2013[36]	Hamilton 2012[37]	Kelly 2012[38]	Mattila 2012[39]	Mellow 2011[40]	Rohlke 2010[41]	Yoon 2010[42]
Fecal Material	NR	NR	6-8 tablespoons	NR	50 g	6-8 tablespoons	20-30 mL	NR	NR	NR
Liquid (Saline unless noted)	NR	NR	1 L tap water	NR	250 mL	800-900 mL sterile water or saline	100-200 mL water	NR	200-300 cc	NR
Amount Delivered/ Location	90 cc of inoculum to right colon then further diluted to 250 cc for adults (160 cc for pediatric patients)	250-500 mL	400-500 cc At farthest point (cecum or terminal ileum) then 50-60 cc every 10 cm during withdrawal	NR Terminal ileum or cecum	220-240 mL Terminal ileum and cecum; 50 mL to areas of diverticulosis for some patients	500-960 mL Starting at terminal ileum or cecum	100 mL Cecum	300-600 mL Terminal ileum (100mL), cecum (50%), areas of diverticular disease (remainder)	Initially infused during withdrawal; later all material instilled at proximal-most extent of exam	250-400 cc Injected in 10-20 cc increments every 5-10 cm during withdrawal

Outcomes (Figure 3, Table 8, Appendix C, Tables 2 and 3)

Reported resolution of symptoms with follow-up of 3 months or less ranged from 73% to 100% (Figure 3, Table 8). The resolution rate was 90% when actual values were used for studies with 100% resolution.[34,42] Across studies, the definitions of response varied and included resolution of diarrhea with success rates of 92% and 96%,[38,40] resolution of multiple signs and symptoms (including diarrhea, fever, cramps, white cell count, and vitals) (92%, 94%, and 100% success),[35,39,42] resolution of infection (95% success),[41] resolution of symptoms and absence of relapse within 8 weeks (80% and 100% success),[29.34] resolution of diarrhea and negative stool testing (86% success),[37] and resolution or greater than 75% improvement in symptoms (73% success).[36]

One study reported overall success rate as well as results based on 2 month success with individual patient-identified donor (n=10, 70% success), standard donor with fresh feces (n=12, 92% success), or standard donor with frozen feces (n=21, 90% success).[37] No significant differences were noted based on either donor source (individual vs. standard donor) or fresh versus frozen donor material. Another study reported the effect of FMT based on *C. difficile* strain type.[39] The study involved 70 subjects (approximately equally split between the NAP1/027 epidemic strain and non-epidemic strains). All 4 subjects who did not have a favorable response to FMT had the epidemic strain, although the authors also note that all 4 had a pre-existing serious condition.

Figure 3. Reported Resolution of Symptoms after Initial FMT for Recurrent CDI, Studies Using Colonoscopic Infusion of Donor Feces

*Due to small sample sizes in 2 studies that reported 100% success (Cammarota 2014,[34] Yoon 2010[42]) the software used to generate this figure lowered the estimates for these 2 studies from 100% to 88% and 96% to allow the upper limit of the 95%CI to be 1.0.

Six studies reported outcomes at greater than 3 months after the first FMT.[35,36,38-41] One study followed 6 of the original 31 patients to one year, and all remained free of CDI.[36] Another followed 9 of the original 12 patients for one year and 7 (78%) remained free of CDI.[40] Four studies reported outcomes for all patients beyond 3 months.[35,38,39,41] There were a total of 127 patients, 114 of which (90%) had long-term success.

Table 8. Outcomes – Recurrent CDI, Studies Using Colonoscopic Infusion of Donor Feces

Outcome	Mean (Range) Unless Noted	Number of Trials Reporting
Number of patients (n)	Total = 237[a]	10
Resolution without recurrence:		
≤3 months with first FMT (%)	90 (73-100)	10
>3 months after first FMT (%)	90 (83-95)	4[b]
Recurrence (%)	10 (0-14)	8
All-Cause mortality (%)	11 (0-25)	6[c]

[a]One patient lost to follow up (Patel 2013[36]), one patient with refractory disease reported under KQ2 (Mellow 2011[40]), additional 7 patients reported in Addendum with success after initial FMT in 6 of 7(86%) and remaining patient achieving resolution after repeat FMT with feces from a different donor (Mellow 2011[40])
[b]Includes only the 4 studies with complete follow-up
[c]One additional study reported 2 deaths in 20 patients (10%) including 10 patients treated via upper GI tract and 10 patients treated via colonoscopy[29]

A median time to resolution of symptoms of 3 days was reported in one series.[36] One small series reported that 2 patients resolved in 2 days but did not report time to resolution for the third patient.[34] Two studies reported resolution within 48 hours,[35,38] one definition of resolution required resolution in 3 to 5 days,[42] and one series reported "almost all" patients resolved within 7 days.[40]

Six series reported all-cause mortality with values ranging from 0%[34,373] to 25%.[40] A small series (n=12 with recurrent FMT) identified 3 deaths (25%) with follow-up of one to 8 months.[40] One study reported 4 deaths within 3 months (4/70, 6%); all were patients who did not respond to FMT and 3 had severe CDI.[39] By one year follow-up, an additional 10 patients had died of unrelated illness - a total of 14 deaths (20%). Another report found one death among 31 participants (3%). The death was considered unrelated to FMT.[36] A recent series reported one death among 12 patients. Following resolution of symptoms after 2 FMTs, the patient had an episode of CDI associated with antibiotic treatment for a urinary tract infection and refused further treatment.[35]

Ten of 24 patients (42%) who failed initial FMT had a second FMT. The success rate with a follow-up of 3 months or less was 100%. One study reported that the one patient in the series who underwent repeat FMT remained successful beyond 3 months.[41] One of the repeat procedures was via push enteroscopy instead of colonoscopy, and was successful.[37] In the RCT comparing nasogastric and colonoscopy approaches and in 2 other series an upper GI route was used in the repeat procedures.[29,35,36]

Harms were not consistently defined or reported. One study reported a microperforation during the procedure (1/31, 3%).[36] Another study reported "no serious events" but one third of patients had bowel movement irregularity and excessive flatulence after FMT.[37] Five studies reported no adverse events.[34,35,38,39,42] The RCT reported one case of transient fever in a pediatric patient treated via colonoscopy.[29]

Immunocompromised Patients

One case series included only patients (n=80) with immunocompromised status.[56] Patient data were obtained from 16 national and international medical centers; some of the patients had been included in previously published case series. The patients underwent FMT for what was

described as recurrent (55%), refractory (11%), severe/complicated (1%), or a combination of recurrent/refractory and severe/complicated (33%) CDI that was unresponsive to standard therapy. It was noted that 79% were treated as outpatients and therefore it was likely they were clinically stable at the time of the FMT. Twelve of the 16 medical centers administered FMT exclusively by colonoscopy. To be included in the series, at least 12 weeks of follow-up data were required. The reasons for immunocompromise included 1) use of immunosuppressive agents for inflammatory bowel disease (n=36), 2) solid organ transplant (n=19), 3) HIV/AIDS (n=3), 4) cancer and treatment with antineoplastic agents (n=7), and 5) other chronic medical conditions including rheumatoid arthritis, end-stage liver or renal disease, end-stage chronic obstructive pulmonary disease on chronic steroids, and Sjogren's disease (n=15).

The series included 75 adults (mean age 53 years) and 5 children (mean age 11 years); 52% were male. Most patients (99%) had been treated with vancomycin, many (84%) with multiple, prolonged, or tapering courses. Metronidazole (69%), fidaxomicin (29%), rifaximin (16%), and probiotics (38%) had also been tried without success.

Resolution of CDI was reported for 62 patients (78%) after one FMT. Of the 36 patients with inflammatory bowel disease, resolution of CDI after one FMT was noted for 31 (86%). A total of 12 patients with either failed FMT or recurrence of CDI underwent a second procedure with resolution of CDI in 8 (67%).

Serious adverse events (death, life-threatening experience, unplanned hospitalization, or important medical event within 12 weeks of FMT) were observed in 12 patients (15%). There were 2 deaths (at one day and 13 days post-FMT) and 10 hospitalizations; one of the deaths and 6 of the hospitalizations were considered unrelated or probably unrelated to the FMT. None of the patients experienced infectious complications directly related to FMT. Non-serious adverse events were also reported for 12 patients (15%). Four were related to FMT, 5 were possibly related, and 3 were unrelated.

Another recent report[57] presented outcomes for 2 solid organ transplant patients who received FMT for "refractory diarrhea due to multiply recurrent CDI." One patient was a female, 73 years old, who received a kidney transplant. Approximately 19 months after kidney transplant, following multiple recurrences of CDI, she underwent FMT via nasojejunal tube. Following initial clinical improvement in diarrhea, CDI recurred and a second FMT, via colonoscopy, was performed approximately 3 weeks after the first FMT. The patient was recurrence-free at one year after the second FMT. The second patient, a 65 year old female, had a bilateral lung transplant. CDI was noted at 27 months post-transplant. Approximately 40 months after the lung transplant, following multiple recurrences of CDI, the patient underwent FMT via outpatient colonoscopy. Diarrhea recurred at 3 weeks and a second FMT was done, this time via nasojejunal tube. The patient's diarrhea resolved but only 5 days of follow-up were reported as the patient transferred to hospice and ultimately died likely related to progressive bronchiolitis obliterans.

Recurrent CDI – Enema

Key Findings

- FMT via enema was associated with resolution of symptoms after initial treatment in 78% (range 50% to 100%) of cases over 3 months follow-up (5 series, total n=45) and

80% to 100% over follow-up greater than 3 months (3 series).
- In successfully treated cases, symptoms generally resolved within 4 days (2 series).
- In patients undergoing a second transplantation after initial failure, resolution was observed in 25% to 100% (3 series).
- No adverse events were reported (2 series).

Overview of Studies (Tables 9 and 10; Appendix C Table 1)

Patient Characteristics and Selection

Five case series included 45 patients with recurrent CDI who were treated with FMT administered via an enema. Two studies were done in Sweden,[43,45]and one each in Canada,[44] Denmark,[47] and Australia.[46] The treatment setting was not reported in 2 studies.[46,47] Of the remaining studies, patients were treated in the hospital,[45] a GI clinic,[43] or at home.[44]

The number of patients enrolled ranged from 2[47] to 23[43] with only one[43] of the 5 series enrolling more than 7 patients. Mean ages ranged from 56 years[46] to 72 years.[44] Four studies reported gender; 38%[43] to 83%[45] of the patients were male.

None of the studies specified a number of recurrences of CDI required before FMT was considered. The diagnosis was made with a positive *C. difficile* toxin in 3 studies[44-46] or a positive toxin or culture in 2 studies.[43,47] All patients had received vancomycin and/or metronidazole for CDI. Other attempted treatments included saccharomyces,[44] cholestyramine and/or fusidic acid,[47] and bacitracin and/or cholestyramine.[46]

Table 9. Summary of Patient Baseline Characteristics – Recurrent CDI, Studies of Enema for Infusion of Donor Feces

Patient Characteristic	Mean (range) Unless Otherwise Noted	Number of Trials Reporting
Number of patients	Total = 45 (range 2-23)	5
Age (years)	65 (56-72)	5
Gender, male (%)	49 (38-83)	4
Time from diagnosis to FMT (months)	8 (5-17)	3
Recurrences prior to FMT	3	3
Treatment location (% inpatient)	17% inpatient, 64% outpatient, 19% home	3
Follow-up (months)	16	4

Donor Selection

In 2 studies, the number of donors was not specifically reported but donors were relatives (including spouses).[43,46] Two other studies also used related donors but specified that there was one donor per patient.[44,47] In the remaining study, one volunteer donor was used.[45] All but one of the studies reported screening donors for HIV, hepatitis, and other conditions.[43-46] No study reported screening donors for auto-immune disease and only one screened for or excluded donors with cancer.[44] Other exclusion criteria included GI disease or recent antibiotics,[43] history of GI illness, or antibiotic use or hospitalization in the past 3 months.[44]

Patient Preparation

Three studies reported on patient preparation for FMT. Antibiotic therapy was stopped 24 to 48 hours before FMT in 2 series.[43,44] In the home treatment series, patients were also given an oral probiotic with *Saccharomyces boulardii* prior to FMT and they were instructed to continue taking the probiotic during FMT and for 60 days post-treatment.[44] The authors commented that the antibiotic and probiotic therapy before FMT was to ensure that patients were asymptomatic until 24 to 48 hours before FMT.[44] The third series enrolled patients hospitalized because of diarrhea.[45] Their last dose of antibiotics was given 7 to 60 days prior to FMT.

Fecal Material Preparation and Delivery

The amount of material used in the FMT procedure varied greatly among the studies (Table 10). All but one series[45] used fresh feces.

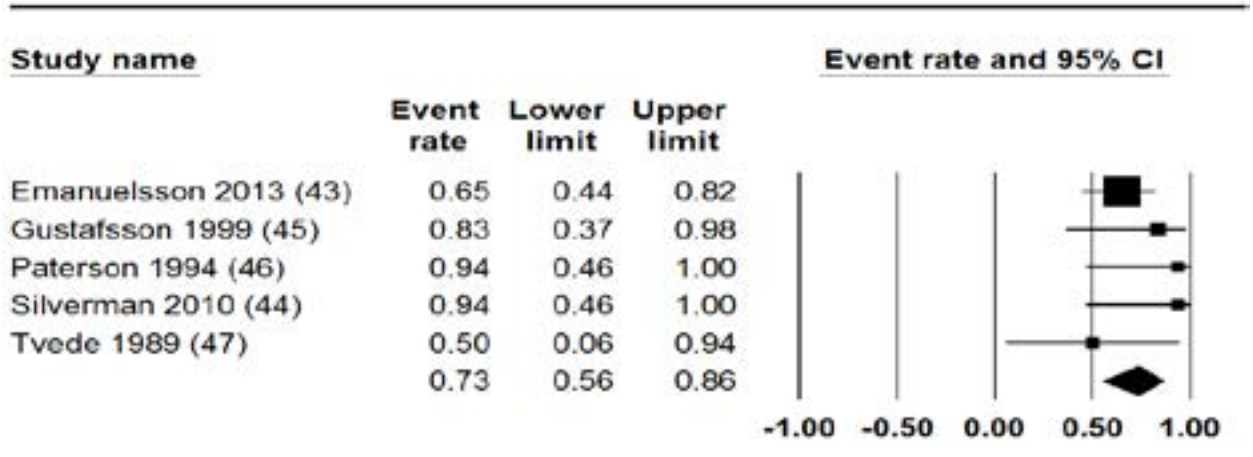
Table 10. Amount of Fecal Material and Liquid Used in FMT – Recurrent CDI, Studies of Enema for Infusion of Donor Feces

	Emanuelsson 2013[43]	Silverman 2010[44]	Gustafsson 1999[45]	Paterson 1994[46]	Tvede 1989[47]
Fecal Material	50 grams or more	50 mL	5 to 10 grams	200 mL	50 grams
Liquid (Saline unless noted)	Combined with to reach 500 mL	200 mL	20 mL pasteurized cows' milk	200 mL	500 mL
Amount Delivered	NR	Approximately 250 mL	NR	NR	NR

Outcomes (Figure 4, Table 11, Appendix C, Tables 2 and 3)

In 2 of the series, 100% of the patients experienced resolution of symptoms after first exposure to FMT with follow-up of 3 months or less;[44,46] one of these series also reported 100% resolution with follow-up of greater than 3 months.[44] In one series, although details were only reported for one of the 7 patients, it is likely that initial exposure consisted of daily treatment for 3 days.[46]

Figure 4. Reported Resolution of Symptoms after Initial FMT for Recurrent CDI, Studies of Enema for Infusion of Donor Feces



*Due to small sample sizes in 2 studies that reported 100% success (Silverman 2010,[44] Paterson 1994[46]), the software used to generate this figure lowered the estimates for these 2 studies from 100% to 94% to allow the upper limit of the 95%CI to be 1.0.

One series reported that 15/23 (65%) patients had loss of perception of illness and discontinuation of diarrhea within 3 days of FMT and there were no signs of recurrence (notes in the patient record) for 3 months.[43] One of the successful patients received 2 installations as part of the initial therapy. Of the 15 patients with resolution of symptoms after initial treatment, follow-up data for greater than 3 months were available for 12 with all remaining free of recurrence. Similarly, in a series of 6 patients, 5 of the 6 (83%) were "clinically well" with follow-up of 3 months or less and all 5 continued to be free of recurrence with follow-up of greater than 3 months.[44] The series with 2 patients reported 50% resolution of symptoms with no stool *C. difficile* toxin with a follow-up of 3 months or less.[47]

Two series reported time to successful treatment after FMT although the reporting was not exact. In one series, it was reported that most resolved within 4 days (range 2 to 6 days).[45] In the second series, resolution was defined as discontinuation of diarrhea within 3 days.[43]

Three series reported no recurrences among patients with an initial response to FMT.[44,45,47] In another series, a recurrence was reported a few weeks after an initial response to FMT and the authors rated the treatment as a failure.[43]

One small series (n=2) reported all-cause mortality with no deaths.[47] Two series reported that there were no adverse events.[43,44] Readmission and/or hospitalization data were not reported.

Repeat FMT procedures were reported in 3 series. In the series with 8 of 23 patients experiencing failure of the initial treatment, 2 patients had a repeat procedure with resolution in one patient (50%).[43] One small series (n=6) reported one initial failure; that patient experienced resolution following a second procedure.[45] In the series with 2 patients, the patient who failed to resolve after the first treatment also did not resolve after the second treatment.[47]

Table 11. Outcomes – Recurrent CDI, Studies of Enema for Infusion of Donor Feces

Outcome	Mean (Range) Unless Noted	Number of Trials Reporting
Number of patients (n)	Total = 45	5
Resolution without recurrence:		
≤3 months with first FMT (%)	78 (50-100)[a]	5
>3 months after first FMT (%)	89 (80-100)	3
Recurrence (%)	3 (0-4)	4
All-Cause mortality (%)	0	1

[a]Resolution result different from Figure due to software limitation (see Figure footnote)

Recurrent CDI – Upper Gastrointestinal Tract and Colonoscopy

Key Findings

- A combined jejunal and colonic approach was associated with resolution of symptoms in 100% of 27 cases.
- No recurrences were reported with mean follow-up of 21 months (range 10 to 34 months).
- Minor adverse events (*ie,* low-grade fever and bloating) were observed.

Patient Characteristics and Selection

One series of patients with recurrent CDI and treated with FMT via both the upper GI tract and colonoscopy has been reported (Appendix C, Table 1).[48] The study was conducted in the United States and enrolled 27 patients with a mean age of 65 years. Treatment setting was not reported.

Patients were included if they had 3 or more recurrences of CDI (mean=4.6 recurrences). Diagnosis was by positive toxin. Nineteen percent of the participants were male. By race/ethnicity, 74% were Caucasian, 22% African-American, and 4% Asian. Prior treatment included metronidazole (89%), vancomycin (92%), fidaxomicin (48%), rifaximin (22%), nitazoxanide (4%), and cholestyramine (4%).

Donor Selection

Donors included spouses, children, and parents, all of whom were screened for medical history and underwent physical and blood testing to exclude transmissible diseases.

Fecal Material Preparation and Delivery

Treatment consisted of 180cc of material placed in the jejunum via enteroscopy and 270cc placed in the colon via colonoscopy. The solution included 25 to 30 grams of fecal material.

Outcomes (Appendix C, Tables 2 and 3)

All of the patients achieved resolution of diarrhea and disappearance of stool *C. difficile* toxin after one treatment. The response was reported at 3 months or less and at greater than 3 months. The time to resolution of symptoms was 3 days (range one to 15 days). All-cause mortality was not reported. Following the procedure, low-grade fever was reported by 19% and bloating by 11%. Neither hospitalizations nor readmissions were reported.

KEY QUESTION #2: What is the effectiveness of fecal microbiota transplantation for refractory CDI compared to standard therapy? Does effectiveness vary by method of transplantation?

We found no studies that compared the effectiveness of FMT for refractory CDI to standard therapy or that compared different methods of transplantation. We summarize below findings from case series of patients with refractory CDI treated via colonoscopy or enema.

Refractory CDI – Colonoscopy

Key Findings

- Data are extremely limited in quantity and quality.
- In 4 patients with severe, refractory CDI, FMT delivered via colonoscopy reduced symptoms in 100% of patients but all subsequently experienced recurrence. A second FMT procedure produced a lasting resolution of symptoms in the 2 patients who completed the procedure.
- One patient with refractory CDI, from a case series of patients with predominantly recurrent CDI, experienced resolution without recurrence.
- No major adverse effects associated with the procedure were noted.

Patient Characteristics and Selection

One case series from the US detailed treatment of 4 patients with severe, refractory CDI (Appendix C, Table 1).[49] The mean age of the patients was 73 years and one of the patients was male (25%). Race/ethnicity was not reported. All of the patients were hospitalized. Prior treatment included oral and intravenous metronidazole and oral vancomycin.

Donor Selection

One volunteer donor was recruited. The donor was screened for HIV, hepatitis, auto-immune disease, cancer, and other conditions. The donor had no risk factors for HIV or hepatitis, no current communicable disease, no recent travel to an endemic diarrhea area, no antibiotic use in the past 3 months, and no GI disease. Metabolic syndrome, autoimmunity, and allergic diseases were relative exclusion criteria.

Patient Preparation

Systemic antibiotics were discontinued at least 48 hours prior to FMT; oral antibiotics were discontinued 12 to 24 hours prior to FMT. On the day before or the day of FMT, patients were given 2 to 3 liters of polyethylene glycol electrolyte solution either orally or via nasogastric tube.

Fecal Material Preparation and Delivery

The FMT procedure was performed via colonoscopy. A mixture of 50 grams of fecal material in 250ml of saline was used. The material was fresh for one patient and had been frozen for the other 3.

Outcomes (Appendix C, Tables 2 and 3)

In the series of 4 patients, all patients showed improvement over "several days" following the initial FMT.[49] No adverse events were reported. However, recurrence of symptoms was noted in all patients, 3 of whom were taking antibiotics.

Repeat FMT was considered for all patients. One patient refused and ultimately died. Another patient underwent surgery instead of a second FMT procedure because the endoscopist was not available to perform the second FMT. The remaining 2 patients had a second FMT procedure and both experienced resolution of symptoms over a follow-up period of over 3 months.

All 4 patients were discharged from the hospital (2 to a rehabilitation facility and one to a nursing home). One of the 4 patients was readmitted to the hospital and the readmission was related to CDI. The duration of hospitalization associated with the initial FMT procedure was 8 to 27 days.

In addition, we report on one patient from a case series of patients predominantly with recurrent CDI.[40] The patient was hospitalized at the time of treatment. Antibiotics were discontinued 48 hours before FMT. Treatment was via colonoscopy with stool from a donor identified by the patient. The patient experienced resolution of diarrhea and had been followed for 9 months.

Refractory CDI – Enema

Key Findings

- Data are very limited in quantity and quality.
- Response rates for patients with refractory CDI treated via enema ranged from 48% to 100%, however, in the 2 series with higher response rates, patients received more than one enema as part of the initial treatment protocol.
- All-cause mortality was 13% (2 deaths, neither patient had evidence of infection) in one series and 6% (6 deaths, none attributable to FMT or directly due to CDI) in another. No serious adverse events were reported.

Overview of Studies (Appendix C, Table 1)

Three series enrolled patients with refractory CDI who underwent FMT via an enema.[18,50,51] One of these series, from Canada, enrolled 94 patients.[50] It is unclear how many were categorized as refractory CDI cases but it was noted that 75% were hospitalized with "severe CDI and refractory disease." The diagnosis of CDI was by positive toxin. The mean age of the patients was 72 years and 44% were male. Patients had completed a mean of 2.1 courses of antibiotics (metronidazole, vancomycin, or a combination). Donors were volunteers; whether they were related to the patients was not reported. Donor feces were screened for *C. difficile* toxin gene, ova and parasites, enteric bacterial pathogens, and viruses; donor blood was tested for HIV, hepatitis B and C, human T-cell lymphotropic virus, and syphilis. Patients were treated with 100 mL of supernatant component of the feces.

The other 2 series, with only refractory CDI cases, were conducted in hospitals in the United States and enrolled 15[51] and 3[18] adult patients. The mean age of patients in the larger series was 59 years and 40% were male.[51] Race/ethnicity were not reported. In the smaller series, the mean age was 52 years and 67% were male.[18]One patient was Hispanic, one patient was white, and race/ethnicity was not reported for one patient. In the larger series, diagnosis was based on direct visualization of pseudomembranes.[51] In both series, a wide range of antibiotics had been used in attempts to treat the refractory condition; in the smaller series, some treatments were continued through the FMT treatment period.[18]

No information was provided about the donor(s) in the smaller series.[18] In the larger series,[51] the donors were an unspecified number of in-house family members, medical students, and residents who were screened for HIV, hepatitis, amoebiasis, and "other enteric diseases." There was no screening for auto-immune disease or cancer.

In the small series, retention enemas were used to deliver the fecal material. No information was provided on preparation of the enemas.[18] One patient received a second FMT procedure on the same day; all 3 patients received another FMT on the day after the first but it was unclear whether this was due to recurrence.

In the other series, most patients received enemas twice daily with one reported to have continued treatment for 12 days. One patient was treated via a cantor tube to the midjejunum.[51] Neither series provided information about the preparation of the fecal material other than use of fresh stool in the larger series.[51]

Outcomes (Appendix C, Tables 2 and 3)

In the mixed refractory/recurrent CDI series, resolution of diarrhea with no recurrence at 6 months follow-up after one FMT was reported for 45 of 94 patients (48%).[50] Forty eight patients had from one to 10 repeat procedures including 9 who received antibiotics for ongoing diarrhea between FMT treatments. Resolution of diarrhea was observed in 41 of the 48 patients with repeat procedures (85%). If all patients with resolution are considered (single or multiple FMTs with or without antibiotics), the response rate was 92%. There were 6 deaths (6%); none were attributable to FMT or directly due to CDI. Transient constipation and excess flatulence were reported in 10%.

In the small series of refractory CDI cases, all 3 patients (100%) experienced a markedly improved clinical course.[18] Symptom resolution was reported in 1-2 days and no deaths were reported. Adverse events were not reported. Hospitalization continued for 2 to 10 days after the last FMT procedure; there was no follow-up after the hospitalization period.

In the larger series of refractory CDI cases, 13 of 15 patients (87%) responded to the initial FMT series (decreases in diarrhea, temperature, and white blood cell counts) although the duration of the response was not reported.[51] Symptoms resolved in one to 12 days. All cause morality was 13% (2 deaths); "no ill effects" of the enemas were reported. It was not reported whether any patients experienced recurrence, hospitalization, or repeat FMT beyond the initial treatment period.

Additionally, we report use of FMT in 2 cases of fulminant CDI. In one, the patient was described as having fulminant *C. difficile* enterocolitis and was successfully treated with FMT delivered via retention enema.[58] In the second, a patient status post stem-cell transplant with fulminant CDI was also successfully treated, by FMT delivered via nasojejunal tube.[59] Further data regarding the treatment of fulminant CDI with FMT are needed.

KEY QUESTION #3: What is the effectiveness of fecal microbiota transplantation as initial therapy for CDI compared to standard therapy? Does effectiveness vary by method of transplantation?

We found no studies that compared FMT as initial therapy for CDI to standard therapy. Overall, there is little information about use of FMT as initial therapy; we found data from one patient (part of a series of 4 patients) treated via enema. No data on other methods of transplantation were identified by our search.

Initial Therapy – Enema

Key Findings

- Data are limited to a single case report. In one patient (part of a small case series), resolution of symptoms was reported within 48 hours after a single FMT procedure.

One patient in the small case series reported above[18] received FMT as initial therapy. The patient was a 68 year old white male. As noted above, little information was provided about the donor or the protocol followed in this series. This patient received a single FMT procedure and

experienced an improved clinical course within 48 hours. The patient was discharged from the hospital 5 days after the procedure and no further follow-up was reported. The authors described this case as a "milder variety of staphylococcal enterocolitis" (Appendix C, Tables 1-3).

KEY QUESTION #4: What are the harms of fecal microbiota transplantation therapy compared to standard therapy for initial, recurrent, or refractory CDI? Do the harms vary by method of transplantation?

Harms (mortality, adverse events, hospitalizations) were identified in the RCTs and case series included under Key Questions 1, 2, and 3 above. Notably, data regarding the long-term safety of FMT are lacking.

In the RCT comparing FMT to standard therapy, only mild adverse events were reported after FMT and included diarrhea, cramping, belching, nausea, abdominal pain, and dizziness.[20] Three patients reported constipation during the 10-week follow-up period. Few and only mild events were noted in the vancomycin and vancomycin plus bowel lavage groups. The only death in the study was in the vancomycin group and was attributed to known severe heart failure and chronic obstructive pulmonary disease.

In the RCT comparing one method of transplantation to another, the authors identified mild abdominal discomfort and bloating in 4 patients (20%); the FMT method was not reported.[29] Transient fever was noted in one pediatric patient treated via colonoscopy. Several serious adverse events were reported but none were attributed to FMT and method of transplantation was provided for only one of these events, a patient treated via nasogastric tube was hospitalized with Fournier's gangrene.

Data reported in case series did not suggest a difference in harms between methods of transplantation. All-cause mortality ranged from 0% to 13% in the 4 case series of upper GI FMT for patients with recurrent CDI. Among patients treated via colonoscopy, all-cause mortality ranged from 0% to 25% in 6 case series of patients with recurrent CDI, and 0% to 25% in 2 small series of patients with refractory CDI. Only one of 5 series of patients with recurrent CDI treated via enema reported mortality with no deaths while in 3 series of patients with refractory CDI treated via enema, mortality ranged from 0% to 13%. None of the deaths was attributed to FMT.

There were few reports of procedure-related harms in the case series. In the upper GI tract case series (recurrent CDI), there were reports of GI bleed, peritonitis, and pneumonia, each in one patient. In the colonoscopy case series, there was one reported microperforation. Transient adverse events were reported in one series of patients with recurrent CDI treated via colonoscopy (bowel movement irregularity and excess flatulence in 33%), the series of patients with recurrent CDI treated via both upper GI tract and colonoscopy (bloating in 11%, low-grade fever in 19%), and one series of patients with refractory CDI treated via enema (constipation and excess flatulence in 10%).

To further understand possible harms associated with FMT, we examined case reports for information about adverse events. A 73 year old female patient with recurrent CDI and comorbid

conditions developed a herpes zoster infection 2 months following FMT via colonoscopy. The donor was the patient's granddaughter. Donor screening included blood tests for HIV; hepatitis A, B, and C; syphilis; cytomegalovirus; and Epstein-Barr virus and stool tests for *C. difficile* toxin, bacterial stool pathogens, worm eggs, parasites, and viruses. The authors considered the infection to be a reactivation of an infection.[60]

A 61 year old male patient with a history of Crohn's disease, acute diverticulitis, CDI, and bacteremia for multidrug-sensitive Escherichia *coli* (MDSEC) underwent FMT via colonoscopy. The relationship of the donor to the patient was not reported but donor screening was described as "exhaustive." The patient experienced a high fever and positive blood cultures for MDSEC strain 24 hours after FMT.[61]

A 78 year old male patient with a history of quiescent ulcerative colitis and other comorbid conditions underwent FMT via colonoscopy following 3 episodes of CDI within a few months. The donor was the patient's wife who was tested for numerous transmissible pathogens. There were no immediate complications of the procedure but 9 days later the patient developed abdominal cramping, tenesmus, and diarrheal symptoms although the presentation was different than in prior episodes of CDI. Sigmoidoscopy revealed characteristics consistent with a flare of ulcerative colitis.[62]

An 80 year old male and a 78 year old female developed norovirus gastroenteritis following FMT via colonoscopy.[63] The donor for the male patient was his son. The patient was discharged following the FMT procedure but was hospitalized with diarrhea 2 days later. Patient and donor stool were negative for enteric pathogens, *C. difficle* toxin PCR, and ova and parasites. The patient tested positive for norovirus. The donor for the female patient was her granddaughter. Nausea, vomiting, and diarrhea developed 12 days after FMT and norovirus was detected in the patient's stool. The donor was not tested but remained asymptomatic. It was noted that an endoscopy suite employee had norovirus-like symptoms the day before FMT for the male patient. It was speculated that the female patient may have acquired norovirus in the community. Both patients recovered.

With limited long-term follow-up data available, concerns have been raised about the safety of FMT.[64] The possibility for transmission of disease is high but donor screening is not standardized and the scope of diseases to be screened for is unknown. Additional randomized trials and an adverse-events registry have been recommended.[64] As reported above, a recent multi-site series that collected reports of use of FMT in immunocompromised patients found serious adverse events (2 deaths and 10 hospitalizations) in 12 patients (15%).[56] There were no infectious complications directly related to FMT. Non-serious adverse events were also reported for 12 patients (15%); 4 were related to FMT and 5 were possibly related.

KEY QUESTION #5: Is the procedure acceptable to patients? Does patient acceptability vary by method of transplantation?

Several of the included studies commented on the acceptability of FMT to patients. The RCT was designed to enroll patients with any recurrence of CDI, however, only 8 of the included 43 patients were enrolled after a first recurrence.[20] The authors commented that the low enrollment of patients

at an early stage of recurrence reflected a reluctance to undergo FMT at that point. Ten of 102 patients who were being assessed for eligibility decline to participate in the trial. The trial used a nasoduodenal approach.

A case series conducted in Norway reported that patients expressed no concerns with either the practical or aesthetic aspects of FMT.[31] All but 2 of the 40 FMT procedures were done via duodenal instillation. It was also noted that very few patients who presented in the clinic with recurrent CDI refused to undergo FMT and that there was greater initial skepticism among the staff than among patients.

A high level of patient acceptance was also reported in a series of 15 patients treated with a nasogastric approach.[32] Similar findings were reported in a series of 18 patients.[33] The authors reported that patients were receptive to the treatment and none objected to FMT for aesthetic reasons.

Among patients contacted to complete a follow-up survey at least 3 months after FMT, it was reported that 97% of the patients indicated that they would be willing to undergo FMT in the future.[55] Furthermore, 53% indicated that they would choose FMT as first-line treatment, before antibiotics. Patients received FMT via colonoscopy in this series.

One series offered patients an option – use fecal material from a self-identified potential donor or from an anonymous screened donor.[37] The authors noted that patients immediately preferred the anonymous donor option.

The authors of one series of 31 patients noted that patients were "miserable" due to health problems associated with CDI and therefore had no concerns about the acceptability of FMT.[36] It was reported that some participants had considered home treatment. In addition, some of the patients in the series preferred the colonoscopy approach used in this series and had refused FMT via a nasogastric approach at other treatment sites.

A survey of patients' perceptions of FMT and whether they would consider it as a treatment option for themselves was conducted on a convenience sample of adult outpatients and family members who accompanied them to a medical or surgical appointment.[21] Of 400 surveys distributed, 192 (48%) were completed. Responses from one individual who had experienced an episode of CDI were considered separately from the responses of those with no history of CDI. Demographic data were reported by 184 respondents; 30% were male, 94% were white, and 59% were 50 years old or above. Patients were presented with 2 scenarios. The only difference was the first scenario described FMT as "floral reconstitution" (FR) while the second gave more detailed information about FMT. After reading the first scenario, 85% of the patients chose antibiotics plus FR as their preferred therapy and 15% chose antibiotics alone. After reading the second scenario, 81% of the patients chose antibiotics plus FR and 19% chose antibiotics alone. If FR was colorless and odorless, the percentage choosing antibiotics plus FR increased to 83%. If FR was provided as a colorless, odorless pill, antibiotics plus FR was chosen by 90%. If FR was recommended by their physician, 94% would choose antibiotics plus FR. For those who *would consider FMT* despite finding it unappealing, the most unappealing aspects were having to discuss the illness with a donor (identified by 74%) and having to find a donor (identified by 72%). Getting FMT by enema (68%) or colonoscopy (69%), the brown color of the FMT liquid

(56%), and the odor of the FMT liquid (52%) were other aspects of FMT rated as unappealing by more than 50% of respondents. For those who rated *FMT as too unappealing to consider*, getting FMT by nasogastric tube (74%) and the need to handle stool (65%) were the aspects rated as unappealing by more than 50% of respondents. Differences were noted between men and women with women rating all aspects of FMT more unappealing than did men. Significant differences were noted in the aspects "need to handle stool," "odor of the FR liquid," and "getting FR by nasogastric tube." Respondents age 65 and older were less likely than younger respondents to rate "need to handle stool," "odor of the FR liquid," and "brown color of the FR liquid" as very unappealing or too unappealing to deal with. No other aspects were significantly different between the younger and older respondents. Among those who would consider FMT, the preferred setting was a hospital for 48%, a physician's office for 39%, and in their own home for 13%. The respondent who reported a prior episode of CDI preferred treatment with antibiotics alone. The individual had been treated with antibiotics and CDI had not recurred.

A second survey included patients with ulcerative colitis who had an outpatient appointment at an inflammatory bowel disease (IBD) center.[65] Surveys were completed by 95% of those invited (95 of 100) and participants ranged in age from 19 to 80 years (median 39 years) with 47% male. Most patients were currently either in remission (59%) or experiencing mildly to moderately active disease (36%). Overall, 46% of respondents were willing to undergo FMT, 43% were unsure, and 11% were unwilling. Participants with more severe disease or who had been hospitalized were more willing. Effectiveness, safety, physician recommendation, and concerns about failure of conventional treatments were factors in considering FMT. Regarding a donor, participants were evenly divided with 46% preferring whomever the physician recommended and 46% preferring a family member or spouse. Participants preferred that FMT be performed via a single session, sedated colonoscopy (77%) or daily enema for 5 days (20%) rather than a single session nasogastric tube (3%).

SUMMARY AND DISCUSSION

SUMMARY OF EVIDENCE

In this systematic review of FMT for the treatment of CDI, we identified a total of 25 case series and 2 RCTs providing evidence regarding the efficacy of FMT for recurrent, refractory, or an initial episode of CDI, with the bulk of the studies dealing with recurrent CDI. One RCT (n=43) compared FMT to standard therapy and was discontinued early due to a significant difference in recurrence between the FMT group and the 2 control groups, driven in part by lower-than-expected response rates in the control groups. The second RCT (n=20) compared FMT via nasogastric tube to FMT via colonoscopy finding no statistically significant difference between the two approaches. The overall low quality of the available evidence evaluating FMT is one important finding of this report and indicates that additional research is needed. Also important, however, is the large positive effect seen with FMT for CDI, both in the RCTs and in the case series. Overall success (as defined by resolution of symptoms at 3 months or less) was 83% for recurrent disease, and 53% for refractory disease. These rates are substantially higher than the 30% to 70% success rates typically reported with various medical therapies for CDI,[6-9] although directly comparing such different studies cannot be done with confidence. Additionally, the optimal medical therapy for patients with multiple recurrences of CDI is unknown, since some small series have reported markedly higher success rates, including up to 88% with the combination of vancomycin followed by rifaximin,[11,12] and even 100% with a vancomycin taper.[13] However, neither of these regimens has been studied prospectively, and thus the strength of evidence supporting their use remains low. Overall, the available studies regarding FMT for CDI demonstrate a large effect size, but are limited by the availability of only 2 moderate quality RCTs, with only one comparing FMT to antimicrobial therapy.

Primary outcomes among the included trials varied. Among the 21 studies of FMT for recurrent CDI, 9 had a primary outcome of clinical resolution without recurrence, 7 had an outcome of clinical resolution, and 5 did not state a primary outcome. Since nearly all of these studies reported that subjects were on antimicrobials until the time of (or shortly before) the FMT, it is difficult to determine whether the FMT was contributing to resolution of symptoms, avoiding recurrence of CDI, or both. However, in several studies the authors specified that antimicrobials for CDI were administered to ensure that patients were "asymptomatic" at the time of FMT, or had a "reduction of symptoms." Thus, although stated outcomes included an element of symptom resolution, in most cases FMT appears to be given with the intent to prevent subsequent recurrence, after an initial course of antimicrobial treatment had resolved all or most of the CDI symptoms.

In addition to the reported harms described in Key Question 4, potential harms of FMT include transmission of communicable diseases, procedural complications, immune-modulatory effects, and others. Thus far, the only reported harms clearly attributable to FMT are procedural complications, including minor mucosal tear, microperforation, aspiration, and peritonitis. The other reported potential harms include a flare of previously quiescent ulcerative colitis, potential norovirus acquisition from a healthcare worker, recurrence of bacteremia post-transplant with an organism similar to one seen pre-transplant, and an episode of zoster. The potential link

between any of these episodes and the FMT is tenuous, at best. Two recent reports of FMT in immunocompromised patients reported no infectious complications

Acceptability to patients has not been systematically assessed in a patient population with a prior or current episode of CDI, which is presumably the group that would potentially be considering treatment with FMT. A survey of patients with no CDI history reported largely favorable results, but the response rate of less than 50% raises the possibility that respondents might answer differently than non-respondents.

LIMITATIONS

Our literature search excluded non-English language studies. Hand searching reference lists from recent systematic reviews identified 4 case series, 3 with English language abstracts.[66-68] In one series, enrolling patients with CDI (not specified if initial, recurrent, or refractory CDI), resolution of CDI without relapse was reported in 15 of 18 (83%) patients, 17 of whom had FMT via colonoscope.[66] Another series included 7 patients with recurrent CDI who received FMT via colonoscopy.[67] Initial success was reported for 5 of 7 patients (71%). The other 2 patients achieved a successful outcome after the procedure was repeated with feces from a different donor. The third series reported a success rate of 78% with no deaths or complications.[68] The number of patients treated was not reported. The protocol was adopted from studies using an upper GI tract approach. Findings from these small case series are consistent with findings from the English language studies included in our review and we conclude that exclusion of non-English studies did not bias our findings.

Other limitations include the following.

Publication Bias

Publication bias is a concern for all types of publications, but is likely particularly relevant for case series, including both those reporting the success of FMT, and those reporting regimens such as vancomycin followed by rifaximin and tapering doses of vancomycin. Whereas it has become more accepted for journals to publish RCTs which demonstrate no benefit, or even harms, similar case series are rarely published. The desire to publish a series of successfully treated patients is easily understood, and provides pilot data for future more definitive studies. The desire to publish a series of clinical failures is less easily understood, and the potential benefits to such work are also less tangible.

Study Quality

With only 2 RCTs included, study quality is a serious limitation of this report. Even well-reported case series have significant quality issues, chief among them being the lack of a direct control group. This necessitates the use of historical controls, which is especially problematic for infectious diseases, since the emergence (and subsequent disappearance) of more virulent or aggressive strains can alter the expected response rate with standard therapy and it is often not known which strain is present, in either clinical or research settings. A direct control group eliminates much of this uncertainty, and prevents both under- and over-estimation of the effect of an intervention.

Heterogeneity

Given that this review included 25 case series and 2 RCTs, the presence of heterogeneity is not surprising. Additionally, the inclusion of studies from 1958 to 2014 made it likely that disease definitions, treatments, and study designs were different. Follow-up duration, donor selection, and pre-FMT preparations varied considerably; how this affected the study outcomes is unknown.

APPLICABILITY

Published data on incidence of CDI specific to the VA are more than a decade old.[69] At that time, 1% of all patients hospitalized in the VA were diagnosed with CDI.[69]According to VA administrative data sources, there were approximately 624,858 hospitalizations in VA facilities in FY 2012, meaning that even a 1% incidence of CDI results in 6,249 cases among inpatients alone. With VA-based studies reporting recurrence rates of 22-30%,[70,71] there would be an estimated 1,375 to 1,875 cases of recurrent CDI annually. Actual FY 2012 data regarding CDI diagnoses (available in the inpatient and outpatient treatment files) reveals similar numbers: compared to the estimated 6,249 cases of CDI and 1,375 to 1,875 cases of recurrent CDI among inpatients, 6,046 cases of CDI and 1,517 cases of recurrent CDI were identified using inpatient data sources. When outpatient CDI diagnoses were included, the total number of cases rose from 6,046 to 8,878.

RESEARCH GAPS/FUTURE RESEARCH

Findings from our evidence report suggest a large beneficial effect of FMT in patients with recurrent or refractory CDI. However, the vast majority of evidence to date comes from case series and the total number of cases with reported outcomes remains relatively low. The 2 reported randomized trials enrolled very few individuals. Confirmation (or refutation) of their findings, assessment of long term harms and determination of broader patient applicability and donor criteria are needed. Furthermore, we are unable to determine if data exist from patients treated with FMT having less favorable results and the potential for substantial positive reporting bias exists. Additionally, conventional methods for rating strength of evidence would classify even well-conducted and reported case series as high risk of bias. Therefore, strength of evidence for the effectiveness of any intervention based on case series (even with large reported effect sizes) would typically be considered insufficient or low at best. Thus the available evidence and the clinical importance of this topic indicate that future research is needed to close knowledge gaps.

Research recommendations to close important gaps include:

1) FMT effectiveness and comparative effectiveness: Additional RCTs comparing FMT to antimicrobial therapy are needed to assess the effectiveness and comparative effectiveness of FMT. Ideally patients and providers should be blinded regarding assigned treatment. Various methods could be used to achieve blinding, especially since FMT is generally administered after a course of antimicrobial therapy, when the patient is typically without CDI symptoms. While full details are beyond the scope of our evidence report such methods could include the use of

a placebo enema to be administered after antimicrobial therapy, or even a placebo colonoscopy or nasogastric tube placement. Including 2 FMT arms in such a trial would allow direct comparisons to be made between the different FMT methods chosen, although it would also increase the necessary sample size.

2) Comparison group including more effective pre-FMT treatment: The optimal comparison group for such a study is currently unknown, but based on the low success rate with 2 weeks of vancomycin observed in the recent RCT among individuals with multiple CDI recurrences (with or without the bowel lavage), and the higher success rates reported with other agents or longer courses, any future trials (randomized or not) should carefully consider what agent(s) and duration to use for optimal medical therapy. Further studies of antimicrobial therapy for the treatment of patients with multiple recurrences of CDI would be valuable, both to inform current practice, and to help guide any potential future comparative effectiveness trials.

3) When to offer FMT: If FMT is effective, it is not known whether FMT should be offered after the second, third, fourth, or some other number of recurrences (or possibly even as initial therapy). Thresholds of CDI recurrence that initiate FMT would have a large impact on the number of individuals who are potential candidates for FMT, may alter the balance of benefits to harms, and would have resource implications. In addition to treatment effectiveness, other factors to be considered (and which require more information) include patient preference (including the impact of altering the name of the treatment modality [from fecal microbial transplantation to *eg*, gastrointestinal recolonization] to enhance patient acceptability), FMT availability, and safety, costs and cost-effectiveness.

4) Donor selection: Information is needed to identify donor selection criteria and screening methods to optimize FMT effectiveness, avoid transmission of harms from FMT donor to recipient, and determine whether patients should be provided with a new donor in the event of having a recurrence after their initial FMT.

5) Fecal material processing and delivery methods: The optimal dose as well as methods to obtain, process and deliver the fecal material are not known. Trials to identify these features would enhance treatment efficacy while minimizing harms.

6) Assessing longer term FMT harms: Little data exist on long-term harms including potential for transmission of diseases from donor to recipient and risk of subsequent CDI.

Research options to evaluate these evidence gaps could include randomized or controlled clinical trials. Additionally, development of a national registry of FMT treated patients and their donors that record standardized assessments of baseline demographics, condition and treatment related characteristics and outcomes could provide valuable additional information. Ongoing trials, evaluating FMT and registered in clinicaltrials.gov for adults or adults and children (Table 12), will provide some important information.

CONCLUSIONS

We found low strength evidence from small RCTs and case series that FMT may have a substantial effect and few short-term adverse events for adults with recurrent CDI. One small

moderate quality RCT study found that FMT reduced symptom recurrence compared to standard CDI therapy that included vancomycin and one very small moderate quality RCT found FMT resulted in high symptom resolution rate that did not differ by delivery routes (nasogastric tube vs. colonoscopy). There is insufficient evidence on FMT for patients with refractory CDI and only a single case report for initial treatment of CDI. Evidence is insufficient whether treatment effects vary by FMT donor, preparation or delivery method.

Table 12. Open Trials of FMT for Adults or Adults and Children[a]

Trial Number Design	Title	CDI	Route of FMT
NCT01226992 RCT	Oral Vancomycin Followed by Fecal Transplant Versus Tapering Oral Vancomycin	Recurrent	Enema
NCT01958463 Single Group Assignment	Transplantation of Fecal Microbiota for *Clostridium Difficile* Infection	Initial, refractory, or recurrent	Colonoscopy
NCT01914731 Single Group Assignment	Fecal Microbiota Transplant for Relapsing *Clostridium Difficile* Infection in Adults and Children Using a Frozen Encapsulated Inoculum	Refractory, recurrent, or relapsing	Oral capsule
NCT01398969 RCT	Multi-Centre Trial of Fresh vs. Frozen-and-Thawed HBT(Fecal Transplant)for Recurrent CDI	Recurrent	Enema
NCT01905709 Single Group Assignment	Fecal Microbiota Transplantation for *C Diff* Infection	Recurrent or refractory	Colonoscopy, sigmoidoscopy, or enema
NCT01942447 Non-randomized	Fecal Microbiota Transplantation in Recurrent or Refractory *Clostridium Difficile* Colitis	Recurrent or refractory	Not specified
NCT01703494 RCT	Fecal Transplant for Relapsing *C. Difficile* Infection	Relapsing	Colonoscopy

[a]Source: clinicaltrials.gov; accessed 24 June 2014

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APPENDIX A. SEARCH STRATEGY

Database: Ovid MEDLINE(R)

Search Strategy:

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1 exp Feces/ or (fecal or faecal or feces or faeces or stool or microbiota).mp.

2 (donor or transplant$).mp. or exp Transplants/

3 1 and 2

4 exp Clostridium Infections/ or exp Clostridium difficile/ or exp Enterocolitis, Pseudomembranous/ or (c difficile or c diff or clostridium difficile).mp.

5 3 and 4

6 limit 5 to (english language and humans and yr="1980 -Current")

APPENDIX B. PEER REVIEW COMMENTS/AUTHOR RESPONSES

REVIEWER COMMENT	RESPONSE
1. Are the objectives, scope, and methods for this review clearly described?	
Yes	No response needed
Yes	No response needed
Yes. This review aims to answer questions regarding the efficacy of fecal microbiota transplantation (FMT) for initial, recurrent or refractory C difficile infection (CDI) compared to standard therapy as well as potential harms and patient acceptability. The Methods (source of data and data abstraction/assessment/analysis) are clearly described.	Thank you
Yes; they were well spelled-out.	Thank you
Yes	No response needed
Yes. The purposes of the review, as indicated by the "Key Questions," are specific and are clearly important.	Thank you
Yes	No response needed
2. Is there any indication of bias in our synthesis of the evidence?	
No	No response needed
No	No response needed
No. In general your synthesis of the evidence was accurate and did not appear overly supportive or opposed to FMT. The overwhelmingly positive results from these numerous series and the clinical experiences of many physicians who've used FMT are admittedly "low quality" evidence. Unfortunately, RCTs of this therapy are difficult to perform and, as the use of FMT has expanded rapidly over the past few years, finding subjects willing to be enrolled in a placebo-controlled study will become increasingly difficult. Meanwhile, the large number of patients with recurrent C. difficile infection who've failed standard therapies should be offered FMT based on the evidence we have so far. Inclusion of some of the data on MECHANISMS of effect would be a valuable addition to this systematic review. Researchers have done sequencing of the fecal microbiome of FMT treated patients before and after FMT. Recurrent C. difficile patients have characteristic low diversity of species and lack normally dominant populations of anaerobes. Post-FMT, this dysbiosis is remedied and this coincides with clinical cure. Papers that I suggest including discussion of: Khoruts A. et al. J Clin Gastroenterol; 2010 & Song Y, et al. PLoS One 2013	We have included a brief discussion on the mechanism of FMT in the introduction, including the suggested references.
No. The reviewers took care to point out limitations/possible sources of bias in the available literature	Thank you.
No. There is no bias, although systematic review is obligatorily affected by publication bias.	No response needed
No. Very cautious.	No response needed

Possibly. I believe that some of the authors have previously submitted a letter of intent for a VA CSP on FMT. This raises some concern that the authors might use the ESP process to try to impact funding decisions for their grant proposal. Therefore, I suggest that the ESP leadership consider whether or not further review or action is needed. Specific lines that suggest bias on the part of the authors include: Page 3, line 2: why do they describe the RCT as "one small high risk of bias RCT"? Later, they study is described as "moderate quality" (page 14, line 6). Page 4, line 36: they call for more RCTs. This may be completely appropriate, but is also self-serving and leads the reader to wonder if they would have made the same recommendation if they weren't trying to get funding for an RCT. Page 10, lines 14-17: they say that the strength of evidence is insufficient or low at best but seem to be ignoring the RCT here. It is not clear why the RCT is not included in this section. Page 33, lines 7-9: again, they call for more RCT's. The description of the RCT here and earlier in the review focus on the low response to antibiotics. The study was stopped early because a review by the data monitoring committee felt that they should (or perhaps I don't fully know the story). If it was scientifically inappropriate to stop the study, then they have a case. But if it was deemed unethical to continue the study due to a dramatic difference, shouldn't the focus be on that fact? Page 34, lines 9-14: it is unlikely that the emergence of more virulent or aggressive strains would lead to lower responses with standard therapy, right? So the argument about historical controls is not bolstered by this statement. Page 34, line 22: The urgent call for RCTs can be self-serving here.	Regarding potential COI. We thank the reviewer for highlighting this point and agree that we should disclose the information noted. We take real or potential COI very seriously as ESP reports must be free of significant conflict to be credible and useful for practice and policy. After discussion with ESP leadership we agree that transparency would be enhanced if we include notation that Drs. Drekonja and Shaukat have submitted a proposal to VA-CSP for a randomized trial assessing FMT: "The Veterans Affairs Fecal Microbiota Therapy Trial for Recurrent Clostridium difficile Infection: A Planning Request for a VA Cooperative Study" The LOI proposes a blinded randomized controlled trial to compare FMT (via enema) to a placebo enema, both administered as an adjunctive treatment after a standard course of oral fidaxomicin (10 days) for recurrent CDI, for efficacy in preventing subsequent episodes of recurrent CDI. We now include this disclosure information in the Preface. Of note, Dr. Drekonja had previously submitted a similar proposal that was not approved for VA planning. Subsequent to our being awarded the contract for, and during the conduct of, the FMT ESP review Drs. Drekonja and Shaukat were informed of an opportunity for additional FMT studies through VA-CSP and encouraged by this reviewer to submit a revised proposal for consideration. Drs. Drekonja and Shaukat did this. and have not yet received reviewer comments or funding decisions. Page 3: The discrepancy was an error. We apologize and have corrected this so that the study is appropriately rated as moderate quality and as moderate risk of bias. Study quality and strength of evidence is assessed solely by our ESP core staff who are methodologically trained in these assessment methods. Our methodology is consistent with that widely used in the ESP and the AHRQ-EPC program. Content collaborators (in this case Drs. Shaukat, Drekonja, Reich and Gezahegn) do not perform these assessments. We make them aware of our findings and discuss our rationale. We routinely employ 2 individuals (Dr. Greer and Mr. MacDonald to independently assess study quality and overall strength of evidence). The ESP director reviews and resolves through discussion any discrepancies. Page 4: Please see our comment above regarding assessment methods for study quality and strength of evidence. We continue to believe that the current evidence is insufficient to fully address the effectiveness and comparative effectiveness of FMT. Randomized controlled trials are the highest quality studies to accurately assess effectiveness and comparative effectiveness. We have further refined our future research needs section to identify specific gaps that might be addressed by RCTs as well as other potential study designs that are needed to close additional gaps in knowledge. Page 10: We have included mention of the 2 RCTs in this sentence but strength of evidence would typically be considered low even taking into account the contributions of the 2 RCTs. Page 33: Information about the early stopping of the RCT has been added. Page 34: We have clarified the statement about historical controls. Page 34: We have deleted the word "urgent" and modified the research needs sections of both the Executive Summary and the full report.

3. Are there any published or unpublished studies that we may have overlooked?	
No	
The review is complete for the time period studied. However, there is a paper published subsequent to the review period, which is a small (n=20), randomized, nonblinded trial of FMT using frozen stool comparing delivery via NG tube to delivery via colonoscopy (Youngster I et al. Clin Infect Dis 2014 Apr 23; epub ahead of print).	Thank you for the suggested reference. We have added this paper.
Yes. Key Question #1 (recurrent CDI by colonoscopy) Rohlke F, Surawicz C, Stollman N. Fecal Flora Reconstitution for Recurrent Clostridium difficile infection: Results and Methodology. J Clin Gastroenterol 2010;44:567-70. Key Question #4 (harms) Our paper was recently accepted and would be an important addition to your safety discussion. In this multicenter series of 80 immunocompromised patients treated with FMT and at least 12 weeks of post FMT follow up, there were no infections transmitted. Kelly C. Ihunnah C. Fischer M, et al. Fecal Microbiota Transplant for Treatment of Clostridium difficile Infection in Immunocompromised Patients. Am J Gastro Accepted 2014. This data was also presented orally at the American College of Gastroenterology 2013 meeting in San Diego	Thank you for the suggestions. KQ#1 We have added the Rohlke data (and deleted the Brandt paper which included some patients from the Rohlke series). KQ#4 We have added the Kelly 2014 paper to the report.
No	No response needed
Yes. Yoon et al. J Clin Gastroenterol 2010; 44; 562-66	We have added the Yoon data (and deleted the Brandt paper which included some patients from the Yoon series).
Not sure. This web site (section on C diff in this author's briefing) may be worth considering: http://haicontroversies.blogspot.com/2014/05/the-year-in-infection-control-2014.html.	Thank you for the suggestion. Our review protocol specifies that we include data from peer-reviewed journal publications.
The authors may wish to include this paper: Kelly et al. "Fecal Microbiota Transplant for Treatment of *Clostridium difficile* Infection in Immunocompromised Patients." *The American Journal of Gastroenterology*. advance online publication 3 June 2014; doi: 10.1038/ajg.2014.133.	Thank you for the suggested reference. We have added this paper.
No	
4. Please write any additional suggestions or comments below. If applicable, please indicate the page and line numbers from the draft report.	
Well done and thorough review and interpretation of peer reviewed published literature on FMT. I would recommend that the authors provide distinguishing definitions for recurrent CDI and refractory CDI.	Thank you for the suggestion. We have added definitions in the Methods section where we describe our Population.
It is unclear to me why the event rate for the VanNood trial is cited at 0.81 since the overall rate of cure was >0.90 when patients who received >1 FMT were included. All of the patients had received multiple courses of antibiotics, so it could be argued that FMT is being held to a higher standard. This may be important because unlike a drug, which is highly standardized, human stool is not, and it may be that a small fraction of donors do not have the flora necessary to cure C. difficile, and subsequent transplant with a different donor may be curative. This phenomenon is seen in clinical practice.	Patients in the control arms of the van Nood trial were considered to have failed after a single course of antimicrobial therapy, and were then offered treatment with donor feces off protocol. Thus, we believe that it is most appropriate to apply the same criteria for FMT (assessment of the primary endpoint after one treatment course). Otherwise, the comparison becomes biased, in that one treatment (FMT) is allowed to have 2 attempts at success, whereas the control treatments are allowed only one. We do separately report the success rates observed after multiple attempts of FMT, which we think conveys more information to our readers.

Page 18 lines 24-28. Note: Patients included in the Brandt series from 2012 (long-term follow up study) INCLUDED overlap of cases reported in Mellow 2011, Kelly 2012, Yoon 2012 AND Rohlke 2010. It would be better to analyze each of these series individually (which have more complete data on these patients) rather than Brandt's long term f/u study (which pools all of these other studies). The question of FMT for severe/complicated CDI comes up very frequently. There is much less literature to support use of FMT in these severe and/or complicated cases. You included some of this in with the "refractory" efficacy discussion (Weingarden 2013), but it should really be a separate discussion and analysis. Weingarden 2012, Neemann K, et al. Transpl Infect Dis 2012 You DM, et al. Ann Intern Med 2008 and Aroniadis O, et al. DDW 2013 (oral presentation and abstract) are other cases/series that specifically were performed for severe disease. In Research gaps/future research (page 34) you could include list of ongoing clinical trials (clinicaltrials.gov), including a double blind-sham controlled RCT of FMT via colonoscopy being conducted at Brown (PI-Kelly) and Montefiore (Brandt).	Page 18 Thank you for the suggestions. We have deleted the Brandt series and now report each of the series individually. We agree that the question of FMT for severe/complicated CDI is common. We did not specifically create such a category for analysis, but note that the reports identified also are described as being "refractory to medical therapy" (You 2008), and "this patient's refractory CDI" (Neeman 2012). Thus, we believe that this is an appropriate place to discuss these cases. The cases presented in You 2008 and Neeman 2012 are briefly discussed, but since they are single case reports they did not meet our inclusion criteria. Similarly, the Aroniadis abstract is not included since we did not include unpublished data. We were unable to locate the citation for Weingarden 2012. We have added a list of ongoing trials from clinicaltrials.gov.
- Is there a specific microbiota population dynamics reference for p6/line 41-end of paragraph (post-CDI treatment microbiome perturbations)? - It may be useful to include references regarding resilience of microbiota post-antibiotic treatment or in setting of C. difficile e.g. a C. difficile/FMT microbiota dynamics study by Song et al (PLOSOne 2013)) - It could also be helpful to specifically invoke the term microbial diversity in discussing alteration of the gut microbiome.	The issue of microbial diversity has been added to the executive summary.
In general, the document is very well-written and provides an exhaustive (perhaps a bit too exhaustive) review of the literature. Specific comments follow: - The review should compare and contrast its findings more clearly with the meta-analysis by Kassam et al. Am J Gastro 2013. In this study, the RCT by van Nood was not included but the systematic review included 273 patients with pooled resolution rate for CDI of 89%, and lower route FMT performing better than upper route FMT (91% vs 80.6%). - Key question 3 probably does not merit equal footing as a "key" question such as FMT for recurrent or refractory CDI. The scarcity of pertinent literature illustrates this, and standard of care is specific antibiotic therapy. - The van Nood RCT, despite its limitations, is still the only RCT available, and is referred variably in the review as low quality, moderate quality, and high risk of bias. The quality description should be consistent, and the RCT provides valuable information despite its limitations and the fact it was stopped early because most patients in the control arms developed CDI recurrence. Furthermore, the RCT used upper route FMT in its active arm, which is probably less effective than lower route FMT based on Kassam meta-analysis results and less desirable by patients. Overall, I think the review needs to state more explicitly that the pooled literature shows that lower route FMT particularly colonoscopy is associated with very high-about 90%- cure rate for recurrent CDI. - Data regarding long-term safety of FMT are lacking, and this should be better highlighted in KQ4, particularly in the summary statements. This is probably a more relevant question than short-term adverse events (which are otherwise well detailed in the document). - A relevant point is to address is effectiveness of FMT based on CDI severity/C difficile strain (specifically the virulent NAP1/027 strain). This is addressed in the study by Mattila et al. - FMT has been used for a variety of indications unrelated to CDI which are probably beyond the scope of this review. It could be worth mentioning this in the preamble.	Since the only trial that directly compared to methods of transplantation demonstrated no significant difference, we are hesitant to endorse one route of administration over another based on overall success rates. We have provided the overall success rates for each route, but again caution that direct comparisons are difficult to make between studies. We have clarified this in the executive summary and in the results section. The Key Questions were developed *a priori* and therefore we present the available evidence on FMT for recurrent or refractory CDI We have corrected the discrepancy on the reporting of the risk of bias of the van Nood RCT. We rated the study as moderate risk of bias. See comment above regarding upper route vs. lower route. We have added a statement regarding the lack of long-term safety data to the relevant section. We have added a statement about *C. Difficile* strain to the results from the Matilla et al. study. We agree that it is beyond the scope of this review, and since CDI is the only indication for FMT for which the FDA does not require an investigational new drug application, we opted to not discuss such investigational uses

Figures 2, 3, and 4 should probably be changed to go from 0 to 1 not from -1 to 1 because the data represent rates, and rates can't be less than zero. If I'm misunderstanding the data please ignore this comment.	Your understanding of the data is correct. We are unable to correct this with the software we have available to generate the plots.
- The authors do a nice job describing the response rates with FMT. However, there is little to no discussion of the expected rate of response with additional courses of antibiotics. There is only a brief mention of this toward the very end of the document, other than some mention that the response rate to antibiotics in the RCT was lower than expected. It seems that some additional data on the response rate with antibiotics would be appropriate to put in context the results with FMT in the case series. For example, if studies of antibiotics show 75% response rates, then the FMT results are not very impressive. But if the response rates are around 30%, then the FMT results seem more impressive. - The authors state that the RCT on FMT was stopped due to a low rate of response to antibiotics in the control group. This statement only tells half the story. The study was not stopped simply due to a low response rate in the control group. The study was stopped because a planned interim analysis showed a significant difference, which required the data safety monitoring board to terminate the study early. The statistical methods used in this study are rigorous and the authors of the ESP should not downplay the dramatically significant results here. The authors need to be careful in how they describe this study so as not to bias the readers, or the conclusions of the ESP analysis. - The section on side-effects doesn't review the potential adverse events that were summarized earlier in the document. I wonder why the authors didn't simply put all of the adverse events in this section, rather than make the reader look through the entire document.	We have included data regarding the expected rate of response to additional antibiotic courses in the introduction. -As described in the online appendix to the article by van Nood et al., the interim analysis was not planned, but rather was requested by the principle investigator when multiple individuals involved with the trial became aware of an "(unexpected) extremely low response rate in the 2 control arms, which seemed much lower than the 60% used in the sample size calculation. The principle investigator subsequently requested the data safety monitoring board (DSMB) for advice." We believe that our characterization of the study is accurate. We have clarified that this discussion is regarding potential side effects beyond those observed and reported in the section on harms. Since much is written about these potential harms, and they also may be relevant with regard to future FDA regulations, we believe that a discussion of these potential harms is appropriate in the discussion section.
One major comment is that the document doesn't review the data on the expected "cure" rates with antibiotic therapy. Given that there is only one RCT of FMT vs. antibiotics and the rest of the data is case-series, it would seem appropriate to include a discussion of the effectiveness of antibiotics for recurrent CDI. This can put the case-series data in perspective (acknowledging the limitations of historical controls). The data on this topic are only briefly mentioned on page 33, lines 11-15. Page 2, line 30-34: why did the initial search miss those 15 articles? That is >50% of the included articles and is concerning. Minor comments:) Page 1, line 22: add "cases" after "500") Page 1, line 23: add "been reported" after "have") Page 11, figure 1: under "Excluded", I would suggest changing the order of the third bullet to state "Not case report with adverse event or case series" since case series don't need adverse events to be included) Page 17, line 19: suggest expanding on the case of possible peritonitis and pneumonia) Page 22, line 31: should it read "with only two OTHER of the six…"?) Page 29, line 24: why not move all discussion of harms into this section so they are all described in one place in the review?) Page 38, line 34: "toward" is misspelled	We have added information on expected "cure" rates with antibiotic therapy. Please see the 2nd paragraph of the introduction in the executive summary (page 1), the introduction to main report (page 7), and the summary and discussion (page 42). Page 2: We, too, were concerned about articles missed during our search. We looked at MeSH terms used to index the missed articles and concluded that the issue was use of different terminology (*eg,* instillation instead of transplantation) over the years. We searched multiple recent systematic reviews and reference lists of all included studies in an attempt to not miss any eligible publications. Minor Comments: Thank you for your careful read of the report.) change has been made) sentence has been modified) change has been made) we have noted that little information was provided by the authors of the series reporting this possible adverse event) we believe this sentence is clear as is) we have moved a summary of harms to KQ4) change has been made
5. Please provide any recommendations on how this report can be revised to more directly address or assist implementation needs.	

No specific recommendations beyond correcting a few typos (eg. C. Diff vs. C. diff used interchangeably in the text).	We have attempted to locate and correct all typographical errors.
None at this time, as the review was not designed to specifically support or not support implementation. However, as acknowledged in the review, there is likely to be ongoing trepidation about the 'unknowns' of manipulating the gut microbiome, particularly as new research is constantly emerging about its varied roles in our physiology. It's definitely helpful to present this as an opportunity for expediting high-quality research (as opposed to a potential source of liability).	Thank you.
None. Best to get a final copy edit, check references, etc. and release, ASAP than to make a lot of minor changes. Timeliness is important.	We agree.

APPENDIX C. EVIDENCE TABLES

Appendix C, Table 1. Study Characteristics

Author, year Country Design Funding Source Risk of Bias (RCTs)	Inclusion/Exclusion Criteria	Intervention Treatment Location Definition of Response Follow-up Duration	Patient Characteristics (means unless otherwise noted)	Donor Characteristics (means unless otherwise noted)
RECURRENT CDI – UPPER GASTROINTESTINAL TRACT VS. COLONOSCOPY				
Youngster, 2014[29] Country: USA Design: RCT Funding Source: National Institute of Allergy and Infectious Diseases Risk of Bias Assessment: *Allocation concealment:* adequate *Blinding:* open label *Intention to treat analysis*: yes (last outcome carried forward) *Withdrawals/ dropouts adequately described*: no *Overall:* Moderate risk of bias	Inclusion: Age 7 to 90 years; refractory or recurrent CDI (relapse after at least 3 episodes of mild/moderate CDI and failure of 6-8 week taper of vancomycin OR at least 2 episodes of severe CDI resulting in hospitalization Exclusion: presence of anatomic contraindications to nasogastric tube or colonoscopy; delayed gastric emptying syndrome, recurrent aspirations, pregnancy, significantly compromised immunity, history of significant allergy to foods not excluded from donor diet Method of diagnosis: (+) toxin	Intervention: Group 1) Bowel preparation (4 L polyethylene glycol electrolyte solution); colonoscopic administration of 90 cc thawed inoculum to the right colon; further diluted to 250 cc for adults and 160 cc for pediatric patients; instructed to retain material as long as possible; oral loperamide given at time of procedure Group 2) 2 mg/kg/day (up to 20 mg) oral omeprazole for 48 hrs prior to procedure; nasogastric tube placement documented by radiography; administration of 90 cc inoculum; tube removed; patients drank glass of water Treatment Location: 25% inpatient; 75% outpatient Definition of Response: clinical resolution of diarrhea off antibiotics for *C. difficile,* without relapse within 8 weeks Follow-up duration: 6 months	N=20 Age (yr): 55 Gender (Male%): 45% Race/Ethnicity (%): NR BMI: NR *Immune Status*: NR *Time from first CDI diagnosis to FMT (days*): 289 *Number of CDI Recurrences:* 4.5 (median); range = 2 to 16 *Prior Treatment*: 95% had vancomycin taper, 60% had previous use of fidaxomicin *Current Treatment with Antimicrobials*: Antimicrobials discontinued at least 48 hours prior to procedure	N=5 *Relationship to Patients*: Not related *Inclusion*: volunteers, healthy, non-pregnant, 19-50 years old, on no medications, normal BMI (18.5-25 kg/m^2), no significant past medical history, no use of antibiotics in past 6 months Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* exposure to infectious agents, blood count, liver function, lipid profile, antinuclear antigen, FOBT HIV: Yes Hepatitis: A, B, C Auto-Immune Disease: NR but excluded significant medical history Cancer: FOBT *Other:* enteric bacterial pathogens, *Treponema pallidum* NOTE: donors were asked to refrain from eating common allergens (tree nuts, eggs, peanuts, shellfish) within 5 days of stool donation; donations were escrowed for 5 weeks to allow retesting of donors for HIV, Hep B, and Hep C

Author, year Country Design Funding Source Risk of Bias (RCTs)	Inclusion/Exclusion Criteria	Intervention Treatment Location Definition of Response Follow-up Duration	Patient Characteristics (means unless otherwise noted)	Donor Characteristics (means unless otherwise noted)
RECURRENT CDI – UPPER GASTROINTESTINAL TRACT				
van Nood, 2013[20] Country: Netherlands, Finland Design: RCT Funding Source: Netherlands Organiza-tion for Health Research and Devel-opment; Organization for Scientific Research Risk of Bias Assessment: *Allocation concealment:* Adequate *Blinding:* Open label; outcome assessed by adjudication committee *Intention to treat analysis*: Modified (excluded 1 patient with no treatment) *Withdrawals/ dropouts adequately described*: Yes *Overall:* Moderate Risk of Bias	Inclusion: Age >18 yrs, >3 month life expectancy, diarrhea with + *C. difficile*, at least one course of vancomycin at 125mg QID x 10+ days or metronidazole 500mg TID x 10+ days Exclusion: prolonged compromised immunity d/t recent chemo, HIV+ with CD4 < 240, prolonged prednisolone at least 60mg daily, pregnancy, current antibiotics for something other than *C. difficile*, ICU admission, need for vasopressors Method of diagnosis: + toxin by PCR and diarrhea	Intervention: Bowel lavage followed the next day with nasoduodenal infusion of donor feces (FMT, n=16) Comparators: 1) vancomycin x 14 days (V, n=13); 2) vancomycin + bowel lavage (VB, n=13) Feces collected day of, diluted w/500cc NS, stirred, supernatant strained and poured into sterile bottle; 141+/-71g of donor stool at 50mL/min over 2-3 min Treatment Location: Hospital: FMT: 5/16 (31%), V 4/13 (31%), VB 4/13 (31%) Definition of Response: Cure without relapse within 10 weeks after initiation of therapy; blinded committee decided which patients were cured Duration of Follow-up: 10 weeks, another 10 weeks if 2nd transplant Withdrawals (%): 0 Lost to Follow-up (%): 0	N=43 (Patient characteristics for N=42 with one patient excluded) Age (yr): 70 FMT: 73 +/-13 Vanc: 66+/-14 VB: 69+/-16 Gender (Male%): 58% FMT: 8 (50%) V: 6(46%) VB: 10 (77%) Race/Ethnicity (%): NR BMI: 23 FMT: 22+/-3 V: 22+/-4 VB: 24+/-4 *Immune Status*: excluded immunocompromised *Time from first diagnosis to FMT:* NR *Number of Recurrences of CDI*: FMT 3 (1-5), V 3 (1-4), VB 2 (1-9) (mean = 2.7) *Prior Treatment*: vancomycin and/ or metronidazole *Current Antibiotic Treatment*: Abbreviated vancomycin 500mg QID x 4-5 days with until day before transplant.	N=15 *Relationship to Patients*: NR *Inclusion:* See below Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis:A-C Auto-Immune Disease:n Cancer: no *Other: Questionnaire re: transmissible diseases* Stool for enteric pathogens, parasites (*Blastocystis hominis* and Dientamoeba fragilis), *C. difficile* Serum HTLV 1&2, cytomegalovirus, Epstein-Barr virus, *Treponema, Strongyloides, Entamoeba*

Author, year Country Design Funding Source Risk of Bias (RCTs)	**Inclusion/Exclusion Criteria**	**Intervention Treatment Location Definition of Response Follow-up Duration**	**Patient Characteristics (means unless otherwise noted)**	**Donor Characteristics (means unless otherwise noted)**
Rubin, 2013[30] Country: USA Design: RCS Funding Source: Duluth Clinic Foundation	Inclusion: All patients undergoing FMT for lab confirmed toxin + CDI with ≥2 recurrences, had FMT via protocol, follow up ≥60 days after procedure Exclusion: Non-CDI FMT, surgically shortened GI tract, data had already been reported Method of diagnosis: + toxin (EIA) with diarrhea	Intervention: Proton pump inhibitor the evening before and morning of FMT; FMT via nasogastric tube, gastroscope (7) or already present PEG (4); approx. 30 g stool mixed in 50-70 ml saline, transplant ~ 25mL of stool/ saline mix Treatment Location: NR Definition of Response: Resolution of diarrhea without recurrence within 60 days of FMT Duration of Follow-up: 60 days	N=74 (72 adults, 2 children) Age (yr): 63 (median) Gender (Male%): 35% Race/Ethnicity (%): NR BMI:NR *Immune Status:* malignant illness (8), active corticosteroid (7) *Time from first diagnosis to FMT:* 206 days (51-1282) *Number of Recurrences of CDI:* NR *Prior Treatment:* at least 2 courses metronidazole and/or vancomycin and/or fidaxomicin *Current Antibiotic Treatment:* Vancomycin 125mg QID ≥3 days pre-FMT stopped day prior	N=NR *Relationship to Patients:* "healthy close household member" *Inclusion:* No antibiotics within 3 months Age (yr):NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis: yes Auto-Immune Disease: no Cancer: no *Other: C. difficile, Treponema pallidum,* ova and parasites, "enteric pathogens
Garborg, 2010[31] Country: Norway Design: RCS Funding Source: None stated	Inclusion: First or second recurrence of CDAD Exclusion: NR Method of Diagnosis: (+) *C. difficile* toxin (37), clinical (2), pseudomembranous colitis (1)	Intervention: Gastroscope or colonoscopic installation of 200mL of donor stool solution collected day of procedure Treatment Location: Inpatient and ambulatory Definition of Response: No further hospital contact due to CDAD symptoms within 80 days of FMT Duration of Follow-up: 80 days	N=40, one patient had 2 courses in 2 years; treated as a separate case Age (yr): 75 (53-94) Gender (Male%): 47% Race/Ethnicity (%):NR BMI: NR *Immune Status:* NR (one with acute myelogenous leukemia) *Time from first diagnosis to FMT:* NR *Number of Recurrences of CDI*: NR *Prior Treatment:* metronidazole and/or vancomycin *Current Antibiotic Treatment*: metronidazole or vancomycin until symptoms resolved; stopped evening prior to intervention	N=NR Relationship to Patients: Close relatives or other household members. Inclusion: No symptoms of GI disease or a history of chronic infectious disease Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis: A-C Auto-Immune Disease: no Cancer: no *Other:* enteric bacterial pathogens

Author, year Country Design Funding Source Risk of Bias (RCTs)	Inclusion/Exclusion Criteria	Intervention Treatment Location Definition of Response Follow-up Duration	Patient Characteristics (means unless otherwise noted)	Donor Characteristics (means unless otherwise noted)
MacConnachie, 2009[32] Country: UK Design: RCS Funding Source: None reported	Inclusion: At least one 10-day course each of vancomycin and metronidazole and recurrence of loose stool following successful antibiotics treatment in a patient recently treated for toxin positive CDAD Exclusion: NR Method of diagnosis: + toxin	Intervention: Proton pump inhibitor prior to FMT; 30g donor stool obtained, blended w/150mL of normal saline; 30mL of solution administered via nasogastric tube Treatment Location: Hospital Definition of Response: Not stated Duration of Follow-up: 16 weeks (median) (range 4-24 weeks)	N=15 Age (yr): 82 (68-95) Gender (Male%): 7% Race/Ethnicity (%): NR BMI: NR *Immune Status*: NR *Time from first diagnosis to FMT*: NR *Number of Recurrences of CDI:* 4 (3-7) *Prior Treatment*: metronidazole, vancomycin, IV immunoglobulin *Current Antibiotic Treatment*: Vancomycin 125mg QID until 12 hrs before procedure	N= NR *Relationship to Patients:* "related" *Inclusion:* "healthy" and negative screen as below Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* blood borne viruses, syphilis, enteropathogens
Aas, 2003[33] Country: USA Design: RCS Funding Source: St. Mary's Duluth Clinic	Inclusion: *C. difficile* with ≥2 lab confirmed relapses, adequate clinical and lab documentation of post-transplant course Exclusion: NR Method of Diagnosis: (+) *C. difficile* toxin	Intervention: 20mg omeprazole the evening before and morning of FMT; nasogastric administration of donor stool (25mL) Treatment Location: Hospital (5/18, 28%) and GI clinic (13/18, 72%) Definition of Response: No laboratory documentation of *C.* difficile colitis during 90 days after FMT; clinical response to FMT; no treatment for *C. difficile* colitis during 90 days after FMT; no record of repeated hospitalization for diagnosis and treatment of diarrhea Duration of Follow-up: 90 days	N=18 Age (yr): 73 (51-88) Gender (Male%): 28% Race/Ethnicity (%): NR BMI: NR *Immune Status*: Crohn's colitis (1), leukemia (1) *Time from first diagnosis to FMT:* 102 +/- 24 days (25-497) *Number of Recurrences of CDI:* 3.6 antibiotic courses (2-7) *Prior Treatment*: metronidazole, vancomycin *Current Antibiotic Treatment:* ≥4 day pretreatment with vancomycin 250mg every 8 hours to reduce *C. difficile* load; stopped evening prior	N=16 Relationship to Patients: Spouse, partner, household family member (15) or healthy donor (1) Inclusion: No antimicrobials within 6 months Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: y Hepatitis: y Auto-Immune Disease: no Cancer: no *Other: C. difficile, Treponema pallidum,* ova and parasites, "enteric pathogens
RECURRENT CDI – COLONOSCOPY				

Author, year Country Design Funding Source Risk of Bias (RCTs)	Inclusion/Exclusion Criteria	Intervention Treatment Location Definition of Response Follow-up Duration	Patient Characteristics (means unless otherwise noted)	Donor Characteristics (means unless otherwise noted)
Cammarota, 2014[34] Country: Italy Design: RCS Funding Source: NR	Inclusion: Recurrent or relapsing CDI or moderate CDI not responding to standard therapy; severe colitis with no response to standard therapy after 48 hours Exclusion: NR Method of diagnosis: + toxin (reported for 2 cases)	Intervention: Large volume bowel preparation; colonoscopy, fresh stool (within 6 hours) mixed with saline, 250 to 500 mL administered Treatment Location: Inpatient (33%), outpatient (33%), unclear (33%) Definition of Response: Resolution of symptoms and absence of relapse within 8 weeks Duration of Follow-up: 4 to 5 months NOTE: unclear if protocol for intervention, definition of response, and protocol for donor screening were developed before or after this series of patients	N=3 Age (yr): 67 Gender (Male%): 66% Race/Ethnicity (%): NR BMI: NR *Immune Status:* NR *Time from first diagnosis to FMT:* NR *Number of Recurrences of CDI:* 1-5 *Prior Treatment:* metronidazole, vancomycin *Current Antibiotic Treatment:* NR	N=NR *Relationship to Patients*: Child (1), sibling (1), NR (1) *Inclusion*: Excluded - risk of infectious agent, high risk sexual behaviors, use of illicit drugs, GI co- morbidities, recent antibiotic therapy, immunosuppressive medications, major surgery, metabolic syndrome, multiple sclerosis, atopic diseases Age (yr): NR Gender (Male%): both reported donors were male Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis: A-C Auto-Immune Disease: NR Cancer: no *Other: CD toxin, enteric pathogens, giardia, cryptosporidium, ova and parasites, syphilis*
Pathak, 2014[35] Country: USA Design: RCS Funding Source: NR	Inclusion: Recurrent CDI not responding to standard therapy Exclusion: GI tract could not be used for FMT (*ie,* malignancy, obstruction, perforation) Method of diagnosis: NR	Intervention: Colonoscopy (n=11) or nasoduodenal tube (n=1); standard bowel preparation the night before procedure; fresh feces (within 6 hours of procedure); 6 to 8 tablespoons in 1 liter tap water; colonoscope advanced to cecum or terminal ileum when possible; 400-500 cc instilled at farthest point then 50-60 cc every 10 cm during withdrawal of colonoscope; 2 tablets of diphenoxylate/atropine to slow excretion Treatment Location: Community hospital Definition of Response: Resolution of diarrhea, fall in white cell count, absence of fever, improvement in vital signs Duration of Follow-up: 2 to 29 months	N=12 Age (yr): 72 Gender (Male%): 33% Race/Ethnicity (%): NR BMI: NR *Immune Status:* NR *Time from first diagnosis to FMT:* 4 months to 2 years *Number of Recurrences of CDI:* NR *Prior Treatment:* metronidazole (4), vancomycin (12), fidaxomicin (8) *Current Antibiotic Treatment:* Stopped 24 hours prior to procedure	N=12 *Relationship to Patients*: Spouse (2), child (8), sibling, niece *Inclusion*: Preferred family members or first-degree relatives; excluded for HIV, STDs, Hepatitis B and C, high-risk sexual behaviors, drug use, tattoos or body piercing, imprisonment, known current communicable disease, GI comorbidities, antibiotic use in past 90 days Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis: A-C Auto-Immune Disease: no Cancer: excluded for GI malignancy *Other: STDs, enteric pathogens, ova and parasites, C. difficile toxins A, B*

Author, year Country Design Funding Source Risk of Bias (RCTs)	Inclusion/Exclusion Criteria	Intervention Treatment Location Definition of Response Follow-up Duration	Patient Characteristics (means unless otherwise noted)	Donor Characteristics (means unless otherwise noted)
Patel, 2013[36] Country: USA Design: RCS Funding Source: NR	Inclusion: ≥2 prior episodes of CDI and ongoing diarrhea in the absence of antimicrobial therapy Exclusion: NR Method of diagnosis: + toxin by PCR or EIA	Intervention: Standard split-dose bowel preparation; colonoscopy, fresh stool mixed with saline within 6 hours, into TI or cecum. 360mL (180-600). 4mg loperamide peri-procedure Treatment Location: Outpatient (n=30), inpatient Definition of Response: Improvement (>75%) or resolution of diarrhea and other symptoms (weight loss, abdominal pain, fatigue) Duration of Follow-up: 1 week to 1 year (n=6)	N=31[a] Age (yr): 61.3 +/- 19.3 Gender (Male%): 45% Race/Ethnicity (%): NR BMI: NR *Immune Status:* Immunosupressed, (prednisone use (n=3), hypogamma-globulinemia (n=2), liver transplant (n=1), renal transplant (n=1), methotrexate use (n=1)) Also UC (n=3), Crohn (n=2) *Time from first diagnosis to FMT:* 340 days (18-2205) *Number of Recurrences of CDI:* 4 (2-7) *Prior Treatment:* metronidazole (31), vancomycin (31), fidaxomicin (6), rifaximin (10), probiotic (23) *Current Antibiotic Treatment:* discontinued 4 hrs prior to bowel prep	N=33 *Relationship to Patients*: Spouse (n=14), child (n=9), sibling (n=5), parent (n=3), niece, friend *Inclusion*: No chronic GI disorder, IBD or IBS, history of colon cancer or polyps, antibiotics or hospitalization within 3 months Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis: A-C Auto-Immune Disease: no Cancer: no *Other: HTLV I/II, rapid plasma regain or syphilis EIA, stool bacterial culture, ova and parasites, cryptosporidium antigen, microsporidia smear, C. difficile toxin (PCR or EIA)*
Hamilton, 2012[37] Country: USA Design: RCS Funding Source: Minnesota Medical Foundation, NIH, MinnCRest Postdoctoral Fellowship	Inclusion: History of symptomatic toxin positive *C. difficile* with 2+ subsequent recurrences; minimum of 6wks tapered or pulsed vancomycin or 1 month vancomycin followed by a minimum of 2 week rifaximin “chaser” Exclusion: Age <18, medical fragility from non *C. difficile* problems resulting in life expectancy <1 year Method of Diagnosis: (+) toxin	Intervention: Standard split-dose bowel preparation; colonoscopy with 220-240 ml to terminal ileum and cecum; some also received 50 ml to areas of maximal diverticulosis Stool sample collected 1-2 hrs before procedure 50g stool 250mL normal saline in blender Alternate: 2 volunteers, with frozen stool thawed 2-4 hrs before procedure (used immediately or stored 1-8 wks before transplant) Treatment Location: Colonoscopy suite Definition of Response: Resolution of diarrhea and negative stool testing for *C. difficile* at 2 months following FMT Duration of Follow-up: 2 months	N=43 Age (yr): 59 +/- 21 Gender (Male%): 28% Race/Ethnicity (%): NR BMI: NR *Immune Status*: IBD in 14/43 *Time from first diagnosis to FMT*: 12.2 +/- 10.3 months *Number of Recurrences of CDI*: 5.9 +/- 3.3 *Prior Treatment*: vancomycin, metronidazole, fidaxomicin (n=1), nitazoxanide (n=3) *Current Antibiotic Treatment*: Vancomycin until 2 days before.	N=12 *Relationship to Patients*: Mother (n=2), daughter (n=1), son (n=3), wife (n=1), husband (n=1), friend (n=2), volunteer (n=2) I*nclusion*: No risk factors for HIV, hepatitis, current communicable disease, travel to endemic diarrhea area, antibiotics within 3 months, other GI disease, metabolic syndrome, autoimmunity, allergic diseases (last 2 relative). Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis: B & C Auto-Immune Disease: yes via questionnaire Cancer: yes *Other:* enteric pathogens, *C. difficile* toxin B, O&P, Giardia, cryptosporidium antigens

Author, year Country Design Funding Source Risk of Bias (RCTs)	Inclusion/Exclusion Criteria	Intervention Treatment Location Definition of Response Follow-up Duration	Patient Characteristics (means unless otherwise noted)	Donor Characteristics (means unless otherwise noted)
Kelly, 2012[38] Country: USA Design: RCS Funding Source: None	Inclusion: At least 3 recurrences of CDI Exclusion: NR Method of diagnosis: NR	Intervention: Standard bowel preparation; colonoscopy to TI or cecum, 500-960mL most to R colon; avoid defecating 30-45 mins; fresh specimen within 6 hours mixed in sterile water; Treatment Location: Outpatient Definition of Response: Did not suffer documented *C. difficile* relapse and/ or free of significant diarrhea requiring vancomycin Duration of Follow-up: 10.7 months (range 2-30 months)	N=26 Age (yr): 59 (19-86) Gender (Male%): 8% Race/Ethnicity (%): White 100% BMI: NR *Immune Status*: NR *Time from first diagnosis to FMT*: 12.6 mo (4-84) *Number of Recurrences of CDI*: "at least 3" *Prior Treatment:* Metronidazole (n=25), saccharomyces (n=23), tapering vancomycin (n=25). rifaximin (n=19), lactobacillus (n=4), IVIG (n=2) *Current Antibiotic Treatment*: vancomycin or metronidazole discontinued 2-3 days prior	N=26 *Relationship to Patients*: Partner (n=2), sibling (n=3), spouse (n=10), child (n=9), cousin (n=1), friend (n=1) *Inclusion*: No antibiotics within 90 days Age (yr): NR Gender (Male%): 54% Race/Ethnicity (%): NR BMI: NR *Screen for: See questionnaire*[b] HIV: yes Hepatitis: A-C Auto-Immune Disease: no Cancer: no *Other: Syphilis, Stool culture for enteric pathogens, ova and parasites, giardia antigen, C. difficile A and B*
Mattila, 2012[39] Country: Finland Design: RCS Funding Source: Finnish Foundation for Gastroenterological Research	Inclusion: Lab confirmed recurrent CDI despite antimicrobial treatment Exclusion: FMT not meeting above criteria and not done via colonoscopy per protocol Method of diagnosis: + culture and toxin	Intervention: Standard bowel preparation; 100mL infused via colonoscopy into the cecum; donor stool obtained within 6 hrs; 20-30mL homogenized in 100-200mL of saline Treatment Location: 60 (86%) outpatient Definition of Response: No persistent diarrhea with positive toxin stool test Duration of Follow-up: 12 mo	N=70 Age (yr): 73 (22-90) Gender (Male%): 40% Race/Ethnicity (%): NR BMI: NR *Immune Status*: NR *Time from first diagnosis to FMT*: 133 days (46-360) *Number of Recurrences of CDI:* 3.5 (1-12) *Prior Treatment:* 4.5 (2-12) Vancomycin, metronidazole, fidaxomicin, IVIG (n=1) *Current Antibiotic Treatment*: 4+ days of pretreatment with vancomycin or metronidazole until a reduction of symptoms occurred; discontinued at least 36 hrs prior	N=62 *Relationship to Patients*: Close relative or household contact (n=61), volunteer (n=1) *Inclusion:* No antibiotics last 6 months and no intestinal symptoms Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis: B,C Auto-Immune Disease: no Cancer: no *Other: Ova and parasites, C. difficile, enteric pathogens, Treponema pallidum, total blood count, C-reactive protein, creatinine, liver enzymes*

Author, year Country Design Funding Source Risk of Bias (RCTs)	Inclusion/Exclusion Criteria	Intervention Treatment Location Definition of Response Follow-up Duration	Patient Characteristics (means unless otherwise noted)	Donor Characteristics (means unless otherwise noted)
Mellow, 2011[40] Country: USA Design: RCS Funding Source: NR	Inclusion: Recurrent (at least 3 recurrences, n=12) or refractory (n=1) CDI; active CDI or on treatment Exclusion: Terminally ill Method of diagnosis: *C. difficile* toxin by EIA & diarrhea	Intervention: Standard bowel preparation; colonoscopy; 300-600mL stool infused - 100mL to TI, remaining 50% cecum, last bit throughout colon Treatment Location: Outpatient endoscopy suite; 8/13 in hospital or homebound at time of procedure Definition of Response: Not stated Duration of Follow-up: 5 months (range 1-10 months)	N=13 Age (yr): 67 (32-87) Gender (Male%): 54% Race/Ethnicity (%): NR BMI: NR *Immune Status*: NR. Colon cancer, lymphoma, radiation proctitis, Crohn's (n=1 each), insulin dependent diabetes (n=2) *Time from first diagnosis to FMT:* 10.7 (1-24) *Number of Recurrences of CDI*: 4 (3-7) *Prior Treatment*: metronidazole, vancomycin *Current Antibiotic Treatment*: NR, discontinued 48 hrs before FMT if taking antibiotics	N=NR *Relationship to Patients*: Person chosen by patient *Inclusion:* No antibiotics last 8 wks, acute or chronic diarrhea, immunosuppressant use or known immune disorder, current or prior chemotherapy Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis: A-C Auto-Immune Disease: screening questions Cancer: no *Other: C. difficile EIA, Treponema pallidum, enteric pathogens, ova and parasites*
Rohlke, 2010[41] Country: USA Design: RCS Funding Source: No funding support	Inclusion: *C. difficile* toxin positivity, consistently recurring symptoms over at least 6 months despite at least 3 courses of traditional treatments (including pulsed and tapered vancomycin) Exclusion: None reported Method of diagnosis: Toxin (+)	Intervention: 4.0L polyethelyne glycol purge evening before procedure; max of 350cc mixed with saline (generally 200-300cc) via colonoscopy under moderate sedation (intent was ileal intubation); stool infused during withdrawal initially; later all material instilled at proximal most extent of exam; patients at one site took 2 tablets diphenoxylate and atropine immediately after procedure and 5 hours later; bed rest at least several hours after procedure Treatment Location: 2 "medical centers"; treated as outpatients Definition of Response: Not stated Follow-up duration: 27.2 months (range 6 months to 5 years)	N=19 Age (yr): 49 (29-82) Gender (Male%): 11% Race/Ethnicity (%): NR BMI: NR *Immune Status*: NR *Time from first CDI diagnosis to FMT (day*s): NR *Number of CDI Recurrences: NR* *Prior Treatment*: "generally vancomycin" *Current Treatment with Antimicrobials*: NR; stopped 1 to 3 days before FMT	N=19 *Relationship to Patients*: 74% partners, 21% family members, 5% housemates *Inclusion*: no recent antibiotic use, no current or recent diarrheal illness, no hospital or health care workers, no at-risk sexual behaviors Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* Screening was selective based on recipient's discretion and desires HIV: NR Hepatitis: NR Auto-Immune Disease: NR Cancer: NR *Other:* NR

Author, year Country Design Funding Source Risk of Bias (RCTs)	Inclusion/Exclusion Criteria	Intervention Treatment Location Definition of Response Follow-up Duration	Patient Characteristics (means unless otherwise noted)	Donor Characteristics (means unless otherwise noted)
Yoon, 2010[42] Country: USA Design: RCS (5 patients excluded) Funding Source: No funding support	Inclusion: *C. difficile* + toxin diarrhea and recurrence despite standard therapies Exclusion: colitis (tests suggestive of IBD, n=1); cloaco-genic rectal carcino-ma (n=1); colon-oscopy (aphthous ulcers and biopsy specimens showing lymphoid aggregates and focal cryptitis , n=1); Crohn's (n=1); unable to contact for follow-up data (n=1) Method of diagnosis: (+) toxin	Intervention: Colonoscopy with 250-400cc injected in 10-20 cc increments every 5 to 10 cm of withdrawal distance; encouraged patients with retain infused stool for at least 4 hours Treatment Location: NR Definition of Response: Absence of diarrhea, cramps, and fever within 3 to 5 days of FMT Follow-up duration: 3 weeks to 8 years	N=12 Age (yr): 66 (30-86) Gender (Male%): 25% Race/Ethnicity (%): NR BMI: NR *Immune Status*: None immune suppressed based on comorbid conditions listed *Time from first CDI diagnosis to FMT (days):* 79 to 1532 days (mean 351 days, median 209 days) *Number of CDI Recurrences: NR* *Prior Treatment:* metronidazole (oral n=12, IV n=3); vancomycin (n=12); nitazoxanide (n=3), rifaximin (n=4), cholestyramine (n=4), *lactobacilil (n=4), Saccharomyes boulardii (n=7)* *Current Treatment with Antimicrobials*: advised patients to discontinue 3 days before procedure but not controlled	N=12 *Relationship to Patients*: spouse/ partner 67%; son/daughter/grand-daughter 33% *Inclusion*: No GI symptoms; "healthy" Age (yr): NR Gender (Male%): 50% Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: at discretion of treating physician; 3/12 screened Hepatitis: at discretion of treating physician; 3/12 screened Auto-Immune Disease: NR Cancer: NR *Other: C. difficile* toxin assay (8/12), stool culture and ova and parasites study (3/12) at discretion of treating physician
RECURRENT CDI –ENEMA				
Emanuelsson, 2013[43] Country: Sweden Design: RCS Funding Source: R&D Council at Skaraborgs Hospital Skovde	Inclusion: "all patients treated with FMT or RBT d/t severe relapsing and therapy-resistant CDI" between 1994-2011 Exclusion: NR Method of diagnosis: + culture and/or toxin by EIA	Intervention: At least 50g fresh feces mixed with saline to 500mL then flushed into rectal catheter (enema); patients lie on left side for 20 min, stomach another 20 min Treatment Location: GI clinic Definition of Response: Sustained resolution of symptoms (loss of perception of illness and discontinuation of diarrhea within 3 days and no signs of recurrence within 3 months) Duration of Follow-up: 18 months (range 0-21 months)	N=23* Age (yr): 67 (25-93) Gender (Male%): 38% Race/Ethnicity (%): NR BMI: NR *Immune Status*: uterine cancer, TB (2), PMR (2), DLBCL (2, one BMT), prostate ca, *Time from first diagnosis to FMT*: 5 months (1-16) *Number of Recurrences of CDI*: 3 antibiotics courses (1-5) *Prior Treatment*: Metronidazole and/or vancomycin (some tapered dosing) *Current Antibiotic Treatment*: NR; stopped morning of FMT	N=NR *Relationship to Patients*: Spouse or close relative *Inclusion*: "good health, no GI disease, no recent antibiotics use" Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis: B and C Auto-Immune Disease: no Cancer: no *Other: Salmonella, Shigella, Campylobacter, enterohemolytic Escherichia coli, C. difficile*

Author, year Country Design Funding Source Risk of Bias (RCTs)	Inclusion/Exclusion Criteria	Intervention Treatment Location Definition of Response Follow-up Duration	Patient Characteristics (means unless otherwise noted)	Donor Characteristics (means unless otherwise noted)
Silverman, 2010[44] Country: Canada Design: RCS Funding Source: NR	Inclusion: Recurrent CDI, living at home Exclusion: NR Method of diagnosis: *C. difficile* toxin	Intervention: 50mL of stool with 200mL saline, family to administer via enema, patient to lay on left side as long as possible; may repeat procedure if diarrhea recurs within 1 hour Treatment Location: Home Definition of Response: Clinical success Duration of Follow-up: Clinic visit at 2 weeks; follow-up 8.6 months (range 4-14 months)	N=7 Age (yr): 72 (30-88) Gender (Male%): 57% Race/Ethnicity (%): NR BMI: NR *Immune Status*: NR *Time from first diagnosis to FMT*: 13 months (6-23) *Number of Recurrences of CDI*: NR *Prior Treatment*: vancomycin, metronidazole, saccharomyces and *S. boulardii* prior to FMT to ensure patients were asymptomatic until 24-48 hours before FMT *Current Antibiotic Treatment*: metronidazole 500mg TID or vancomycin 125mg QID with saccharomyces 500mg BID stopped 24-48 hrs before transplant	N=7 *Relationship to Patients*: child (n=4), sibling (n=1), spouse (n=1), grandchild (n=1) *Inclusion*: No history of GI illness, malignancy, antibiotic use or hospitalization within 3 months Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis: A-C Auto-Immune Disease: no Cancer: no *Other: HTLV I/II, syphilis EIA, H pylori antibody, C. difficile, culture, ova and parasites, cryptosporidia, microspora*
Gustafson, 1999[45] Country: Sweden Design: Prospective case series Funding Source: Swedish Medical Research Council & Karolinska Institute funds	Inclusion: Hospitalized patients with antibiotic associated diarrhea; 6 had + C diff toxin Exclusion: NR Method of diagnosis: toxin	Intervention: Coloscope with 20mL enema of homogenized donor stool and pasteurized cow milk into the rectum Treatment Location: Hospital Definition of Response: “Clinically well” defined as <3 stools per day and normal consistency Duration of Follow-up: 18 months	N=6 (with CDI +) Age (yr): 60.8 (30-83) Gender (Male%): 83% Race/Ethnicity (%): NR BMI: NR *Immune Status*: NR *Time from first diagnosis to FMT:* NR *Number of Recurrences of CDI*: NR *Prior Treatment:* Metronidazole (n=2) *Current Antibiotic Treatment:* none (last antibiotic dose was 7 to 60 days before FMT)	N=1 *Relationship to Patients*: Healthy donor *Inclusion*: NR Age (yr): NR Gender (Male%): 0% Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis: A-C Auto-Immune Disease: no Cancer: no *Other: cytomegalovirus, Epstein-Barr virus, C difficile, “bacterial pathogens”*

Author, year Country Design Funding Source Risk of Bias (RCTs)	**Inclusion/Exclusion Criteria**	**Intervention Treatment Location Definition of Response Follow-up Duration**	**Patient Characteristics (means unless otherwise noted)**	**Donor Characteristics (means unless otherwise noted)**
Paterson, 1994[46] Country: Australia Design: RCS Funding Source: NR	Inclusion: Relapsing toxin + *C. difficile* Exclusion: NR Method of diagnosis: +toxin	Intervention: Rectal tube infusion of 400mL of mixed feces and saline daily for 3 days[c] Treatment Location: NR Definition of Response: Not stated Duration of Follow-up: NR	N=7 Age (yr): 56 (30-80) Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Immune Status*: NR, multiple myeloma (n=1) *Time from first diagnosis to FMT*: NR *Number of Recurrences of CDI:* 3 (1-4) *Prior Treatment*: Vancomycin, metronidazole, bacitracin or cholestyramine *Current Antibiotic Treatment*: NR	N=NR *Relationship to Patients*: "relative" I*nclusion*: NR Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis: B+C Auto-Immune Disease: no Cancer: no *Other: C. difficile, enteric pathogens*
Tvede, 1989[47] Country: Denmark Design: RCS Funding Source: NR	Inclusion: Relapsed CDI Exclusion: NR Method of diagnosis: Culture and toxin	Intervention: Enema, 50g stool with 500mL saline Treatment Location: NR Definition of Response: Not stated Duration of Follow-up: 12 months	N=2 Age (yr): 60 (59-60) Gender (Male%): 50% Race/Ethnicity (%): NR BMI: NR *Immune Status*: NR *Time from first diagnosis to FMT:* 17 (15-18) months *Number of Recurrences of CDI:* 3 (2-4) *Prior Treatment*: Vancomycin, cholestyramine, metronidazole, fusidic acid *Current Antibiotic Treatment*: NR	N=2 *Relationship to Patients*: Husband (n=1), daughter (n=1) *Inclusion*: NR Age (yr): NR Gender (Male%): 50% Race/Ethnicity (%): NR BMI: NR *Screen for: NR*

Author, year Country Design Funding Source Risk of Bias (RCTs)	Inclusion/Exclusion Criteria	Intervention Treatment Location Definition of Response Follow-up Duration	Patient Characteristics (means unless otherwise noted)	Donor Characteristics (means unless otherwise noted)
RECURRENT CDI –UPPER GASTROINTESTINAL TRACT AND COLONOSCOPY				
Dutta, 2014[48] Country: USA Design: Prospective case series Funding Source: Gastroenterology Research Fund, Sinai Hospital Baltimore. Institute for Genome Sciences, University of Maryland	Inclusion: ≥3 recurrences of CDI ages 18-90 Exclusion: Critically ill, cancer and immunocompromised patients Method of diagnosis: Toxin by ELISA with diarrhea ≥ 3 stools/day	Intervention: 180cc into JEJUNUM via enteroscopy and 270cc via colonoscopy Treatment Location: NR Definition of Response: Resolution of diarrhea and disappearance of stool *C. difficile* toxin Duration of Follow-up: 21 months (range 10-34)	N=27 Age (yr): 65 (18-89) Gender (Male%): 19% Race/Ethnicity (%): Caucasian (74), African American (22), Asian (4) BMI: NR *Immune Status*: NR *Time from first diagnosis to FMT*: 12.9 months (2.5-27) *Number of Recurrences of CDI*: 4.6 (3-5) *Prior Treatment*: metronidazole (n=24), vancomycin (n=26), fidaxo-micin (n=13), rifaxomycin (n=6), ni-tazoxanide, cholestyramine (n=1) *Current Antibiotic Treatment*: NR	N=27 *Relationship to Patients*: Spouse (n=10), Child (n=13), parent (n=4) *Inclusion*: NR Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Other: Screen for "history, physical and blood testing to exclude any transmissible diseases"*
REFRACTORY CDI – COLONOSCOPY				
Weingarden, 2013[49] Country: USA Design: RCS Funding Source: NIH	Inclusion: Severe CDI refractory to antibiotics[d] Exclusion: NR Method of diagnosis: NR	Intervention: Colonoscopy admin of stool; 50g stool with 250mL saline either thawed (n=3) or fresh (n=1); 220-240 ml to terminal ileum and cecum; 50 ml to colonic areas with maximum diverticulosis Treatment Location: Hospital Definition of Response: Not stated Duration of Follow-up: Up to one year	N=4 Age (yr): 72.8 (66-83) Gender (Male%): 25% Race/Ethnicity (%): NR BMI: NR *Immune Status*: ovarian cancer on chemo (n=1) *Time from first diagnosis to FMT*: NA *Number of Recurrences of CDI*: NA *Prior Treatment*: metronidazole (oral & IV), vancomycin (oral) *Current Antibiotic Treatment*: metronidazole held 48hrs prior, vancomycin 12-24 hrs prior	N=1 *Relationship to Patients*: Volunteer *Inclusion:* No risk factors for HIV, hepatitis, communicable disease, travel to endemic diarrhea area, antibiotics (3 months), GI disease, metabolic syndrome, autoimmunity, allergy (last 2 relative) Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis: yes Auto-Immune Disease: yes via questionnaire Cancer: yes *Other: enteric pathogens, C. difficile toxin B, ova and parasites, Giardia, cryptosporidium antigens*

Author, year Country Design Funding Source Risk of Bias (RCTs)	Inclusion/Exclusion Criteria	Intervention Treatment Location Definition of Response Follow-up Duration	Patient Characteristics (means unless otherwise noted)	Donor Characteristics (means unless otherwise noted)
REFRACTORY CDI –ENEMA				
Lee, 2014[50] Country: Canada Design: RCS Funding Source: Natural Sciences and Engineering Research Council of Canada and National Science Foundation through Statistical and Applied Mathematical Sciences Institute	Inclusion: Recurrent (symptom resolution for at least 2 days after discontinuation of treatment with recurrence of diarrhea) or refractory (ongoing diarrhea despite treatment with at least 5 days oral vancomycin) CDI Exclusion: NR Method of diagnosis: + toxin by EIA or PCR	Intervention: 150g of stool emulsified in 300mL of sterile water; 100 mL of supernatant administered rectally by enema Treatment Location: 70/94 (74.5%) were hospitalized Definition of Response: Clinical resolution of CDI Duration of Follow-up: 6 to 24 months	N=94 Age (yr): 72 (range 24-95) Gender (Male%): 44% Race/Ethnicity (%): NR BMI: NR *Immune Status*: NR *Time from first diagnosis to FMT:* NR *Number of Recurrences of CDI*: NR *Prior Treatment*: Mean of 2.1 courses of antibiotics (metronidazole (79%), vancomycin (75%), vancomycin taper (15%), combination (17%) *Current Antibiotic Treatment*: NR	N=NR *Relationship to Patients*: Unknown volunteers *Inclusion*: No antibiotics in the preceding 6 months Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: yes Hepatitis: B,C Auto-Immune Disease: no Cancer: no *Other: H. pylori serology, HTLV-1&2, C. difficile, ova and parasites,, syphilis serology, "enteric bacterial pathogens"*
Bowden, 1981[51] Country: USA Design: RCS Funding Source: NR	Inclusion: Pseudo-membranous colitis Exclusion: NR Method of diagnosis: Pseudomembranes on direct visualization and diarrhea	Intervention: BID fecal enemas (n=13) or jejunal infusion with cantor tube (n=1), "enteric infusion" (n=1) until symptoms improved; stool prepared in saline and given as retention enema Treatment Location: Hospital Definition of Response: Resolution of symptoms (decrease in number of stools, temperature, white blood cell count); in some cases resolution of pseudomembrane; improvement in well being Duration of Follow-up: NR	N=15 Age (yr): 59 (43-85) Gender (Male%): 40% Race/Ethnicity (%): NR BMI: NR *Immune Status*: NR *Time from first diagnosis to FMT:* NR *Number of Recurrences of CDI*: NR *Prior Treatment*: Kanamycin, tetracycline, neomycin, sulfasuxidine, sulfathalidine, keflin, chloramphenicol, gentamicin, clindamycin, lactobacillus, albumin *Current Antibiotic Treatment*: NR	N=NR *Relationship to Patients*: In-house family, medical students and residents *Inclusion*: NR Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: no Hepatitis: yes Auto-Immune Disease: no Cancer: no *Other: amoebiasis, "other enteric diseases"*

Author, year Country Design Funding Source Risk of Bias (RCTs)	Inclusion/Exclusion Criteria	Intervention Treatment Location Definition of Response Follow-up Duration	Patient Characteristics (means unless otherwise noted)	Donor Characteristics (means unless otherwise noted)
Eiseman, 1958[18] Country: USA Design: Case Series Funding Source: NR	Inclusion: Pseudo-membranous enterocolitis Exclusion: NR NOTE: report of 4 cases – 3 refractory CDI, 1 initial therapy (see below)	Intervention: Retention fecal enema using donor feces from a "normal" subject Treatment Location: Hospital Definition of Response: Not stated Follow-up duration: 2 to 10 days (until hospital discharge)	N=3 Age (yr): 52 Gender (Male%): 67% Race/Ethnicity (%): white 33%, Hispanic 33%, NR 33% BMI: NR *Immune Status*: NR *Time from first CDI diagnosis to FMT (days):* 8 (range 1 to 20) *Number of CDI Recurrences:* NR *Prior Treatment*: albamycin, erythromycin, chloromycetin *Current Treatment with Antimicrobials*: NR	N=NR *Relationship to Patients*: NR *Inclusion*: "Normal" subject, no antimicrobials during previous several months Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: NR Hepatitis: NR Auto-Immune Disease: NR Cancer: NR *Other:* NR
INITIAL THERAPY FOR CDI - ENEMA				
Eiseman, 1958[18] Country: USA Design: Case Series Funding Source: NR	Inclusion: See above (1 case in series was FMT as initial therapy) Exclusion: NR	Intervention: Retention fecal enema using donor feces from a "normal" subject Treatment Location: Hospital Definition of Response: Not stated Follow-up duration: 5 days	N=1 Age (yr): 68 Gender (Male%): 100% Race/Ethnicity (%): white 100% BMI: NR *Immune Status*: NR *Time from first CDI diagnosis to FMT (days):* 7 *Number of CDI Recurrences:* NR *Prior Treatment*: albamycin, erythromycin, chloromycetin *Current Treatment with Antimicrobials*: NR	N=NR *Relationship to Patients*: NR *Inclusion*: "Normal" subject, no antimicrobials during previous several months Age (yr): NR Gender (Male%): NR Race/Ethnicity (%): NR BMI: NR *Screen for:* HIV: NR Hepatitis: NR Auto-Immune Disease: NR Cancer: NR *Other:* NR

USA = United States of America; UK = United Kingdom; RCS = retrospective case series; RCT = randomized controlled trial; NR = not reported; N = number of subjects; BID = two times a day; BMI = body mass index; CDAD = *Clostridium difficile* associated diarrhea; DI = *Clostridum difficile* infection; EIA = enzyme immunoassay; FMT = fecal microbiota transplantation; FOBT = fecal occult blood test; GI = gastrointestinal; HTLV = human T-cell lymphotropic virus; IV = intravenous; O&P = ova and parasites; PCR = polymerase chain reaction; PEG = percutaneous endoscopic gastroscopy; QID = four times a day; TID = three times a day

[a]Only 30 patients of 31 had diarrhea, which was the primary outcome

[b]Donor Screening Questionnaire

Exclusion Criteria: Risk of infectious agent; Known exposure to HIV or viral hepatitis (within the previous 12 mo); High-risk sexual behaviors (examples: sexual contact with anyone with HIV/AIDS or hepatitis, men who have sex with men, sex for drugs or money); Use of illicit drugs; Tattoo or body piercing within 6mo; Incarceration within previous 12mo; Known current communicable disease; Risk factors for variant Creutzfeldt-Jakob disease; GII comorbidities; History of inflammatory bowel disease; History of irritable bowel syndrome, idiopathic chronic constipation, or chronic diarrhea; History of GI malignancy

Other: Antibiotic use within the preceding 90 d; Recent ingestion of a potential allergen (*eg*, nuts) where recipient has a known allergy to this agent; Systemic autoimmunity, for example, multiple sclerosis, connective tissue disease; Chronic pain syndromes, for example, chronic fatigue syndrome, fibromyalgia

[c]Protocol reported for one of the patients, unclear if others followed same protocol

[d]WBC >20, albumin <2.5, fever, abdominal pain, distension, colonic thickening on CT, ascites

Appendix C, Table 2. Outcomes after Initial Transplant and Adverse Events

Study, yesear Country Design N=	Reported Resolution of Symptoms after Initial FMT - n/N (%)		Time to Resolution of Symptoms, days	Recurrence n/N (%)	All-Cause Mortality n/N (%)	Adverse Events n/N (%)
	3 months or less	Greater than 3 months				
RECURRENT CDI – UPPER GASTROINTESTINAL TRACT VS. COLONOSCOPY						
Youngster 2014[29] USA RCT N=20 (3 pediatric)	Colonoscopy; 8/10 (80) Nasogastric: 6/10 (60) P=.63	NR	NR	0/20 (in 8 week follow-up)	2/20 (10) (at 12 and 21 weeks after FMT)	Mild abdominal discomfort and bloating 4/20 (20) Transient fever: 1/20 (5) (pediatric patient) Adenocarcinoma of esophagus: 1/20 (5) Fournier's gangrene: 1/20 (5)
RECURRENT CDI – UPPER GASTROINTESTINAL TRACT						
Van Nood, 2013[20] Netherlands RCT N=43 (17 FMT, 13 Vancomycin, 13 Vancomycin+BL) NOTE: 1 patient in FMT group was excluded from analysis because of a clinically-driven protocol violation	FMT: 13/16 (81) Vancomycin: 4/13 (31) Vancomycin+BL: 3/13 (23) P<.01	NR	NR	FMT: 3/16 (19) Vancomycin: 8/13 (62) Vancomycin+BL: 7/13 (54)	FMT: 0/16 Vancomycin: 1/13 (8) Vancomycin+BL: 0/13	FMT - day of infusion[a] Diarrhea: 15/16 (94) Cramps: 5/16 (31) Belching: 3/16 (19) Nausea: 1/16 (6) FMT – follow-up Constipation: 3/16 (19) Other (considered un-related to FMT) Infection: 2/16 (13) Hospitalization: 1/16 (6) Vancomycin, Vancomycin+BL: few and mild adverse events only
Rubin, 2012[30] USA RCS N=74 (72 adults)[b]	58/72 (81)	NR	NR	NR	0/72	0/72
Garborg, 2010[31] Norway RCS N=40	29/40 (73)	NR	Usually within 24 hrs	NR	5/40 (13)	NR
MacConnachie, 2009[32] UK RCS N=15	11/15 (73)	NR	NR	4/15 (27)	0/15	Upper GI bleeding: 1/15 (7)
Aas, 2003[33] USA RCS N=18	15/18 (83)	NR	Most reported resolution within 12-24 hrs	1/18 (6)	2/18 (11)	Possible peritonitis day 3 s/p FMT: 1/18 (6) Pneumonia: 1/18 (6)
TOTAL[c]	**132/171 (77)**			**8/59 (14) (4 studies)**	**7/161 (4)[d] (5 studies)**	

Study, yesear Country Design N=	Reported Resolution of Symptoms after Initial FMT - n/N (%)		Time to Resolution of Symptoms, days	Recurrence n/N (%)	All-Cause Mortality n/N (%)	Adverse Events n/N (%)
	3 months or less	Greater than 3 months				
RECURRENT CDI – COLONOSCOPY						
Cammarota 2014[34] Italy RCS N=3	3/3 (100)	NR	2 days after procedure for 1 patient; NR for 2 patients	NR	0/3	0/3
Pathak 2014[35] USA RCS N=12	11/12 (92)	10/12 (83%)	Within 48 hours	0/12	1/12 (8)	0/12
Patel, 2013[36] USA RCS N=31	Diarrhea symptoms 22/30 (73)[e]	Diarrhea symptoms 6/6 (100) who followed up at 1 year	Median: 3 days (1-18)	3/30 (10)	1/31 (3)	Microperforation during procedure 1/31 (3)
Hamilton, 2012[37] USA RCS N=43	37/43 (86) Individual donor: 7/10 (70) Standard donor: Fresh 11/12 (92) Frozen 19/21 (90) P=.127	NR	NR	6/43 (14)	0/43	No serious events Short lived bowel movement irregularity and excessive flatulence in approximately 1/3 of patients
Kelly, 2012[38] USA RCS N=26	25/26 (96)	24/26(92)	Hours to few days	2/26 (8)	NR	NR
Mattila, 2012[39] Finland RCS N=70	66/70 (94)	62/70 (89)	NR	8/70 (11)	3 months: 4/70 (6) 12 months: 14/70 (20)	0/70
Mellow, 2011[40] USA RCS N=12[f]	11/12 (92)	7/9 (78) who were followed for over 3 months or who relapsed prior	Almost all within 7 days	1/12 (8)	3/12 (25)	NR

Study, yesear Country Design N=	Reported Resolution of Symptoms after Initial FMT - n/N (%)		Time to Resolution of Symptoms, days	Recurrence n/N (%)	All-Cause Mortality n/N (%)	Adverse Events n/N (%)
	3 months or less	Greater than 3 months				
Rohlke, 2010[41] USA RCS N=19	18/19 (95)	18/19 (95)	NR	1/19 (5)	NR	NR
Yoon, 2010[42] USA RCS N=12	12/12 (100%)	NR (available follow-up ranged from 3 weeks to 8 years)	NR (by definition, symptoms resolved in 3 to 5 days)	NR	NR	0/12
TOTAL[g]	**213/237 (90)**			**21/222 (10) (8 studies)**	**19/171 (11)[d] (6 studies)**	
RECURRENT CDI –ENEMA						
Emanuelsson, 2013[43] Sweden RCS N=23	15/23 (65)	12/15 (80) (3 had only <3 months follow-up)	NR (success defined as discontinuation of diarrhea within 3 days)	1/23 (4) recurrence a few weeks after initial treatment (treatment was rated as failure)	NR	0/23
Silverman, 2010[44] RCS N=7	7/7 (100)	7/7 (100)	NR	0/7	NR	0/7
Gustafsson, 1999[45] Sweden PCS N=6 CDI	5/6 (83)	5/5 (100)	Most within 4 days (range 2 to 6)	0/6	NR	NR
Paterson, 1994[46] Australia RCS N=7	7/7 (100)[h]	NR	NR	NR	NR	NR
Tvede, 1989[47] Denmark RCS N=2	1/2 (50)	NR	NR	0/2	0	NR
TOTAL	**35/45 (78)**			**1/38 (3) (4 studies)**	**0/2 (1 study)**	

Study, yesear Country Design N=	Reported Resolution of Symptoms after Initial FMT - n/N (%)		Time to Resolution of Symptoms, days	Recurrence n/N (%)	All-Cause Mortality n/N (%)	Adverse Events n/N (%)
	3 months or less	Greater than 3 months				
RECURRENT CDI –UPPER GASTROINTESTINAL TRACT AND COLONOSCOPY						
Dutta, 2014[48] USA PCS N=27	27/27 (100)	27/27 (100)	3 days (range 1-15)	0/27	NR	Low-grade fever: 5/27 (19) Bloating: 3/27 (11)
REFRACTORY CDI – COLONOSCOPY						
Weingarden, 2013[49] USA RCS N=4	0/4 All patients had improvement in symptoms but then recurrence	NA	Improvements noted in 1 to "several" days	4/4 (100) All patients were considered for 2nd procedure; 3/4 were on antibiotics	1/4 (25)	NR
Mellow, 2011[40] USA RCS N=1 (see Recurrent CDI – Colonoscopy)	1/1 (100)	1/1 (100)	NR	0/1	0/1	NR
Total	**1/5 (20)**			**4/5 (80)**	**1/5 (20)**	
REFRACTORY CDI – ENEMA						
Lee, 2014[50] Canada RCS N=94	45/94 (48)	45/94 (48)	NR	0/45	6/94 (6) None attributable to FMT or CDI	Transient constipation and excess flatulence: 10%
Bowden, 1981[51] USA RCS N=16[b] (15 adults)	13/15 (87)[i]	Duration of response not reported	1-12 days	NR	2/15 (13)[j]	"No ill effects from the fecal enemas"
Eiseman, 1958[18] USA RCS N=4 (3 with refractory CDI)	3/3 (100)[j]	NR	1-2 days	Unclear[k]	0/3	NR
TOTAL	**61/112 (54)**			**0/45 (1 study)**	**8/112 (7)**	

Study, yesear Country Design N=	Reported Resolution of Symptoms after Initial FMT - n/N (%)		Time to Resolution of Symptoms, days	Recurrence n/N (%)	All-Cause Mortality n/N (%)	Adverse Events n/N (%)
	3 months or less	Greater than 3 months				
INITIAL THERAPY FOR CDI - ENEMA						
Eisemen, 1958[18] USA RCS N=4 (1 as initial therapy)	1/1 (100)	NR	Within 48 hours	0/1	0/1	NR

BL = bowel lavage; CDI = *C. difficile* infection; FMT = fecal microbiota transplant; GI = gastrointestinal; NR = not reported; PCS = prospective case series; RCS = retrospective case series; s/p = status post

- [a]All lasted less than 3 hrs after infusion
- [b]Children were excluded; 2 patients for Rubin 2012[30] and 1 patient for Bowden 1981[51]
- [c]Includes 10 patients from nasogastric group reported by Youngster 2014[29]
- [d]Does not include 2 deaths reported by Youngster 2014[29] because treatment group was not reported
- [e]One patient lost to follow-up after FMT
- [f]One additional patient had refractory CDI that was successfully treated >3 months (See Refractory CDI – Colonoscopy section); additional 7 patients reported in Addendum with success after initial FMT in 6 of 7(86%) with the remaining patient achieving resolution after repeat FMT with feces from a different donor
- [g]ncludes 10 patients from colonoscopy group reported by Youngster 2014[29]
- [h]All had daily FMT for unspecified amount of time, likely 3 days
- [i]Most patients received fecal enema twice daily for up to 12 days
- [j]One additional patient died of cerebrovascular accident 1 month after treatment
- [k]One patient received 2nd transplant on same day; all 3 patients received another transplant the day after the first but unclear whether the repeat procedures were related to treatment failure

Appendix C, Table 3. Outcomes after Repeat Transplant

Study, year Country Design N=	Repeat Transplant after Initial FMT Failure n/N (%)	Reported Resolution of Symptoms after Repeat Transplant n/N (%)	
		≤ 3 months	> 3 months
RECURRENT CDI – UPPER GASTROINTESTINAL TRACT VS. COLONOSCOPY			
Youngster 2014[25] USA RCT N=20	5/6 (83) (2/2 from colonoscopy group, 3/4 from nasogastric group; all requested nasogastric administration)	4/5 (80%) (2/2 from original colonoscopy group, 2/3 from original nasogastric group	NR
RECURRENT CDI – UPPER GASTROINTESTINAL TRACT			
Van Nood, 2013[16] Netherlands RCT N=43 (16 FMT)	3/3 (100)	2/3 (66.7)	NR
Rubin, 2012[26] USA RCS N=74 (72 adults)	0/14	NA	NA
Garborg, 2010[27] Norway RCS N=40	6/11 (55)	4/6 (67)	NR
MacConnachie, 2009[28] UK RCS N=15	1/4 (25)	1/1 (100)	NR
Aas, 2003[29] USA RCS N=18	0/3	NA	NA
RECURRENT CDI – COLONOSCOPY			
Cammarota 2014[30] Italy RCS N=3	NA	NA	NA
Pathak 2014[31] USA RCS N=12	1/1 (100) (Nasoduodenal approach)	1/1 (100)	NR

Study, year Country Design N=	Repeat Transplant after Initial FMT Failure n/N (%)	Reported Resolution of Symptoms after Repeat Transplant n/N (%)	
		≤ 3 months	> 3 months
Patel, 2013[32] USA RCS N=31	3/8 (38)[a] 2 via upper endoscopy due to subtotal colectomy	3/3 (100)	NR
Hamilton, 2012[33] USA RCS N=43	4/6 (67)	4/4 (100) One had push enteroscopy into jejunum because of colostomy	NR
Kelly, 2012[34] USA RCS N=26	0/1	NA	NA
Mattila, 2012[35] Finland RCS N=70	0/4	NA	NA
Mellow, 2011[36] USA RCS N=12	0/1	NA	NA
Rohlke, 2010[37] USA RCS N=19	1/1 (100)	1/1 (100)	1/1 (100)
Yoon, 2010[38] USA RCS N=12	NA	NA	NA
RECURRENT CDI –ENEMA			
Emanuelsson, 2013[39] Sweden RCS N=23	2/8 (25)	1/2 (50)	1/2 (50)
Silverman, 2010[40] RCS N=7	NA	NA	NA

Study, year Country Design N=	Repeat Transplant after Initial FMT Failure n/N (%)	Reported Resolution of Symptoms after Repeat Transplant n/N (%)	
		≤ 3 months	> 3 months
Gustafsson, 1999[41] Sweden PCS N=6 CDI	1/1 (100)	1/1 (100%)	1/1 (100%)
Paterson, 1994[42] Australia RCS N=7	NA	NA	NA
Tvede, 1989[43] Denmark RCS N=2	1/1 (100)	0/1	NA
RECURRENT CDI –UPPER GASTROINTESTINAL TRACT AND COLONOSCOPY			
Dutta, 2014[44] USA PCS N=27	NA	NA	NA
REFRACTORY CDI – COLONOSCOPY			
Weingarden, 2013[45] USA RCS N=4	2/4 (50%)	2/2 (100%)	2/2 (100%)
Mellow, 2011[36] USA RCS N=1 (see Recurrent CDI - Colonoscopy)	NA	NA	NA
REFRACTORY CDI – ENEMA			
Lee, 2014[46] Canada RCS N=94	48/49 (98)[b,c]	41/48 (85)[b]	41/48 (85)[b]
Bowden, 1981[47] USA RCS N=16 (15 adults)	0/2	NA	NA

Study, year Country Design N=	Repeat Transplant after Initial FMT Failure n/N (%)	Reported Resolution of Symptoms after Repeat Transplant n/N (%)	
		≤ 3 months	> 3 months
Eiseman, 1958[14] USA RCS N=4 (3 with refractory CDI)	NA	NA	NA
INITIAL THERAPY FOR CDI - ENEMA			
Eisemen, 1958[14] USA RCS N=4 (1 as initial therapy)	NA	NA	NA

CDI = *C. difficile* infection; FMT = fecal microbiota transplantation; NA = not applicable; NR = not reported; PCS = prospective case series; RCS = retrospective case series

[a]One patient lost to follow-up after FMT

[b]includes 9 patients treated with antibiotics for ongoing diarrhea between repeat FMTs

[c]20 patients received 2 FMTs, 17 patients received 3 FMTs, and 11 patients received 4 or more FMTs