

Fecal microbiota transplantation: donor relation, fresh or frozen, delivery methods, cost-effectiveness

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Abstract

Fecal microbiota transplantation (FMT) has evolved into a robust and efficient means for treating recurrent *Clostridium difficile* infection (CDI). Our narrative review looks at the donor selection, preparation, delivery techniques and cost-effectiveness of FMT. We searched electronic databases, including PubMed, MEDLINE, Google Scholar, and Cochrane Databases, for studies that compared the biological effects of donor selection, fresh or frozen fecal preparation, and various delivery techniques. We also evaluated the cost-effectiveness and manually searched references to identify additional relevant studies. Overall, there is a paucity of studies that directly compare outcomes associated with related and non-related stool donors. However, inferences from prior studies indicate that the success of FMT does not depend on the donor-patient relationship. Over time, the use of unrelated donors has increased because of the formation of stool banks and the need to save processing time and capital. However, longitudinal studies are needed to clarify the optimal freezing time before microbial function declines. Several FMT techniques have been developed, such as colonoscopy, enema, nasogastric or nasojejunal tubes, and capsules. The comparable and high efficacy of FMT capsules, combined with their convenience, safety and aesthetically tolerable mode of delivery, makes it an attractive option for many patients. Cost-effective models comparing these various approaches support the use of FMT via colonoscopy as being the best strategy for the treatment of recurrent CDI.

Keywords *Clostridium difficile*, fecal microbiota transplantation, donor selection, capsule, colonoscopy, enema

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Introduction

Clostridium difficile infection (CDI) represents a major clinical and economic burden on healthcare systems [1]. The management of treatment failure and recurrent CDI poses a significant challenge, which drives the cost of healthcare because of their associated morbidity and mortality [2]. Recurrent CDI is reported in 10-30% of patients after initial treatment, with recurrence approaching 60% after the third episode of CDI [3]. Restoration of gut diversity through fecal microbiota transplantation (FMT) has emerged as an effective treatment for CDI-associated diarrhea in patients with recurrent disease after initial antibiotic therapy [4]. A variety of approaches to FMT have been studied, including outcomes associated with donor selection, fecal samples and various delivery techniques, including upper or lower gastrointestinal routes [5]. We herein review current knowledge on FMT and in particular its relationship to donor selection, use of frozen or fresh fecal samples, and delivery systems. We also review the cost-effectiveness of FMT by various delivery systems.

Materials and methods

In this narrative review, studies were searched in electronic databases according to article titles, abstract contents, and relevance in the field of FMT through the end of April 2018. The databases used in this review included PubMed, MEDLINE, Google Scholar, and Cochrane Databases. The main terms applied were *Clostridium difficile*, *Clostridium difficile* infection, fecal microbiota transplantation, fecal transplantation, fecal bacteriotherapy, intestinal microbiota transplantation, floral reconstitution, infectious diarrhea, donor selection, related donor, fresh stool, frozen stool, capsules, colonoscopy, enema, and management. We also manually searched references to identify additional relevant studies. Articles published in languages other than English were excluded.

Related versus unrelated donors

Early FMT practices offered patients the opportunity to select relatives as a source of stool for transplantation [6,7]. In the event the patient could not identify a donor, a healthy volunteer was chosen. The selected volunteers were often other hospital patients, medical students, or residents [6-9]. Early reviews noted the preference for related donors [10-12] due to their genetic similarity and shared environment, both of which are known to influence gut diversity [13]. A shared environment also reduced the risk of transferring infectious agents to the patient [10,14,15]. However, it was noted that there was no rationale for excluding healthy volunteers [16], and subsequent systematic reviews [4,17] and meta-analysis [18] did not report a statistically significant difference in outcomes based on donor selection. Recently, with the use of stool banks, the use of unrelated donors has increased significantly [19,20].

There are limited data on direct comparisons of related and unrelated donors. Inferences from randomized controlled trials (RCTs) are also limited, as those trials were not structured to investigate the donor-patient relationship and their outcomes (Table 1) [5,23-29]. Retrospective studies from the United States [21] and Finland [22] were limited by small sample sizes and found no significant difference in outcomes

after eight weeks and one year, respectively (100% vs. 78.6% resolution; 70% vs. 92% resolution, related and unrelated donors respectively). Six RCTs used exclusively unrelated or related donors, or a mixture [5,23,24,26-28], while two RCTs used almost exclusively related donors [25,29]. The rate of resolution in 7 of 8 RCTs ranged from 87-96.2%; one study that utilized a single enema infusion reported a resolution of 43.8%. When compared to the resolution rate of other studies that utilized a single enema infusion, it did not appear to be an outlier (47.9% [30] and 51.6% [31]). Overall, current evidence indicates that the success of FMT does not depend on the donor-patient relationship; however, larger studies should be designed to explore this area in greater detail.

The advantages of using unrelated donors stem from their easy access and availability from stool banks. It can take weeks to screen a donor [4], thus time and capital are saved by treating patients with donations from an established source. Furthermore, accessibility to FMT is increased by removing the burden of donor screening and processing from healthcare providers [21,32,33]. However, ethical concerns regarding the privacy and ownership of stool have been raised [34,35]. It is unclear how these issues affect patients or stool banks.

Additional benefits of using unrelated donors include the avoidance of unpleasing or difficult conversations with related donors [36,38,39]. A survey of 183 FMT-naïve patients found that 28% of patients found selecting their own donor too unappealing to consider FMT as a treatment [37]. On the other hand, experience from another institution found that, when given a choice after switching to using frozen stool from unrelated donors, all patients preferred the unrelated donor option [21]. These data suggests that some patients struggle with discussing FMT with related donors and may prefer using unrelated donors.

A third option, the autologous donor, involves stool taken from an individual when their disease is in remission [40,41]. Stool can be used as treatment for that individual when the disease relapses. Although implementing this form of personalized medicine has been made easier by the creation of stool banks, its practicality and effectiveness have yet to be evaluated. Regardless of the donor utilized, the recommendation from consensus and working groups around the world emphasizes that every donor should be carefully and thoroughly screened before FMT is performed [42-46].

Table 1 Summary of randomized controlled trials of fecal microbiota transplantation for recurrent *Clostridium difficile* infection

Publication	# of patients	Donor	Preparation	Mode	Overall resolution rate (%)	Follow-up duration
Van Nood et al 2013 [23]	16	UR	Fresh	NDT	94	10 weeks
Youngster et al 2014 [24]	20	UR	Frozen	NGT, colonoscopy	90	6 months
Cammarota et al 2015 [25]	20	R & UR	Fresh	Colonoscopy	90	10 weeks or longer
Kelly et al 2016 [26]	22	R & UR	Fresh	Colonoscopy	90.9	6 months
Lee et al 2016 [5]	178	R & UR	Fresh, frozen	Enema	96.1	13 weeks - 1 year
Hota et al 2017 [29]	16	R & UR	Fresh	Enema	43.8	4 months
Kao et al 2017 [27]	105	UR	Frozen	Colonoscopy, capsule	96.2	3 months or longer
Jiang et al 2017 [28]	72	UR	Fresh, frozen, lyophilized	Colonoscopy	87	5 months

UR, unrelated; R, related; NDT, nasoduodenal tube; NGT, nasogastric tube

Frozen versus fresh fecal preparation

Another significant evolution in the practice of fecal transplantation has been the use of frozen fecal matter. The earliest records can be traced to a report in 1998 by a group in Norway [47,48]. Frozen cultures had been used 9 years previously by Tvede and Rask-Maden to treat 5 patients, but their transplant material was referred to as “synthetic stool” as it was a limited combination of cultured bacterial strains [49]. The overall efficacy of the studies performed in Norway ranged from 83-100% [17,47,48].

Since then, most studies involving frozen fecal matter have reported an overall CDI cure rate between 81-100% [5,21,22,24,28,31,50-54] (Table 2). Two retrospective analyses [21,22] and three RCTs [5,24,28] directly compared fresh and frozen stool. All five studies reported primary outcomes that did not differ between fresh and frozen stool. No significant differences were noted, despite the range in the storage time of frozen fecal matter (1 week to 6 months). One small case series

involving 3 patients [55] and a pilot clinical trial involving 7 patients who received frozen stool [56] reported lower resolution rates (67% and 71.4% respectively). Besides the significant limitation of small sample sizes, the case series involved patients suffering from severe CDI, one who refused a second transplant and ultimately passed away from fulminant disease [55]. The pilot trial treated patients suffering an initial episode of CDI, some of whom were concomitantly or recently on antibiotics for other indications, with a protocol that did not include a bowel lavage [56]. These differences may have contributed to a lower resolution rate. Regardless, current evidence appears to indicate similar efficacy among frozen and fresh fecal preparations.

A central question related to the use of frozen stool is the viability of the microbiome over time. Costello *et al* tested bacterial viability after six months of storage [52]. The study showed that the microbiome remained largely unchanged after six months. CDI resolution has been achieved following 10 months of storage, while other studies have reported successful outcomes of FMT after six months [28,50] and up

Table 2 Summary of studies of fecal microbiota transplant utilizing frozen stool

Publication	# of patients	Mode	Stool amount (g)	Duration of storage	Overall resolution rate (%)	Follow-up period
Gustafsson <i>et al</i> 1999 ^a [48]	14	Enema	5-10	<2 weeks	100	2-3 weeks up to 18 months
Hamilton <i>et al</i> 2012 ^b [21]	21	Colonoscopy, colostomy, push enteroscopy	50	1-8 weeks	90.5-100	3-12 months
Weingarden <i>et al</i> 2013 ^c [55]	3	Colonoscopy	50	Not reported	67	6 weeks - 1 year
Youngster <i>et al</i> 2014 [24]	20	NGT, colonoscopy	41	29-156 days	90	6 months
Satokari <i>et al</i> 2015 ^d [22]	23	Colonoscopy	30	Up to 16 weeks	96	12 weeks - 1 year
Youngster <i>et al</i> 2014 [90]	20	Capsule	48	30-252 days	90	6 months
Orenstein <i>et al</i> 2016 [31]	31	Enema	50	Not reported	87.1	6 months
Hirsch <i>et al</i> 2015 [51]	19	Capsule	2.3	49-63 days	89	90 days
Costello <i>et al</i> 2015 ^e [52]	20	Colonoscopy, push enteroscopy	30	227 days (170-272)	100	3-14 months
Youngster <i>et al</i> 2016 [50]	180	Capsule	48	Up to 6 months	93	Up to 6 months
Lee <i>et al</i> 2016 ^f [5]	91	Enema	100	Up to 30 days	95.6	13 weeks - 1 year
Camacho-Ortiz <i>et al</i> 2017 [56]	7	EGD, colonoscopy, PEG	881.62	Not reported	71.4	30 days
Lahtinen <i>et al</i> 2017 [53]	13	Colonoscopy, gastroscopy	30	Up to 16 weeks	84.6	1 month
Staley <i>et al</i> 2017 ^g [54]	49	Capsule	50	Up to 1 year	87.8	Up to 12 months
Kao <i>et al</i> 2017 [27]	105	Colonoscopy, capsule	80-100	Up to 2 months	96.2	At least 3 months
Jiang <i>et al</i> 2017 ^h [28]	72	Colonoscopy	≥50	Up to 6 months	80.8	5 months

All studies utilized frozen, homologous stool from unrelated donors unless otherwise specified

^aAt least one patient had a second enema

^bStudy also had related donors (10) and utilized fresh stool (22 cases); data shown for patients treated with frozen stool only

^cFresh stool used for 1 patient; data shown for patients treated with frozen stool only; all patients had severe CDI

^dAn additional 26 patients received fresh stool (total of 49 patients); data only shown for patients who received frozen stool

^eIQR range in brackets

^fSome patients received stool from a related donor (number unknown); only data for frozen patients shown

^gLyophilized (Freeze-dried) stool used

^hFresh, frozen and lyophilized stool used (25:24:23 patients); data shown for frozen and lyophilized patients only

EGD, esophagogastroduodenoscopy; NGT, nasogastric tube; PEG, percutaneous endoscopic gastrostomy

to 1 year of storage [54]. Similar results have been reported in mice models, though a decline in quantity and diversity was observed after seven months of storage [57]. Given the benefits of frozen fecal transplant material and evidence to support its durability, clinicians trained in the use of FMT may be more inclined to use frozen preparations.

In 2015, an innovation in fecal preparation involved the use of freeze-dried stool [59]. Also known as lyophilized stool, a fresh suspension is transferred to a vacuum drier that produces a powdered product, which is then encapsulated. The motivation behind the creation of lyophilized stool was to develop a more concentrated and conveniently stored product with the hope that patients could utilize it at home. Various studies, including a case report [59], a retrospective study [60], pragmatic cohort study [54] and an RCT [28], have reported on the use of lyophilized stool with resolution rates ranging from 78-100%. The RCT by Jiang *et al* found lyophilized stool to be statistically less effective than fresh stool (78% vs. 100%, $P=0.022$) but equally effective as frozen stool (78% vs. 83%, $P=0.255$) in resolving recurrent CDI [28]. Further studies are needed to determine the efficacy and safety of lyophilized stool.

Delivery methods

Until 1990, enema was the method of choice for fecal transplant. Since then, various routes have been tested; however, the most optimal route of administration remains unclear. Delivery can be broadly classified into upper and lower gastrointestinal routes. Common upper gastrointestinal routes include esophagogastroduodenoscopy via enteric tubes (nasogastric, nasoduodenal, and nasojejunal tubes), and oral capsules [32,52,61-64]. Common lower gastrointestinal

methods include colonoscopy and enemas [21,65-67]. There are benefits and pitfalls for each modality and physicians often choose one that best fits a combination of their patients' needs, their expertise and availability (Table 3).

The major advantage that colonoscopy offers over other modalities is the ability to visualize the entire colon [40,68-72]. It also enables reliable delivery of stool to affected segments of the bowel [71,73,74] and possibly better retention of stool [73]. This can be particularly important, since it has been observed that the proximal colon has more severe pseudomembranous changes [75]. Furthermore, colonoscopy can deliver larger amounts of stool per transplant procedure [40,71,74,76], associated with higher success rates [17]. Bowel preparation before the procedure is suggested to increase the likelihood of resolution of CDI by decreasing the number of spores and residual organisms [74]. However, there is a risk of bowel perforation, and those who are severely ill may not tolerate the procedure or anesthesia [69,77,78,79].

Enemas are less invasive, easier to perform, and relatively less expensive [80]. The ease and simplicity of an enema allows it to be used in the hospital, ambulatory offices, and even at home [81,82]. However, there are greater concerns regarding retention of stool, as well as the risk that stool would not reach beyond the splenic flexure [72], which may require multiple infusions to achieve efficacy [83]. Greater facility time and personnel are sometimes required to maintain and rotate the patient between various positions to compensate for poor retention [70]. Additionally, patients with poor sphincter tone or issues with incontinence may augment concerns about retention [80].

Upper gastrointestinal routes are typically faster, less expensive and better tolerated compared to colonoscopy, though not as esthetically pleasing to some patients [12,15,16,61,68,70]. Typically, less stool sample is used when upper gastrointestinal

Table 3 Summary of studies of fecal microbiota transplantation delivered via oral capsules

Publication	# of patients	Amount of stool (g)	Capsule preparation	Duration of storage (days)	Capsules/treatment	Overall cure rate %	Duration of follow-up
Louie <i>et al</i> 2013 [88]	27	approx. 100	Fresh	Within hours	24-34	100	6 months
Youngster <i>et al</i> 2014 [90]	20	48	Frozen	30-252	30	90	6 months
Tian <i>et al</i> 2015 ^a [59]	1	50	Lyophilized	Not reported	10	100	>14 days
Hirsch <i>et al</i> 2015 [51]	19	2.3	Frozen	49-63	6-22	89	90 days
Hecker <i>et al</i> 2016 ^b [60]	20	40	Lyophilized	Not reported	20-40	95	204 days (31-408)
Youngster <i>et al</i> 2016 [50]	180	48	Frozen	Up to 180	30	93	Up to 6 months
Staley <i>et al</i> 2017 ^c [54]	49	50	Lyophilized	Up to 365	2-27	87.8	Up to 12 months
Kao <i>et al</i> 2017 ^d [27]	53	80-100	Frozen	Up to 60	40	96.2	At least 3 months

All studies used homologous stool from unrelated donors

A multicenter retrospective publication by Hagel *et al* includes 13 patients treated by capsule FMT, but not enough information is provided to include in the chart

^aFollow up unknown

^bAverage number of days followed-up, range in brackets

^cThe protocol evolved over time, partly because of limited resources: 6 patients received 24-27 capsules/treatment (taken over 2-3 days), 14 patients received 14 capsules/treatment (taken within one day), and 30 received 2-3 capsules/treatment (taken in one single ingestion)

^dTotal number of patients in the study was 105; 52 patients received fecal microbiota transplantation via colonoscopy. Cure rate shown is only for participants who received capsules

routes are used, possibly to avoid regurgitation as well as better retention rates [61,84]. On the other hand, this has also been suggested as a reason why some transplants fail [17]. Common concerns include degradation by the gastric milieu, aspiration, hemorrhage and perforation of the upper gastrointestinal system [68,85-87]. This was supported by Wang *et al* who demonstrated in a systematic review that the rate of adverse events was more common when upper compared to lower gastrointestinal routes were used (43.6% vs. 17.7%) [58].

The most recently developed mode of stool delivery is in the form of oral capsules [88,89]. It involves the delivery of stool mixed with a cryoprotectant, most commonly glycerol, and double- or triple-encapsulated to protect the stool from stomach acidity. Capsules are minimally invasive, convenient, and eliminate the risk of perforation by endoscopic procedures. Additionally, capsules are more esthetically pleasing, as patients have shown a preference for this mode of delivery over others [27,37].

Studies comparing the different routes of FMT have had mixed results, most likely due to sample size and research design [92]. Postigo *et al* compared the efficacy of upper and lower routes of delivery. Using a pooled analysis of 182 patients, the study did not show a significant difference between lower gastrointestinal and upper gastrointestinal delivery of FMT 95% (95% confidence interval [CI] 92-97%) vs. 88% (95%CI 82-94%), respectively ($P=0.162$) [93]. An observational follow-up study by Gundacker *et al* found that FMT by nasogastric tube (NGT) was less effective than colonoscopy [65]. Subgroup analysis revealed that NGT was equally effective for patients who were severely ill (Charleston comorbidity index [CCI]>5) or moderately ill (CCI<5), although there was a trend towards increasing effectiveness with colonoscopy for severely ill patients. However, a small randomized study of 20 patients by Youngster *et al* found colonoscopy and NGT to be equally successful [24]. A larger study by Kao *et al* involving 116 patients (57 patients randomized to the capsule group and 59 to the colonoscopy group) found that the use of capsules was non-inferior to colonoscopy [27]. The study showed that 96.2% of patients achieved prevention of recurrent CDI after a single treatment in both groups (capsule=51/53, colonoscopy=50/52; difference 0%; 1-sided 95%CI -6.1% to infinity; $P<0.001$). Evidence from these comparisons largely indicates that upper gastrointestinal methods of delivery can be equally effective as lower gastrointestinal methods. Furthermore, the high efficacy of FMT capsules, combined with their convenience, safety and esthetics, make them an attractive option for many patients.

Cost-effectiveness of FMT

CDI places a large burden on the healthcare system and makes it imperative to develop guidelines that emphasize cost-effective therapies [93-97]. A meta-analysis estimated the total financial burden of inpatient management of CDI in the United States to be \$6.3 billion in 2015 [94]. In Europe, the economic burden of CDI was estimated to be roughly €3 billion [98], with costs per episode ranging between €5798 and €11,202 [97]. Given

the effectiveness of FMT in the management of recurrent CDI, several studies have evaluated its cost-effectiveness [99-104].

The first cost-effective analysis compared three types of FMT (colonoscopy, duodenal infusion, and enema) and standard antibiotic therapy in the US. The analysis began with the first episode of recurrence and utilized contemporary guidelines to model two additional episodes of recurrence. At a willingness-to-pay threshold of \$50,000/quality-adjusted life year (QALY), they found that FMT via colonoscopy was cost-effective compared to vancomycin and dominant (both cheaper and more effective) compared to the other therapies [99]. Of the several assumptions that went into the model, the choice to model FMT with only a single infusion of stool per treatment should be noted. If multiple infusions were permitted, the resolution rates for FMT via enema or duodenal infusion might have been higher (0.813 vs. 0.926 and 0.815 vs. 0.94, respectively), which may have significantly altered the conclusions of the study.

Two other cost-effectiveness analyses have led to mixed conclusions. A decision-analytic model involving Markov processes compared colonoscopy, enema, NGT and standard antibiotic therapy, beginning with the first recurrence of CDI. The analysis, from the perspective of the ministry of health in Ontario, Canada, concluded that FMT via colonoscopy dominated all other strategies. Sensitivity analysis revealed it to be dominant in 87% of simulations. FMT via enema was preferred if colonoscopy was not available [100]. Another decision-analytic model, from France, compared various methods of FMT (colonoscopy, duodenal infusion, enema), vancomycin and fidaxomicin, for the second recurrence of CDI. Using the WHO's commission on macroeconomics and health to set the willingness-to-pay threshold at \$32,000, they found FMT via enema to be highly cost-effective (incremental cost-effectiveness ratio [ICER] \$18,092/QALY) compared to vancomycin. Although FMT via colonoscopy was still cost-effective according to WHO guidelines, it was not as cost-effective as FMT via enema (ICER \$73,653/QALY) [101].

Other cost-effectiveness studies for recurrent CDI have limited their scope to comparing specific methods. One study compared FMT via colonoscopy to vancomycin for the third recurrence of CDI. They found that FMT dominated vancomycin unless the cure rate with vancomycin was greater than 90% or the costs of FMT exceeded \$3,205 (2011 USD) [102]. Another study used Markov's model to compare two methods of FMT (nasoduodenal infusion and colonoscopy) and vancomycin for the first recurrence of CDI. From the perspective of the healthcare system in Australia, the study found both methods of FMT to be dominant over vancomycin, with an estimated savings of over AU\$1.37 million (2015 Australian dollars) per year. While no significant differences were reported between the various methods of FMT, the study did not incorporate the risks associated with nasoduodenal infusion into their model [103].

Additionally, a decision-analytic model by Varier *et al* compared FMT via colonoscopy to metronidazole and vancomycin, from the perspective of a third-party payer. Given the lack of published data on the effectiveness of FMT for initial CDI, the authors assumed that the procedure was as

effective as it was for recurrent CDI [104]. At a willingness-to-pay threshold of \$100,000 (2011 US dollars), the base case of FMT was not cost-effective when compared to metronidazole (ICER \$124,964/QALY) but was dominant over vancomycin. FMT would have dominated metronidazole if the cost of the procedure was less than \$584, the cost of metronidazole was over \$559, or the cure rate with metronidazole was less than 71% [104]. Recently, a small RCT in Norway showed that, when FMT was used as primary therapy for CDI, overall response to treatment was achieved in 7 (n=9) patients in the FMT group (78%; 95%CI 40-97), compared with 5 (n=11) in the metronidazole group (45%; 95%CI 17-77) (P=0.20) [105]. However, the study did not show statistical significance. Longitudinal studies are needed to define the role of FMT in the management of primary CDI. Currently, it appears that FMT may not be a cost-effective strategy for initial cases of CDI.

Concluding remarks

FMT is an effective and robust strategy for treating recurrent CDI. Our narrative review has shown that the success of FMT does not depend on the donor-patient relationship. To this end, the use of unrelated donor stool is becoming widely accepted with the creation of stool banks. However, further studies are needed to clarify storage requirements and the optimal freezing time before declining microbial function and diversity. Furthermore, several FMT techniques are used in the process of fecal transplantation. Based upon current data, we believe colonoscopy to be the most effective strategy. However, capsule FMT offers patients a more convenient and esthetically pleasing option. Cost-effectiveness models comparing these various approaches support the use of fecal transplant using colonoscopy over antibiotic therapy for treating recurrent CDI. However, there remains a knowledge gap regarding the cost-effectiveness of capsule FMT.

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