MASSACHUSETTS

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Medical Policy

Fecal Microbiota Transplantation

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Policy Number: 682

BCBSA Reference Number: 2.01.92
NCD/LCD: N/A

Related Policies

Fecal Analysis in the Diagnosis of Intestinal Dysbiosis, #556

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue^{SM} and Medicare PPO Blue^{SM} Members

Fecal microbiota transplantation may be considered **MEDICALLY NECESSARY** for treatment of patients with recurrent *Clostridium difficile* infection under the following conditions:

- There have been at least 3 episodes of recurrent infection; **AND**
- Episodes are refractory to appropriate antibiotic regimens, including at least 1 regimen of pulsed vancomycin.

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

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is **not required**.
Commercial PPO and Indemnity	Prior authorization is **not required**.
Medicare HMO Blue^{SM}	Prior authorization is **not required**.
Medicare PPO Blue^{SM}	Prior authorization is **not required**.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

CPT codes:	Code Description
44705	Preparation of fecal microbiota for instillation, including assessment of donor specimen

HCPCS Codes

HCPCS codes:	Code Description
G0455	Preparation with instillation of fecal microbiota by any method, including assessment of donor specimen

The following ICD Diagnosis Codes are considered medically necessary when submitted with the CPT and HCPCS codes above if medical necessity criteria are met:

ICD-10 Diagnosis Codes

ICD-10 CM diagnosis codes:	Code Description
A04.71	Enterocolitis due to Clostridium difficile, recurrent
A04.72	Enterocolitis due to Clostridium difficile, not specified as recurrent

DESCRIPTION

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 (ie, 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 300000 cases of CDI in 2006 compared with fewer than 150000 cases in 2000. Moreover, CDI causes an estimated 15000 to 20000 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 2 patients with recurrent CDI.[4] The product is made from 33 bacterial isolates developed from culturing stool from a healthy donor.

Summary

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.

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 2small 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 (7 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 History

Date	Action
1/2020	BCBSA National medical policy review. Description, summary and references updated. Policy statements unchanged.
1/2019	BCBSA National medical policy review. Description, summary and references updated. Policy statements unchanged.
1/2018	New references added from BCBSA National medical policy.
10/2017	Clarified coding information.
12/2016	New references added from BCBSA National medical policy.
1/2016	New references added from BCBSA National medical policy.
6/2015	New references added from BCBSA National medical policy.
10/2014	New policy describing medically necessary and investigational indications. Effective 10/1/2014.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References

1. Kachrimanidou M, Malisiovas N. Clostridium difficile infection: a comprehensive review. Crit Rev Microbiol. Aug 2011;37(3):178-187. PMID 21609252
2. Nelson RL, Kelsey P, Leeman H, et al. Antibiotic treatment for Clostridium difficile-associated diarrhea in adults. Cochrane Database Syst Rev. Sep 07 2011(9):CD004610. PMID 21901692
3. Gough E, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent Clostridium difficile infection. Clin Infect Dis. Nov 2011;53(10):994-1002. PMID 22002980
4. Petrof EO, Gloor GB, Vanner SJ, et al. Stool substitute transplant therapy for the eradication of Clostridium difficile infection: 'RePOOPulating' the gut. Microbiome. Jan 09 2013;1(1):3. PMID 24467987
5. Food and Drug Administration (FDA). Guidance for Industry: Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat

Clostridium difficile Infection Not Responsive to Standard Therapies. 2013; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enforcement-policy-regarding-investigational-new-drug-requirements-use-fecal-microbiota. Accessed September 23, 2019.
6. Food and Drug Administration (FDA). Fecal Microbiota Transplantation: Safety Communication - Risk of Serious Adverse Reactions Due to Transmission of Multi-Drug Resistant Organisms. 2019; https://www.fda.gov/safety/medwatch-safety-alerts-human-medical-products/fecal-microbiota-transplantation-safety-communication-risk-serious-adverse-reactions-due. Accessed September 23, 2019.
7. Tariq R, Pardi DS, Bartlett MG et al. Low Cure Rates in Controlled Trials of Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection: A Systematic Review and Meta-analysis. Clin. Infect. Dis., 2019 Apr 9;68(8). PMID 30957161
8. Khan MY, Dirweesh A, Khurshid T et al. Comparing fecal microbiota transplantation to standard-of-care treatment for recurrent Clostridium difficile infection: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol, 2018 Aug 24;30(11). PMID 30138161
9. Quraishi MN, Widlak M, Bhala N, et al. Systematic review with meta-analysis: the efficacy of faecal microbiota transplantation for the treatment of recurrent and refractory Clostridium difficile infection. Aliment Pharmacol Ther. Sep 2017;46(5):479-493. PMID 28707337
10. Drekonja D, Reich J, Gezahegn S, et al. Fecal microbiota transplantation for Clostridium difficile Infection: a systematic review. Ann Intern Med. May 5 2015;162(9):630-638. PMID 25938992
11. Guo B, Harstall C, Louie T, et al. Systematic review: faecal transplantation for the treatment of Clostridium difficile-associated disease. Aliment Pharmacol Ther. Apr 2012;35(8):865-875. PMID 22360412
12. Sofi AA, Silverman AL, Khuder S, et al. Relationship of symptom duration and fecal bacteriotherapy in Clostridium difficile infection-pooled data analysis and a systematic review. Scand J Gastroenterol. Mar 2013;48(3):266-273. PMID 23163886
13. Chapman BC, Moore HB, Overbey DM, et al. Fecal microbiota transplant in patients with Clostridium difficile infection: A systematic review. J Trauma Acute Care Surg. Oct 2016;81(4):756-764. PMID 27648772
14. Kelly CR, Khoruts A, Staley C, et al. Effect of fecal microbiota transplantation on recurrence in multiply recurrent Clostridium difficile infection: a randomized trial. Ann Intern Med. Nov 01 2016;165(9):609-616. PMID 27547925
15. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. N Engl J Med. Jan 31 2013;368(5):407-415. PMID 23323867
16. Lee CH, Steiner T, Petrof EO, et al. Frozen vs fresh fecal microbiota transplantation and clinical resolution of diarrhea in patients with recurrent Clostridium difficile Infection: a randomized clinical trial. JAMA. Jan 12 2016;315(2):142-149. PMID 26757463
17. Moayyedi P, Surette MG, Kim PT, et al. Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a randomized controlled trial. Gastroenterology. Jul 2015;149(1):102-109 e106. PMID 25857665
18. Rossen NG, Fuentes S, van der Spek MJ, et al. Findings from a randomized controlled trial of fecal transplantation for patients with ulcerative colitis. Gastroenterology. Jul 2015;149(1):110-118 e114. PMID 25836986
19. Youngster I, Sauk J, Pindar C, et al. Fecal microbiota transplant for relapsing Clostridium difficile infection using a frozen inoculum from unrelated donors: a randomized, open-label, controlled pilot study. Clin Infect Dis. Jun 2014;58(11):1515-1522. PMID 24762631
20. Lee CH, Chai J, Hammond K et al. Long-term durability and safety of fecal microbiota transplantation for recurrent or refractory Clostridioides difficile infection with or without antibiotic exposure. Eur. J. Clin. Microbiol. Infect. Dis., 2019 Jun 6;38(9). PMID 31165961
21. Paramsothy S, Paramsothy R, Rubin DT et al. Faecal Microbiota Transplantation for Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. J Crohns Colitis, 2017 May 10;11(10). PMID 28486648
22. Sha S, Liang J, Chen M, et al. Systematic review: faecal microbiota transplantation therapy for digestive and nondigestive disorders in adults and children. Aliment Pharmacol Ther. May 2014;39(10):1003-1032. PMID 24641570

23. Costello SP, Hughes PA, Waters O et al. Effect of Fecal Microbiota Transplantation on 8-Week Remission in Patients With Ulcerative Colitis: A Randomized Clinical Trial. JAMA, 2019 Jan 16;321(2). PMID 30644982
24. Aziz I, Törnblom H, Palsson OS et al. How the Change in IBS Criteria From Rome III to Rome IV Impacts on Clinical Characteristics and Key Pathophysiological Factors. Am. J. Gastroenterol., 2018 Jun 9;113(7). PMID 29880963
25. Ford AC, Bercik P, Morgan DG et al. Validation of the Rome III criteria for the diagnosis of irritable bowel syndrome in secondary care. Gastroenterology, 2013 Sep 3;145(6). PMID 23994201
26. Ianiro G, Eusebi LH, Black CJ et al. Systematic review with meta-analysis: efficacy of faecal microbiota transplantation for the treatment of irritable bowel syndrome. Aliment. Pharmacol. Ther., 2019 May 29;50(3). PMID 31136009
27. Holster S, Lindqvist CM, Repsilber D et al. The Effect of Allogenic Versus Autologous Fecal Microbiota Transfer on Symptoms, Visceral Perception and Fecal and Mucosal Microbiota in Irritable Bowel Syndrome: A Randomized Controlled Study. Clin Transl Gastroenterol, 2019 Apr 23;10(4). PMID 31009405
28. Johnsen PH, Hilpüsch F, Cavanagh JP et al. Faecal microbiota transplantation versus placebo for moderate-to-severe irritable bowel syndrome: a double-blind, randomised, placebo-controlled, parallel-group, single-centre trial. Lancet Gastroenterol Hepatol, 2017 Nov 5;3(1). PMID 29100842
29. Rossen NG, MacDonald JK, de Vries EM, et al. Fecal microbiota transplantation as novel therapy in gastroenterology: A systematic review. World J Gastroenterol. May 7 2015;21(17):5359-5371. PMID 25954111
30. Vrieze A, Van Nood E, Holleman F, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology. Oct 2012;143(4):913-916 e917. PMID 22728514
31. Rubin DT, Ananthakrishnan AN, Siegel CA et al. ACG Clinical Guideline: Ulcerative Colitis in Adults. Am. J. Gastroenterol., 2019 Mar 7;114(3). PMID 30840605
32. McDonald LC, Gerding DN, Johnson S et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin. Infect. Dis., 2018 Feb 21;66(7). PMID 29462280