MEDICAL POLICY

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MEDICAL POLICY DETAILS	
Medical Policy Title	**Fecal Microbiota Transplantation**
Policy Number	**2.01.48**
Category	**Technology Assessment**
Original Effective Date	**08/16/12**
Committee Approval Date	**08/15/13, 07/17/14, 07/16/15, 06/16/16, 06/15/17, 09/20/18, 09/19/19, 09/17/20, 09/16/21, 09/15/22, 09/21/23**
Current Effective Date	**09/21/23**
Archived Date	**N/A**
Archive Review Date	**N/A**
Product Disclaimer	• *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan or Child Health Plus product), medical policy criteria apply to the benefit.* • *If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.* • *If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.* • *If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.*

POLICY STATEMENT

I. Based upon our criteria and assessment of the peer-reviewed literature, fecal microbiota transplantation (FMT) (also known as fecal bacteriotherapy) has been medically proven to be effective and, therefore, is considered **medically appropriate** for the treatment of recurrent *Clostridioides* (formerly *Clostridium) difficile* infection (CDI), when **ALL** the following criteria have been met:
   A. Patient has had at least three (3) episodes of recurrent CDI (an initial episode and two recurrences) despite the standard antibiotic therapy;
   B. Patient is not immunocompromised; **and**
   C. The appropriate donor stool screening has been completed (see guidelines below).

II. Based upon our criteria and assessment of the peer-reviewed literature, fecal microbiota transplantation (FMT) has not been medically proven to be effective and, therefore, is considered **investigational** for all other indications, including but not limited to, the first line treatment for CDI or the treatment of inflammatory bowel disease.

Refer to Corporate Medical Policy #11.01.03 Experimental or Investigational Services

This policy does not address the pharmaceutical treatment of CDI (e.g., Rebyota [fecal microbiota, live – jslm]). Refer to the Pharmacy Management Drug Policy Pharmacy-63

POLICY GUIDELINES

I. Careful evaluation of all candidate stool donors is important to minimize the risk for infection and to maximize the likelihood of successful treatment outcome; therefore, the designated stool donor should undergo screening of blood and feces prior to the stool donation (McDonald et al., 2017) (Bakken et al, 2011).

II. The U.S. Food and Drug Administration (FDA) has issued safety communication alerts to inform health care providers and patients of the potential risk of serious or life-threatening infections with the use of FMT. The FDA

indicates the need for additional screening protections of donor stool (e.g., multi-drug resistant organisms [MDROs], *Escherichia coli*, SARS-Co-V-2, COVID-19, and monkeypox virus (FDA, 2019, 2020, 2022).

DESCRIPTION

To date, the major potential clinical application of FMT is in the treatment of *Clostridioides 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. Disruption of the normal colonic flora occurs most commonly following the administration of oral, parenteral, or topical antibiotics. Standard treatment for CDI is antibiotic therapy; however, symptoms recur in up to 35% of patients.

Recurrent CDI is a difficult and common challenge associated with the CDI. An initial episode of CDI is followed by a recurrent episode, and the risk of recurrence significantly increases after two or more recurrences. Risk factors for CDI recurrence include the administration of other antibiotics during or after initial treatment of CDI, a defective humoral immune response against C. *difficile* toxins, advancing age, increasingly severe underlying disease, and continued use of PPIs has been associated with an increased risk of recurrence (McDonald et al., 2018).

FMT is a proposed treatment for refractory CDI, which involves the administration of intestinal microorganisms via the transfer of stool from a healthy person into a diseased patient, with the intent of restoring normal intestinal flora. FMT can be administered as a liquid suspension into a patient's upper gastrointestinal tract through a nasogastric tube or gastroscopy, into the colon through a colonoscope or rectal catheter, or orally via capsules.

FMT is being investigated as a potential treatment of conditions in which altered colonic flora may play a role (e.g., inflammatory bowel disease, irritable bowel syndrome, idiopathic constipation) and non-gastrointestinal diseases (e.g., multiple sclerosis, obesity, autism, type 2 diabetes mellitus, fatty liver, and chronic fatigue syndrome). However, for these conditions, the contribution of alterations in colonic flora to the disorder is uncertain or controversial.

The principal potential risk associated with FMT is transmission of contagious agents contained in the donor stool. There are risks of transmitting agents that do not cause a disease immediately after transplantation but may complicate the treatment of the patient in the future. The fecal transplant material (donor stool) must be appropriately screened for infectious diseases and pathogens.

Due to the potential for serious adverse reactions with FMT, the U.S. Food and Drug Administration (FDA) has determined that additional protections are needed for use of FMT. Along with FDA guidelines for donors of human cells, tissues, and cellular- and tissue-based products (FDA, 2007), the FDA has published several safety alerts for additional screening for other diseases (FDA, 2019, 2020, and 2022). Stool testing should include, but may not be limited to, routine bacterial culture for enteric pathogens; C. *difficile* toxin; fecal Giardia antigen; fecal Cryptosporidium antigen; acid-fast stain for Cyclospora and Isospora (acid-fast for cryptosporidium if no antigen is available); ova and parasites; and Heliobacter pylori fecal antigen. In addition, the FDA has recommended that donor stool should be specifically tested for multi-drug-resistant organisms (MDROs), including extended-spectrum, beta-lactamase-producing Enterobacteriaceae; vancomycin-resistant enterococci; carbapenem-resistant Enterobacteriaceae; and methicillin-resistant staphylococcus aureus), and should not be used, if positive. Serologic testing should include blood testing for HIV (type I and II); testing for hepatitis A, B and C; and rapid plasma regain (PR) and florescent treponemal antibody absorption test (FTA-ABS) for syphilis.

RATIONALE

Based on published outcomes from case series/case reports and randomized controlled trials (RCT), FMT is a highly effective therapy for refractory, recurrent CDI when standard treatments have failed. Overall, FMT resulted in resolution for 92% of patients (89% after a single treatment). FMT as a first-line therapy for CDI is currently being investigated but has not been studied sufficiently.

FMT has been shown to have some effect in alleviating symptoms in patients with other, difficult-to-treat conditions (e.g., irritable bowel syndrome, inflammatory bowel diseases such as Crohn's disease and ulcerative colitis. However, most studies of these diseases mainly consist of case series, case reports, and cohort studies. While outcome data are promising, there is insufficient evidence currently to implement FMT as a treatment regimen. Additional randomized, control trials

and longer-term studies are still needed, to determine efficacy and safety profiles for patients with diseases other than recurrent CDI.

Irritable Bowel Syndrome (IBS)

For individuals who have IBS who receive FMT, the evidence includes systematic reviews and RCTs. One systematic review with meta-analysis involving 19 studies reported that FMT was superior to placebo in improving quality of life through 24 weeks; however, there was no difference in the IBS Severity Scoring System or symptom improvement between FMT and placebo (Elhusein et al., 2022). Another systematic review with meta-analysis reviewed 5 RCTs and reported mixed outcomes for FMT in patients with IBS (Ianioro et al., 2019). When all studies were pooled, nonet benefit was found for active FMT.

Madsen et al (2021) reported the results of a double-blind RCT evaluating the efficacy of FMT capsules (n=26) versus placebo capsules (n=25) in patients with moderate-to-severe IBS (IBS-SSS score ≥175 points). Both groups administered capsules for 12 days and patients were allowed to continue any concomitant IBS medications, including laxatives or agents for constipation. Patients tracked their symptoms in a diary and were followed for 6 months. The primary outcome was not specified, but investigators evaluated abdominal pain, stool frequency, and stool form. Subgroup analyses by IBS subtype were not performed.

Holvoet et al (2020) reported the results of a double-blind RCT evaluating the efficacy of FMT in patients with IBS-D or IBS-M and severe bloating (mean abdominal bloating sub-score of ≥3). The intervention group (n=43) received donor FMT via the nasojejunal route and the control group (n=19) received autologous FMT placebo via the same route. A daily symptom diary was used to assess IBS-related symptoms and improvement in IBS symptoms at 12 weeks was the primary outcome of the trial. After a single FMT, more patients in the treatment group versus placebo reported efficacy for more than 1 year (21% vs. 5%). A second FMT reduced symptoms in 67% of patients with an initial response to donor stool, but not in patients with a prior non-response.

Lahtinen et al (2020) reported the results of a double-blind RCT evaluating the efficacy of FMT in patients with IBS. The intervention group (n=23) received donor FMT via colonoscopy and the control group (n=26) received autologous FMT placebo via the same route. Approximately 35% of patients experienced adverse events with no significant difference between groups.

Inflammatory Bowel Disease (IBD)

For individuals who have IBD who receive FMT, the evidence includes systematic reviews and RCTs. Systematic reviews have generally shown favorable clinical remission and response with FMT in patients with IBD while acknowledging limitations (e.g., small sample size, short term follow up, and/or lack of control arm) and the need for further RCTs with long-term follow-ups to assess long-term effectiveness and safety (Wu et al., 2022; Tan et al., 2022; Zhou et al., 2021, and Fehily et al., 2021).

Randomized controlled trials have not resulted in sufficient evidence to permit conclusions on the efficacy of FMT for IBD. All studies acknowledged study strengths and limitations that require further research. Additionally, questions remain about the optimal route of administration, donor characteristics, and the number of transplants.

Shabat et al (2022) published results from the CRAFT UC trial, a single, blinded, three-arm RCT in Italy that concluded the ulcerative colitis exclusion diet (UCED) alone arm appeared to achieve higher clinical remission and mucosal healing than single donor FT with or without diet. The study was terminated early due to futility. Crothers et al (2021) published results of a small (n=12), single-center, placebo-controlled RCT in the US investigating long-term encapsulated delivery of FMT in patients with mild to moderate ulcerative colitis (UC). Fang et al (2021) published results of a small (n=10), single-center, open-label RCT in China investigating monotherapy with FMT for recurrent UC. Sokol et al (2020) published results of a small (n=8), multicenter, single-blind, placebo-controlled RCT in France investigating endoscopic delivery of FMT in patients with Crohn's disease (CD). Sood et al (2019) published results of a 48-week, small (n=8), single-center RCT in India evaluating maintenance FMT (n=31) versus placebo (n=30) in patients with UC receiving standard of care therapies who are in clinical remission after prior FMT sessions.

Professional Guidelines

In 2021, the ACG published a guideline on the management of *Clostridioides difficile* infection (CDI). This guideline makes the following recommendations:

- "We suggest fecal microbiota transplantation (FMT) be considered for patients with severe and fulminant CDI refractory to antibiotic therapy, particularly, when patients are deemed poor surgical candidates (strong recommendation, low quality of evidence)."
- "We recommend patients experiencing their second or further recurrence of CDI be treated with FMT to prevent further recurrences (strong recommendation, moderate quality of evidence)."
- "We recommend FMT be delivered through colonoscopy (strong recommendation, moderate quality of evidence) or capsules (strong recommendation, moderate quality of evidence) for treatment of CDI; we suggest delivery by enema if other methods are unavailable (conditional recommendation, low quality of evidence)."
- "We suggest repeat FMT for patients experiencing a recurrence of CDI within 8 weeks of an initial FMT (conditional recommendation, very low quality of evidence)."
- "FMT should be considered for recurrent CDI in patients with IBD (strong recommendation, very low quality of evidence)."

In 2021, the ACG published a guideline on the management of irritable bowel syndrome (IBS). This guideline recommended against the use of fecal transplant for the treatment of global IBS symptoms (strong recommendation; very low quality of evidence) (Lacy et al., 2021).

In 2019, the American College of Gastroenterology (ACG) published guidelines on the management of adults with ulcerative colitis (UC), noting that "fecal microbiota transplantation (FMT) requires more study and clarification of treatment before use as therapy for UC" (Rubin et al., 2019).

In 2021, the American Society of Colon and Rectal Surgeons (ASCRS) published a guideline on the management of CDI, stating:

- "Patients with recurrent or refractory CDI should typically be considered for fecal bacteriotherapy (e.g., intestinal microbiota transplantation) if conventional measures, including appropriate antibiotic treatment, have failed (Grade of recommendation: Strong recommendation based on moderate-quality evidence, 1B)."
- "Patients with 3 or more CDI episodes can be managed with a vancomycin tapered and pulsed course or fidaxomicin followed by a microbiome-based therapy such as fecal microbiota transplantation."
- "In general, conventional antibiotic treatment should be used for at least 2 recurrences (ie, 3 CD episodes) before offering fecal microbiota transplantation."

In 2017, the Infectious Diseases Society of America and Society for Healthcare Epidemiology of America updated clinical practice guidelines for the diagnosis and treatment of CDI in children and adults (McDonald et al., 2018) and a 2021 focused update echoes the previous recommendations (Johnson et al., 2021):

- "Consider fecal microbiota transplantation for pediatric patients with multiple recurrences of CD following standard antibiotic treatments. (Weak recommendation, very low quality of evidence)"
- "Fecal microbiota transplantation is recommended for patients with multiple recurrences of CDI who have failed appropriate antibiotic treatments. (Strong recommendation, moderate quality of evidence)"
- "Potential candidates for FMT include patients with multiple recurrences of CDI who have failed to resolve their infection despite treatment attempts with antibiotic agents targeting CDI. Although there are no data to indicate how many antibiotic treatments should be attempted before referral for FMT, the opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (i.e., 3 CD episodes) should be tried."

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*
- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).*

CPT Codes

Code	Description
44705	Preparation of fecal microbiota for instillation, including assessment of donor specimen
0780T	Instillation of fecal microbiota suspension via rectal enema into lower gastrointestinal tract *(Effective date 01/01/23)*

HCPCS Codes

Code	Description
G0455	Preparation with instillation of fecal microbiota by any method, including assessment of donor specimen

ICD10 Codes

Code	Description
A04.7 - A04.72	Enterocolitis due to Clostridium difficile (code range)

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*Key Article

KEY WORDS

Fecal microbiota therapy (FMT), Fecal transfusion, Fecal transplant, Human probiotic infusion (HPI), Intestinal microbiota Transplantation (IMT), Microbiome, Stool transplant, inflammatory bowel disease, irritable bowel disease

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

Based upon our review, fecal bacteriotherapy is not addressed in National or Regional CMS coverage determinations or policies.