

MEDICAL POLICY		Fecal Microbiota Transplantation	
Effective Date: 4/1/2020  <div style="text-align: right;">4/1/2020</div>		Section: MED	Policy No: 223
		Technology Assessment Committee Approved Date: 3/13; 7/13; 7/14; 6/15; 11/15; 7/16; 8/16 Medical Policy Committee Approved Date: 12/15; 9/17; 7/18; 8/19; 3/2020	
Medical Officer	Date		

See Policy CPT/HCPCS CODE section below for any prior authorization requirements

SCOPE:

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayn Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:

All lines of business

BENEFIT APPLICATION

Medicaid Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

POLICY CRITERIA

- I. Fecal microbiota transplantation may be considered **medically necessary and covered** for the treatment of Clostridium difficile (C. difficile) infection when **all** of the following criteria are met (A. - C.):
 - A. A patient has had at least three episodes (initial episode plus two recurrences) of C. difficile infection that have not responded with appropriate treatment with antibiotics; **and**
 - B. Testing confirms diagnosis of C. difficile infection by **both** of the following (1. and 2.):
 1. Recurrent diarrhea (>3 unformed stools in ≤24 hours); **and**
 2. Either of the following:
 - a. Stool sample positive for C. difficile or it’s toxins; **or**
 - b. Colonoscopic or histopathological evidence of pseudomembranous colitis; **and**
 - C. The patient does not have **any** of the following contraindications (1. -5.):
 1. Patient is immunocompromised, including any of the following (a. – e.):

- a. Patients on major immunosuppressive agents (e.g., high-dose corticosteroids, calcineurin inhibitors, mammalian target of rapamycin (mTOR) inhibitors, lymphocyte-depleting biological agents, anti-tumor necrosis factor agents, chemotherapeutic antineoplastic agents)
 - b. Advanced HIV/acquired immune deficiency syndrome
 - c. Recent bone marrow transplant
 - d. Decompensated liver cirrhosis
 - e. Other causes of severe immunodeficiency
2. Anatomic contraindications to nasogastric tube, enema, or colonoscopy (dependant on route of administration)
 3. Pregnancy
 4. Use of ongoing antibiotics for indications other than CDI
 5. Toxic megacolon or ileus
- II. Fecal microbiota transplantation is considered **investigational and not covered** when criterion I. above is not met, including but not limited to treatment for **any** of the following (A.-C.):
- A. Initial episode/occurrence of CDI
 - B. When one of the contraindications noted above is present
 - C. For conditions other than CDI, including but not limited to, any of the following (1. - 11.):
 1. Chronic fatigue syndrome
 2. Constipation
 3. Graft-versus-host disease of the gut
 4. Hepatic encephalopathy
 5. Inflammatory bowel disease (including ulcerative colitis Crohn's disease)
 6. Intestinal multidrug-resistant bacterial decolonization
 7. Irritable Bowel Syndrome
 8. Metabolic syndrome
 9. Obesity
 10. Parkinson's disease
 11. Pouchitis

Link to [Policy Summary](#)

BILLING GUIDELINES

- Fecal microbiota transplantation pills should be billed with HCPCS code J7999.
- Colonoscopy (or other instillation methods) may not be billed separately, as HCPCS code G0455 includes "instillation by any method."
- Use of codes other than HCPCS code G0455 for this procedure (e.g., 44705 or 44799) is not appropriate.

CPT/HCPCS CODES

All Lines of Business	
Prior Authorization Required	
G0455	Preparation with instillation of fecal microbiota by any method, including assessment of donor specimen
Not Covered	
44705	Preparation of fecal microbiota for instillation, including assessment of donor specimen
Unlisted Codes	
All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then it will be denied as not covered .	
44799	Unlisted procedure, small intestine

DESCRIPTION

Fecal microbiota transplantation (FMT), also known as fecal bacteriotherapy, involves using one of several methods to introduce fecal matter from a healthy donor into the gastrointestinal tract of a patient with recurrent clostridium difficile (*C. difficile*) infection (CDI) to recolonize the patient's colon with nonpathogenic bacteria.

Alternatives to FMT include surgical treatment (eg, colectomy), conventional antibiotic agents (metronidazole and vancomycin), alternative antibiotics (e.g., rifaximin, Fidaxomicin, fusidic acid), pulsed dosing of vancomycin, probiotics, and intravenous immunoglobulin against *C difficile* toxin.

FMT is administered by a gastroenterologist via nasogastric tube, nasoduodenal/jejunal tube, an upper-tract endoscope, a colonoscope, retention enema, or a combination of upper and lower methods. Recently, oral capsulized FMT has been introduced, which involves ingestion of several prepared capsules under direct supervision. At this time, no consensus exists on the preferred administration route, and no clear superiority of one method over another has been demonstrated.¹

Alleged benefits of FMT include lower cost than several courses of antibiotics and hospitalization, rapid treatment and resolution compared to several weeks of antibiotics, mild to no side effects, and reduced risk of antibiotic-associated bacterial resistance.

REVIEW OF EVIDENCE

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of fecal microbiota transplantation (FMT) as a treatment for any indication. Below is a summary of the available evidence identified through February 2020.

Clostridium difficile Infections (CDI)*Recurrent CDI*

In 2016 (updated 2018; archived 2019), Hayes published a review of FMT for refractory or recurrent CDI, including four randomized controlled trials (RCTs) and eight retrospective series on adult populations.² Because studies including pediatric patients were limited, they were not included in the review. Overall, the review indicated that a small but moderate-quality body of evidence consistently reported that the use of FMT cures a large proportion of patients with refractory or recurrent CDI who had failed standard antibiotic treatment. The review stated that adverse events associated with FMT were generally rare and self-limiting. Two fair quality, moderately sized (n=39 and 43 adult patients) both reported a large magnitude of benefit among those receiving FMT compared with controls. In both RCTs, between 65-94% of patient who underwent FMT were cured after 10 weeks, compared to 23-26% of patients in control groups (p.0.01-0.0001). As a result, Hayes assigned a **rating of “B”** for use of FMT in adult patients with relapse of CDI after ≥ 1 courses of ≥ 10 days of oral vancomycin at 125 milligrams (mg) 4 times daily or > 10 days of oral metronidazole at 500 mg 3 times daily.

Similar conclusions were drawn by the 2017 Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review, the Washington State Health Care Authority technology assessment on FMT, and the ECRI emerging technology report, all of which included three of the same RCTs as the Hayes review above.^{1,3,4}

Additional systematic reviews published after the Hayes review reported similar conclusions regarding the use of FMT as a treatment for recurrent/refractory CDI.⁵⁻⁹ All recent systematic reviews on this therapy are in agreement that FMT is an effective treatment for recurrent and refractory CDI, independent of preparation and route of delivery, with a relatively low rate of serious adverse events.

No additional studies were identified that evaluated FMT as a treatment for recurrent CDI since the most recent systematic reviews included above.

Initial CDI

The evidence for the use of FMT for treatment of an initial CDI is limited mainly to case reports and small case series, since the majority of studies have evaluated its use in the setting of recurrent infection. These small studies have been small (n<7) and have reported mixed results.¹⁰

There has been one small RCT published that has evaluated the use of FMT (donor-unrelated donor mix) to treatment CDI, but included patients with both initial and recurrent CDI.¹¹ The trial included 19 adult patients (16 available for analysis) that evaluated FMT as a first-line treatment compared to oral vancomycin. Symptoms resolved in 8/9 patients (88.9%) in the vancomycin group, while symptoms resolved in 4/7 patients (57.1%) after the first course of FMT and in 5/7 patients (71.4%) after the second course. Cure rates were not significantly different between treatment arms and patients treated with FMT did not have higher cure rates than those treated with conventional vancomycin therapy in this setting.

Other Indications*Inflammatory Bowel Disease (IBD) (Ulcerative colitis [UC] and Crohn's disease [CD])*

- In 2014, Colman and Rubin conducted a systematic review on the use of FMT as a primary therapy for IBD, including 18 studies (9 cohort studies, 8 case studies and 1 RCT).¹² In total, 122 patients were described [79 ulcerative colitis (UC); 39 Crohn's disease (CD); 4 IBD unclassified]. Overall, 45% (54/119) of patients achieved clinical remission. Pooled estimates of clinical remission were 22% (95% CI 10.4%-40.8%) for UC and 60.5% (95% CI 28.4%-85.6%) for CD. Of note, there was significant heterogeneity ($I^2 = 37%$) between the cohort studies. The review concluded that there was variability between studies regarding FMT efficacy and that more RCTs are needed.
- One 2015 systematic review by Rossen et al., included seven case series (n= 6 cases of CD and 106 cases of UC) and reported clinical remission rates of 0-68% (n=3 case series) and clinical improvement rates between 20% and 92% (n=6 case series).¹³ All seven studies were deemed of poor quality: small case series that were heterogenous in terms of site of IBD, measures of therapeutic response, clinical evaluation tools used, and inclusion of patients with CD. As a result, the review concluded that although FMT shows promise for IBD, additional studies are needed.
- In 2016, the Washington State Health Care Authority technology assessment on FMT, described above, evaluated its use as a treatment for IBD, including studies on ulcerative colitis (UC) and Crohn's disease (CD).³ The assessment only included two RCTs, and neither found any significant differences concerning clinical response or remission rates for FMT compared to placebo. Both studies had significant limitations. One study did not blind the patients, was small in size (n=38), and did not report confidence intervals. The larger RCT (n=75) was deemed to have a high risk of bias and had short-term follow-up (1.75 months). Overall, the technology assessment stated that there was sufficient evidence to evaluate the use of FMT for IBD, but that the studies suffered from methodological limitations and the quality of evidence was poor.
- Recent systematic reviews focused on the use of FMT for IBD and/or UC treatment have reported clinical remission rates between 28% and 40.5% in pooled analyses.¹⁴⁻¹⁹ These reviews all suffer from the same methodological limitation: including mainly case series that have small patient cohorts and lack a comparator group. Some reviews have also included case reports and conference abstracts. In addition, both sub-group and/or pooled analyses have been reported in these reviews to have modest but significant between-study heterogeneity. All reviews have indicated that additional, better-designed RCTs are still required to confirm efficacy in this population.

No additional comparative studies, including RCTs, were identified that evaluated FMT as a treatment for IBD and/or UC since the most recent systematic reviews included above.

Other Conditions

In the 2015 systematic review by Rosset al. described above, studies were included which evaluated the use of FMT to treat constipation, pouchitis and irritable bowel syndrome (IBS). However, only one small

case series was identified and evaluated for each of these conditions, and it were all determined to be of poor quality. The review also included one small RCT (n=18 male patients) which reported on the use of FMT for metabolic syndrome, evaluating patients six -weeks post FMT. The review concluded that there was insufficient evidence to draw conclusions about the efficacy of FMT as a treatment for any of these conditions.

Only two RCTs were identified after the publication of the Rossen et al. systematic review on conditions other than CDI and IBD. these are described below. However, these are the first RCTs to evaluate the use of FMT for these conditions, and additional larger RCTs with longer term follow-up are needed.

In 2017, Tian et al. published a small RCT on the use of FMT to treat constipation, including patients randomly assigned to conventional treatment alone (n = 30) or FMT (n = 30) through a nasointestinal tube.²⁰ The authors reported modestly significant differences between the intervention group and control group in the clinical cure rate (36.7% vs. 13.3%, p = 0.04), and additional outcome measures. However, the FMT group had more treatment-related adverse events than did the control group (50 vs. 4 cases) and the study had limited follow-up (12 weeks).

In 2018, Bajaj et al. published a small RCT (n=20 patients, 10 per treatment group) evaluating FMT for treatment of hepatic encephalopathy compared to standard of care.²¹ The authors only reported adverse events, not patient-specific health outcomes such as cure rate, and noted that treatment with placebo antibiotics, sham FMT or autologous FMT, may have been more appropriate for the control arm. This RCT was limited by the fact that the FMT treatment group was also treated with pretreatment antibiotics, making it difficult to discern the precise role of FMT alone. Given the given the selected donor approach used in this study, the results may not be generalized to FMT from different donors and administration routes.

In addition to the conditions addressed above, FMT has also been evaluated in small case series and case reports as a potential treatment for chronic fatigue syndrome,²² graft-versus-host disease of the gut,^{23,24} intestinal multidrug-resistant bacterial decolonization,²⁵ irritable bowel syndrome,²⁶ hepatic encephalopathy,²⁷ and Parkinson's disease.²⁸ Due to the small number of patients evaluated for these conditions, conclusions cannot be drawn regarding the efficacy of FMT for these conditions.

CLINICAL PRACTICE GUIDELINES

Infectious Diseases Society of America (IDSA)/ Society for Healthcare Epidemiology of America (SHEA)

In 2018, the IDSA/SHEA published joint clinical practice guidelines for clostridium difficile infection in adults and children.²⁹ This was an update to the previous 2010 guidelines and was completed in 2017. This high quality guideline was informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options, including literature published up to the end of 2016.

Initial Occurrence of CDI:

“Either vancomycin or fidaxomicin is recommended over metronidazole for an initial episode of CDI.” This was a strong recommendation based on high quality evidence and was recommended regardless of disease severity.

“In settings where access to vancomycin or fidaxomicin is limited, we suggest using metronidazole for an initial episode of nonsevere CDI only.” This was a strong recommendation based on moderate quality evidence.

For fulminant CDI, previously referred to as severe, complicated CDI, “vancomycin administered orally is the regimen of choice (strong recommendation, moderate quality of evidence). If ileus is present, vancomycin can also be administered per rectum (weak recommendation, low quality of evidence).”

Recurrent or Recalcitrant CDI:

First recurrence: Treatments included either vancomycin or fidaxomicin, depending on antibiotic used during the first occurrence. These were weak recommendations, based on moderate to low quality evidence.

Second or subsequent recurrence: FMT was listed as an option for recurrent CDI, with the guideline stating “[FMT] is recommended for patients with multiple recurrences of CDI who have failed appropriate antibiotic treatments.” This was a strong recommendation, but is only to be considered after the second recurrence. The guideline stated, “the opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (i.e., 3 CDI episodes) should be tried prior to offering fecal microbiota transplantation.” This same recommendation was extended to children, but was a weak recommendation, based on low quality evidence.

American Society of Colon and Rectal Surgeons (ASCRS)

In 2015, the ASCRS published evidence-based practice parameters for the management of *Clostridium difficile* infection that recommended the following:³⁰

Initial Occurrence of CDI:

“Both metronidazole and vancomycin are acceptable first-line agents for an initial bout of CDI, with selection normally based on disease severity.” This was a strong recommendation based on moderate-quality evidence (RCTs with limitations).

“Surgery [] should typically be reserved for patients with severe colitis that fails to improve with medical therapy, for generalized peritonitis, or for rare cases of colonic perforation.” This was a strong recommendation, but was based on low-quality evidence (observational studies or case series with limited long term follow-up).

Recurrent or Recalcitrant CDI:

First line treatments for recurrent CDI (defined as recurrent diarrhea AND a positive fecal sample for *C. diff.* or its toxins, or colonoscopic/histopathologic evidence of pseudomembranous colitis) include either metronidazole or vancomycin. This was a strong recommendation, but was based on low quality evidence.

FMT was listed as one of several alternative treatments, with the guideline stating:

“Patients with refractory CDI may be considered for fecal bacteriotherapy (intestinal microbiota transplantation) if conventional measures have failed.” This was a strong recommendation based on low quality evidence. However, the guideline indicated that “it is recommended that conventional methods of treatment should be sequentially exhausted before considering fecal bacteriotherapy”.

The guideline also noted that, “best practices for this treatment modality still need to be developed with regard to patient selection, donor selection, and fecal transplant protocol as further experience with this technique evolves.”

National Institute for Health and Care Excellence (NICE)

In 2014, NICE issued an interventional procedure guidance for fecal microbiota transplant (FMT) for the treatment of recurrent CDI, stating the following:³¹

“Current evidence on the efficacy and safety of [FMT] for recurrent *C. difficile* infection is adequate to support the use of this procedure.... The procedure should only be considered for people with recurrent *C. difficile* infections that have failed to respond to antibiotics and other treatments.”

The guidance stated that first line treatment includes rehydration and antibiotic therapy, but did not expand further.

American College of Gastroenterology (ACG)

In 2013, the ACG published evidence-based practice guidelines for the diagnosis, treatment and prevention of *Clostridium difficile* infection.³²

Initial Occurrence of CDI:

Either metronidazole or vancomycin were recommended as first-line agents, depending on disease severity and intolerance/allergies. These were typically strong recommendations based on high- to moderate-quality evidence. Severe CDI treatment recommendations included modified vancomycin protocols (strong recommendation based on low quality evidence) and surgery in select patients (strong recommendation based on moderate quality evidence).

Recurrent or Recalcitrant CDI:

First-line treatment for recurrent CDI, defined as recurrence within 8 weeks of completion of therapy, is metronidazole or pulsed vancomycin regimen. The ACG cautioned against the use of fidaxomicin due to insufficient evidence of superiority over vancomycin.

Fecal transplant should be considered, “if there is a third recurrence following a pulsed vancomycin regimen”. This was a conditional (moderate strength) recommendation (uncertainty exists about the risk-benefit ratio) based on moderate-quality evidence.

The ACG noted that long-term follow-up for any treatment of recurrent CDI is limited and the potential for transmission of infectious agents is a concern.

CENTERS FOR MEDICARE & MEDICAID

As of 2/19/2020, no Centers for Medicare & Medicaid (CMS) coverage guidance was identified which addresses fecal microbiota transplantation for any indication.

POLICY SUMMARY

There is sufficient evidence that the use of fecal microbiota transplantation (FMT) as a treatment for recurrent *Clostridium difficile* infections (CDI), when previous occurrences have been refractory to antibiotic regimens, leads to higher cure rates (clinical remission) than additional treatments with antibiotic therapies. In addition, all recent clinical practice guidelines support the use of FMT in this setting.

There is insufficient evidence that use of FMT as a treatment for an initial occurrence of CDI improves cure rates when compared with antibiotic treatment. The majority of the evidence consists of small case series and case reports. Only one comparative study was identified, which reported no difference in cure rates between FMT and standard vancomycin therapy. In addition, none of the clinical practice guidelines address the use of FMT in this setting.

There is insufficient evidence that use of FMT as a treatment for inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, improves cure rates when compared with other treatments or placebo. The majority of the evidence consists of small case series that were heterogeneous in terms of the site of IBD, measures of therapeutic response, clinical evaluation tools used, and inclusion/exclusion of patient's with Crohn's disease. Only two RCTs were identified, neither found any significant differences concerning clinical response or remission rates for FMT compared to placebo. Systematic reviews of the use of FMT for IBD report that conclusions regarding the efficacy of FMT in this setting cannot be drawn at this time. No clinical practice guidelines were identified that address FMT as a treatment option for inflammatory bowel disease, Crohn's disease or ulcerative colitis.

There is insufficient evidence that use of FMT as a treatment for other conditions not addressed above, including but not limited to constipation and metabolic syndrome, improves cure rates when compared with other treatments or placebo. No clinical practice guidelines were identified that address FMT as a treatment option for any indication other than CDI.

INSTRUCTIONS FOR USE

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days' notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

REGULATORY STATUS

U.S. Food and Drug Administration (FDA) Regulation of Fecal Microbiota for Transplantation

Currently, the FDA has classified human stool as a biological agent and determined that its use in fecal microbiota transplantation (FMT) therapy and other research should be regulated to ensure patient safety. To use FMT to treat recurrent *Clostridium difficile* infection (CDI), an investigational new drug (IND) permit is not required, but is strongly encouraged. Therefore, the use of FMT for recurrent CDI does not require FDA-approval.

However, the use FMT for research or to treat any condition other than recurrent CDI, required an IND permit approved by the FDA.

Per the FDA **Draft** Guidance for Industry on FMT for refractory CDI (published in March 2016):³³

“FMT administered to treat *C. difficile* infection meets the definition of a biological product, as defined in section 351(i) of the PHS Act (42 U.S.C. 262(i)), in that it is a regulated article applicable to the prevention, treatment, or cure of a disease or condition of human beings. It also meets the definition of a drug within the meaning of section 201(g) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(g)), in that it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or is intended to affect the structure or any function of the body of man. As a biological product, FMT administered to treat *C. difficile* infection is subject to the licensing requirements set forth in section 351 of the PHS Act (42 U.S.C. 262). It is, however, exempt from these licensing requirements when administered pursuant to an IND application and in compliance with the IND regulations set forth in 21 CFR Part 312. (See 42 U.S.C. 262(a)(3)).”

This guidance is in draft form only, is still open for comments and has not been approved by the FDA in its final form.

In June 2019, the FDA advised that stool donors for fecal microbiota transplantation be screened with questions that specifically address risk factors for colonization with Multi Drug Resistant Organisms (MDROs), and individuals at higher risk of colonization with MDROs should be excluded as donors.³⁴ In addition, FDA scientists advised that donor stool should be specifically tested for MDROs and not used if positive.

Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

REFERENCES

1. ECRI Institute. Emerging Technology Report. Fecal Microbiota Transplantation for Treating Recurrent Clostridium difficile Infection. Published: 3/16/2012. Updated: 7/21/2016. <https://www.ecri.org/components/Target/Pages/12037.aspx?tab=2#>. Accessed 2/21/2020.
2. Hayes Inc. Fecal Microbiota Transplant for Refractory or Recurrent Clostridium Difficile Infection in Adults. https://www.hayesinc.com/subscribers/displaySubscriberArticle.do?articleId=48366&searchSto re=%24search_type%3Dall%24icd%3D%24keywords%3Dfecal%2Cmicrobiota%2Ctransplantation %24status%3Dall%24page%3D1%24from_date%3D%24to_date%3D%24report_type_options%3 D%24technology_type_options%3D%24organ_system_options%3D%24specialty_options%3D% 24order%3DasearchRelevance. Published 2016 (updated 2018; archived 2019). Accessed 2/19/2020.
3. Washington State Health Care Authority. Health Technology Clinical Committee. Health Technology Assessment: Fecal microbiota transplantation (FMT). Final evidence report. Published: September 30, 2016. <https://www.hca.wa.gov/assets/program/fmt-final-report-20161005.pdf>. Accessed 2/19/2020.
4. Agency for Healthcare Research and Quality (AHRQ). Effective Health Care Program. Comparative effectiveness review. Early Diagnosis, Prevention, and Treatment of Clostridium difficile: Update. Published: 03/29/2016. https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/c-difficile-update_research.pdf. Accessed 2/19/2020.
5. 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. *Alimentary pharmacology & therapeutics*. 2017;46(5):479-493. <https://onlinelibrary.wiley.com/doi/epdf/10.1111/apt.14201>.
6. Moayyedi P, Yuan Y, Baharath H, Ford AC. Faecal microbiota transplantation for Clostridium difficile-associated diarrhoea: a systematic review of randomised controlled trials. *The Medical journal of Australia*. 2017;207(4):166-172. <https://www.mja.com.au/journal/2017/207/4/faecal-microbiota-transplantation-clostridium-difficile-associated-diarrhoea>.
7. Iqbal U, Anwar H, Karim MA. Safety and efficacy of encapsulated fecal microbiota transplantation for recurrent Clostridium difficile infection: a systematic review. *European journal of gastroenterology & hepatology*. 2018. https://journals.lww.com/eurojgh/Abstract/publishahead/Safety_and_efficacy_of_encapsulated_fecal.98073.aspx.
8. Tang G, Yin W, Liu W. Is frozen fecal microbiota transplantation as effective as fresh fecal microbiota transplantation in patients with recurrent or refractory Clostridium difficile infection: A meta-analysis? *Diagnostic microbiology and infectious disease*. 2017;88(4):322-329. <https://www.clinicalkey.com#!/content/playContent/1-s2.0-S0732889317301529?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0732889317301529%3Fshowall%3Dtrue&referrer=https:%2F%2Fwww.ncbi.nlm.nih.gov%2Fpubmed%2F28602517>.
9. Chapman BC, Moore HB, Overbey DM, et al. Fecal microbiota transplant in patients with Clostridium difficile infection: A systematic review. *The journal of trauma and acute care surgery*. 2016;81(4):756-764. <https://www.ncbi.nlm.nih.gov/pubmed/27648772>.

10. Lee CH, Belanger JE, Kassam Z, et al. The outcome and long-term follow-up of 94 patients with recurrent and refractory *Clostridium difficile* infection using single to multiple fecal microbiota transplantation via retention enema. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology*. 2014;33(8):1425-1428.<https://www.ncbi.nlm.nih.gov/pubmed/24627239>.
11. Camacho-Ortiz A, Gutierrez-Delgado EM, Garcia-Mazcorro JF, et al. Randomized clinical trial to evaluate the effect of fecal microbiota transplant for initial *Clostridium difficile* infection in intestinal microbiome. *PloS one*. 2017;12(12):e0189768. Safety and efficacy of encapsulated fecal microbiota transplantation for recurrent *Clostridium difficile* infection: a systematic review.
12. Colman RJ, Rubin DT. Fecal microbiota transplantation as therapy for inflammatory bowel disease: a systematic review and meta-analysis. *Journal of Crohn's & colitis*. 2014;8(12):1569-1581.<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4296742/>.
13. Rossen NG, MacDonald JK, de Vries EM, et al. Fecal microbiota transplantation as novel therapy in gastroenterology: A systematic review. *World journal of gastroenterology*. 2015;21(17):5359-5371.<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4419078/>.
14. Sun D, Li W, Li S, et al. Fecal Microbiota Transplantation as a Novel Therapy for Ulcerative Colitis: A Systematic Review and Meta-Analysis. *Medicine*. 2016;95(23):e3765.<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4907653/>.
15. Narula N, Kassam Z, Yuan Y, et al. Systematic Review and Meta-analysis: Fecal Microbiota Transplantation for Treatment of Active Ulcerative Colitis. *Inflammatory bowel diseases*. 2017;23(10):1702-1709.<https://academic.oup.com/ibdjournal/article-abstract/23/10/1702/4791645?redirectedFrom=fulltext>.
16. Costello SP, Soo W, Bryant RV, Jairath V, Hart AL, Andrews JM. Systematic review with meta-analysis: faecal microbiota transplantation for the induction of remission for active ulcerative colitis. *Alimentary pharmacology & therapeutics*. 2017;46(3):213-224.<https://www.ncbi.nlm.nih.gov/pubmed/28612983>.
17. Shi Y, Dong Y, Huang W, Zhu D, Mao H, Su P. Fecal Microbiota Transplantation for Ulcerative Colitis: A Systematic Review and Meta-Analysis. *PloS one*. 2016;11(6):e0157259.<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4905678/>.
18. Imdad A, Nicholson MR, Tanner-Smith EE, et al. Fecal transplantation for treatment of inflammatory bowel disease. *Cochrane Database of Systematic Reviews*. 2018(11).<https://doi.org/10.1002/14651858.CD012774.pub2>.
19. Myneedu K, Deoker A, Schmulson MJ, Bashashati M. Fecal microbiota transplantation in irritable bowel syndrome: A systematic review and meta-analysis. *United European Gastroenterol J*. 2019;7(8):1033-1041
20. Tian H, Ge X, Nie Y, et al. Fecal microbiota transplantation in patients with slow-transit constipation: A randomized, clinical trial. *PloS one*. 2017;12(2):e0171308.<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5291446/>.
21. Bajaj JS, Kassam Z, Fagan A, et al. Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: A randomized clinical trial. *Hepatology (Baltimore, Md)*. 2017;66(6):1727-1738.<https://www.ncbi.nlm.nih.gov/pubmed/28586116>.
22. Borody TJ, Nowak A, Finlayson S. The GI microbiome and its role in chronic fatigue syndrome: A summary of bacteriotherapy. *Journal of the Australasian College of Nutritional and Environmental Medicine*. 2012;31(3):3
23. Kakhana K, Fujioka Y, Suda W, et al. Fecal microbiota transplantation for patients with steroid-resistant acute graft-versus-host disease of the gut. *Blood*. 2016;128(16):2083-2088.<https://www.ncbi.nlm.nih.gov/pubmed/27461930>.

24. Kakihana K. Fecal microbiota transplantation for acute graft-versus-host disease of the gut. [*Rinsho ketsueki*] *The Japanese journal of clinical hematology*. 2017;58(5):499-505. <https://www.ncbi.nlm.nih.gov/pubmed/28592766>.
25. Davido B, Batista R, Michelon H, et al. Is faecal microbiota transplantation an option to eradicate highly drug-resistant enteric bacteria carriage? *The Journal of hospital infection*. 2017;95(4):433-437
26. Borody TJ, George L, Andrews P, et al. Bowel-flora alteration: a potential cure for inflammatory bowel disease and irritable bowel syndrome? *The Medical journal of Australia*. 1989;150(10):604. <https://www.ncbi.nlm.nih.gov/pubmed/2783214>.
27. Kao D, Roach B, Park H, et al. Fecal microbiota transplantation in the management of hepatic encephalopathy. *Hepatology (Baltimore, Md)*. 2016;63(1):339-340. <https://www.ncbi.nlm.nih.gov/pubmed/26264779>.
28. Ananthaswamy A. Faecal transplant eases symptoms of Parkinson's disease. In: Elsevier; 2011.
29. 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). *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2018;66(7):987-994. <https://academic.oup.com/cid/article/66/7/e1/4855916#113830989>.
30. Steele SR, McCormick J, Melton GB, et al. Practice parameters for the management of Clostridium difficile infection. *Diseases of the colon and rectum*. 2015;58(1):10-24. https://www.fascrs.org/sites/default/files/downloads/publication/practice_parameter_clostridium_difficile_infection.pdf.
31. National Institute for Health and Care Excellence (NICE) Guidance. Faecal microbiota transplant for recurrent Clostridium difficile infection. Interventional procedures guidance [IPG485]. Published : March 2014. <https://www.nice.org.uk/guidance/ipg485>. Accessed 2/21/2020.
32. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. *The American journal of gastroenterology*. 2013;108(4):478-498; quiz 499. <http://gi.org/guideline/diagnosis-and-management-of-c-difficile-associated-diarrhea-and-colitis/>.
33. U.S. Food and Drug Administration. Guidance Document: Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat Clostridium difficile Infection Not Responsive to Standard Therapies. <https://www.fda.gov/media/96562/download>. Published 2016. Accessed 2/21/2020.
34. U.S. Food and Drug Administration. Important Safety Alert Regarding Use of Fecal Microbiota for Transplantation and Risk of Serious Adverse Reactions Due to Transmission of Multi-Drug Resistant Organisms. <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/important-safety-alert-regarding-use-fecal-microbiota-transplantation-and-risk-serious-adverse>. Published 2019. Accessed 2/20/2020.