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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 <i>Clostridium difficile</i> 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 pouchitis, irritable bowel syndrome, constipation, 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 infusion 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 *Clostridium difficile* infection (CDI) and other conditions, including inflammatory bowel disease.

SUMMARY OF EVIDENCE

For individuals who have recurrent CDI refractory to antibiotic therapy who receive FMT, the evidence includes randomized controlled trials (RCTs), multiple systematic reviews, and observational studies. The relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. The RCTs found that FMT was more effective than standard treatment or placebo for patients with recurrent CDI. Other RCTs did not find the

superiority of any route of administration over another or the superiority of fresh vs. frozen feces. Case reports and case series have reported high rates of resolution of recurrent CDI following treatment with FMT. Few treatment-related adverse events have been reported. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have inflammatory bowel disease who receive FMT, the evidence includes a large-scale systematic review and meta-analysis, two RCTs in patients with ulcerative colitis, as well as observational studies. The relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Two small RCTs on FMT for treatment of ulcerative colitis were discontinued due to futility, which restricted data analysis to patients already enrolled. Of the two small RCTs, one found a statistically significant higher remission rate after active FMT than after a control intervention, but this trial had few patients in remission (n=11) and short follow-up (seven weeks); the other trial reported no difference in remission rates. Data on a small number of patients with Crohn disease are available; however, there are no controlled studies of FMT in this population. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have irritable bowel syndrome who receive FMT, the evidence includes a systematic review and RCTs. The relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. The systematic review found mixed outcomes; in a pooled analysis of three RCTs utilizing autologous FMT as a placebo, the relative risk of irritable bowel syndrome symptoms not improving decreased and was statistically superior compared to donor FMT. 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 the effects of the technology on health outcomes.

For individuals who have pouchitis, constipation, multi-drug resistant organism infection, or metabolic syndrome who receive FMT, the evidence includes a small number of case series and RCTs. The relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Data are available for only a limited number of patients and there is a lack of comparative studies. Current comparative studies are small and either do not report clinical outcomes or fail to demonstrate a significant benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

POLICY

Fecal microbiota transplantation may be considered **medically necessary** for treatment of patients with recurrent *Clostridium difficile* infection under the following conditions (see Policy Guidelines):

- There have been at least three episodes of recurrent infection; AND
- Episodes are refractory to appropriate antibiotic regimens, including at least one regimen of pulsed vancomycin.

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.

Among the two published randomized controlled trials evaluating FMT for treatment of *Clostridium difficile* infection (CDI), the van Nood study (2013) included patients with at least one recurrence of CDI; the other study, the Youngster study (2014), included patients with a relapse after at least three episodes of mild-to-moderate CDI or at least two episodes of severe CDI.

The 2013 American College of Gastroenterology guidelines recommended that FMT be considered second-line therapy for a third recurrence of CDI.

BACKGROUND

FECAL MICROBIOTA

Fecal microbiota transplantation (FMT), also called donor feces infusion, intestinal microbiota transplantation, and fecal bacteriotherapy involves the 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, or the stool can be infused into the colon through a colonoscope or rectal catheter.

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

Clostridium difficile Infection

To date, the major potential clinical application of FMT is the treatment of *Clostridium 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. The incidence of CDI in North America has increased substantially. For example, according to hospital discharge diagnosis data, there were more than 300,000 cases of CDI in 2006 compared with fewer than 150,000 cases in 2000. Moreover, CDI causes an estimated 15,000 to 20,000 deaths per year in U.S. hospitals.^{1,2}

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.³

Other Applications

Other potential uses of FMT include treatment of conditions in which altered colonic flora may play a role. They include 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 two patients with recurrent CDI.⁴ 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.⁵ 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).⁶ 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 two 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.**

REFERENCES

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

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