Protocol

Fecal Microbiota Transplantation

(20192)

Medical Benefit		**Effective Date**: 10/01/21	**Next Review Date**: 07/23
Preauthorization	Yes	**Review Dates**: 07/14, 07/15, 07/16, 07/17, 07/18, 07/19, 07/20, 07/21, 07/22	

Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

RELATED PROTOCOL

Fecal Analysis in the Diagnosis of Intestinal Dysbiosis

Populations	Interventions	Comparators	Outcomes
Individuals: • With recurrent *Clostridium difficile* infection refractory to antibiotic therapy	Interventions of interest are: • Fecal microbiota transplantation	Comparators of interest are: • Standard antibiotic regimens	Relevant outcomes include: • Symptoms • Change in disease status • Treatment-related morbidity
Individuals: • With inflammatory bowel disease	Interventions of interest are: • Fecal microbiota transplantation	Comparators of interest are: • Standard of care	Relevant outcomes include: • Symptoms • Change in disease status • Treatment-related morbidity
Individuals: • With irritable bowel disease	Interventions of interest are: • Fecal microbiota transplantation	Comparators of interest are: • Standard of care	Relevant outcomes include: • Symptoms • Change in disease status • Treatment-related morbidity
Individuals: • With pouchitis, constipation, multi-drug resistant organism infection, or metabolic syndrome	Interventions of interest are: • Fecal microbiota transplantation	Comparators of interest are: • Standard of care	Relevant outcomes include: • Symptoms • Change in disease status • Treatment-related morbidity

DESCRIPTION

Fecal microbiota transplantation (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. Fecal transplant is proposed for treatment-refractory Clostridioides (formerly Clostridium) difficile infection (CDI) and other conditions, including inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), pouchitis, constipation, multi-drug resistant organism (MDRO) infection, or metabolic syndrome.

SUMMARY OF EVIDENCE

For individuals who have recurrent CDI refractory to antibiotic therapy who receive FMT, the evidence includes systematic reviews with meta-analyses and observational studies. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Meta-analyses have found that FMT is more effective than standard treatment or placebo for patients with recurrent CDI. A long-term prospective study found that FMT for recurrent or refractory CDI appears to be durable at 4 to 8 years following treatment, even for patients who had subsequently received non-CDI antibiotic therapy. A meta-analysis comparing several routes of FMT delivery for the treatment of recurrent CDI found that cure rates were significantly higher with colonoscopy or oral capsules versus nasogastric tube or enema, while colonoscopy and capsules were equally effective. Similar success rates have been demonstrated with FMT using fresh versus frozen feces. Conversely, data regarding the superiority of FMT using donor versus autologous feces are conflicting. Few treatment-related adverse events have been reported. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have IBD who receive FMT, the evidence includes systematic reviews and randomized controlled trials (RCTs). Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Two systematic reviews with meta-analysis concluded that FMT had shown promise in treating patients with ulcerative colitis (UC), but 1 meta-analysis recommended caution about using FMT to treat patients with Crohn disease (CD). A 48-week RCT in patients with UC in clinical remission after prior FMTs found conflicting results for remission outcomes with additional courses of FMT. This current evidence is not sufficient to permit conclusions on the efficacy of FMT for UC. Another RCT in patients with recurrent active UC found a median remission time of 24 months in both FMT and standard of care treatment groups. Additionally, questions remain about the optimal route of administration, donor characteristics, and the number of transplants. A small RCT in patients with CD failed to find a difference in the achievement of remission with FMT versus placebo. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have IBS who receive FMT, the evidence includes a systematic review and RCTs. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. The systematic review with meta-analysis reviewed 5 RCTs and reported mixed outcomes for FMT in patients with IBS. When all studies were pooled, no net benefit was found for active FMT. In a pooled analysis of 3 RCTs utilizing autologous FMT as a placebo, patients were less likely to experience an improvement in IBS symptoms with donor FMT (i.e., active treatment). Two additional RCTs published after the meta-analysis also utilized autologous FMT as a placebo, and did not find a significant reduction in symptoms of IBS using donor FMT; both trials also found reduced durability of response 1 year following donor FMT. An additional placebo-controlled RCT administered FMT via oral capsules and found no improvement in abdominal pain scores, stool frequency, or stool form in a mixed population of patients with IBS. Few treatment-related adverse events have been reported. Data are limited by small study sizes and heterogeneity in utilized outcome measurement scales and definitions of treatment response. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have pouchitis, constipation, MDRO infection, or metabolic syndrome who receive FMT, the evidence includes systematic reviews, a RCT, and prospective cohort studies. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Systematic reviews of data from patients who received FMT for constipation, pouchitis, MDRO infections, and metabolic syndrome have all concluded that more data are needed before FMT can be applied in clinical practice for these populations. In a meta-analysis assessing the use of FMT in obese and metabolic syndrome patients, the initial improvements of several metabolic parameters failed to demonstrate sustained durability at 12 weeks after treatment. While cohort studies have demonstrated FMT to be fairly effective in eradicating MDRO colonization, a RCT comparing FMT to no intervention in patients with MDROs failed to demonstrate improved rates of decolonization with treatment. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

POLICY

Fecal microbiota transplantation may be considered **medically necessary** for treatment of patients with recurrent *Clostridioides difficile* infection under the following conditions (see Policy Guidelines section for U.S. Food and Drug Administration Guidance):

- There have been at least two recurrences that are refractory to standard antibiotic treatment.

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

POLICY GUIDELINES

There is a lack of consensus on the number of recurrences that warrants consideration of FMT.

The 2021 Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) guidelines for *Clostridioides difficile* infection (CDI) states that patients with multiple recurrences of CDI who have failed to resolve their infection with standard of care antibiotic treatments are potential candidates for FMT.[1] It was the opinion of guideline panelists to have patients try appropriate antibiotics for at least two recurrences (i.e., three CDI episodes) before FMT is considered. The optimal timing between multiple FMT sessions is not discussed in the guidelines.

The 2021 American Society of Colon and Rectal Surgeons (ASCRS) guideline for CDI recommends that patients with 3 or more CDI episodes be managed with a vancomycin tapered and pulsed course or fidaxomicin followed by a microbiome-based therapy such as FMT.[2] Per the guideline: "Conventional antibiotic treatment should be used for at least 2 recurrences (i.e., 3 CDI episodes) before offering fecal microbiota transplantation."

The 2021 American College of Gastroenterology (ACG) guideline for CDI recommends FMT for patients experiencing their second or further recurrence of CDI (i.e., third or later CDI episode) to prevent further recurrences.[3] This guideline also specifically recommends a repeat FMT for patients experiencing a recurrence of CDI within 8 weeks of an initial FMT session.

Per the 2021 IDSA and Society for Healthcare Epidemiology of America (SHEA) guidelines, a recurrent case occurs within two to eight weeks of the incident case and requires both clinical plus laboratory evidence of disease for diagnosis; the 2021 IDSA/SHEA guideline does not provide an update to this definition. The 2021 guidelines from the ASCRS and ACG define a recurrent case as one occurring within 8 weeks after the completion of a course of CDI therapy and requiring both clinical plus laboratory evidence of disease for diagnosis.[2,3]

Due to the potential for serious adverse reactions with FMT, the U.S. Food and Drug Administration (FDA) has determined that the following protections are needed for use of FMT:

- Donor screening with questions that specifically address risk factors for colonization with multi-drug resistant organisms (MDROs), and exclusion of individuals at higher risk of colonization with MDROs.
- MDRO testing of donor stool and exclusion of stool that tests positive for MDRO. FDA scientists have determined the specific MDRO testing and frequency that should be implemented.
- Consent for the use of FMT is obtained from the patient or a legally authorized representative in accordance with FDA guidance.[4]

On April 9, 2020, the FDA published additional safety information regarding the potential risk of transmission of SARS-CoV-2 via FMT. Recommendations for additional screening and testing procedures are outlined in this publication.[5]

BACKGROUND

FECAL MICROBIOTA

Fecal microbiota transplantation (FMT), also called donor feces infusion, intestinal microbiota transplantation, and fecal bacteriotherapy involves the duodenal infusion of intestinal microorganisms via the 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, into the colon through a colonoscope or rectal catheter, or administered orally via capsules (i.e., encapsulated FMT).

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

Clostridioides difficile Infection

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. *C.difficile* occurs naturally in the intestinal flora. According to the 2019 Centers for Disease Control and Prevention (CDC) report, *Antibiotic Resistance Threats in the United States,* CDI continues to be an urgent threat.[6] In 2017, there were an estimated 223,900 cases of CDI in hospitalized patients and an estimated 12,900 CDI-associated deaths. Interestingly, the overall number of cases of healthcare-associated CDI cases has been trending down since 2012 when the number of cases was estimated at 251,400.

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 the 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.[7]

OTHER APPLICATIONS

Other potential uses of FMT include the treatment of conditions in which altered colonic flora may play a role: inflammatory bowel disease, irritable bowel syndrome, idiopathic constipation, and non-gastrointestinal diseases 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.[8] The product is made from 33 bacterial isolates developed from culturing stool from a healthy donor.

REGULATORY STATUS

In 2016, the U.S. Food and Drug Administration (FDA) issued updated draft guidance on investigational new drug requirements for the use of FMT to treat CDI not responsive to medication therapy.[4] The draft guidance is similar to the 2013 guidance and states that the FDA 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 FDA 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 the use of fecal transplant for treating conditions other than treatment-resistant CDI.

In 2019, the FDA issued a safety alert regarding the use of FMT due to the potential risk of serious or life-threatening infections caused by the transmission of multi-drug resistant organisms (MDROs).[9] Two immunocompromised individuals received investigational FMT and developed invasive infections caused by the transmission of extended-spectrum beta-lactamase-producing *Escherichia coli*. One of the affected individuals died. The donor stool used in each patient's FMT procedures had not been tested for extended-spectrum beta-lactamase-producing gram-negative organisms prior to use. Follow-up testing verified donor stool was positive for MDROs identical to the organisms isolated from the 2 patients. Due to these events, the FDA has determined that the following additional protections are required for any investigational use of FMT:

- Donor screening that specifically addresses risk factors for colonization with MDROs and exclusion of individuals at higher risk of colonization with MDROs (e.g., health care workers, persons who have recently been hospitalized or discharged from long-term care facilities, persons who regularly attend outpatient medical or surgical clinics, and persons who have recently engaged in medical tourism).
- MDRO testing of donor stool and exclusion of stool testing positive for MDROs. At a minimum, tests should include:
    - extended-spectrum beta-lactamase-producing *Enterobacteriaceae*
    - vancomycin-resistant enterococci
    - carbapenem-resistant *Enterobacteriaceae*
    - methicillin-resistant *Staphylococcus aureus*
- All FMT products currently in storage for future use must be quarantined until donor MDRO carriage risk can be assessed and FMT products are tested and found negative for MDROs.
- The informed consent process for FMT treatment subjects should describe the risk of MDRO transmission and infection and the measures being implemented for donor screening and stool testing.

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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