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

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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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TABLE OF CONTENTS

FIGURES

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

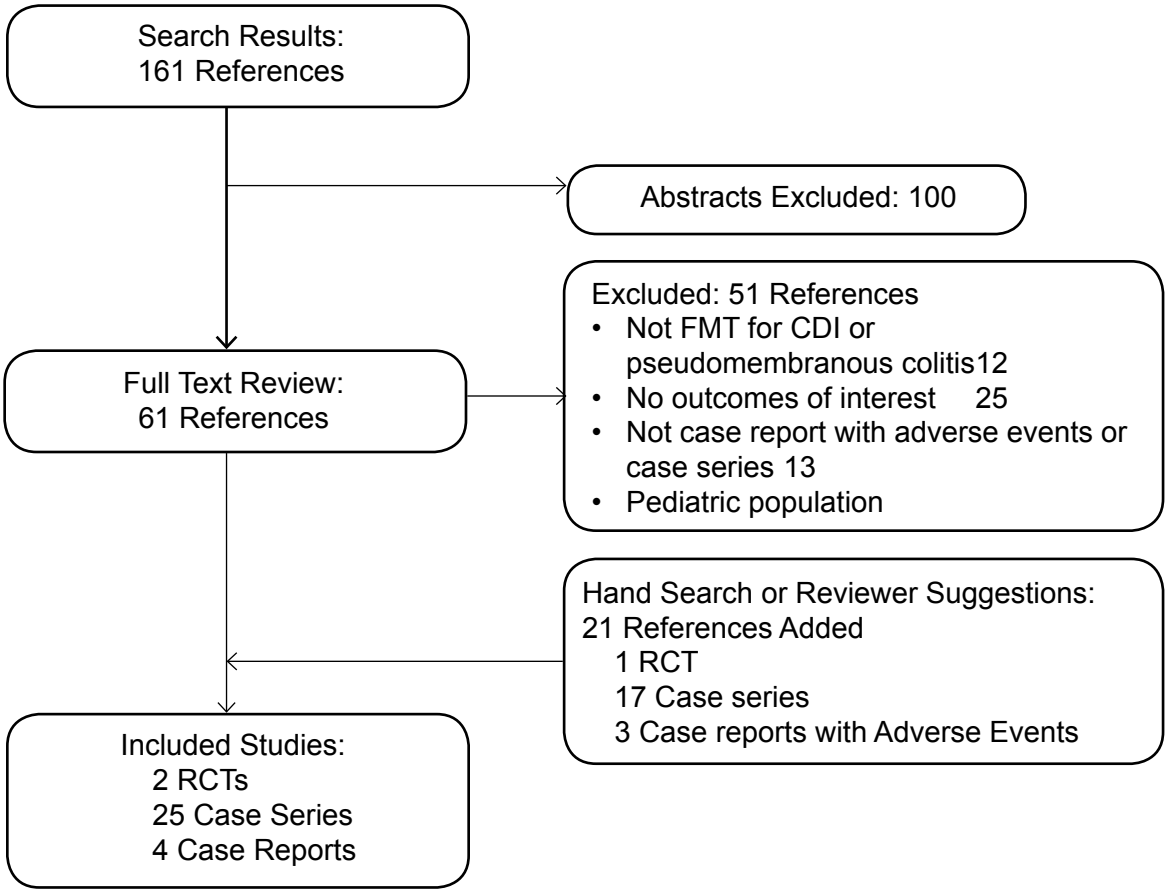


Table 1. Outcomes Reported by CDI Status and Method of Transplantation

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

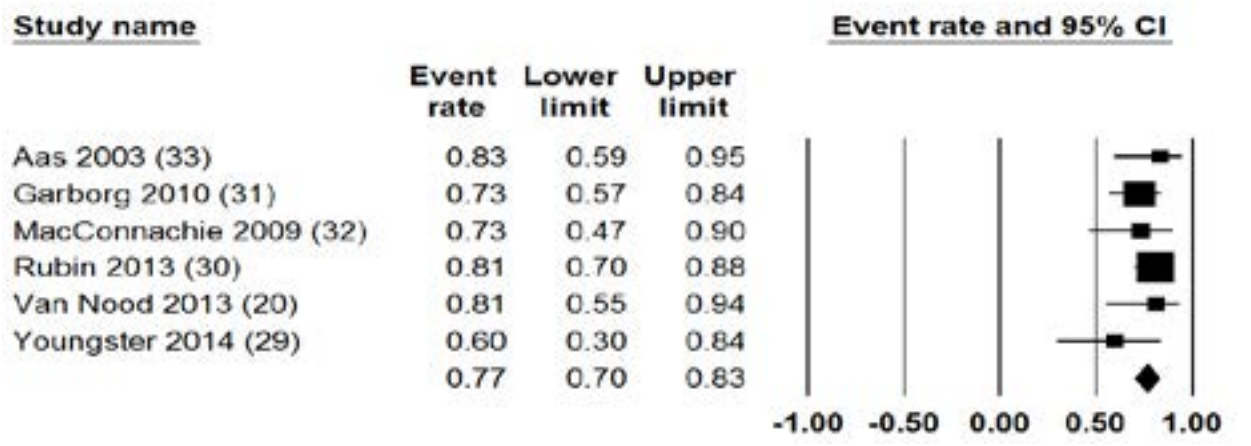
PEG = percutaneous endoscopic gastrostomy

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.

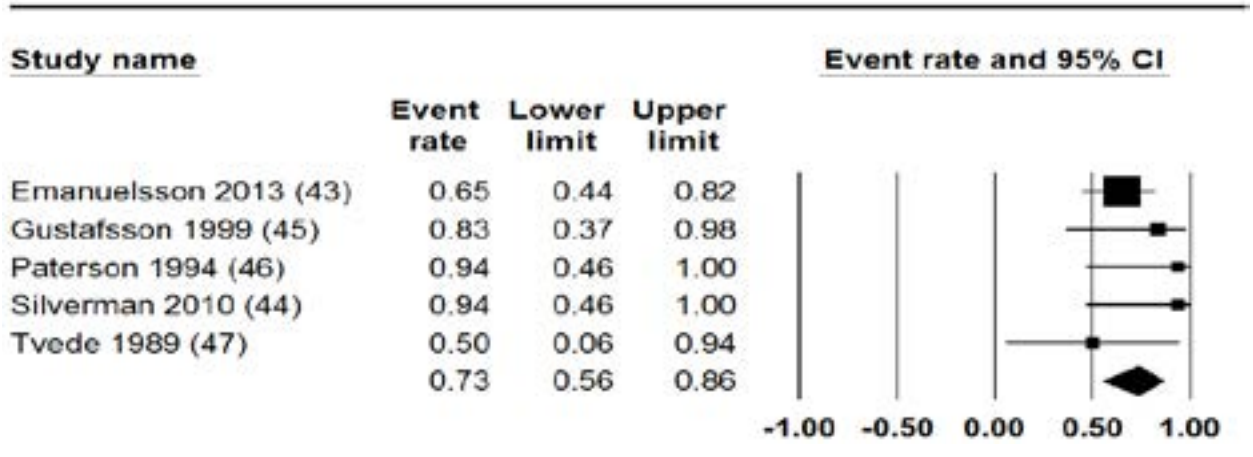
Table 10. Amount of Fecal Material and Liquid Used in FMT – Recurrent CDI, Studies of Enema for Infusion of Donor Feces

	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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