REVIEW

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Fecal Microbiota Transplantation for *Clostridium difficile* Infection

A Systematic Review

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Background: The role of fecal microbiota transplantation (FMT) for *Clostridium difficile* infection (CDI) is not well-known.

Purpose: To assess the efficacy, comparative effectiveness, and harms of FMT for CDI.

Data Sources: MEDLINE (1980 to January 2015), Cochrane Library, and ClinicalTrials.gov, followed by hand-searching references from systematic reviews and identified studies.

Study Selection: Any study of FMT to treat adult patients with CDI; case reports were only used to report harms.

Data Extraction: Data were extracted by 1 author and verified by another; 2 authors independently assessed risk of bias and strength of evidence.

Data Synthesis: Two randomized, controlled trials (RCTs); 28 case-series studies; and 5 case reports were included. Two RCTs and 21 case-series studies (516 patients receiving FMT) reported using FMT for patients with recurrent CDI. A high proportion of treated patients had symptom resolution; however, the role of previous antimicrobials is unclear. One RCT comparing FMT with 2 control groups ($n = 43$) reported resolution of symptoms in 81%, 31%, and 23% of the FMT, vancomycin, or vancomycin-plus-bowel lavage groups, respectively ($P < 0.001$ for both control groups vs. FMT). An RCT comparing FMT route ($n = 20$) reported no difference between groups (60% in the nasogastric tube group and 80% in the colonoscopy group; $P = 0.63$). Across all studies for recurrent CDI, symptom resolution was seen in 85% of cases. In 7 case-series studies of patients with refractory CDI, symptom resolution ranged from 0% to 100%. Among 7 patients treated with FMT for initial CDI, results were mixed.

Limitation: Most studies were uncontrolled case-series studies; only 2 RCTs were available for analysis.

Conclusion: Fecal microbiota transplantation may have a substantial effect with few short-term adverse events for recurrent CDI. Evidence is insufficient on FMT for refractory or initial CDI treatment and on whether effects vary by donor, preparation, or delivery method.

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Since its discovery as the cause of pseudomembranous colitis in 1978 (1, 2), *Clostridium difficile* has become an increasingly important pathogen. Initially largely confined to patients with health care exposure, *C. difficile* infection (CDI) now also affects persons with no or limited contact with the health care system (3). In 2013, the Centers for Disease Control and Prevention placed *C. difficile* into the top threat category ("urgent") in its threat report on antimicrobial resistance (4).

The high rate of recurrence—15% to 30% of patients after their initial CDI episode and increasing thereafter—is a major challenge (5, 6). Several treatment or recurrence episodes may result in repeated hospitalizations, clinic visits, deconditioning, malnourishment, and fecal incontinence. Antimicrobial treatment of recurrent disease yields success rates between 30% and 80%, depending on the number of recurrences and the agent and treatment duration selected (5–8). These suboptimal response rates have spurred investigation of additional treatment options, including fecal microbiota transplantation (FMT).

Severe colonic microbiome (normal colonic bacteria) alterations are characteristic of CDI. Restoring the microbiome has been proposed to prevent recurrence, and probiotics are the most widely used intervention. However, probiotic microorganisms are less diverse than those of the organisms that characterize the colonic microbiome in healthy persons (9). Fecal microbiota transplantation is increasingly used as a treatment of recurrent CDI on the basis of the idea that importing the colonic microbiome of a healthy person is a simple method of reconstituting the normal colonic flora. Most FMT cases in the medical literature are from noncontrolled case-series studies (10). Reported success rates of up to 100% and the publication of a randomized, controlled trial (RCT) comparing FMT with antimicrobial treatment (11) have increased interest in FMT, even as regulations have evolved. The U.S. Food and Drug Administration currently requires an investigational new drug application for human studies of FMT but not for clinical use in treating CDI.

The first reported use of FMT (delivered via enema) in medical literature was a small case-series study of hospitalized patients. Since then, various reports have described performing the procedure outside of the hospital, including at home by means of self-administered enema (12). Timing and frequency of FMT has also varied; most are administered in a single session, whereas others have relied on serial administration over several days. Several guidelines and reviews are available to help providers select appropriate patients for FMT, guide the selection and screening of stool donors, and choose from among the delivery

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methods (13–15). The 2 most recent guidelines differ about the strength of evidence supporting FMT—a European guideline stated that FMT is "strongly recommended (A-I)" after a second recurrence of CDI (13), whereas a guideline from the American College of Gastroenterology offered a more cautious recommendation, stating that "if there is a third recurrence after a pulsed vancomycin regimen, fecal microbiota transplant (FMT) should be considered. (Conditional recommendation, moderate-quality evidence)" (14).

We did a systematic review of the evidence about the effectiveness of FMT for recurrent, refractory, and initial CDI and looked for evidence that effectiveness varied by method of transplantation. We also assessed harms of FMT and procedure acceptability. This report is derived from work done for a larger U.S. Department of Veterans Affairs Evidence-based Synthesis Program review.

Key Summary Points

Fecal microbiota transplantation (FMT) for *Clostridium difficile* infection (CDI) is increasingly used, primarily for recurrent CDI but also for refractory CDI and treatment of the initial CDI episode.

Although 35 studies of FMT for CDI were identified, only 2 were randomized, controlled trials (RCTs), with only 1 RCT having a non-FMT comparator group.

Among the 36 patients who received FMT for recurrent CDI in the 2 RCTs, 27 (75%) had resolution of symptoms without recurrence.

Among the 480 patients in 21 case-series studies who received FMT for recurrent CDI, 85% had resolution of symptoms without recurrence.

Few studies reported on FMT for refractory CDI or for treatment of the initial CDI episode; among these, success rates were highly variable.

METHODS

Search Strategy

We searched MEDLINE for articles published in English from 1980 to January 2015 that enrolled human participants and described FMT for known or suspected CDI (**Appendix Table**, available at www.annals.org). We also searched the Cochrane Library and ClinialTrials.gov through January 2015. Our search included studies of any design, although we excluded case reports unless they reported harms. Additional articles, including some predating our search period or using nonstandard descriptors for CDI or FMT, were identified from hand-searching reference lists of existing systematic reviews and included studies as well as from suggestions by a technical expert panel.

Study Selection and Definitions

Titles, abstracts, and articles were independently reviewed by 2 investigators, and disagreements were resolved by discussion and involvement of a third investigator, if needed. We considered initial CDI to be the first occurrence of CDI in a particular patient, recurrent CDI to be an episode occurring after previous treatment and favorable response for at least 1 previous episode, and refractory CDI to be an episode that did not respond to antimicrobial treatment.

Data Abstraction and Quality Assessment

Study characteristics, patient characteristics, and outcomes data were abstracted from included articles. Because all but 2 of the included studies were case-series studies, we did not formally assess quality but rather noted that conventional methods for rating strength of evidence would classify even well-conducted and reported case-series studies as high risk of bias (16). Therefore, strength of evidence would typically be considered insufficient or low. For the 2 RCTs, quality was assessed on the following criteria: allocation concealment, blinding, analysis approach, and description of withdrawals—a modification of the Cochrane approach to determining risk of bias (17). Our key outcomes included resolution of symptoms (primary outcome), time to resolution of symptoms, recurrence, all-cause mortality, and adverse events. We report results after a single administration of FMT or, in the case of studies that specified serial administration of FMT on successive days, a single prespecified series of administrations. In several studies, patients having recurrence were offered repeated FMT; these patients were categorized as having unsuccessful FMT because they met the recurrence outcome.

Data Synthesis and Analysis

Most findings are summarized narratively. Because the included studies report outcomes on small numbers of patients derived largely from case-series studies, any pooled estimate of the effect size and a surrounding CI was considered to be of questionable validity. Therefore, we report descriptive summaries of each included study and an overall percentage of patients remaining free of recurrent CDI.

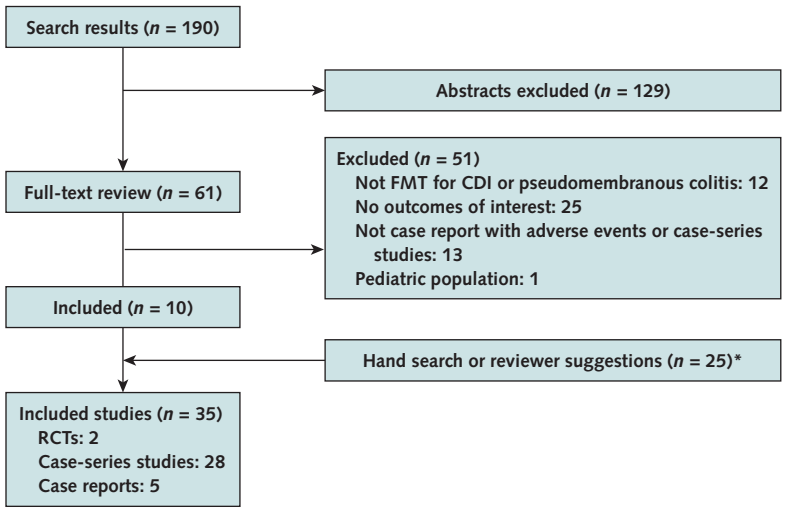
Role of the Funding Source

This review was funded by the U.S. Department of Veterans Affairs. The funding source had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. Members of a technical expert panel and peer reviewers of the evidence report provided advice and feedback. Technical expert panel members and peer reviewers were not compensated for their contributions.

RESULTS

Our literature search yielded 190 abstracts or titles. We excluded 129 articles after abstract review and performed full-text reviews of 61 articles; of those, we ex-

Figure. Summary of evidence search and selection.



CDI = *Clostridium difficile* infection; FMT = fecal microbiota transplantation; RCT = randomized, controlled trial.
* Included 1 RCT.

cluded 51, leaving 10 articles. From hand-searching reference lists of systematic reviews and included studies and suggestions from technical expert panel members, we identified another 25 articles for a total of 35 included studies: 2 RCTs, 28 case-series studies, and 5 case reports (Figure).

FMT for Recurrent CDI

Data From RCTs

Two small RCTs with moderate risk of bias (11, 18) reported use of FMT for patients with recurrent CDI. The first compared FMT using a nasoduodenal tube with 2 control groups (43 patients; 1 withdrew after random assignment); 81% of FMT patients achieved resolution of symptoms within 3 months compared with 31% and 23% for the vancomycin and vancomycin-plus-bowel lavage control groups, respectively ($P < 0.001$ for FMT vs. both control groups) (11). The study, which we rated as moderate quality, was unblinded and done in the Netherlands. It was terminated after the investigators saw "extremely low" response rates in the control groups, which differed substantially from the 60% rate used for calculations of sample sizes. Patients had a mean age of 70 years, and 58% were men. Previous CDI episodes were numbered from 1 to 9. Administration of FMT was done after 4 to 5 days of oral vancomycin (500 mg 4 times daily), whereas the control groups received the same dose of vancomycin for 14 days. The second RCT compared 2 FMT treatment approaches, nasogastric tube and colonoscopy, in 20 patients. Overall, 70% of patients had resolution of symptoms; the difference between treatment approaches was not significant (60% in the nasogastric tube group and 80% in the colonoscopy group; $P = 0.63$) (18). This moderate-quality study was unblinded, did not include a non-FMT control group, and was done in the United States. The patients in this trial were younger than those in the other RCT, with a mean age of 50 years in the colonoscopy group and 59 years in the nasogastric tube group. Most patients (55%) were women, with 3 to 17 previous CDI episodes. Fecal microbiota transplantation was administered 3 days after stopping antimicrobial treatment of CDI. This study was a feasibility study and was not adequately powered to detect clinically significant differences in outcomes. Overall, recurrent CDI treated in the setting of an RCT resulted in 27 of 36 patients (75%) having resolution of symptoms without recurrence.

Data From Case-Series Studies

We identified 21 case-series studies reporting on FMT for the treatment of recurrent CDI (12, 19–38), delivered by means of various methods (Table 1). Patient characteristics varied, but overall patients were older, were mostly women, and had several (3 to 12) previous CDI recurrences. The initial CDI episode was 3 to 27 months before FMT. Outcome reporting was variable, particularly about resolution of symptoms. Although some version of this outcome was usually reported, resolution of symptoms and recurrence were often combined as "resolution of diarrhea without relapse" or "durable resolution." In addition, authors commonly reported that antimicrobials for CDI were given before FMT to ensure that patients were asymptomatic or had a "reduction in symptoms" at the time of FMT. Thus, in most cases, FMT was administered when patients were largely asymptomatic, with the FMT possibly contributing to further symptom resolution, recurrence prevention, or both. Overall, in case-series studies, patients treated with FMT for recurrent CDI remained without recurrence in 85% of episodes (Table 2).

FMT for Refractory CDI

We identified 7 studies (27, 39–43) reporting on patients with refractory CDI treated with FMT using var-

ious methods; none compared FMT with standard therapy or different methods of administration. Reported resolution of symptoms ranged widely (0% to 100%; overall resolution rate, 55%). In 1 study (37) with both recurrent and refractory cases, separating the 2 types of patients was impossible. Because the authors stated that "the majority of patients (74.5%) were hospitalized at the time of FMT," we placed this study in the "refractory" category.

FMT for Initial CDI

We identified 7 cases of FMT used as treatment during the initial episode of CDI, all from case-series studies. Six cases were part of a series of 14 patients with refractory CDI (39), and 1 case was part of a series of 4 patients (43). Among the 6 cases, 1 was cured after FMT. The other patient received FMT as initial treatment of an episode of postantibiotic-associated colitis and was described to have symptom resolution within 48 hours of the procedure. This series predated the discovery of *C. difficile*, and few details were reported.

Harms of FMT

The 2 included RCTs reported mild adverse events attributed to FMT, including diarrhea, cramping, belching, nausea, abdominal pain, bloating, transient fever, and dizziness (11, 18). Serious adverse events were also described, including a case of Fournier gangrene (18), but none were attributed to the FMT.

Case-series studies reported few harms. Eight case-series studies (reporting on 70 patients) did not explicitly mention harms; all others specifically commented on harms (or lack thereof). Possible procedure-related harms, including microperforation with colonoscopy (26) and gastrointestinal bleeding (29), peritonitis (38), and pneumonia (38) with use of the upper gastrointestinal tract route, were rarely reported. One case-series study reported on FMT use in 80 immunocompromised patients (44). Although serious adverse events (2 deaths and 10 hospitalizations) occurred in 12 patients (15%), none seemed to be directly related to FMT. Nonserious adverse events were reported for 12 patients (15%); 4 were considered related to FMT, and 5 were possibly related.

Because rare adverse events may be first reported as a case report, we examined case reports for such events. One report (45) described a patient with abdominal pain and hypotension 3 days after FMT by means of a gastrojejunostomy tube placed through an indwelling gastric tube. The patient had pneumoperitoneum, toxic megacolon, and polymicrobial bacteremia and subsequently died. Other potential harms included development of herpes zoster 2 months after FMT (46), recurrence of *Escherichia coli* bacteremia (47), a flare of previously quiescent ulcerative colitis (48), and 2 cases of norovirus gastroenteritis (49). In one of these cases, an endoscopy suite employee had norovirus-like symptoms the day before the FMT was administered in the suite. Long-term data on harms were not reported.

Patient Acceptance of FMT

The RCT comparing FMT with standard therapy was designed to enroll patients with any recurrence of CDI; however, only 8 of 43 included patients were enrolled after a first recurrence (11). The authors commented that the low enrollment of patients at an early stage of recurrence reflected a reluctance to receive FMT at that point. Several case-series studies reported that patients expressed no concern with any aspect of FMT (26, 29, 34, 38). Among patients contacted for a survey at least 3 months after FMT, 97% indicated that they would be willing to receive FMT in the future (50).

DISCUSSION

We identified 2 RCTs and 28 case-series studies about the efficacy of FMT for recurrent CDI, refractory CDI, or an initial episode of CDI, with most studies dealing with recurrent CDI. The paucity of RCTs is notable, particularly considering that only 1 compared FMT with standard antimicrobial therapy. As a result, there is a dearth of high-quality evidence to guide clinicians and policymakers on how to apply this promising but largely untested therapy.

The overall low quality of the available evidence evaluating FMT is important and indicates that additional research is needed. However, the large positive effect seen with FMT for CDI, both in the RCTs and case-series studies, is also important. Overall success was 85% for recurrent disease and 55% for refractory disease. These rates are substantially higher than the 30% to 80% success rates typically reported with various medical therapies for CDI, although directly comparing such different studies cannot be done with confidence. In addition, the optimal medical therapy for patients with several recurrences of CDI is unknown because some small series have reported markedly higher success rates, including up to 88% with vancomycin followed by rifaximin (51) and even 100% with tapered vancomycin (52). The success rates from the RCTs are lower (75%) than those from case-series studies of similar patients (85%); if future studies confirm this finding, enthusiasm for FMT may be tempered, especially if similar success rates can be obtained with antimicrobial treatment.

Our primary outcome was resolution of symptoms, and recurrence was a secondary outcome. However, many studies reported a primary outcome that combined these outcomes, such as "cure without relapse" or "resolution of diarrhea without recurrence." In addition, FMT was administered after standard antimicrobial therapy, with patients often specified as being "asymptomatic" or having had "a reduction of symptoms" at FMT administration. Although stated outcomes included an element of symptom resolution, in most cases FMT seemed to be given with the intent to prevent recurrence after antimicrobial treatment had resolved all or most CDI symptoms. Future FMT studies should carefully consider their primary outcome (resolution of symptoms vs. prevention of recurrence)

Table 1. Overview of Studies

Study, Year (Reference)	Country	Study Design	Participants Enrolled, *n*	Patient Characteristics	
				Age, *y**	CDI Recurrences (Range), *n*
Recurrent CDI; FMT via upper GI tract (7 studies; *n* = 214 [187 receiving FMT])					
Youngster et al, 2014 (19)‡	United States	PCS	16	60	2 (1 to 5)
Youngster et al, 2014 (18)§	United States	RCT	10	55‖	4.5 (2.0 to 16.0)
van Nood et al, 2013 (11)	Netherlands	RCT	43 (16 FMT)	70¶	3 (1 to 5); FMT group
Rubin et al, 2013 (22)	United States	RCS	74 (72 adults)	Median: 63	NR
Garborg et al, 2010 (34)	Norway	RCS	40	75	NR
MacConnachie et al, 2009 (29)	United Kingdom	RCS	15	82	4 (3 to 7)
Aas et al, 2003 (38)	United States	RCS	18	73	3.6 (2.0 to 7.0)
Recurrent CDI; FMT via colonoscopy (11 studies; *n* = 257)					
Khan et al, 2014 (30)	United States	RCS	20	66	5.1
Youngster et al, 2014 (18)	United States	RCT	10	55‖	4.5 (2.0 to 16.0)
Cammarota et al, 2014 (37)	Italy	RCS	3	67	1 to 5
Pathak et al, 2013 (24)	United States	RCS	12 (11 via colonoscopy)	72	NR
Patel et al, 2013 (26)	United States	RCS	31	61	4 (2 to 7)
Hamilton et al, 2012 (32)	United States	RCS	43	59	5.9
Kelly et al, 2012 (31)	United States	RCS	26	59	≥3
Mattila et al, 2012 (28)	Finland	RCS	70	73	3.5 (1.0 to 12.0)
Mellow and Kanatzar, 2011 (27)	United States	RCS	13 (12 recurrent)	67	4 (3 to 7)
Rohlke et al, 2010 (23)	United States	RCS	19	49	NR
Yoon and Brandt, 2010 (20)	United States	RCS	12	66	NR
Recurrent CDI; FMT via enema (5 studies; *n* = 45)					
Emanuelsson et al, 2014 (35)	Sweden	RCS	23	67	3 (1 to 5)**
Silverman et al, 2010 (12)	Canada	RCS	7	72	NR
Gustafsson et al, 1999 (33)	Sweden	RCS	6	61	NR
Paterson et al,1994 (25)	Australia	RCS	7	56	3 (1 to 4)
Tvede and Rask-Madsen, 1989 (21)	Denmark	RCS	2	60	3 (2 to 4)
Recurrent CDI; FMT via upper GI tract and colonoscopy (1 study; *n* = 27)					
Dutta et al, 2014 (36)	United States	PCS	27	65	4.6 (3.0 to 5.0)
Refractory CDI; FMT via upper GI tract (2 studies; *n* = 12)					
Youngster et al, 2014 (19)‡	United States	PCS	4	72	3 (1 to 5)
Zainah et al, 2015 (40)	United States	RCS	8	74	3.3 (2.0 to 5.0)
Refractory CDI; FMT via colonoscopy (2 studies; *n* = 5)					
Weingarden et al, 2013 (41)	United States	RCS	4	73	NR
Mellow and Kanatzar, 2011 (27)	United States	RCS	1 (from series)	NR	1
Refractory CDI; FMT via enema (3 studies; *n* = 112)					
Lee et al, 2014 (39)	Canada	RCS	94	72	2.1**
Bowden et al, 1981 (42)	United States	RCS	16 (15 adults)	59	NR
Eiseman et al, 1958 (43)	United States	RCS	3 (patients 1, 2, and 4)	52	NR
Initial therapy for CDI; FMT via upper GI tract (1 study; *n* = 6)					
Zainah et al, 2015 (40)	United States	RCS	6	72	0
Initial therapy for CDI; FMT via enema (1 study; *n* = 1)					
Eiseman, 1958 (43)	United States	RCS	1 (patient 3)	68	NR

CDI = *Clostridium difficile* infection; FMT = fecal microbiota transplantation; GI = gastrointestinal; NR = not reported; PCS = prospective case series; RCS = retrospective case series; RCT = randomized, controlled trial.
* Mean except where noted.
† At ≤3 mo.
‡ Oral ingestion of encapsulated stool.
§ Upper GI tract.
‖ Among 20 patients enrolled (10 treated via upper GI tract route and 10 treated via colonoscopy) and donors.
¶ Among 42 patients enrolled (16 receiving FMT).
** Courses of antibiotics.

Table 1–Continued

Donor Characteristics			Resolution of Symptoms After Initial FMT, *n/N (%)*†	Reported Length of Follow-up (Range)
Donors, *n*	**Relationship to Patients**	**Stool Volume**		
4	Not related	Mean of 48 g of sieved and concentrated material	13/16 (81)	6 mo
5‖	Not related	340 cc	6/10 (60)	6 mo
15	NR	500 cc	13/16 (81)	10 wk
NR	Healthy close household member	25 mL	58/72 (81)	60 d
NR	Close relative or other household member	200 mL	29/40 (73)	80 d
NR	Related	30 mL	11/15 (73)	16 wk (4 to 24 wk)
16	Spouse, partner, household family member	25 mL	15/18 (83)	90 d
20	Spouse, partner, first-degree relative, not related	NR	18/20 (90)	6 mo
5‖	Not related	340 cc	8/10 (80)	6 mo
3	Child, sibling, not specified	250 to 500 mL	3/3 (100)	4 to 5 mo
12	Spouse, child, sibling, niece	400 to 500 cc	11/12 (92)	2 to 29 mo
33	Spouse, child, sibling, parent, niece, friend	NR	22/30 (73)	1 wk to 1 y
12	Parent, child, spouse, friend, volunteer	220 to ≥240 mL	37/43 (86)	2 mo
26	Partner, sibling, spouse, child, cousin, friend	500 to 960 mL	25/26 (96)	11 mo (2 to 30 mo)
62	Relative or household contact, volunteer	100 mL	66/70 (94)	12 mo
NR	Chosen by patient	300 to 600 mL	11/12 (92)	5 mo (1 to 10 mo)
19	Partner, family member, housemate	NR	18/19 (95)	27 mo (6 mo to 5 y)
12	Spouse, partner, child/grandchild	240 to 400 cc	12/12 (100)	3 wk to 8 y
NR	Spouse or close relative	NR	15/23 (65)	18 mo (0 to 21 mo)
7	Child/grandchild, spouse, sibling	250 mL	7/7 (100)	8.6 mo (4 to 14 mo)
1	Not related	NR	5/6 (83)	18 mo
NR	Relative	NR	7/7 (100)	NR
2	Spouse, child	NR	1/2 (50)	12 mo
27	Spouse, child, parent	340 cc	27/27 (100)	21 mo (10 to 34 mo)
3	Not related	Mean of 48 g of sieved and concentrated material	1/4 (25)	6 mo
NR	Family member or unrelated	120 to 180 mL	8/8 (100)	100 d
1	Not related	250 mL	0/4 (0)	Up to 12 mo
1	Chosen by patient	300 to 600 mL	1/1 (100)	9 mo
NR	Not related	100 mL	45/94 (48)	6 to 24 mo
NR	Household relative, volunteer	NR	13/15 (87)	NR
NR	NR	NR	3/3 (100)	2 to 10 d
NR	Family member or unrelated	120 to 180 mL	1/6 (17)	100 d
NR	NR	NR	1/1 (100)	5 d

and also report symptoms of CDI present at FMT administration.

Fecal microbiota transplantation may be safe and well-tolerated, with few serious adverse events, even though it is often administered to patients with significant medical comorbid conditions. As FMT increases in frequency, reports of procedural complications will likely increase, as expected when any invasive procedure is performed more frequently (53). In addition to studies confirming the efficacy of FMT, studies are

needed to determine the safety of FMT. Although prospective trials will be able to address the efficacy of FMT, harms seem to be sufficiently rare; therefore, comparing the safety of different methods will likely require ongoing surveillance, possibly by means of a publicly accessible registry. The optimal source of donor feces, amount and processing method of donor stool, preferred timing of the procedure relative to preceding antimicrobial use, and other technical aspects that have varied across studies also need further study.

Fecal microbiota transplantation for CDI is a topic of considerable research. A search of ClinicalTrials.gov for "fecal microbiota transplantation AND *Clostridium difficile*" (accessed 27 January 2015) yielded 26 studies, 13 of which are currently recruiting. Among these studies, 3 are for non-CDI conditions, 4 are studies of FMT for CDI without a comparator group, 1 is to administer autologous FMT in patients having stem cell transplantation to prevent CDI, and 1 is to characterize the microbiota in patients having received FMT. One study (NCT02299570) is a trial of a stool-derived commercial product administered via enema versus sham enema. The remaining 3 studies are trials of FMT versus a comparator agent. One (NCT01703494) is a study of FMT via colonoscopy versus sham FMT (instilling the patient's own stool via colonoscopy); planned enrollment is 53 patients. Another (NCT02255305) is an open-label study of FMT via enema versus antimicrobial treatment, with planned enrollment of 60 patients. The final is a pediatric study (NCT01972334) of FMT via endoscopy versus sham endoscopy, with planned enrollment of 46 patients. Although these studies will provide some additional efficacy data, a large blinded RCT comparing FMT with placebo, both administered after standard antimicrobial therapy, is needed. If efficacy is established, further studies powered to detect meaningful differences by administration route would be needed.

Our search excluded non–English-language studies; hand-searching reference lists from recent systematic reviews identified 4 case-series studies, 3 of which had English-language abstracts (54–56). These studies were small (7 and 18 patients or number not reported). Success rates for FMT ranged from 71% to 83%, which are consistent with the studies included in our review. We do not believe that their exclusion biases our findings. Publication bias is a concern, particularly because most included studies are case-series studies. The desire to publish a series of successfully treated patients is easily understood and provides pilot data for more definitive studies. The desire to publish a series of clinical failures is less easy to understand and may result in preferential reporting of successful cases. Our search strategy, developed with input from a trials search coordinator, did not identify many eligible case-series studies. This is likely due to the varied and evolving terminology used to describe both CDI and FMT. We thoroughly searched reference lists from existing studies and systematic reviews to identify references not identified in our search.

A further limitation is the lack of blinding in the single RCT that compared FMT with antimicrobial therapy. Although recurrence of CDI may seem to be a hard clinical outcome, for which blinding may be desirable but not mandatory, there are reasons to be skeptical of this approach. *Clostridium difficile* is known to persist after symptom resolution, which may represent residual genetic material to be amplified by newer molecular tests or asymptomatic colonization with viable organisms. This has important implications because if patients with recent CDI are tested for *C. difficile*, it is expected that a sizable percentage will test positive. Most studies and clinical practice guidelines address this by only testing patients with 3 or more loose stools daily. However, stool frequency can be influenced by many factors, including diet and anxiety. Other examples of promising treatments that have not survived the scrutiny of placebo-controlled trials serve as cautionary examples, including knee arthroscopy for meniscal tears (57) and renal vein denervation for hypertension (58). In each case, early enthusiasm gave way to reality when rigorously conducted RCTs found no benefit to standard therapy or a sham procedure. Redberg (59) recently argued that evidence is mounting that "medical procedures can produce a strong placebo effect that can be mistaken for actual effectiveness" and called for renewed emphasis on ensuring that procedures and devices provide benefit.

In summary, low-strength evidence supports FMT as having a substantial effect and few short-term adverse events for adults with recurrent CDI. There is insufficient evidence about FMT for patients with refractory CDI or for initial treatment of CDI. Evidence is insufficient about whether treatment effects vary by FMT donor, preparation, or delivery method.

Table 2. Summary Results for Reported Resolution of Symptoms After Initial FMT for Recurrent CDI, Overall and by FMT Method

FMT Method	Patients With Resolution of Symptoms Without Recurrence, %*	Studies/Total Studies Analyzed, *n/N*
Upper GI tract	77	7/187†
Colonoscopy	90	11/257†
Enema	78	5/45
Upper GI tract and colonoscopy	100	1/27
All methods	85	23/516‡

CDI = *Clostridium difficile* infection; FMT = fecal microbiota transplantation; GI = gastrointestinal.
* Because of small sample sizes and the abundance of data from case-series studies, 95% CIs were considered to be unreliable and were not calculated.
† Includes 10 patients from reference 18.
‡ Total number of studies is 1 less than the sum of individual rows.

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Appendix Table. Search Strategy

Database: Ovid MEDLINE
1 exp Feces/ or (fecal or faecal or feces or faeces or stool or microbiota).mp.
2 (donor or transplant$).mp. or exp Transplants/
3 1 and 2
4 exp Clostridium Infections/ or exp Clostridium difficile/ or exp Enterocolitis, Pseudomembranous/ or (c difficile or c diff or clostridium difficile).mp.
5 3 and 4
6 limit 5 to (english language and humans and yr="1980-Current")