# MEDICAL POLICY

| MEDICAL POLICY DETAILS | |
|---|---|
| **Medical Policy Title** | **Fecal Microbiota Transplantation** |
| **Policy Number** | **2.01.48** |
| **Category** | **Technology Assessment** |
| **Original Effective Date** | **08/16/12** |
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| **Current Effective Date** | **09/19/24** |
| **Archived Date** | **N/A** |
| **Archive Review Date** | **N/A** |
| **Product Disclaimer** | • *Services are contract dependent; if a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.*<br>• *If a commercial product (including an Essential Plan or Child Health Plus product), medical policy criteria apply to the benefit.*<br>• *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.*<br>• *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.*<br>• *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) has been medically proven to be effective and, therefore, is considered **medically appropriate** for the treatment of adults with recurrent *Clostridioides difficile* infection (CDI), when **BOTH** the following criteria have been met:
   A. Patient has a history of two (2) or more recurrences after the initial episode, despite standard antibiotic treatment (total of three [3] or more episodes);
   B. The appropriate donor stool screening has been completed.

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, please refer to the following Pharmacy Management Drug Policies:*

- *Pharmacy-63 Clinical Review Prior Authorization (CRPA) Medical for Rebyota (fecal microbiota, live - jslm)*
- *Pharmacy-09 Clinical Review Prior Authorization (CRPA) Rx for Vowst (fecal microbiota spores, live-brpk)*

## POLICY GUIDELINES

I. FMT should be performed with appropriately screened donor stool. Rigorous evaluation of all candidate stool donors is important to minimize the risk for transmitting infection and to maximize the likelihood of successful treatment outcome.

II. Although multiple professional guidelines recommend conventional FMT to prevent CDI in patients with a history of two (2) or more recurrences, the American Gastroenterological Association (AGA) intentionally refrains from this

limit as some patients are at increased risk of recurrence or morbid recurrence and may benefit from FMT after the initial CDI episode or first recurrence (Peery et al., 2024).

III. Fecal microbiota products that are used to diagnose, prevent, treat, or cure a disease or condition in humans are biological products and the Center for Biologics Evaluation and Research has oversight of the safety and effectiveness of these products. The U.S. Food and Drug Administration (FDA) issued safety alerts on the potential risk of serious or life-threatening infections with the use of FMT, and additional safety protections for screening protections of donor stool (e.g., multi-drug resistant organisms [MDROs], Escherichia coli, SARS-Co-V-2, COVID-19, and monkeypox virus (FDA, 2023).

## DESCRIPTION

Fecal microbiota–based therapies include conventional fecal microbiota transplant (FMT) and U.S. Food and Drug Administration–approved pharmaceutical treatment of CDI (e.g., fecal microbiota live-jslm and fecal microbiota spores live-brpk. This policy addresses FMT only.

Fecal microbiota transplantation (FMT), also called fecal bacteriotherapy, donor feces infusion, and intestinal microbiota transplantation is a proposed treatment for refractory *Clostridioides difficile* (*C difficile*) infection (CDI). FMT 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.

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.

To date, the major potential clinical application of FMT is for patients who have treatment-refractory 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 an initial and subsequent recurrences of CDI is antibiotic therapy.

Recurrent CDI is defined by resolution of CDI symptoms while on appropriate therapy, followed by reappearance of symptoms, usually within two months of discontinuing treatment. Recurrent CDI is 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).

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.

## RATIONALE

Based on published outcomes from case series/case reports and randomized controlled trials (RCT), FMT is a highly effective therapy for recurrent CDI when standard treatments have failed. In 2023, Minkoff et al. conducted a Cochrane review by compared donor FMT (dFMT) to control for the management of recurrent CDI in immunocompetent individuals, six RCTs were included (N=320); the route of administration was the upper gastrointestinal tract via a nasoduodenal tube in 1 study, enema only in 2 studies, colonoscopic only in 2 studies, and either nasojejunal or colonoscopic delivery in 1 study. The controls included vancomycin (5 studies), fidaxomicin (1 study), autologous FMT (aFMT]) (1 study), and rectal bacteriotherapy (1 study). Results demonstrated that dFMT significantly increased the

likelihood of recurrent CDI resolution when compared to control. The risk of serious adverse events or mortality did not differ between dFMT and control groups.

FMT as a first-line therapy for CDI is currently being investigated however, the evidence is insufficient to determine that the therapy results in an improvement in the net health outcome.

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 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 RTCs and longer-term studies are still needed, to determine efficacy and safety profiles for patients with diseases other than recurrent CDI (e.g., irritable bowel syndrome and inflammatory bowel disease).

Irritable Bowel Syndrome (IBS)

For individuals who have IBS who receive FMT, the evidence includes systematic reviews and RCTs.

Wang et al. (2023) performed a systematic review and meta-analysis of nine RCTs (n = 516) to investigate the efficacy and safety of FMT for people diagnosed with IBS. The route of FMT administration included nasojejunal probe, gastroscope, colonoscopy, and oral capsules. Results demonstrated that when compared to placebo, a single FMT significantly decreased the IBS-SSS score (primary outcome) at months 1, 3, 6, 24, and 36. The clinical response rate was also significantly improved with FMT at months 3, 24, and 36 months, as was the IBS-QoL score at months 3, 24, and 36. FMT did not increase the risk of adverse events. The authors conclude that a single FMT is effective and safe for patients with IBS, however, the authors noted that some factors may affect the effectiveness of FMT, and that the relationship between the gut microbiome and the effect of FMT for IBS is still unclear.

A 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 (Ianiro 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).

A 2023 Cochrane review by Imdad et al. included 12 studies (N=550) that evaluated the efficacy and safety of FMT for the treatment of IBD. The follow-up duration across studies ranged from 6 to 12 weeks for the evaluation of induction and from 48 to 56 weeks for the evaluation of remission. Comparators included autologous FMT, placebo, standard medication, and no intervention. FMT was administered in the form of capsules or suspensions for oral administration, nasoduodenal tube, enema, or colonoscopy. The results demonstrated that FMT significantly increased the likelihood of induction of clinical remission in UC compared to the control (risk ratio, 1.79; 95% CI, 1.13 to 2.84). However, FMT did not significantly improve the likelihood of induction of endoscopic remission. FMT did not significantly improve the maintenance of clinical or endoscopic remission of UC. There were no statistically significant differences in the rates of adverse events or serious adverse events.

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 Society Guidelines

In 2024, the AGA developed a clinical practice guideline to provide recommendations on the use of fecal microbiota–based therapies for select gastrointestinal diseases (Peery et al., 2024). The guideline notes that these recommendations supersede prior AGA guideline recommendations around FMT in ulcerative colitis (UC). The AGA:

- suggests the use of fecal microbiota-based therapies upon completion of standard of care antibiotics over no fecal microbiota–based therapies in:
  - immunocompetent adults with recurrent C *difficile* infection (Conditional recommendation, low certainty evidence
  - mildly or moderately immunocompromised adults with recurrent C *difficile* infection, (Conditional recommendation, low certainty evidence)
- suggests against the use of fecal microbiota–based therapies upon completion of standard of care antibiotics over no fecal microbiota–based therapies for severely immunocompromised adults with recurrent C difficile infection. (Conditional recommendation, very low certainty of evidence)
- suggests the use of conventional fecal microbiota transplant over no fecal microbiota transplant in adults hospitalized with severe or fulminant C *difficile* infection not responding to antimicrobial therapy, (Conditional recommendation, low certainty of evidence)
- suggests against the use of conventional FMT except in the context of clinical trial in adults with ulcerative colitis, Crohn's disease, pouchitis, and irritable bowel syndrome. (Conditional recommendation, very low certainty of evidence)

The AGA defines immunocompromised as:

- Mildly or moderately immunocompromised patients are immunocompromised but do not meet the definition of severe.

- Severely immunocompromised patients are those patients receiving active cytotoxic therapy for solid tumors and hematologic malignancies, patients who have received chimeric antigen receptor T-cell therapy or hematopoietic cell transplant (only when neutropenic), any neutropenia, patients with severe primary immunodeficiency, patients with advanced or untreated HIV infection (CD4 counts <200/mm$^3$, AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV).

The AGA did not identify any RCTs or comparative observational studies that directly compared FMT with placebo or standard of care in immunocompromised adults with nonsevere, nonfulminant recurrent CDI. Observational studies suggest the effect of FMT on reducing the risk of recurrence was similar to the immunocompetent adults with recurrent CDI and that FMT appears to be well tolerated with no differences in the risk of serious adverse events.

The American College of Gastroenterology (ACG) clinical practice guideline (Kelly et al., 2021) noted that conventional FMT is considered the best treatment option for multiply recurrent CDI and that rigorous donor screening is critical in immunocompromised populations. Stating that although there has been concern that immunocompromised patients may be at higher risk of infectious complications after FMT, this concern has not been corroborated by published studies to date. Serious adverse events have rarely been reported, even among immunocompromised patients, although risk of infection is an important consideration.

In 2021, the American College of Gastroenterology (ACG) published a guideline on the management of *Clostridioides difficile* infection (Kelly et al., 2021). The ACG considers FMT to the be the best treatment option for multiple recurrent CDI, including immunocompromised patients who are seronegative for cytomegalovirus (CMV) and Epstein-Barr virus (EBV). The 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 recommends against the use of fecal transplant for the treatment of global irritable bowel syndrome (IBS) symptoms. (strong recommendation; very low quality of evidence) (Lacy et al., 2021).

In 2019, the ACG recommends against the use of fecal transplant adults with ulcerative colitis (UC), noting 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 (Poylin et al., 2021):

- 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 three (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 two (2) recurrences (i.e., 3 CD episodes) before offering fecal microbiota transplantation.

In 2021, the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) published a focused update guideline echoing the 2017 recommendations for FMT. FMT is recommended only for patients with multiple recurrences of CDI who have failed appropriate antibiotic treatments and where appropriate

screening of donor and donor fecal specimens have been performed, in accordance with these newer FDA recommendations (Johnson et al., 2021).

The American College of Gastroenterology (ACG) clinical practice guideline (Kelly et al., 2021) noted that conventional FMT is considered the best treatment option for multiply recurrent CDI and that rigorous donor screening is critical in immunocompromised populations. Stating that although there has been concern that immunocompromised patients may be at higher risk of infectious complications after FMT, this concern has not been corroborated by published studies to date. Serious adverse events have rarely been reported, even among immunocompromised patients, although risk of infection is an important consideration.

In 2018, the IDSA and SHEA published clinical practice guidelines for the diagnosis and treatment of CDI in children and adults (McDonald et al., 2018) indicating:

- 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 CDI 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 |



**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 or fecal microbiota transplant are not addressed in National or Regional CMS coverage determinations or policies.