MEDICAL POLICY

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Medical Policy Title	**Fecal Microbiota Transplantation**
Policy Number	**2.01.48**
Current Effective Date	**September 18, 2025**
Next Review Date	**September 2026**

Our medical policies are based on the assessment of evidence based, peer-reviewed literature, and professional guidelines. Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract. (Link to Product Disclaimer)

POLICY STATEMENT(S)

I. Fecal microbiota transplantation (FMT) 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. Fecal microbiota transplantation (FMT) 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.

RELATED POLICIES

Corporate Medical Policy

11.01.03 Experimental or Investigational Services

Pharmacy Policy

Pharmacy-09 Clinical Review Prior Authorization (CRPA) Rx, for Vowst (fecal microbiota spores, live-brpk)

Pharmacy-63 Clinical Review Prior Authorization (CRPA) Medical, for Rebyota (fecal microbiota, live - jslm)

POLICY GUIDELINE(S)

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 2024).

DESCRIPTION

Fecal microbiota–based therapies include conventional fecal microbiota transplant (FMT), and U.S. Food and Drug Administration (FDA) 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 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.

SUPPORTIVE LITERATURE

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.

FMT as a first-line therapy for CDI is currently being investigated. The evidence is insufficient to determine that first-line FMT therapy results in an improvement in the net health outcome. The American Gastroenterological Association's clinical practice guidelines indicate that trials are needed

to assess FMT therapies as primary prevention in patients at high risk of CDI and as first-line treatment after short course of anti-CDI therapy (Perry 2024).

Camacho-Ortiz et al (2017) conducted a small, open, two-arm pilot RCT to evaluate the impact of fecal donor-unrelated donor mix (FMT-FURM) transplantation as first-line therapy for CDI. Patients were randomized in a 1: 1 ratio to either oral vancomycin (n=10) or FMT-FURM (n=9). From each patient, a fecal sample was obtained at days 0, 3, and 7 after treatment. Symptoms resolved in 8/9 patients (88.9%) in the vancomycin group, while symptoms resolved in 4/7 patients (57.1%) after the first FMT-FURM dose (P = 0.26) and in 5/7 patients (71.4%) after the second dose (P = 0.55).

Baunwall et al (2022) conducted the EarlyFMT trial, a small randomized, double-blind, placebo-trial to compare the efficacy and safety of fecal microbiota transplantation compared with placebo after vancomycin for first or second C difficile infection. Eligible patients were aged 18 years or older with first or second C difficile infection. Patients were randomly assigned (1:1) to fecal microbiota transplantation (n=21) or placebo (n=21) administered on day 1 and between day 3 and 7, after they had received 125 mg oral vancomycin four times daily for 10 days. The trial was stopped prematurely, after the 8-week interim analysis, for ethical reasons. Significantly lower rate of resolution was identified in the placebo group compared with the fecal microbiota transplantation group (Haybittle-Peto boundary limit p<0.001). Resolution of C difficile-associated diarrhea week 8 was achieved in 19 of 21 patients in the FMT group and seven of 21 patients in the placebo group (p=0.00031). The absolute risk reduction for recurrence following fecal microbiota transplantation compared with placebo was 57%. The study examined the additive effect of FMT after vancomycin; therefore, the authors indicated that the results should not be interpreted as evidence for FMT alone, but for its use in combination with antibiotics. The authors concluded that FMT after vancomycin is superior to standard-of-care vancomycin alone in achieving sustained cure of first or second C difficile infection.

Irritable Bowel Syndrome (IBS)

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.

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.

Elhusein et al (2022) performed 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. Another systematic review with meta-analysis reviewed 5 randomized control trials (RCTs) and reported mixed outcomes for FMT in patients with IBS (Ianiro 2019). When all studies were pooled, nonet benefit was found for active FMT.

El-Salhy et al (2022) published 3-year follow-up results of a double-blind, placebo-controlled study that randomized 165 patients with IBS, which was published in 2020 by the same researcher. The current study included 125 patients (n=38 from the placebo group; n=42 who received 30 grams (g) of donor feces; n=45 who received 60-g of donor feces). Response rates were 26.3%, 69.1%, and 77.8% in the placebo, 30-g, and 60-g groups, respectively, at 2 years after FMT, and 27.0%, 64.9%, and 71.8%, respectively, at 3 years after FMT. The response rates were significantly higher in the 30-g and 60-g groups than in the placebo group. Patients in the 30-g and 60-g groups had significantly fewer IBS symptoms and fatigue, and a greater quality of life both at 2 and 3 years after FMT. No long-term adverse events were recorded.

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.

Inflammatory Bowel Disease – Crohn's Disease

Sokol et al (2020) conducted a pilot RCT investigating endoscopic delivery of FMT in patients with Crohn's disease (CD). This small, multicenter, single-blind, placebo-controlled RCT was conducted in France and randomized patients to FMT (n=8) and sham transplantation (n=9). The primary endpoint was the colonization of donor microbiota at week 6, which was not reached by any patient. The rate of clinical flares in the 24 weeks following FMT was a secondary endpoint in the study. Only those patients who achieved clinical remission within the 3 weeks following the commencement of corticosteroids were randomized to treatment or placebo. The treatment group received FMT after colon cleansing with polyethylene glycol. The steroid-free clinical remission rate at 10 and 24 weeks was 44.4% (4/9) and 33.3% (3/9) in the sham transplantation group and 87.5% (7/8) and 50.0% (4/8; one patient loss of follow-up while in remission at week 12 and considered in flare at week 24) in the FMT group. Crohn's Disease Endoscopic Index of Severity decreased 6 weeks after FMT (p =

0.03) but not after sham transplantation (p = 0.8). Conversely, the CRP level increased 6 weeks after sham transplantation (p = 0.008) but not after FMT (p = 0.5). None of the adverse events observed in the trial was related to FMT. These results must be confirmed in larger studies.

Zhou et al (2023) conducted a systematic review and meta-analysis to examine the safety and effectiveness of FMT in patients with CD. Eleven cohort studies and one RCT involving 228 patients were included. In a meta-analysis, the pooled proportion of adult patients with active CD that achieved clinical remission 2 to 4 weeks after FMT was 57%. Results showed that FMT reduced Crohn's disease activity index scores 4 to 8 weeks after FMT. Subgroup analyses showed no difference between FMT methodologies, except for pre-FMT treatment with antibiotics (P = 0.02). Most adverse events were self-limiting and disappeared spontaneously within hours or days after FMT. The authors concluded that FMT could be a promising therapy in the short-term treatment of active CD; however, more placebo-controlled RCTs, with long-term-up follow-up, are necessary.

Kao et al (2024) conducted the first placebo-controlled, randomized, multicenter trial to evaluate the efficacy of FMT on patients with active Crohn's disease (CD). Patients with mild-to-moderate CD were randomized 1:1 and received FMT (n=17) or placebo (n=12). The first treatment was administered by colonoscopy followed by weekly oral capsules for 7 weeks. Primary end point was clinical and endoscopic remission at week 8. Secondary outcomes included clinical and endoscopic response, adverse events, and health-related quality of life using generic and disease-specific instruments. At week 8, 0% (0/15) of patients in the FMT group versus 8.3% (1/11) in the placebo group reached the primary end point of combined clinical and endoscopic remission as per protocol analysis. There were no differences between the groups in clinical or endoscopic responses. One patient in each group had worsening of CD. Although both groups experienced statistically significant improvements in health-related quality of life, only the FMT group had a significant decrease in activity impairment. FMT was not effective at inducing clinical and endoscopic remission in CD using the FMT regimen in this study. Future studies should use an adequately powered multicenter trial and use a longer intervention period to improve the clinical efficacy.

Inflammatory Bowel Disease – Ulcerative Colitis

Several small single-center studies have been conducted. 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 ulcerative colitis (UC) receiving standard of care therapies who are in clinical remission after prior FMT sessions. 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 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.

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.

A Cochrane review (Imdad 2023) included 12 studies (N=550 participants) 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 showed that FMT may increase rates of induction of clinical remission in UC compared to the control (risk ratio, 1.79; 95% CI, 1.13 to 2.84; low certainty). 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. The authors concluded that FMT may increase the proportion of people with active UC who achieve clinical and endoscopic remission. The evidence was very uncertain about whether use of FMT in people with active UC impacted the risk of serious adverse events or improvement in quality of life. The evidence was also very uncertain about the use of FMT for maintenance of remission in people with UC, as well as induction and maintenance of remission in people with CD, and no conclusive statements could be made in this regard. Further studies are needed to address the beneficial effects and safety profile of FMT in adults and children with active UC and CD, as well as its potential to promote longer-term maintenance of remission in UC and CD.

Caenepeel et al (2025) conducted a multi-centric, double-blind, sham-controlled, randomized trial with repeated FMTs to induce clinical remission in patients with active UC through rigorous donor screening and by applying an anerobic workflow to create cell-density-standardized FMT preparations. Thereby, targeting the identification and characterization of potentially highly effective donors (also referred to as 'superdonors') for treatment of UC. Patients (n=66) were randomized to receive 4 infusions of allogenic donor or autologous FMT (allogenic FMT, n=30; and autologous FMT, n=36). At week 8, respectively, 3 and 5 patients reached the primary endpoint of steroid-free clinical remission (P= .72), indicating no treatment difference of at least 5% in favor of allogenic FMT. The trial did not meet its primary endpoint of increased steroid-free clinical remission and was halted at 66% of intended inclusions due to futility. The authors concluded, strict allogenic donor selection could not increase the efficacy of FMT in active UC. Nevertheless, key lessons for future research were learned.

Gefen et al (2025) indicated that FMT has been shown to restore gut microbiome composition with an acceptable safety profile. A systematic review and meta-analysis of randomized control trials was conducted to assess the efficacy of FMT in inducing UC remission. A total of 14 studies (n= 600 patients with a median age of 40.7 years) were assessed. FMT was used in 299 patients and associated with significantly higher odds of combined clinical and endoscopic remission (OR 2.25, 95% CI 1.54, 3.3; p<0.0001), clinical remission (p-0.0003) and endoscopic remission (p=0.011). Compared with baseline, FMT was more effective when biologics, steroids, or methotrexate were used as pre-FMT treatment. Oral delivery of FMT and pooled donors led to higher odds of remission. On meta-regression, pooled donors and methotrexate pre-treatment were associated with an increased likelihood of remission. Current evidence shows that oral delivery of FMT and multi-donor FMT may confer better results than transanal delivery and single-donor FMT. Standardization of the administration method, dosage, donors, and pre-FMT treatment is needed.

Other Indications

FMT has been shown to have some effect in alleviating symptoms in patients with other difficult-to-treat conditions (e.g., diabetes, obesity and metabolic syndrome, neurological disorders); 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.

Pediatric Population

Ulcerative colitis (UC) and FMT in children was studied in the first pilot RCT, the Pediatric FEcal microbiota Transplant in ulcerative Colitis (PediFETCh) (Pai 2021). During a 36-month study period, patients aged 4 to 17 years with active UC for less than 1-year were randomized to FMT (n=13) or placebo (n=12) arms. Seven patients randomized to the placebo arm crossed over to the open-label arm, and six patients completed the 30-week arm. The study did not reach the primary feasibility outcome of achieving recruitment targets (50 patients over 2 years), which suggests that recruitment remains the most significant challenge. There had several study limitations, however, the authors indicated that this pilot RCT offers evidence that FMT may have an important role in improving symptoms and inflammatory indices in the pediatric UC.

Tun et al (2022) performed a systematic review and meta-analysis to assess the efficacy of FMT for the treatment of CDI in pediatric patients 21 years old or younger. The analysis included 904 children across 14 observational studies (5 prospective, 5 retrospective, and 4 case series); 12 studies included children with recurrent CDI and 2 studies included children with recurrent CDI or first episode of CDI. The most common route of FMT administration was colonoscopy (49.79%). The primary outcome was the efficacy of FMT in treating CDI or recurrent CDI. Results demonstrated a rate of success ranging between 66% and 100%. The pooled rate of clinical success in the overall cohort was 86% ($p<.001$). There were 47 adverse events in 45 patients and 38 serious adverse events in 36 patients; the causes of serious adverse events were variable and there was no single predominant cause. The authors stated that despite its efficacy, FMT still remains relatively poorly regulated and standardized. Limitations of this study include the lack of any RCT and the inability to control for confounding variables in patient qualities and procedural protocols (e.g., route of administration). It was concluded that FMT is an effective and safe therapy in pediatric and adolescent patients with C. difficile infection.

Intractable constipation in children and FMT was studied in a double-blind RTC aimed to determine the safety and efficacy of retrograde colonic enema (RCE)-based FMT in the treatment of intractable constipation in children (Gu 2024). A total of 110 children were randomized to the FMT with RCE group or the placebo with RCE group. All participants received a daily RCE, followed by a 4-week FMT treatment (twice a week) and a 12-week follow-up period. Spontaneous bowel movements ≥ 3 per week were the main outcome. At the end of the follow-up period, 22 patients (40.0%) in the FMT with RCE group and 10 patients (18.2%) in the placebo with RCE group had ≥ 3 spontaneous bowel movements per week ($P < 0.05$). Both RCE and FMT enriched the intestinal bacterial diversity of patients with constipation. The adverse events were all mild self-limiting gastrointestinal symptoms. The authors concluded that FMT enhances the efficacy of RCE, and the use of RCE-based FMT is a safe and effective method in the treatment of intractable constipation in children.

PROFESSIONAL GUIDELINE(S)

Adult Population

In 2024, the American Gastroenterology Association (AGA) developed a clinical practice guideline to provide recommendations on the use of fecal microbiota–based therapies for select gastrointestinal diseases (Peery 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)
- 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)
- 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)
- 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 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 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 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 2019)

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

The American College of Gastroenterology (ACG) clinical practice guideline (Kelly 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 Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) published a focused update guideline echoing the recommendations for FMT published in 2018. 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 2021)

In 2018, the IDSA and SHEA published updated clinical practice guidelines for the diagnosis and treatment of CDI in children and adults (McDonald 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.

<u>Pediatric Population</u>

In 2018, an international multidisciplinary panel of experts in pediatric oncology and infectious diseases performed systematic reviews of RTCs for the prevention or treatment of CDI in any population and considered the directness of the evidence to children with cancer and pediatric hematopoietic stem-cell transplantation (HSCT) patients (Diorio 2018). A strong recommendation to not use FMT was made in this population.

In 2019, a joint position paper on FMT for recurrent CDI (rCDI) and other conditions in children was issued from the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (Davidovics 2019). The group of experts acknowledge that controlled trials with FMT for rCDI have not been performed in children, and numerous clinical and regulatory considerations have to be considered when using

this untraditional therapy. In general, the group concurs with current adult guidelines when considering FMT for the treatment of rCDI in children and propose FMT be considered in children with one of the following:

- For rCDI (recurrence of symptoms within 8 weeks of treatment for CDI), either:
  - At least 3 episodes of mild to moderate CDI and failure of a 6- to 8- week taper with vancomycin with or without an alternative antibiotic (eg, rifaximin, nitazoxanide), or
  - At least 2 episodes of severe CDI resulting in hospitalization and associated with significant morbidity.
- For moderate CDI not responding to standard therapy (including vancomycin) for at least 1 week. We recommend caution, however, in such cases, with repeated testing for etiologies other than CDI such as IBD.
- For severe CDI or fulminant C difficile colitis with no response to standard therapy after 48 hours.

In 2023, the American Academy of Pediatrics (AAP) published a clinical report on FMT to provide the general pediatrician with a broad overview to enable appropriate guidance to families seeking FMT as treatment of a child's condition. (Oliva-Hemker 2023). The AAP's summary states that, to date, controlled trials are not available and there are no prospective pediatric clinical trials using FMT to treat CDI. The long-term effects of FMT are unknown. Cohort studies support the use of FMT in pediatric patients with moderate to severe or recurrent CDI but is not recommended for the clinical treatment of any other medical condition.

REGULATORY STATUS

The U.S. Food and Drug Administration (FDA) placed the study and use of FMT under the guidance of the Center for Biologics Evaluation and Research (CBER), which is the same section that monitors vaccines, blood products, and gene therapy. The FDA views FMT as both a biologic and as a drug with the applicable regulations in respect to procedures and monitoring.

The FDA issued safety alerts on the potential risk of serious or life-threatening infections with the use of FMT and 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).

CODE(S)

- Codes may not be covered under all circumstances.
- Code list may not be all inclusive (AMA and CMS code updates may occur more frequently than policy updates).
- (E/I)=Experimental/Investigational
- (NMN)=Not medically necessary/appropriate

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

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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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SEARCH TERMS

Not Applicable

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

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

PRODUCT DISCLAIMER

- Services are contract dependent; if a product does not cover a service, medical policy criteria do not apply.
- If a commercial product (including an Essential Plan or Child Health Plus product) covers a specific service, 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 HISTORY/REVISION	
Committee Approval Dates	
08/16/12, 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, 09/19/24, 09/18/25	
Date	**Summary of Changes**
09/18/25	• Annual review, policy intent unchanged.
01/01/25	• Summary of changes tracking implemented.
08/16/12	• Original effective date