

2.01.92	Fecal Microbiota Transplantation		
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Section:	2.0 Medicine	Page:	Page 1 of 17

Policy Statement

Fecal microbiota transplantation (FMT) may be considered **medically necessary** for treatment of patients with recurrent *Clostridium difficile* infection under **both** of the following conditions (see Policy Guidelines section):

- Episodes are refractory to appropriate antibiotic regimens, including at least 1 regimen of pulsed vancomycin
- There have been at least 3 episodes of recurrent infection

Fecal microbiota transplantation (FMT) is considered **investigational** in all other situations.

Policy Guidelines

Coding

Effective October 1, 2019, a new CPT PLA code describes a qualitative test for *Clostridium difficile* toxin testing from a stool sample:

- **0107U**: *Clostridium difficile* toxin(s) antigen detection by immunoassay technique, stool, qualitative, multiple-step method

The following CPT code is specific for preparation of fecal microbiota transplantation (FMT):

- **44705**: Preparation of fecal microbiota for instillation, including assessment of donor specimen

The following HCPCS code includes the preparation as well as the instillation:

- **G0455**: Preparation with instillation of fecal microbiota by any method, including assessment of donor specimen

There is a lack of consensus on the number of recurrences that warrants consideration of fecal microbiota transplantation (FMT).

Among the published randomized controlled trials evaluating FMT for treatment of *Clostridium difficile* infection (CDI), the van Nood study (2013) included patients with at least 1 recurrence of CDI; the other study, the Youngster study (2014), included patients with a relapse after at least 3 episodes of mild-to-moderate CDI or at least 2 episodes of severe CDI (both studies are described in the Rationale section.)

The 2013 American College of Gastroenterology guidelines have recommended that FMT be considered second-line therapy for a third recurrence of CDI.

Description

Fecal microbiota transplantation (FMT) involves the infusion of intestinal microorganisms via transfer of stool from a healthy person into a diseased patient, with the intent of restoring normal intestinal flora. Fecal transplant is proposed for treatment-refractory *Clostridium difficile* infection (CDI) and other conditions, including inflammatory bowel disease.

Related Policies

- Fecal Analysis in the Diagnosis of Intestinal Dysbiosis

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

In 2016, the U.S. Food and Drug Administration issued updated draft guidance on investigational new drug requirements for the use of FMT to treat CDI not responsive to medication therapy.⁵ The draft guidance is similar to the 2013 guidance and states that the Food and Drug Administration is continuing to consider how to regulate FMT and that, during this interim period, the agency will use enforcement discretion regarding the use of fecal transplant to treat treatment-resistant CDI. The Food and Drug Administration requires that physicians obtain adequate informed consent from patients or their legal representative before performing the intervention. The document also noted that selective enforcement does not apply to use of fecal transplant for treating conditions other than treatment-resistant CDI.

Rationale

Background

Fecal Microbiota

Fecal microbiota transplantation (FMT), also called donor feces infusion, intestinal microbiota transplantation, and fecal bacteriotherapy, involves the infusion of intestinal microorganisms via transfer of stool from a healthy individual into a diseased individual to restore normal intestinal flora. The stool can be infused as a liquid suspension into a patient's upper gastrointestinal tract through a nasogastric tube or gastroscopy, or the stool can be infused into the colon through a colonoscope or rectal catheter.

The goal of FMT is to replace damaged and/or disordered native microbiota with a stable community of donor microorganisms. The treatment is based on the premise that an imbalance in the community of microorganisms residing in the gastrointestinal tract (i.e., dysbiosis) is associated with specific disease states, including susceptibility to infection.

The human microbiota, defined as the aggregate of microorganisms (bacteria, fungi, archaea) on and in the human body, is believed to consist of approximately 10 to 100 trillion cells, approximately 10 times the number of human cells. Most human microbes reside in the intestinal tract, and most of these are bacteria. In its healthy state, intestinal microbiota performs a variety of useful functions including aiding in the digestion of carbohydrates, mediating the synthesis of certain vitamins, repressing the growth of pathogenic microbes, and stimulating the lymphoid tissue to produce antibodies to pathogens.

Applications

Clostridium difficile Infection

To date, the major potential clinical application of FMT is the treatment of *Clostridium difficile* infection (CDI). Infection of the colon with *C. difficile* is a major cause of colitis and can cause life-threatening conditions including colonic perforation and toxic megacolon. *C. difficile* occurs naturally in intestinal flora. The incidence of CDI in North America has increased substantially. For

example, according to hospital discharge diagnosis data, there were more than 300,000 cases of CDI in 2006 compared with fewer than 150,000 cases in 2000. Moreover, CDI causes an estimated 15,000 to 20,000 deaths per year in U.S. hospitals.^{1,2}

It is unclear what causes *C. difficile* overgrowth, but disruption of the normal colonic flora and colonization by *C. difficile* are major components. Disruption of the normal colonic flora occurs most commonly following administration of oral, parenteral, or topical antibiotics. Standard treatment for CDI is antibiotic therapy. However, symptoms recur in up to 35% of patients, and up to 65% of patients with recurrences develop a chronic recurrent pattern of CDI.³

Other Applications

Other potential uses of FMT include treatment of conditions in which altered colonic flora may play a role. They include inflammatory bowel disease, irritable bowel syndrome, idiopathic constipation, and non-gastrointestinal disease such as multiple sclerosis, obesity, autism, and chronic fatigue syndrome. However, for these conditions, the contribution of alterations in colonic flora to the disorder is uncertain or controversial.

There is interest in alternatives to human feces that might have the same beneficial effects on intestinal microbiota without the risks of disease transmission. In a proof of principle study, Petrof et al (2013) evaluated a synthetic stool product in 2 patients with recurrent CDI.⁴ The product is made from 33 bacterial isolates developed from culturing stool from a healthy donor.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Recurrent *Clostridium difficile* Infection

Clinical Context and Test Purpose

The purpose of fecal microbiota transplantation (FMT) is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with recurrent *Clostridium difficile* infection (CDI) refractory to antibiotic therapy.

The question addressed in this evidence review is: Does the use of FMT improve the net health outcome in patients with recurrent CDI?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is individuals with recurrent CDI refractory to antibiotic therapy.

Interventions

The therapy being considered is FMT.

Comparators

The following therapy is currently being used to treat CDI: standard antibiotic regimens.

Outcomes

The general outcomes of interest are symptoms, change in disease status, and treatment-related morbidity.

Timing

Follow-up can range up to and beyond 12 weeks is of interest to monitor for outcomes.

Setting

Patients with recurrent CDI are actively managed by gastroenterologists, infectious disease specialists and primary care providers in an inpatient setting.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Khan et al (2018) conducted a systematic review of the literature and meta-analysis of pooled data on the use of FMT as a treatment option for recurrent CDI.⁶ Reviewers only selected RCTs comparing FMT (fresh or frozen) with medical treatment. Among the selected studies, there was a nonsignificant trend toward the resolution of diarrhea following a single fresh FMT infusion compared with frozen FMT or medical treatment (odds ratio, 2.45; 95% confidence interval [CI], 0.78 to 7.71; $p=0.12$, $I^2=69%$), but different forms and routes of FMT administration were shown to be equally efficacious. Reviewers concluded that FMT is a promising treatment modality for recurrent CDI. Variability of FMT dose usages, small trial populations, and window to assess treatment success or failure limited analysis data.

Quraishi et al (2017) published a systematic review and meta-analysis of studies (including RCTs) investigating the effect of FMT in patients with recurrent or refractory CDI.⁷ Reviewers deemed the RCTs as having a low risk of bias (including adequate randomization with allocation concealment and intention-to-treat analysis). Reviewers did not report an assessment of bias in terms of blinding, sample size adequacy, or possible differences in baseline characteristics. They argued that none of the trials examining the efficacy of FMT were truly placebo-controlled, and the case series followed patients until resolution of CDI (range, 10 weeks to 8 years), though some had an incomplete follow-up. In the pooled analysis, 92% of patients had a resolution of CDI (95% CI, 89% to 94%); heterogeneity was classified as likely moderate ($I^2=59%$). Additionally, in the 7 trials that evaluated FMT, the intervention overall was associated with an increase in the resolution of recurrent and refractory CDI (relative risk, 0.23; 95% CI, 0.07 to 0.80). The 30 case series reported resolution rates for CDI ranged from 68% to 100%.

The Quraishi review found FMT to be effective in the treatment of recurrent and refractory CDI, and no serious adverse events from FMT were reported in the RCTs through the follow-up period. Most adverse effects in the case series were minor (bloating, belching, abdominal cramps, pain or discomfort, nausea, vomiting, excess flatulence, constipation, transient fever, urinary tract infections, self-limiting diarrhea, irregular bowel movement). However, reviewers noted several

limitations. Based on variability in the definitions of CDI resolution used across the studies, reviewers could not distinguish between recurrent and refractory CDI. There were also variations across studies in terms of recipient preparations, number of infusions, time to resolution, follow-up, overall response, dosing, concurrent use of medications, and other nonspecified biases. Heterogeneity between most studies was considerable.

Drekonja et al (2015) systematically reviewed the literature on FMT for treating CDI.⁸ Twenty-one case series included patients with recurrent CDI in these studies; 85% of patients treated with FMT remained free of symptoms without additional recurrences (the number of patients successfully treated was not reported). Seven case series included patients with refractory CDI, defined as an episode of CDI that did not respond to antimicrobial treatment. Resolution of symptoms in the studies on refractory CDI ranged widely, from 0% to 100%, with an overall resolution rate of 55%. There were reports of only 7 patients treated with FMT for initial CDI. The case series reported few adverse events.

Several systematic reviews of uncontrolled studies on FMT for treating CDI have been published.^{3,9-11} Of these, only Sofi et al (2013) conducted a pooled data analysis.¹⁰ Reviewers searched the literature and could not find any RCTs that evaluated FMT (none had been published at that time). Reviewers did find a total of 25 observational studies, which provided data on adults treated with FMT for CDI. All case series were retrospective. Most studies included recurrent CDI, but several case reports treated patients who were severely ill due to acute CDI. Fecal transplants were performed by the gastroduodenal route in 91 (32%) patients and by the colonic route in 198 (68%) patients. Treatment success was defined as resolution of CDI symptoms at follow-up. Mean follow-up posttransplant ranged from 10 days to 65 months. In a pooled analysis of individual patient data, the overall treatment success rate was 91.2%. Subgroup analyses revealed a significantly higher treatment failure rate in patients treated colonically vs the duodenal route; moreover, these analyses revealed a higher treatment failure rate in patients who experienced symptoms for at least 60 days vs fewer than 60 days.

Table 1 summarizes the characteristics of selected systematic reviews.

Table 1. Characteristics of Systematic Review

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Khan et al (2018) ⁶	To 2018	7	Recurrent CDI treated with FMT	543 (20-178)	RCTs	2008-2016
Quraishi et al (2017) ⁷	To 2016	37	Recurrent or refractory CDI treated with FMT	3518 (NR)	7 RCTs, 30 case series	2003-2016
Drekonja et al (2015) ⁸	To 2015	35	Initial, refractory, and recurrent CDI treated with FMT	679 (1-257)	2 RCTs, 28 case series, 5 case reports	1958-2015
Sofi et al (2013) ¹⁰	To 2012	25	Initial and recurrent CDI treated with FMT	239 (4-70)	15 case series, 10 case reports	NR

CDI: *Clostridium difficile* infection; FMT: fecal microbiota transplantation; NR: not reported.

Randomized Controlled Trials

Kelly et al (2016) published the findings of a multicenter, double-blinded RCT evaluating FMT for recurrent CDI comparing donor with personal stool. There were possible baseline differences in the mean duration of CDI since initial dose, mean CDI recurrences, and the prior use of *Lactobacillus*, fidaxomicin, or proton-pump inhibitor. Forty-three patients completed the 8-week follow-up evaluation, and the principal investigators terminated enrollment after 28 months in light of data on the efficacy of FMT. The intention-to-treat analysis included all enrolled patients.

The primary end point was CDI resolution, defined as the resolution of diarrhea without the need for further anti-CDI therapy throughout the follow-up period. Fecal microbiota analyses of patient and donor stool before and after FMT demonstrated an overall CDI resolution of 90.9% in the heterologous FMT group compared with a CDI resolution of 62.5% in the autologous FMT group ($p=0.042$). However, there were notable differences in efficacy by site. CDI resolution with

heterologous FMT at the first site was 90.0% (95% CI, 51.8% to 98.7%) and 42.9% (95% CI, 20.1% to 69.0%) with autologous FMT. The second site reported CDI resolution with heterologous FMT to be 91.7% (95% CI, 57.2% to 98.9%) compared with 90.0% (95% CI, 51.8% to 98.7%) in the autologous FMT group. The trialists cautioned that the observed variability in efficacy between sites suggested that patients who have a lower risk of CDI recurrence may not benefit from FMT. For patients with clinical failure, failure occurred at a mean of 10 days postprocedure. Rates of adverse events were similar in the 2 groups. Four serious adverse events were reported, but none was attributed to FMT or colonoscopy. Reported study limitations included the following factors:

- no data collection on the severity of previous CDI episodes or antibody titers;
- possibly limited representation of the CDI population due to the exclusion of patients aged 75 or older and due to the inclusion of a younger cohort of patients;
- dosing differences;
- the possibility of overdiagnosis of CDI due to the use of polymerase chain reaction testing of stool to diagnose CDI;
- and the lack of power to assess rare, severe adverse events.

Van Nood et al (2013) published a nonblinded trial that included patients 18 years and older with at least 1 recurrence of CDI.¹² Exclusion criteria included prolonged compromised immunity, admission to an intensive care unit, and need for vasopressor medication. Patients were randomized to 1 of 3 treatment groups: (1) FMT; (2) antibiotic therapy; or (3) antibiotics and bowel lavage. Patients assigned to the FMT group also received a modified course of vancomycin (500 mg orally 4 times a day for 4-5 days) and bowel lavage before infusion. A second infusion was given to patients in the FMT group who relapsed after the first treatment. The trial was initially designed to enroll 120 patients (40 per group), but, because of the high relapse rate in the control groups, the data and safety monitoring group recommended early trial termination.

The primary efficacy outcome was a cure without relapse within 10 weeks of initiating treatment. Cure was defined as the absence of diarrhea that could not be explained by other causes and 3 consecutive negative tests for CDI toxin. Relapse was defined as diarrhea with a positive stool test for CDI toxin during this 10-week period. For the 3 patients who received a second infusion, follow-up was extended to 10 weeks after the second treatment. Patients were questioned about symptoms of diarrhea, and stool tests were performed on days 14, 21, 35, and 70 and when diarrhea was reported. One patient in the FMT group was excluded from analysis.

Fifteen (94%) of 16 analyzed patients in the FMT group were cured (13 after a single infusion, 2 after a second infusion from a different donor). In contrast, only 4 (31%) of 13 patients in the antibiotics-only group and 3 (23%) of 13 patients in the antibiotics and bowel lavage group were cured. The overall cure rate was significantly higher in the FMT group than in the other 2 groups ($p < 0.001$). Most patients in the FMT group experienced short-term adverse events (i.e., diarrhea in 94%, cramping in 31%, belching in 19%) that resolved within 3 hours.

Table 2 summarizes the characteristics of the selected RCTs.

Table 2. Summary of Key Randomized Controlled Trials Characteristics

Study	Countries	Sites	Dates	Participants	Interventions		
					Active 1	Active 2	Comparator
Kelly et al (2016) ¹³	U.S.	2	1987-2013	≥3 recurrences CDI; received full course vancomycin at most recent acute episode	n=22; heterologous donor stool via colonoscopy; 300 mL fecal suspension	n=0	n=24; autologous personal stool via colonoscopy; 300 mL fecal suspension
van Nood et al (2013) ¹²	NL	1	2008-2010	≥1 recurrences CDI	N=17; donor FMT via	n=13; vancomycin and bowel	n=13; Vancomycin only; 500 mg

Study	Countries	Sites	Dates	Participants	Interventions
				nasoduodenal tube; 141 g	lavage; 500 mg orally 4 times daily for 14 d orally 4 times daily for 14 d

CDI: *Clostridium difficile* infection; FMT: fecal microbiota transplantation; NL: Netherlands.

Retrospective Studies

Investigating the long-term clinical outcomes of FMT in patients with CDI, Mamo et al (2018) conducted a retrospective study using a follow-up survey of 137 patients who had received FMT for recurrent CDI at a single center between January 2012 and December 2016.¹⁴ Median time from last FMT to follow-up was 22 months. Overall at follow-up, 82% (113/137) of patients had no recurrence of CDI (nonrecurrent CDI group) and 18% (24/137) of patients had CDI (recurrent CDI group). The survey results suggested that antibiotic exposure for non-CDI infections after FMT were more common in the recurrent CDI group (75%) than in the nonrecurrent CDI group (75 38%; $p < 0.001$). Overall, 82% of patients reported being symptom-free.

In another retrospective study, Meighani et al (2017) assessed outcomes from FMT for recurrent CDI in patients with inflammatory bowel disease (IBD).¹⁵ All patients underwent FMT between December 2012 and May 2014 within a single health care system. Demographic and clinical characteristics as well as treatment outcomes for patients with IBD were compared with those of the general population within this system. Of 201 patients who underwent FMT, 20 had concurrent IBD, and the study found that the response to FMT and CDI relapse rate in the IBD group ($n=20$) did not differ statistically from the rest of the cohort ($n=201$). The overall response rate in the IBD population was 75% at 12 weeks. Study design, lack of a standardized FMT treatment protocol, and variable donors limit certainty in conclusions drawn from these data.

Pediatric Populations

To characterize a pediatric population with recurrent CDI, Aldrich et al (2018) published a retrospective study that included both hospital-acquired CDI and community-acquired CDI cases, comparing the success rates of various treatments used including FMT.¹⁶ The pediatric population consisted of 175 subjects ages 1 to 21 reporting 215 separate CDI episodes. Treatments included oral metronidazole (145/207 [70%]) and oral vancomycin (30/207 [15%]), with recurrent rates of 30% (42/145) and 37% (11/30), respectively. Overall, 29% (63/215) of all CDI cases had at least 1 documented recurrence. Using multivariate analysis, the study showed that subjects with hospital-acquired CDI were 2.6 times less likely to recur than those with community-acquired CDI (odds ratio, 0.39; 95% CI, 0.18 to 0.85; $p=0.018$) and that FMT had an overall success rate of 83% (10/12).

Procedural Approaches

Route of Administration

Systematic Reviews

The review by Quraishi et al (2017), discussed previously, included a subgroup analysis of FMT delivery.⁷ Pooled analysis of 7 RCTs and 25 case series revealed a significant difference between lower gastrointestinal delivery (95%; 95% CI, 92% to 97%) and upper gastrointestinal delivery (88%; 95% CI, 82% to 94%; $p=0.02$). Reviewers concluded that FMT appeared to be effective in the treatment of recurrent and refractory CDI, independent of the delivery route.

Randomized Controlled Trials

An RCT by Youngster et al (2014) compared infusion of donor stools administered by colonoscopy or nasogastric tube.¹⁷ Twenty patients with relapsing and recurrent CDI were included. Patients had to have a CDI relapse following at least 3 episodes of mild-to-moderate CDI and failure of a course of vancomycin, or at least 2 episodes of severe CDI that resulted in hospitalization and was associated with significant morbidity. All patients received donor FMT and were randomized to 1 of 2 infusion routes: colonoscopy or nasogastric tube. Both groups

received thawed inoculum 90 mL. Patients could receive a second FMT if symptoms did not resolve following the initial transplant. The primary efficacy outcome was clinical cure, defined as resolution of diarrhea (i.e., <3 bowel movements per 24 hours) while off antibiotics for CDI, without relapse for 8 weeks. Fourteen patients were cured after the first FMT, eight in the colonoscopy group and six in the nasogastric tube group; the difference between groups was not statistically significant ($p=0.628$). Of the remaining 6 patients, one refused additional treatment and the other five underwent a second transplant. By study protocol, patients could choose the route of administration for the second procedure, and all chose the nasogastric tube. Four other patients were cured after the second transplant, for an overall cure rate of 18 (90%) of 20. This trial did not find either route of administration of donor feces to be superior to the other; however, it was reported that patients preferred a nasogastric tube.

Fresh vs Frozen Feces

Systematic Reviews

The review by Quraishi et al (2017) also included a subgroup analysis of FMT preparation. Only 1 RCT in the review directly compared the effects of fresh stool for FMT ($n=11$) with frozen stool for FMT ($n=108$) on CDI resolution (RR=1.19; 95% CI, 0.77 to 1.84). The remaining 30 case series used frozen stool. Two RCTs and 2 case series used fresh stool to prepare FMT. The pooled analyses found no difference in the response rates between fresh FMT (92%; 95% CI, 89% to 95%; $I^2=54%$) and frozen FMT (93%; 95% CI, 87% to 97%; $p=0.84$; $I^2=19%$). Reviewers concluded that FMT appeared to be effective in the treatment of recurrent and refractory CDI, independent of FMT preparation.

Randomized Controlled Trials

A double-blind RCT by Lee et al (2016) compared fresh with frozen stool used in FMT to treat patients with recurrent CDI.¹⁸ A total of 232 patients were included, with 114 assigned to frozen FMT and 118 to fresh FMT. The primary endpoint was the proportion of patients with no recurrence of CDI-related diarrhea 13 weeks after FMT. The trial was designed as a noninferiority trial, with a margin of 15%. In the per-protocol population ($n=178$), clinical resolution of symptoms was reported in 76 (83.5%) of 91 patients in the frozen FMT group and 74 (85.1%) of 87 in the fresh FMT group (difference, -1.6%; 95% 1-sided CI, -10.5% not reached). In the modified intention-to-treat group, clinical resolution with up to 2 FMT treatments was reported in 81 (75.0%) of 108 patients in the frozen FMT group and 78 (70.3%) of 111 in the fresh FMT group (difference, 4.7%; 95% 1-sided CI, -5.2% not reached). The difference between groups was within the 15% noninferiority margin and thus frozen FMT was considered noninferior to fresh FMT.

Section Summary: Recurrent *Clostridium difficile* Infection

A systematic review and meta-analysis of 7 RCTs and 30 case series concluded that FMT appeared to be effective in the treatment of recurrent and refractory CDI, independent of preparation and route of delivery. A small RCT, which enrolled patients who had failed at least 1 course of antibiotic treatment, reported a large increase in resolution of CDI with FMT plus antibiotics compared with antibiotics with or without bowel lavage. A double-blinded, multicenter RCT used fresh heterologous stool administered via colonoscopy; patients in this RCT had 3 or more CDI recurrences and received a full course of vancomycin. Moreover, trialists found FMT to be effective in preventing further episodes of CDI during an 8-week follow-up period. RCTs evaluating procedural differences found similar success rates with FMT administered via colonoscopy or gastric tube and with fresh or frozen FMT. Uncontrolled studies have reported high rates of resolution of recurrent CDI following treatment with FMT.

Inflammatory Bowel Disease

Clinical Context and Test Purpose

The purpose of FMT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with IBD.

The question addressed in this evidence review is: Does the use of FMT improve the net health outcome in patients with IBD?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is individuals with IBD.

Interventions

The therapy being considered is FMT.

Comparators

The following therapy is currently being used to treat IBD: standard of care.

Outcomes

The general outcomes of interest are symptoms, change in disease status, and treatment-related morbidity.

Timing

Follow-up out to 12 weeks is of interest to monitor for outcomes.

Setting

Patients with IBD are actively managed by gastroenterologists and primary care providers in an outpatient setting.

Study Selection Criteria

Methodologically credible studies were selected using the same principles as outlined for indication 1.

Systematic Reviews

A systematic review and meta-analysis by Paramsothy et al (2017) searched for studies to January 2017 evaluating the efficacy and/or safety of FMT use in treating IBD, distributed across 3 disease subtypes (ulcerative colitis [UC], Crohn disease [CD], pouchitis).¹⁹ Fifty-three studies were selected and analyzed for this review (41 in UC, 11 in CD, 4 in pouchitis). Overall, 36% (201/555) of UC patients, 50.5% (42/83) of CD patients, and 21.5% (5/23) of pouchitis patients achieved the primary outcome of clinical remission. Pooled proportion achieving clinical remission was 33% among cohort studies, with a moderate risk of heterogeneity; among the 4 RCTs selected, there was a significant benefit in clinical remission (odds ratio, 2.89; 95% CI, 1.36 to 6.13; $p=0.006$), with moderate heterogeneity. Transient gastrointestinal complaints comprised most of the adverse events. Reviewers concluded that FMT appeared most promising in treating UC, and use of FMT to treat CD should be interpreted cautiously, due to wide confidence intervals.

Sha et al (2014) published a systematic review of observational data on FMT for treatment of IBD.²⁰ Reviewers identified reports of 111 IBD patients (UC and CD) worldwide who received fecal transplants for IBD. All studies were case series. Remission was achieved in 87 (77.8%) of 111 IBD patients.

Randomized Controlled Trials

In 2015, 2 double-blind placebo-controlled randomized trials evaluated FMT for treatment of UC. Both trials were discontinued due to futility, with one ultimately reporting positive findings. The 2 RCTs varied in their control conditions, outcomes measures, and intervention lengths. Moayyedi et al (2015) enrolled 75 patients ages 18 and older with active UC (Mayo Clinic score ≥ 4 , endoscopic Mayo Clinic score, ≥ 1) and without CDI.²¹ Patients underwent a clinical and endoscopic examination at week 7. The primary outcome was UC remission at week 7, defined as a full Mayo score of less than 3 and a flexible sigmoidoscopy finding of complete healing of the mucosa (endoscopic Mayo score, 0).

The investigators planned to recruit 130 patients. After 50% of participants were enrolled, the data monitoring and safety committee recommended trial discontinuation for futility and completion of the trial for enrolled patients. At the 7-week follow-up, 9 (24%) of 38 patients in the FMT group and 2 (5%) of 37 patients in the placebo group achieved UC remission. The difference between groups was statistically significant ($p=0.03$). There was no significant difference between groups in adverse event rates.

Rossen et al (2015) assessed 50 patients with mild to moderately active UC.²² To participate in this RCT, patients had to have a patient-reported Simple Clinical Colitis Activity Index score between 4 and 11, an endoscopic Mayo score of 1 or more, and stable medication use. FMT was done via a nasoduodenal tube using fecal suspension 500 mL. Patients underwent a clinical and endoscopic examination at baseline, 6 weeks, and 12 weeks. The primary end point was clinical remission at 12 weeks, defined as a Simple Clinical Colitis Activity Index score of 2 or less and at least a 1-point improvement on the combined Mayo endoscopic score of the sigmoid and rectum.

Investigators calculated that a sample size of 42 patients would be needed for the primary outcome analysis. The sample size calculation assumed a response rate of 70% in the treatment group and 22.5% in the control group. At the first interim analysis, after 20 patients had completed 12 weeks of follow-up, a lower response rate was observed and an increase in the sample size was recommended. At the second interim analysis, the data monitoring and safety committee recommended terminating the trial for futility. At study termination, 50 patients had been randomized. Two patients were excluded from the trial postrandomization, leaving 48 patients in the intention-to-treat analysis. Thirty-seven patients completed the trial. In the intention-to-treat analysis of the primary outcome measure, 7 (30.4%) of 23 patients in the active FMT group and 8 (32%) of 25 patients in the control group met criteria for clinical remission. The difference between groups was not statistically significant ($p=1.0$). Four patients (2 in each group) experienced a serious adverse event. Other than 1 case of abdominal pain, the serious adverse events were not considered treatment-related. Most patients experienced mild adverse events during or shortly after treatment, the most common of which were transient borborygmus and an increase in stool frequency.

Table 3 summarizes the characteristics of selected RCTs.

Table 3. Summary of Key Randomized Controlled Trial Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Moayyedi et al (2015) ²¹	Canada	1	NR	UC without CDI	n=38; FMT via donor stool retention enema; weekly for 6 wk	n=37; placebo via retention enema; weekly for 6 wk
Rossen et al (2015) ²²	NL	1	NR	Mild-to-moderate UC	n=25; 2 FMTs via nasoduodenal tube; 500 mL fecal suspension; 3 wk apart	n=25; 2 placebo autologous stool treatments via nasoduodenal tube; 500 mL fecal suspension; 3 wk apart

CDI: *Clostridium difficile* infection; FMT: fecal microbiota transplantation; NL: Netherlands; NR: not reported; UC: ulcerative colitis.

Section Summary: Inflammatory Bowel Disease

A systematic review with meta-analysis reviewed 53 studies and concluded that FMT had shown promise in treating patients with UC, but called cautious about using FMT to treat patients with CD. Two small RCTs on FMT for treatment of UC and both were discontinued for futility, with limited available data for analysis of enrolled patients who completed the trials. One trial found a statistically significant higher remission rate after FMT than after a control intervention, but the implications of this finding are tempered by the low numbers of patients with remission ($n=11$).

and short follow-up (7 weeks). The other trial reported no difference in remission rates. This current evidence is not sufficient to permit conclusions on the efficacy of FMT for UC. Additionally, questions remain about the optimal route of administration, donor characteristics, and a number of transplants. Data on a small number of patients with CD are available, but there are no controlled studies of FMT in this population.

Pouchitis, Irritable Bowel Syndrome, Constipation, or Metabolic Syndrome

Clinical Context and Test Purpose

The purpose of FMT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with pouchitis, irritable bowel syndrome (IBS), constipation, or metabolic syndrome.

The question addressed in this evidence review is: Does the use of FMT improve the net health outcome in patients with pouchitis, IBS, constipation, or metabolic syndrome?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant populations of interest are individuals with pouchitis, IBS, constipation, or metabolic syndrome.

Interventions

The therapy being considered is FMT.

Comparators

The following therapy is currently being used to treat pouchitis, IBS, constipation, and metabolic syndrome: standard of care.

Outcomes

The general outcomes of interest are symptoms, change in disease status, and treatment-related morbidity.

Timing

Though not completely standardized, follow-up for pouchitis, IBS, constipation, or metabolic syndrome symptoms would typically occur in the months to years after starting treatment.

Setting

Patients with pouchitis, IBS, constipation, or metabolic syndrome are actively managed by gastroenterologists and primary care providers in an outpatient setting.

Study Selection Criteria

Methodologically credible studies were selected using the same principles as outlined for indication 1.

Systematic Reviews

A systematic review by Rossen et al (2015) of studies on FMT identified a case series on constipation (N=3 patients), another on pouchitis (N=8 patients), and a third on IBS (N=13 patients).²³ There was also a small RCT (N=18) on FMT for treatment of metabolic syndrome. The RCT by Vrieze et al (2012) compared donor FMT with placebo (reinfusion of own collected feces).²⁴ The trialists found a significantly greater improvement in peripheral insulin sensitivity in the active FMT group but no difference between groups in hepatic insulin sensitivity.

Section Summary: Pouchitis, Irritable Bowel Syndrome, Constipation, or Metabolic Syndrome

There is insufficient evidence on the efficacy and safety of FMT for treating conditions including pouchitis, IBS, constipation, and metabolic syndrome. The evidence consists primarily of a few

small case series; a small RCT on FMT for treating metabolic syndrome had mixed findings and did not report clinical outcomes (e.g., symptom improvement).

Adverse Events

Wang et al (2016) published a systematic review of adverse events associated with FMT.²⁵ Reviewers identified 50 publications (total N=1089 FMT-treated patients). Of these, 831 patients were affected by CDI, 235 had IBD, and the remainder had miscellaneous indications. The overall incidence of adverse events in the studies was 28.5% (310/1089). Most reported adverse events were mild-to-moderate in severity and included abdominal cramping, flatulence, fever, and belching. A total of 9.2% (100/1089) patients developed serious adverse events. Thirty-eight patients died. Reviewers attributed 1 death to be definitely related to FMT, 2 were possibly related, and 35 were unrelated. The definitely related death was due to aspiration during colonoscopy sedation, and the two possibly related deaths were associated with infections (due either to FMT or the patients' immunocompromised state). The incidence of severe infection was 2.5% (27/1089). Reviewers categorized 8 cases of severe infection as probably or possibly related to FMT; the other 19 cases were categorized as unrelated.

Summary of Evidence

For individuals who have recurrent CDI refractory to antibiotic therapy who receive FMT, the evidence includes RCTs, multiple systematic reviews, and observational studies. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. The RCTs found that FMT was more effective than standard treatment or placebo for patients with recurrent CDI. Other RCTs did not find the superiority of any route of administration over another or the superiority of fresh vs frozen feces. Case reports and case series have reported high rates of resolution of recurrent CDI following treatment with FMT. Few treatment-related adverse events have been reported. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have inflammatory bowel disease who receive FMT, the evidence includes a large-scale systematic review and meta-analysis, 2 RCTs in patients with ulcerative colitis, as well as observational studies. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Two small RCTs on FMT for treatment of ulcerative colitis were discontinued due to futility, which restricted data analysis to patients already enrolled. Of the 2 small RCTs, one found a statistically significant higher remission rate after active FMT than after a control intervention, but this trial had few patients in remission (n=11) and short follow-up (7 weeks); the other trial reported no difference in remission rates. Data on a small number of patients with Crohn disease are available; however, there are no controlled studies of FMT in this population. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have pouchitis, irritable bowel syndrome, constipation, or metabolic syndrome who receive FMT, the evidence includes a small number of case series and/or case reports. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Data are available for only a limited number of patients and there is a lack of comparative studies. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests from Blue Cross Blue Shield Association, input was received from 5 clinicians associated with 3 physician specialty societies and from 5 clinicians at 2 academic

medical centers in 2014. There was near consensus that fecal transplantation may be considered medically necessary for treating at least some patients with *Clostridium difficile* infection. There was also near consensus that fecal microbiota transplant (FMT) is considered investigational for inflammatory bowel disease; moreover, there was a consensus that FMT is considered investigational for conditions other than those previously mentioned. Input was mixed on criteria for selecting patients with *Clostridium difficile* infection for fecal transplantation; in general, the number of FMT recurrences was considered an important criterion. There was near consensus among reviewers that there are potential safety concerns associated with FMT, and that these concerns should be studied further before the procedure is offered routinely in clinical practice.

Practice Guidelines and Position Statements

The American College of Gastroenterology (2013) published guidelines on diagnosis, treatment, and prevention of *Clostridium difficile* infection (CDI).²⁶ The guidelines addressed fecal microbiota transplant for treatment of 3 or more CDI recurrences, as follows:

“If there is a third recurrence after a pulsed vancomycin regimen, fecal microbiota transplant (FMT) should be considered. (Conditional recommendation, moderate-quality evidence)”

For treatment of 1 to 2 CDI recurrences, the guidelines recommended:

“The first recurrence of CDI can be treated with the same regimen that was used for the initial episode. If severe, however, vancomycin should be used. The second recurrence should be treated with a pulsed vancomycin regimen. (Conditional recommendation, low-quality evidence)”

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02526849	A Randomized Controlled Study of Efficacy, Safety and Durability of Fecal Microbiota Transplantation in Adult Patients With Slow Transit Constipation	100	Jun 2017 (ongoing)
NCT02255305	Fecal Microbiota Transplantation Versus Standard Medical Therapy for Initial Treatment of Recurrent <i>Clostridium Difficile</i> Infection	60	Dec 2019
NCT02328547	Multicenter, Randomized, Double-blinded, Placebo-controlled Trial of Fecal Microbiota Transplantation (FMT) for Diarrhea-Predominant Irritable Bowel Syndrome (IBS-D)	48	Mar 2018
NCT02743234	Fecal Microbiota Transplantation for Relapsing <i>Clostridium Difficile</i> Infection (FACIT)	64	Apr 2019
NCT02801656	Fecal Microbiota Transplantation for Primary <i>Clostridium Difficile</i> Diarrhea	130	Dec 2019
Unpublished			
NCT01896635	Fecal Microbiota Transplantation in Ulcerative Colitis (FOCUS)	81	Aug 2016 (completed)

NCT: national clinical trial.

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Documentation for Clinical Review

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
 - Number of episodes of recurrent *Clostridium difficile* infection
 - Past treatment regimen(s) including antibiotic used and response(s)
- Procedure report(s)

Post Service

- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

MN/IE

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or

when the code describes application of a product in the position statement that is investigational.

Type	Code	Description
	0107U	Clostridium difficile toxin(s) antigen detection by immunoassay technique, stool, qualitative, multiple-step method (Code effective 10/1/2019)
	44705	Preparation of fecal microbiota for instillation, including assessment of donor specimen
HCPCS	G0455	Preparation with instillation of fecal microbiota by any method, including assessment of donor specimen
ICD-10 Procedure	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
09/30/2014	BCBSA Medical Policy adoption	Medical Policy Committee
09/30/2015	Policy revision without position change	Medical Policy Committee
03/01/2016	Policy revision without position change	Medical Policy Committee
12/01/2016	Policy revision without position change	Medical Policy Committee
10/01/2017	Policy revision without position change	Medical Policy Committee
01/01/2018	Policy revision without position change	Medical Policy Committee
01/01/2019	Policy revision without position change	Medical Policy Committee
11/01/2019	Coding update	Administrative Review

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.