Select Health Medical Policies

Infectious Disease Policies

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MEDICAL POLICY

FECAL MICROBIOTA THERAPY

Policy # 522
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Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for Select Health Commercial, Select Health Medicare (CMS), and Select Health Community Care (Medicaid) plans. Refer to the "Policy" section for more information.

Description

Clostridioides difficile (C. diff), formerly referred to as *Clostridium difficile* (C. diff), is a bacterial infection that results in millions of human infections worldwide annually. The most common clinical presentation of *Clostridioides difficile*-associated Infection (CDI) is mild-to-moderate diarrhea, with some patients having mucus or blood in stool. Manifestations of *Clostridioides difficile*-associated diarrhea with colitis, include watery diarrhea with lower abdominal pain and cramping, low grade fever, and leukocytosis. *Clostridioides difficile* illness often develops during or shortly after a course of antibiotics. But signs and symptoms may not appear for weeks or months afterward.

The Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America define mild, moderate, severe, and complicated C. diff as follows:

Clinical Definition	Supportive Clinical Data
Initial episode, mild or moderate	Leukocytosis with a white blood cell count of 15,000 cells/µL or lower and a serum creatinine level less than 1.5 times the premorbid level
Initial episode, severe	Leukocytosis with a white blood cell count of 15,000 cells/µL or higher and a serum creatinine level greater than 1.5 times the premorbid level
Initial episode, severe, complicated	Hypotension or shock, ileus, megacolon

Clostridioides difficile infection is usually treated with antibiotic therapy, though relapses may occur. The most common antibiotics used are metronidazole and vancomycin. Most recently, fidaxomicin (Dificid) has gained FDA approval for treatment of CDI. Though these agents are effective, increasing resistance by *Clostridioides difficile* has emerged, which has led to an increasing number of antibiotic failures.

Fecal microbiota therapy, also called fecal biotherapy, fecal bacteriotherapy, fecal microbiota transplantation, fecal flora reconstitution, fecal transfer, or stool transplantation, was first described in 1958 as a successful treatment for antibiotic-induced diarrhea in patients who did not respond to other treatments and whose critical condition continued to worsen. Since then, fecal microbiota therapy has continued to be used rarely in the United States and sporadically in other countries, mostly due to aesthetic issues, patient acceptance, and some concerns about disease transmission. Interest in this procedure has grown substantially over the past few years due to the increasing incidence and severity of CDI, as well as the increasing resistance of CDI to current care antibiotic therapy. Fecal microbiota therapy involves the reintroduction of healthy fecal bacteria from a donor into the GI tract of a patient diagnosed with CDI. There have been successful results, defined as clearance of diarrhea or negative *Clostridioides difficile* toxin assays, with fecal microbiota transplantation (FMT) administered to the proximal colon *via* colonoscope, enema, or upper GI tract *via* nasoduodenal (ND) tube, or even orally in

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the case of the newer frozen capsule formulations. Regardless of the delivery method chosen, the initial steps in the procedure are similar: evaluating patient eligibility, patient consent, determining and screening donors, and in most cases, discontinuing the recipient's antibiotics prior to the procedure. The exact preparation and volume of the donated sample and location of delivery can vary.

Clinicians often elect to utilize stool donations from individuals living in the same household, hypothesizing that in close living arrangements—and particularly with intimate partners—potential pathogens would likely already have been widely shared by both parties. Donation from an intimate partner diminishes the risk of transferring an additional infectious agent (to which the recipient has not been previously exposed) into their GI tract. Regardless of the relationship of the recipient and donor, rigorous screening for other infectious agents is recommended.

As this therapy has evolved, attempts at developing standardized commercial preparations of fecal material for transplantation have also evolved. There remain no FDA-approved commercial therapies. One nonprofit stool bank that sells frozen fecal matter in capsule form (Capsule G3) or frozen solutions is called OpenBiome (Somerville, MA). It provides frozen stool preparations in 250 cc frozen solution (Lower Delivery Microbiota Preparation-FMP250) for colonoscopic delivery, 30 cc frozen solution (Upper Delivery Microbiota Preparation-FMP30), and the frozen capsules. The capsules contain concentrated formulations of the same screened and processed microbiota preparations as OpenBiome's other FMT treatments. The recommended number of capsules for treatment of CDI is 30 capsules, swallowed consecutively in a single session. Capsules are size 00, approximately the size of a large multivitamin. OpenBiome provides 2 'placebo' test capsules with each treatment. The patient may be asked to ingest one test capsule prior to the start of treatment, under direct observation of the physician, to ensure the patient's ability to swallow and mitigate the risks associated with aspiration. Regardless of the formulation used, it is kept frozen until time of administration and then warmed to room temperature. The materials are administered in the same fashion as other fresh stool preparations. The stool undergoes extensive preparation including testing for several pathogens. The donors also undergo testing for potentially transmittable conditions. The material has a shelf-life of approximately 6 months when in the frozen state.

COMMERCIAL PLAN POLICY AND CHIP (CHILDREN'S HEALTH INSURANCE PROGRAM)

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

Select Health covers fecal microbiota therapy as a proven therapy for members with *Clostridium difficile* infection in limited circumstances.

Select Health covers OpenBiome capsules/commercially prepared fecal concentrate as a proven therapy for members with *Clostridioides difficile* infection in the same circumstances as fresh stool specimen transplantation.

Recommended Criteria for Coverage:

1. For mild-to-moderate *Clostridioides difficile* infection:
   a. Patient has positive *Clostridioides difficile* infection PCR or toxin assay, **and**
   b. After three episodes of *Clostridioides difficile* infection.
2. Fulminant *Clostridioides difficile* infection (formerly referred to as severe *Clostridioides difficile* infection), as defined by hypotension or shock, ileus, or megacolon (must meet either a or b)
   a. Recurrent infection that is fulminant; **or**
   b. Patient is not improving after three days of antibiotic therapy.

Select Health does not cover fecal microbiota therapy for any other indication; use in other settings is considered investigational.

SELECT HEALTH MEDICARE (CMS)

Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS, and InterQual criteria are not available, the Select Health Commercial policy applies. For the most up-to-date Medicare policies and coverage, please visit their search website http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp& or the manual website

SELECT HEALTH COMMUNITY CARE (MEDICAID)

Select Health Community Care policies typically align with State of Utah Medicaid policy, including use of InterQual. There may be situations where NCD/LCD criteria or Select Health commercial policies are used. For the most up-to-date Medicaid policies and coverage, please visit their website http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

Summary of Medical Information

A technology assessment completed on January 29, 2013, identified six systematic reviews and sixteen peer-reviewed journal articles regarding fecal microbiota therapy which met inclusion criteria for review. These studies involved 391 patients with recurrent or recalcitrant *Clostridioides difficile* infections. The largest study was only 70 patients (Mattila et al.). The severity of diarrheal disease varied in the studies from mild-to-moderate to severe. All studies involved patients with recurrent or recalcitrant disease who had failed multiple courses of antibiotic therapy. The response rate in these studies ranged from 73.3% to 100%. The lowest outcomes tended to be noted for therapies administered via nasogastric tube (i.e., 73.3% and 83.0%). The mean response rate for all studies was 92.5%.

Study duration impacted the ability to determine the durability of the therapy as many studies were of 3 months duration or less. However, Brandt et al. identified a durability of effect extending out to 17 months, and Rohlke et al. identified effectiveness of the therapy to 27.7 months. It was remarkable to note the resolution of the diarrhea occurred in as little as 1-day post-instillation of the microbiota therapy (Kelly et al. and Yoon et al.), but often in 2–3 days (Garborg et al. and Brandt et al.).

Most studies suffered from methodological limitations due to the lack of blinding, or randomization, though either would be difficult to achieve for this therapy. Despite the variability in treatment protocols and patient populations, the available published literature demonstrates fecal microbiota therapy to have high efficacy in the resolution of *Clostridioides difficile* induced disease commensurate with treatment following standard regimens of metronidazole and vancomycin (i.e., resolution of diarrhea > 90% in all patient cohorts).

Most patients in whom fecal microbiota therapy was not efficacious in eliminating symptoms associated with C. diff were immunocompromised, elderly, or had significant secondary illness. In patients who failed conservative treatment, fecal transplantation appears to be a viable last option having good outcomes and a low risk profile as no significant adverse events were reported in the literature.

With regards to commercially prepared frozen stool preparation, four systematic reviews and 4 primary studies were identified for use in the management of fecal microbiota therapy during a review completed in November of 2016. Though the studies were of small size and had some methodological issues, the outcomes demonstrated non-inferior outcomes and adverse events compared to fresh FMT. Follow-up times after therapy ranged from 13 weeks to 6 months.

Billing/Coding Information

CPT CODES

0780T	Instillation of fecal microbiota suspension via rectal enema into lower gastrointestinal tract
44705	Preparation of fecal microbiota for instillation, including assessment of donor specimen

HCPCS Codes

G0455	Preparation with instillation of fecal microbiota by any method, including assessment of donor specimen
J3490	Unclassified drugs
J3590	Unclassified biologics

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Revision History

Revision Date	Summary of Changes
1/15/25	For Commercial Plan Policy, changed required amount of episodes of *Clostridioides difficile* infection in criterion #1b to qualify for this therapy from four to three.