Systematic Review of Intestinal Microbiota Transplantation (Fecal Bacteriotherapy) for Recurrent *Clostridium difficile* Infection

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***Clostridium difficile* infection (CDI) is a gastrointestinal disease believed to be causally related to perturbations to the intestinal microbiota. When standard treatment has failed, intestinal microbiota transplantation (IMT) is an alternative therapy for patients with CDI. IMT involves infusing intestinal microorganisms (in a suspension of healthy donor stool) into the intestine of a sick patient to restore the microbiota. However, protocols and reported efficacy for IMT vary. We conducted a systematic literature review of IMT treatment for recurrent CDI and pseudomembranous colitis. In 317 patients treated across 27 case series and reports, IMT was highly effective, showing disease resolution in 92% of cases. Effectiveness varied by route of instillation, relationship to stool donor, volume of IMT given, and treatment before infusion. Death and adverse events were uncommon. These findings can guide physicians interested in implementing the procedure until better designed studies are conducted to confirm best practices.**

Clostridium difficile infection (CDI) is a gastrointestinal disease believed to be causally related to perturbations to the intestinal microbiota [1]. The term *microbiota* refers to the community of microorganisms that inhabit a particular region of the body [2]. In the human gut, there are ~300–500 species of microorganisms (intestinal microbiota), with roughly 10^{12} bacterial cells per gram of stool [3]. These organisms aid in several functions, including digestion of complex carbohydrates, energy storage, immune functions, and protection against invasion by pathogens [3]. Existing evidence shows that certain classes of antimicrobials have profound effects on the intestinal microbiota [4]. The widely accepted model for *C. difficile* pathogenesis is that the use of broad spectrum antimicrobials alters the balance of the intestinal microbiota, allowing pathogenic strains of *C. difficile* to infect the intestine [1–3].

Primary episodes of CDI are treated with metronidazole or vancomycin after cessation of the antibiotic believed to be related to the infection [4], and up to 35% of patients treated experience a recurrence of symptoms after initial improvement [5, 6]. Up to 65% of these patients develop a chronic recurrent pattern of disease (recurrent CDI) [1, 5]. Recurrent CDI is typically treated using a tapered (31% recurrence rate) or pulsed (14% recurrence rate) regimen of metronidazole or vancomycin [4, 5]. Given the poor treatment outcomes for CDI, especially recurrent CDI, it is not surprising that investigation of treatment alternatives has continued over several decades [2, 4, 7–9].

One potential alternative to standard therapy is the use of indigenous intestinal microorganisms from a healthy donor (via infusion of a liquid suspension of stool) to restore the intestinal microbiota of a diseased individual. First documented in humans in 1958 [10], fecal bacteriotherapy, also called intestinal microbiota transplantation (IMT), may be a useful treatment for CDI through restoration of the intestinal microbiota [5].

IMT has not been widely adopted as a therapeutic tool probably due to concerns regarding safety and acceptability [11]. Despite these concerns, the procedure has been performed in a growing number of patients throughout the world. In addition to treating CDI, IMT has also been used to treat pseudomembranous colitis (PMC), believed to be caused by *C. difficile* toxins, inflammatory bowel disease and irritable bowel syndrome (IBS), 2 diseases also believed to be causally related to the intestinal microbiota [1].

IMT protocols vary with regard to the quantity of donor stool used, preparation of recipients, methods for infusion of donor stool, and measurement of outcomes. To our knowledge, 4 publications have reviewed the literature on the use of this procedure [1, 6, 12, 13], but none were systematic reviews. Additionally, we know of only 1 randomized controlled trial (RCT) currently underway to test the efficacy of IMT in the treatment of CDI [12]. To summarize the literature on the use of IMT and provide direction for future investigations of this still poorly understood intervention, we conducted a systematic review of fecal transplantation in humans as therapy for CDI and PMC.

METHODS

Search Strategy and Selection Criteria

We searched Medline, Embase, and Biosis through Ovid (up to 15 April 2011) for publications, in any language, documenting the infusion of stool from a healthy human donor, into an unhealthy human subject, as treatment for a specified medical condition (Supplementary Appendix 1, online only). Publications of any type were included if they reported original data from such a procedure for CDI or PMC treatment. Bibliographies of all identified reviews [1, 5–8, 12–16] and original research publications were hand searched for additional studies. We also searched Current Contents, Conference Papers Index, Papersfirst, and Web of Science for conference proceedings and abstracts that may not have been indexed in these 3 databases. Terms from the Ovid search were used as keywords with no limits, as shown in Supplementary Appendix 2, online only. All search strings were developed with the assistance of a qualified librarian.

Two investigators (E. G. and H. S.) independently assessed titles and abstracts for eligible publications. If eligibility could not be determined, the full article was retrieved. Publications that did not report original data on the outcome of the IMT procedure, reports describing the use of a cultured bacterial suspension rather than human feces, interviews, and reviews were excluded.

Data Abstraction and Analysis

Once eligibility was determined, 2 reviewers (E. G. and H. S.) independently abstracted data from selected publications using a standardized pretested form. Discrepancies were corrected by consensus. Data from non–English-language publications were simultaneously extracted by 2 reviewers (A. R. M. and Kerstin Tiedemann). The following information was retrieved: number of patients, patient characteristics (average age, number of men), transplantation procedures (patient preparation, choice of donor, dosage, number of infusions, route of instillation, retreatments offered if treatment failed, duration of follow-up, outcomes (death, treatment failure, resolution, relapse), and adverse events. Study period, country, and study design were also abstracted. Three investigators were emailed for unpublished data [17, 18] (Thomas Moore unpublished data). One did not respond [17], and data were no longer available from another [18]. When multiple publications reported on the same patients [18–24], we analyzed the most recent and complete data [18, 20, 24].

Data of interest were often not reported. Agreement between independent reviewers on availability of data, and data abstracted, were computed for 10 key variables using a κ statistic. Data were summarized using Stata software (version 11.0; StataCorp).

Operational Definitions

The following operational definitions were used to standardize data abstraction. A *failure* was defined as the continued occurrence of clinical illness during (1) the period of follow-up subsequent to transplantation but before retreatment or (2) during the period of follow-up subsequent to retreatment. *Resolution* was defined as either complete cessation of clinical symptoms or diagnostic confirmation of the absence of disease, during the period of follow-up after transplantation. When multiple infusions were not given as part of a retreatment for failure, they were counted as part of a single treatment. Resolution after 1 treatment was therefore counted separately from resolution after retreatment due to failure. A *relapse* was defined as resolution, with subsequent return of signs and symptoms during the follow-up period, and was counted only among patients with resolution. *Deaths* were recorded as due to the illness or not, as reported by the authors. Studies varied in the reporting of the IMT dosage given to patients. To make use of all available information related to the amount of donor stool patients were exposed to in a single infusion, *stool weight* was defined as the quantity (in grams) of donor stool used to make the IMT suspension, and *suspension volume* was defined as the volume (in milliliters) of the IMT suspension infused. *Number of infusions* was defined as the number of times donor stool was infused, not including retreatments when treatment failed.

RESULTS

Literature Review

The electronic search identified 2054 titles. All titles and abstracts were reviewed. Of the 66 reports selected for full review, 28 were excluded based on eligibility criteria [1, 4–8, 11–16,

25–40] (Figure 1). An additional 11 titles were excluded because they did not report treatment for CDI or PMC [41–44], reported data from the same subjects as more recent reports [19, 21–23], did not report data on key variables of interest [45], did not report data disaggregated by diagnosis [46], or could not be translated [47] (Figure 1).

### Characteristics of Included Reports

In total, 27 unique reports were included in the analysis [10, 17, 18, 20, 24, 48–68] (Thomas Moore, unpublished data) (Table 1). One article provided 2 abstractions [50] resulting in 28 observations for analysis. Agreement among reviewers on availability of data and data abstracted was high (median κ value, 0.91 and 0.8, respectively). The majority of reports were journal articles (70%); followed by letters (15%), abstracts (12%), and unpublished data (3%). Two-thirds (67%) were case series; the remainder were case reports (data not shown). Periods of data collection spanned 1957–1958 to 2001–2011, providing data on 317 patients (Table 1) from 8 countries. The average patient age was 53 years (range, 2–95 years), and 39% of patients were male. Follow-up ranged from 36 hours to 5 years. In all studies, patients had diagnoses of recurrent or relapsing CDI (91%) or PMC (9%) (Table 1).

IMT Procedures

The majority of patients received the IMT by enema (35%) or by gastroscope or nasojejunal (NJ) tube (23%) from a donor who was a relative (66%). Per treatment, approximately half received 1 infusion (range, 1–48 infusions) and the majority received a ≥200-mL IMT suspension (71%) (range, 25-1500 mL) (Table 1), typically given immediately after preparation (47%). Normal saline was used to prepare most IMT suspensions (62%). Where information was provided, all patients received antibiotic treatment or another procedure before IMT (Table 2). Patients with treatment failure or relapse were given IMT retreatment (44%), vancomycin or metronidazole (28%), or retreatment with antibiotics (3%), or their treatment was not reported (25%) (data not shown).

Outcomes in Patients Treated for CDI

Ninety-two percent of patients experienced resolution (Table 1), 89% after a single treatment (Table 2), and 5% after retreatment due to failure or relapse (data not shown). Eleven (4%) experienced a relapse in symptoms. With a single treatment, resolution rates were lowest with 1 infusion (87.5%); however 23% of these patients received infusion by gastroscope or NJ tube, which also showed the lowest resolution rate by route (76%) (Table 2). IMT
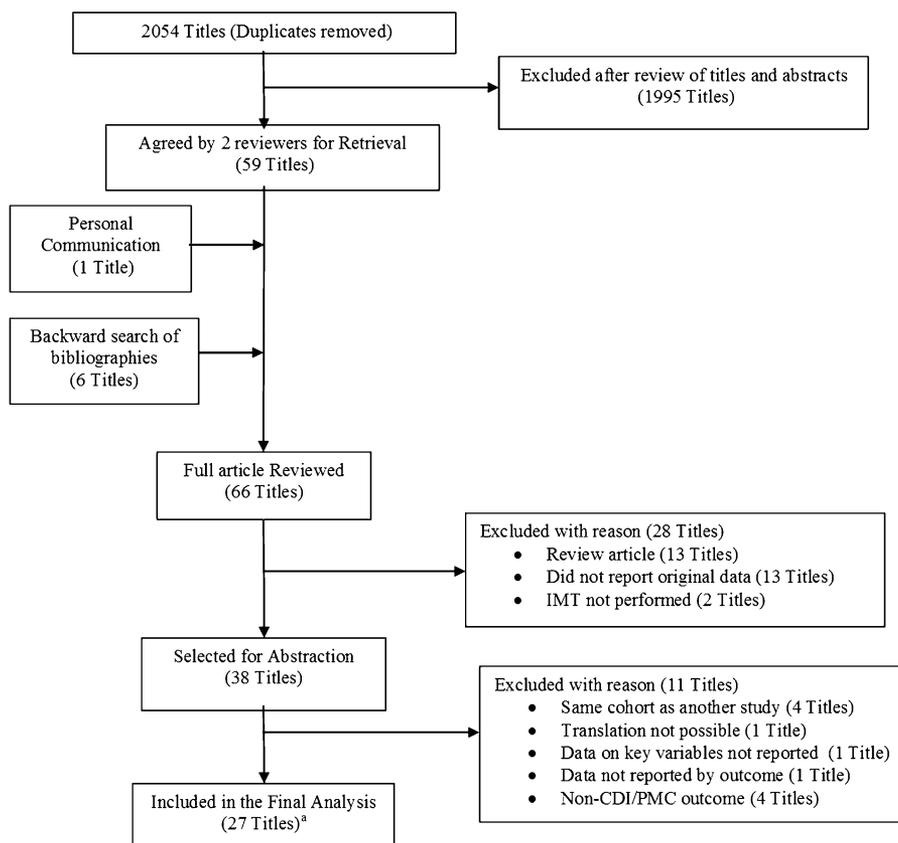
Figure 1. Flow diagram of study selection. [a]The 27 unique publications provided 28 abstractions. CDI, *Clostridium difficile* infection; IMT, intestinal microbiota transplantation; PMC, pseudomembranous colitis.

Table 1. Summary of Case Series and Reports of Intestinal Microbiota Transplantation

Reference	Years of data collection	Diagnosis	No. of patients	Patients with resolution, no. (%)[a]	Age, mean (range), y	Duration of follow-up, mean (range)	Stool, g/suspension volume, mL	Infusions per treatment	Donor relationship (no. of patients)	Instillation method (no. of patients)
Schwan et al [20]	1977–1983	CDI	1	1 (100.0)	67	1 y	NR/450	2	H	Enema
Tvede et al [48]	NR	CDI	2	1 (50.0)	60 (59–60)	12 mo	50/500	1	H (1), D (1)	Enema
Flotterod et al [49]	1982–1985	CDI	1	1 (100.0)	64	NR	10/NR	1	H	Duodenal endoscope
Paterson et al [50]	NR	CDI	1	1 (100.0)	39	2 y	200/200	3	H	Enema
Paterson et al [50]	NR	CDI	6	6 (100.0)	56 (30–80)	NR	NR/NR	NR	R	Enema
Lund-Tonnesen et al [18]	1995–1996	CDI	18	15 (83.3)	64 (27–89)	18 mo[b]	5–10/NR	NR	UR	Colonoscope
Persky et al [51]	NR	CDI	1	1 (100.0)	60	5 y	NR/500	NR	H	Colonoscope
Borody et al [452]	NR	CDI/IBD	6	6 (100.0)	NR (11–59)	8 wk	200–300/200–300	1–14	H	Enema
Aas et al [53]	1994–2002	CDI	18	15 (83.3)	73 (51–88)	90 d	30/25	1	R (15), UR (3)	NJ tube
Jorup- Ronstrom et al [54]	NR	CDI	5	4 (80.0)	83 (79–88)	2 mo (5–21)	NR/30	1	UR	Fecal lavage (3), enema (1), NR (1)
Wettstein et al [55]	NR	CDI	16	15 (93.7)	NR (11–87)	NR (4–6 wk)	200–300/200–300	1–24	R, UR	Colonoscopy, enema
Louie et al [56]	NR	CDI	45	44 (97.7)	62 (30–91)	1 y	300–500/1000–1500	1–3	R (35), UR (10)	Rectal catheter
Nieuwdorp et al [57]	NR	CDI	7	7 (100.0)	67 (48–81)	84 d	150/300–400	NR	S (3), D (4), LA (1), UR (1)	Colonoscope
You et al [58]	NR	CDI	1	1 (100.0)	69	36 h	45/300	1	D	Enema
Hellemans et al [59]	NR	CDI	1	1 (100.0)	59	4 mo	NR/NR	5	B	Colonoscope
MacConnachie et al [60]	NR	CDI	15	12 (80.0)	82 (68–95)	16 wk (4–24)	30/30	1	R	NJ Tube
Khoruts et al [61]	NR	CDI	1	1 (100.0)	61	6 mo	25/250	1	H	Colonoscope
Garborg et al [17]	1994–2008	CDI	40	33 (82.5)	75 (53–94)	80 d	50–100/200	1	R, UR	Gastroscope (38), colonoscope (2)
Rohlke et al [62]	2004–2009	CDI	19	19 (100.0)	49 (29—82)	27 mo (6–65)	NR/200–300	1–2	SP, R, UR	Colonoscope
Russell et al [63]	NR	CDI	1	1 (100.0)	2	6 mo	30/25	NR	F	NJ tube
Silverman et al [64]	NR	CDI	7	7 (100.0)	65 (30–88)	8.6 mo (4–14)	50/250	1	R	Enema
Yoon et al [24]	NR	CDI	12	12 (100.0)	66 (30–86)	NR (3 wk to 8 y)	NR/250–400	1	SP (8), S (1), D (2), GC (1)	Colonoscope
T. Moore (unpublished)	2001–2011	CDI	65	64 (98.5)	68 (18–89)	30 d (30 d to 5 y)	NR/1000	1	SP, P, C, S	Enema
Cutolo et al [65]	NR	PMC/S. aureus	1	1 (100.0)	65	96 d	57/1240 48/59	48[c], 24[d]	UR	Cantor tube
Eiseman et al [10]	1957–1958	PMC/S. aureus	4	4 (100.0)	56 (45–68)	7 d (3–11)	NR/NR	1–3	NR	Enema
Fenton et al [66]	1974	PMC	1	1 (100.0)	57	NR	NR/NR	1	NR	Enema
Bowden et al [67]	NR	PMC	16	13 (81.2)	56 (14–85)	NR (5 d, 3 y)	NR/NR	1–24	R, UR	Enema (14), NJ tube (1), Cantor tube (1)
Faust et al [68]	1992–2001	PMC/CDI	6	6 (100.0)	53 (37–74)	NR (9–50 mo)	NR/NR	NR	R (4), B (1), S (1)	NR

Abbreviations: CDI, *Clostridium difficile* infection; IBD, inflammatory bowel disease; NJ, nasojejunal; NR, not reported; PMC, pseudomembranous colitis; *S. aureus*, *Staphylococcus aureus* infection. Donor relationship abbreviations: B, brother; C, unspecified child; D, daughter; F, father; GC, grandchild; H, husband; LA, in-law; P, unspecified parent; R, unspecified relative or family member; S, son; SP, spouse or partner; UR, unrelated volunteer.

[a] Includes resolution after retreatment for treatment failure.

[b] From Gustafsson et al [21].

[c] By enema.

[d] By Cantor tube.

Table 2. Outcomes Achieved in Patients Treated With Intestinal Microbiota Transplantation for *Clostridium difficile* Infection and Related Conditions, Excluding Retreatments After Treatment Failure, by Characteristics of the Procedure

Procedure characteristics	Studies, no.	Patients with outcome/patients in sample (%)			
		Resolution[a]	Relapse[b]	Deaths due to treated condition	Deaths due to any cause
All procedures	28	284/317 (89.0)	11/284 (3.9)	4/317 (1.3)	13/317 (4.1)
Infusions, no.					
1	12	147/168 (87.5)	7/147 (4.8)	3/168 (1.8)	8/168 (4.8)
≤3	5	67/70 (95.7)	3/67 (4.5)	0/70 (0.0)	0/70 (0.0)
>3	5	36/40 (90.0)	1/36 (2.8)	1/40 (2.5)	5/40 (12.5)
NR	6	34/39 (87.2)	0/34 (0.0)	0/39 (0.0)	0/39 (0.0)
Instillation method[c]					
Colonoscope	9	55/62 (88.7)	3/55 (5.4)	0/62 (0.0)	0/62 (0.0)
Enema	11	105/110 (95.4)	5/105 (4.8)	1/110 (0.9)	5/110 (4.5)
Gastroscope or NJ tube	4	55/72 (76.4)	2/55 (3.6)	3/72 (4.2)	7/72 (9.7)
Rectal catheter	2	44/46 (95.6)	0/44 (0.0)	0/46 (0.0)	1/46 (2.2)
>1 method	2	19/21 (90.5)	1/19 (5.3)	0/21 (0.0)	0/21 (0.0)
NR	1	6/6 (100.0)	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)
Donor[c]					
Related	19	195/209 (93.3)	7/195 (3.6)	0/209 (0.0)	3/209 (1.4)
Unrelated	4	21/25 (84.0)	0/21 (0.0)	0/25 (0.0)	1/25 (4.0)
Mixed[d]	3	57/72 (79.2)	4/57 (7.0)	4/72 (5.6)	9/72 (12.5)
NR	3	11/11 (100.0)	0/11 (0.0)	0/11 (0.0)	0/11 (0.0)
Diluent					
Normal saline	20	169/196 (86.2)	5/169 (3.0)	4/196 (2.0)	11/196 (5.6)
Water	1	64/65 (98.5)	5/64 (7.8)	0/65 (0.0)	1/65 (1.5)
Other[e]	3	31/35 (88.6)	1/31 (3.2)	0/35 (0.0)	1/35 (2.9)
NR	4	20/21 (95.2)	0/20 (0.0)	0/21 (0.0)	0/21 (0.0)
Pre-IMT treatment					
Vancomycin or metronidazole[f]	6	150/164 (91.5)	5/150 (3.3)	3/164 (1.8)	6/164 (3.7)
Antibiotics[g] and bowel lavage	2	33/35 (94.3)	4/33 (12.1)	0/35 (0.0)	0/35 (0.0)
Other[h]	8	43/50 (86.0)	2/43 (4.6)	0/50 (0.0)	3/50 (6.0)
NR	12	58/68 (85.3)	0/58 (0.0)	1/68 (1.5)	4/68 (5.9)
IMT suspension volume, mL					
<200	5	32/40 (80.0)	2/32 (6.2)	0/40 (0.0)	3/40 (7.5)
200–500	13	98/114 (86.0)	4/98 (4.1)	3/114 (2.6)	5/114 (4.4)
>500	2	107/110 (97.3)	5/107 (4.7)	0/110 (0.0)	1/110 (0.9)
NR	8	47/53 (88.7)	0/47 (0.0)	1/53 (1.9)	4/53 (7.5)
Stool weight, g					
<50	9	53/64 (82.8)	2/53 (3.8)	0/64 (0.0)	2/64 (3.1)
≥50	7	100/116 (86.2)	1/100 (1.0)	3/116 (2.6)	6/116 (5.2)
NR	12	131/137 (95.6)	8/131 (6.1)	1/137 (0.7)	5/137 (3.6)

Abbreviations: CDI, *Clostridium difficile* infection; IMT, intestinal microbiota transplantation; NR, not reported.

[a] Resolution was defined as the cessation of symptoms or disappearance of disease without the need for retreatment.

[b] Subset of patients who experienced a return of signs and symptoms.

[c] Patients from the same study are reported in >1 category, so the number of studies do not add up to 28.

[d] Both related and unrelated donors were used.

[e] Other diluents included saline with psyllium (n = 16), milk (n = 18), and yogurt (n = 1).

[f] Vancomycin only (n = 111), vancomycin and metronidazole (n = 7), or vancomycin or metronidazole (n = 46).

[g] Antibiotics not specified.

[h] Other pre-IMT treatments included bowel lavage (n = 2), nitazoxanide and bowel lavage (n = 1), unspecified antibiotic therapy (n = 12), vancomycin and omeprazole (n = 34), and α-tocopheryl quinone (n = 1).

from a related donor showed a slightly higher resolution rate (93%) compared with unrelated donor stool (84%) (Table 2). Relatives included both family members and spouses or partners. Where data were available, IMT from a family member showed 87% resolution (34/39 patients) and 8% relapse (2/24 patients), whereas IMT donated from a spouse or partner showed 96% resolution (23/24 patients) and 13% relapse (2/15 patients). By sex, IMT from a male donor showed 86% resolution (12/14 patients), with no relapses, and IMT from a female donor showed 100% resolution (12/12 patients) but 8% relapse (1/12 patients) (data not shown).

Resolution rates were greater with IMT suspensions prepared using water (98.5%) than for those prepared with normal saline (86%); however, with water, the rate of relapse was >2 times

greater (8% vs 3% for saline) (Table 2). Other diluents used to prepare IMT suspensions included yogurt, milk, and saline with psyllium. Suspensions prepared with milk resulted in 94% resolution (15/16 patients), and saline with psyllium resulted in 94% resolution (15/16 patients) and 1 relapse (7%). The 1 patient treated with a yogurt suspension had resolution without relapse.

Patients who received both bowel lavage and an antibiotic before IMT showed the highest relapse rate (12%) (Table 2). Where treatment before IMT was classified as "other," all failures occurred in patients who received vancomycin and omeprazole (a proton pump inhibitor) before IMT [48, 55, 58]. Thirty-four patients in this group received vancomycin and omeprazole, with 6 failures (18%) (data not shown).

Resolutions increased with the volume of IMT given (97% given >500 mL vs 80% given <200 mL). Where data were reported, there was very little difference in resolution rates when more donor stool (in grams) was used to prepare the IMT suspension. However, the relapse rate was 4 times greater when <50 g of stool was used (4% vs 1% for ≥50 grams) (Table 2).

Of the patients who received retreatment due to failure or relapse, 87.5% (14/16 patients) experienced resolution. Thirteen deaths (4%) occurred during follow-up, of which 3, all from a single study [17], were attributed to CDI (1%). Adverse events included upper gastrointestinal hemorrhage (n = 1) [55], IBS symptoms (n = 4) [51], infectious IBS symptoms (n = 1) [59], constipation (n = 1) [56], and signs of irritable colon (n = 1) [19]. None of these could be directly attributed to IMT (data not shown).

DISCUSSION

We have summarized the literature describing patients treated with IMT for recurrent CDI and PMC. Evidence from 317 patients across 27 case series and reports suggests that IMT is a highly effective therapy for these disorders when standard treatments have failed. IMT resulted in resolution for 92% of patients (89% after a single treatment). Relapses and deaths after IMT were relatively uncommon. When case data were summarized by the characteristics of the procedure, instillation by gastroscope or NJ tube seemed least effective, and stool from a related donor was most effective. The effectiveness of water versus saline suspensions is difficult to interpret because water suspensions resulted in more frequent resolution but also more relapses; however, these were all reported from a single study. A possible dose response was also observed for resolution without retreatment in patients who received increasing volumes of IMT suspension. The slightly lower resolution rate in patients given 1 infusion in a single treatment may be due to the lower rate of resolution in patients infused by gastroscope in 1 study (73%), all of whom received 1 infusion [17]. Excluding this study, resolution

occurred in 91% of patients who received 1 infusion. Thus, outcome rates did not appear to vary with number of infusions given.

Although the exact mechanism of action for IMT therapy is unknown, it is believed to restore the composition and function of the intestinal microbiota in diseased patients [2]. Various reports have documented changes to the intestinal microbiota after IMT [44, 48, 61], and the microbiota of treated patients typically has been shown to resemble that of the donor after infusion [44, 61].

Further support for the efficacy of this procedure is provided by its use in the treatment of other gastrointestinal disorders. Our literature search identified 4 such reports (13 patients treated for inflammatory bowel disease and 5 for IBS) [41–44]. These studies reported 100% resolution and no relapses or deaths. However, 89% of these patients received >3 infusions, and 56% were infused with ≥200 milliliters of fecal suspension. The effectiveness of IMT is also supported by the successful use of cultured bacterial suspensions in the treatment of recurrent CDI and other gastrointestinal disorders [34, 48].

Other alternatives to standard therapies, such as probiotics, toxin-binding molecules, immunoglobulin, and *C. difficile* vaccination remain unproved. Evidence for the use of probiotics in the treatment of CDI is conflicting [69–71]. Only *Saccharomyces boulardii* has been found to reduce the absolute risk of recurrence by 30%–33% [72, 73] and only in combination with antibiotics. Toxin-binding molecules are designed to target specific *C. difficile* toxins and block their pathologic effects [74]. One such treatment, tolevamer, has been shown to reduce the absolute risk of CDI recurrence by 20% and 24% compared with vancomycin and metronidazole but was found to be inferior to both in treating primary CDI (46% cure rate for tolevamer vs 81% and 72% for vancomycin and metronidazole, respectively) [74]. The administration of antibodies against *C. difficile* or its toxins is another alternative treatment approach. RCTs have found monoclonal antibodies to be comparable to metronidazole in preventing recurrence (44% and 45%, respectively) [75] and have found intravenous immunoglobulin to reduce the absolute rate of recurrence by 18% in patients who were receiving metronidazole or vancomycin in parallel [76]. However, immunoglobulin is more costly than other therapies [31]. The evidence supporting vaccination for the prevention of CDI recurrence is limited (3/3 patients were cured with no recurrence after vaccination with a *C. difficile* toxoid A and B vaccine) [7]. Fidaxomicin was also shown to be not inferior to vancomycin in a recent RCT [9].

Limitations

Classification of variables associated with IMT procedure was not standard across studies; therefore, operational definitions were defined a priori for data abstraction. However, publications often did not report data on these variables. Data on weight of stool used were not reported for 43% of patients (12 studies),

and data on pre-IMT treatment were not reported for 21% (12 studies) (Table 2). The volume of suspension and number of infusions given were also not reported for >10% of patients (6 and 8 studies, respectively).

Most patients also received treatment or preparation with another procedure (eg vancomycin or bowel lavage) before IMT was performed, making it difficult to estimate the effect of IMT alone. Available data suggest that resolution rates may be slightly higher in patients treated with vancomycin, metronidazole, or unspecified antibiotics with bowel lavage before IMT (92%) and lower in patients treated with vancomycin and omeprazole (82%). In addition, relapses may be due to reinfection with a new strain rather than relapse of infection with the same strain of *C. difficile* [14]. Distinguishing between these 2 occurrences after IMT therapy is of clinical relevance, but this distinction was made only in 1 study [62] and could not be explored in our analysis.

A final limitation is the heterogeneity of the populations treated. This analysis included patients from 8 countries, including Australia, North America, and Europe, treated over a period of 53 years. The variability in outcomes across procedures may be partly explained by differences in the underlying populations studied and by the small number of patients in some categories. However, methods for pooling data and for a formal exploration of heterogeneity using case reports are very limited [77] and could not be applied to these studies, limiting our analysis to descriptive statistics. Methods to assess study quality or publication bias in case reports are also unavailable. It is possible that cases successfully treated with IMT were more likely to be published. These study designs may also be less subject to peer review, which poses another possible source of bias.

Despite these limitations, these data suggest that IMT may be a highly effective and safe therapy for recurrent CDI and PMC when standard treatments have failed. IMT is also a more readily accessible and less costly procedure than some standard or other alternative therapies [28]. There are also biologically plausible explanations for its action. However, differences in the IMT procedure may influence resolution rates. Instillation by gastroscope or NJ tube may be less effective than other methods. Relatives of patients could be given priority as potential stool donors. One infusion may be sufficient, depending on the route. Physicians who are interested in applying this procedure as an alternative therapy should be guided by evidence from these case reports. However, published case reports can provide very biased evidence of treatment efficacy, and better designed studies, such as RCTs, are necessary to confirm the efficacy of this therapy and define best practices for its use, including standards for pre-IMT treatment.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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