Fecal Transplant

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DESCRIPTION

Fecal transplant also called fecal bacteriotherapy, donor feces infusion, fecal microbiota transplantation (FMT), or duodenal infusion of intestinal microorganisms, involves the administration of intestinal microorganisms via transfer of stool from a healthy individual into a diseased individual, with the intent of restoring 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 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.

Fecal transplant is proposed for the treatment of 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.

Clostridioides difficile Infection

To date, the major potential clinical application of a fecal transplant 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. 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.

Other Applications

Other potential uses of a fecal transplant 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. The product is made from 33 bacterial isolates developed from culturing stool from a healthy donor.

Recurrent Clostridioides Difficile Infection

Clinical Context and Therapy Purpose
The purpose of a fecal transplant is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with
recurrent Clostridioides difficile infection (CDI) refractory to antibiotic therapy.

The question addressed in this evidence review is: Does the use of a fecal transplant improve the net health outcome in patients with recurrent CDI?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with recurrent CDI refractory to antibiotic therapy.

Interventions
The therapy being considered is a fecal transplant.

Comparators
The following therapy is currently being used to treat CDI: standard antibiotic regimens.
Outcomes

The general outcomes of interest are symptoms, change in disease status, and treatment-related morbidity. Follow-up ranging up to and beyond 12 weeks is of interest to monitor for outcomes. Outcomes reported in fecal transplant trials for CDI include clinical cure, resolution of CDI with no further recurrence, or reduced risk of CDI recurrence.

There are inconsistencies across these trials in how CDI resolution (i.e., treatment success) and recurrence are defined and measured.

Treatment success generally required a resolution of diarrhea symptoms with or without laboratory confirmation; up to 3 consecutive negative stool tests for C. difficile toxin have been required to define cure in 1 trial. Conversely, recurrence generally required the presence of diarrhea with or without laboratory confirmation or the need for further treatment for up to 17 weeks after the incident case.

- The 2017 Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America guideline for CDI recommends against repeat testing for C.difficile toxin during the same episode of diarrhea or for asymptomatic patients, since >60% of patients may remain positive for the C. difficile toxin even after successful treatment.
- Per the 2017 IDSA/SHEA guideline, a recurrent case occurs within 2 to 8 weeks of the incident case and requires both clinical plus laboratory evidence of disease for diagnosis. The 2021 update to the IDSA/SHEA guideline does not comment on repeat testing nor does it provide an updated definition of recurrent CDI.

- Per 2 separate 2021 guidelines from the American Society of Colon and Rectal Surgeons (ASCRS) and American College of Gastroenterology (ACG), a recurrent case occurs within 8 weeks after the completion of a course of CDI therapy and requires both clinical plus laboratory evidence of disease for diagnosis.

Du et al (2021) completed a systematic review and meta-analysis by evaluating the efficacy of FMT delivery via oral capsules for the treatment of recurrent CDI. The analysis included 12 case series and 3 RCTs (N=763 patients). Encapsulated delivery of FMT demonstrated an overall efficacy rate of 82.1% (95% CI, 76.2 to 87.4). There was no statistically significant difference in the efficacy of FMT capsules that used lyophilized stool versus frozen stool (p=.37). There was also no statistically significant Hildifference in the efficacy of FMT capsules compared with colonoscopy (RR, 1.01; 95% CI, 0.95 to 1.08). No serious adverse events attributable to oral FMT capsules were reported, other than those associated with treatment failure.

(2020) Ramai et al completed a systematic review and meta-analysis by comparing several routes of FMT delivery for the treatment of recurrent CDI Twenty-six studies (N=1309) were included; colonoscopy was used in 16 studies (n=483), nasogastric/nasoduodenal tube in 5 studies (n=149), enema in 4 studies (n=360), and oral capsules in 4 studies (n=301). The pooled cure rates for colonoscopy, capsules, enema, and nasogastric/nasoduodenal tube were 94.8%, 92.1%, 87.2%, and 78.1%, respectively. Cure rates were significantly higher with colonoscopy versus nasogastric tube or enema (p<.001 for both); capsules were also superior to nasogastric tube (p<.001) and enema (p=.005). The difference in cure rates did not reach statistical significance when comparing colonoscopy and capsules (p=.126).

(2019) Rokkas et al performed a systematic review and meta-analysis to assess the efficacy of FMT for the treatment of recurrent CDI. Six RCTs were included in the analysis (N=348), and 7 interventions were compared (donor FMT [dFMT], autologous FMT [aFMT], vancomycin, vancomycin plus dFMT, vancomycin plus bowel lavage, fidaxomicin, and placebo). The primary outcome was the resolution of CDI-related symptoms. The network meta-analysis demonstrated that dFMT was superior to vancomycin (odds ratio [OR], 20.02; 95% credible interval [CrI], 7.05 to 70.03), vancomycin plus dFMT (OR, 4.69; 95% CrI, 1.04 to 25.22), vancomycin plus bowel lavage (OR, 22.77; 95% CrI, 4.34 to 131.63), and fidaxomicin (OR, 22.01; 95% CrI, 4.38 to 109.63) groups.

(2019) Tariq et al performed a systematic review and meta-analysis to assess the efficacy of FMT as a treatment option for recurrent CDI on the basis of results from open-label studies and placebo-controlled clinical trials. The authors were motivated to perform this analysis based on observations that FMT cure rates for CDI are high in observational studies (eg, >90%) but appear to be consistently lower in open-label studies and clinical trials. Thirteen studies were included for evaluation, including 6 placebo-controlled RCTs

and 7 open-label studies. Out of 610 patients receiving FMT, 439 patients achieved clinical cure (76.1%; 95% confidence interval [CI]: 66.4% to 85.7%); study heterogeneity was significant (I^2 =91.35%). Cure rates were found to be lower in randomized trials (139/216, 67.7%; 95% CI: 54.2% to 81.3%) versus open-label studies (300/394, 82.7%; 95% CI: 71.1% to 94.3%; p<.001). Subgroup meta-analysis by FMT route of administration indicated lower cure rates with enema than colonoscopy (66.3% vs. 87.4%; p<.001). However, no differences between colonoscopy and oral delivery routes were detected (87.4% to 81.4%; p=.17). Lower cure rates were observed for studies that included both recurrent and refractory CDI than those that only included patients with recurrent CDI (63.9% vs. 79%; p<.001).

(2018) Khan et al conducted a systematic review of the literature and meta-analysis of pooled data on the use of FMT as a treatment option for recurrent CDI. Reviewers only selected RCTs comparing FMT (fresh or frozen) with medical treatment. Among the selected studies, there was a nonsignificant trend toward the resolution of diarrhea following a single fresh FMT infusion (nasogastric or nasojejunal tube, upper endoscopy, retention enema, or colonoscopy) compared with frozen FMT infusion or medical treatment (OR, 2.45; 95% CI, 0.78 to 7.71; p=.12, I^2=69%), but different forms and routes of FMT administration were shown to be equally efficacious. Reviewers concluded that FMT is a promising treatment modality for recurrent CDI. Variability of FMT dose usages, small trial populations, and window to assess treatment success or failure limited analysis data.

(2018) Mamo et al conducted a retrospective study to investigate the long-term clinical outcomes of FMT in patients with CDI, using a follow-up survey of 137 patients who had received FMT for recurrent CDI at a single center between January 2012 and December 2016. Median time from last FMT to follow-up was 22 months. Overall, at follow-up, 82% (113/137) of patients had no recurrence of CDI (nonrecurrent CDI group) and 18% (24/137) of patients had CDI (recurrent CDI group). The survey results suggested that antibiotic exposure for non-CDI infections after FMT were more common in the recurrent CDI group (75%) than in the nonrecurrent CDI group (38%; p<.001). Overall, 82% of patients reported being symptom-free.

(2017) Quraishi et al published a systematic review and meta-analysis of studies (including RCTs) investigating the effect of FMT in patients with recurrent or refractory CDI. Reviewers deemed the RCTs as having a low risk of bias (including adequate randomization with allocation concealment and intention-to-treat analysis). Reviewers did not report an assessment of bias in terms of blinding, sample size adequacy, or possible differences in baseline characteristics. They argued that none of the trials examining the efficacy of FMT were truly placebo-controlled, and the case series followed patients until resolution of CDI (range, 10 weeks to 8 years), though some had an incomplete follow-up. In the pooled analysis, 92% of patients had a resolution of CDI (95% CI, 89% to 94%); heterogeneity was classified as likely moderate (I^2=59%). Additionally, in the 7 trials that evaluated FMT, the intervention overall was associated with an increase in the resolution of recurrent and refractory CDI (relative risk [RR],

0.23; 95% CI, 0.07 to 0.80). The 30-case series reported resolution rates for CDI ranging from 68% to 100%.

The review found FMT to be effective in the treatment of recurrent and refractory CDI, and no serious adverse events from FMT were reported in the RCTs through the follow-up period. Most adverse effects in the case series were minor (bloating, belching, abdominal cramps, pain or discomfort, nausea, vomiting, excess flatulence, constipation, transient fever, urinary tract infections, self-limiting diarrhea, irregular bowel movement). However, reviewers noted several limitations. Based on variability in the definitions of CDI resolution used across the studies, reviewers could not distinguish between recurrent and refractory CDI. There were also variations across studies in terms of recipient preparations, number of infusions, time to resolution, follow-up, overall response, dosing, concurrent use of medications, and other nonspecified biases. Heterogeneity among studies was considerable.

(2017) Meighani et al assessed outcomes from FMT for recurrent CDI in patients with inflammatory bowel disease (IBD). All patients underwent FMT between December 2012 and May 2014 within a single health care system. Demographic and clinical characteristics, as well as treatment outcomes for patients with IBD, were compared with those of the general population within this system. Of 201 patients who underwent FMT, 20 had concurrent IBD, and the study found that the response to FMT and CDI relapse rate in the IBD group (n=20) did not differ statistically from the rest of the cohort (n=201). The overall response rate in the IBD population was 75% at 12 weeks. Study design, lack of a standardized FMT treatment protocol, and variable donors limit certainty in conclusions drawn from these data.

(2017) Quraishi et al completed a review by discussed previously, included a subgroup analysis of FMT delivery. Pooled analysis of 7 RCTs and 25 case series revealed a significant difference between lower gastrointestinal delivery (95%; 95% CI, 92% to 97%) and upper gastrointestinal delivery (88%; 95% CI, 82% to 94%; p=.02). Reviewers concluded that FMT appeared to be effective in the treatment of recurrent and refractory CDI, independent of the delivery route.

Prior to the availability of RCTs in this arena, several systematic reviews of uncontrolled studies on FMT for treating CDI were also published. Overall, data from these uncontrolled studies have reported high rates of resolution of recurrent CDI following treatment with FMT.

Recurrent Clostridioides Difficile Infection: Donor Versus Autologous Feces

(2020) Ramai et al completed a review also included a subgroup analysis of donor relation. Results demonstrated that cure rates were not significantly influenced by whether FMT used unrelated or a mix of related and unrelated donors (94.5% and 95.7%, respectively).

(2019) Rokkas et al completed a review by discussed previously, included a subgroup analysis of donor relation. Using data from a single RCT, results demonstrated the superiority of dFMT over aFMT for resolution of CDI symptoms (OR, 6.42; 95% CrI, 1.28 to 57.74). The wide CrI creates uncertainty regarding the difference between these interventions.

Recurrent Clostridioides Difficile Infection: Fresh Versus Frozen Feces
(2020) Ramai et al The review discussed previously, included a subgroup analysis of FMT preparation. The overall cure rates were similar amongst patients treated with FMT that used fresh (n=556) versus frozen (n=753) stool (94.9% and 94.5%, respectively).

(2017) Quraishi et al The review also included a subgroup analysis of FMT preparation. Only 1 RCT in the review directly compared the effects of fresh stool for FMT (n=11) with frozen stool for FMT (n=108) on CDI resolution (RR, 1.19; 95% CI, 0.77 to 1.84). The remaining 30 case series used frozen stool. Two RCTs and 2 case series used fresh stool to prepare FMT. The pooled analyses found no difference in the response rates between fresh (92%; 95% CI, 89% to 95%; I^2=54%) and frozen FMT (93%; 95% CI, 87% to 97%; p=.84; I^2=19%). Reviewers concluded that FMT appeared to be effective in the treatment of recurrent and refractory CDI, independent of FMT preparation.

(2016) Lee et al completed a double-blind RCT review compared fresh with frozen stool used in FMT to treat patients with recurrent CDI.[25,] A total of 232 patients were included, with 114 assigned to frozen FMT and 118 to fresh FMT. The primary endpoint was the proportion of patients with no recurrence of CDI-related diarrhea 13 weeks after FMT. The trial was designed as a noninferiority trial, with a margin of 15%. In the per-protocol population (n=178), clinical resolution of symptoms was reported in 76 (83.5%) of 91 patients in the frozen FMT group and 74 (85.1%) of 87 patients in the fresh FMT group (difference, -1.6%; 95% 1-sided CI, -10.5% to not reached). In the modified intention-to-treat group, clinical resolution with up to 2 FMT treatments was reported in 81 (75.0%) of 108 patients in the frozen FMT group and 78 (70.3%) of 111 patients in the fresh FMT group (difference, 4.7%; 95% 1-sided CI, -5.2% to not reached). The difference between groups was within the 15% noninferiority margin and thus frozen FMT was considered noninferior to fresh FMT.

Recurrent Clostridioides Difficile Infection: Long-term Outcomes
(2019) Lee et al performed a prospective study assessing the long-term durability and safety of FMT for patients with recurrent or refractory CDI. Ninety-four patients underwent FMT via retention enema between 2008 to 2012; 32 patients were unreachable and 37 were deceased 4 to 8 years later for a follow-up survey. Twenty-three of the remaining 25 patients completed the questionnaire. No CDI recurrences were reported in patients treated with FMT. Twelve of 23 participants (52.2%) received at least 1 course of antibiotics for treatment of a condition other than CDI. Nine participants (40.9%) received probiotics. Current health was self-reported as "much better" in 17 patients (73.9%) or "somewhat better" in 3 patients (13.0%). The authors concluded that FMT for

recurrent or refractory CDI appears to be durable at 4 to 8 years following treatment, even after receiving non-CDI antibiotic therapy.

Recurrent Clostridioides Difficile Infection: Pediatric Populations
(2018) Alrdich et al published a retrospective study that included both hospital-acquired CDI and community-acquired CDI cases, comparing the success rates of various treatments used including FMT.21, The pediatric population consisted of 175 subjects ages 1 to 21 years reporting 215 separate CDI episodes. Treatments included oral metronidazole (145/207 [70%]) and oral vancomycin (30/207 [15%]), with recurrent rates of 30% (42/145) and 37% (11/30), respectively. Overall, 29% (63/215) of all CDI cases had at least 1 documented recurrence. Using multivariate analysis, the study showed that subjects with hospital-acquired CDI were 2.6 times less likely to recur than those with community-acquired CDI (OR, 0.39; 95% CI, 0.18 to 0.85; p=.018) and that FMT had an overall success rate of 83% (10/12).

Section Summary: Recurrent Clostridioides difficile Infection
For individuals who have recurrent CDI refractory to antibiotic therapy who receive FMT, the evidence includes systematic reviews with meta-analyses and observational studies. 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.

Inflammatory Bowel Disease

Clinical Context and Therapy Purpose
The purpose of a fecal transplant is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with IBD.

The question addressed in this evidence review is: Does the use of a fecal transplant improve the net health outcome in patients with IBD?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with IBD. Individuals with IBD include subsets of patients with ulcerative colitis (UC) and Crohn disease (CD).

Interventions
The therapy being considered is a fecal transplant.

Comparators
The following therapy is currently being used to treat IBD: standard of care.

Outcomes
The general outcomes of interest are symptoms, change in disease status, and treatment-related morbidity. Follow-up out to 12 weeks is of interest to monitor for outcomes. In clinical trials of a fecal transplant for CD or UC, there are inconsistencies in reported outcomes. Clinical remission was the most reported outcome, but study definitions varied.

According to the 2019 American Gastroenterological Association (AGA) guidelines for moderate to severe UC, the following outcomes should be used for decision-making for adults with moderate to severe UC:

- Induction and maintenance of remission
- Short-term colectomy risk (within 3 months of hospitalization)

Other important outcomes recognized by these guidelines include:

- Induction and maintenance of endoscopic remission
- Maintenance of corticosteroid-free remission
- Serious adverse events (including serious infections and malignancy)
- Treatment tolerability (drug discontinuation due to adverse events).

According to the 2018 AGA guidelines for CD, common outcomes in clinical trials of CD patients include measurements of Crohn disease activity index (CDAI), the Harvey Bradshaw Index, and other patient-reported outcome tools. With regard to remission, the guidelines stress that patients with CD may be in histologic, endoscopic, clinical, or surgical remission. The guidelines note there has been a recent push to more patient-reported outcomes and objective measures of disease (endoscopy findings) versus CDAI. Mucosal healing is an important target in assessing the efficacy of therapies for IBD. In this population, mucosal healing is defined as an absence of ulceration. Endoscopic scoring systems have been developed to quantify the degree of ulceration and inflammation in patients with CD. The Simple Endoscopic Score for Crohn's disease (SES-CD) has been used to assess endoscopic activity in clinical practice.

The 2021 AGA guideline for moderate to severe luminal and perianal fistulizing CD recognizes the following outcomes of interest for decision-making in this arena:

- Induction and maintenance of endoscopic remission
- Maintenance of corticosteroid-free remission
- Serious adverse events (including serious infections and malignancy)
- Treatment tolerability (drug discontinuation due to adverse events).

(2021) Crothers et al published results of a small, single-center, placebo-controlled RCT in the US investigating long-term encapsulated delivery of FMT in patients with mild to

moderate UC. Patients in the FMT group received induction FMT via colonoscopy, followed by 12 weeks of oral maintenance therapy with frozen FMT capsules. Patients were required to be on stable doses of UC-specific medications for at least 6 weeks prior to screening, including tumor necrosis factor inhibitors, oral immunomodulators, oral and topical 5-aminosalicylates, and methotrexate; corticosteroid use was not allowed. Patients in both study groups were pretreated with ciprofloxacin and metronidazole for 7 days prior to randomization to FMT or placebo. No primary outcome was identified; clinical remission (defined as a modified Mayo score ≤2 at 12 weeks plus achievement of several prespecified subscores) and clinical response (defined as a decrease in total Mayo score ≥3 points at 12 weeks plus achievement of several prespecified subscores) were measured. Due to difficulties recruiting patients who met inclusion/exclusion criteria, enrollment was terminated early when only 15 of the expected 20 patients were enrolled; furthermore, 1 patient in the FMT group and 2 in the placebo group did not meet endoscopic criteria for inclusion and were excluded from the study after randomization. The only serious adverse event was a worsening of disease activity, which occurred in 1 patient in each group. Relevant limitations noted are it is unclear whether excluding patients with severe disease is appropriate or matches the intended use profile, the clinically significant difference not prespecified and the follow up is not of sufficient duration for harms.

(2021) Fang et al published results of a small, single-center, open-label RCT in China investigating monotherapy with FMT for recurrent UC. Patients in the FMT group received a single instillation of FMT via colonoscopy; the control group received standard of care UC treatments. Enrolled patients were previously treated with 5-aminosalicylates at stable doses for at least 4 weeks, but had received no other therapy, including immunosuppressive agents or biologics. The primary outcome was steroid-free remission of UC (defined as a total Mayo score ≤2 with an endoscopic Mayo score of ≤1). Patients were followed for up to 24 months after treatment. Overall, FMT was well tolerated with no serious adverse events reported. Relevant limited noted are it is unclear whether excluding patients with comorbidities is appropriate or matches the intended use profile, there is no consort reporting of harms and clinically significant difference is not prespecified. Additional limitations were the investigators and patients were not blinded to treatment and evidence of selective reporting because not all prespecified outcome results were reported.

The same study reported on long-term remission in patients with recurrent active UC who received either a single administration of FMT (n=10) or standard of care UC treatments (n=10). The median remission time was 24 months in both the FMT (range, 6 to 38 months) and control (range, 7 to 35 months) groups (p=.895). No adverse events occurred during long-term follow-up.

(2020) Sokol et al published results of a small, multicenter, single-blind, placebo-controlled RCT in France investigating endoscopic delivery of FMT in patients with CD. Patients could not be on concomitant tumor necrosis factor inhibitors, and those with active disease at screening were treated with oral prednisone. Only those patients who

achieved clinical remission within the 3 weeks following the commencement of corticosteroids (defined as a Harvey Bradshaw Index <5) were randomized to treatment or placebo. The treatment group received FMT after colon cleansing with polyethylene glycol. The primary endpoint was the colonization of donor microbiota at week 6. Colonization was defined as being successful if the fecal microbiota of the recipient 6 weeks after FMT was more similar to the fecal microbiota of the donor than to the recipient before FMT; similarity was assessed using Sorensen's index, and a score ≥0.6 signaled successful colonization. The rate of clinical flares in the 24 weeks following FMT was a secondary endpoint in the study. A clinical flare was defined as any 1 of the following: a CDAI > 220 points, a CDAI between 150 and 220 with an increase >70 compared with baseline, the need for surgery, or the need to start a new medical treatment for CD. Eight patients received FMT and 9 received placebo treatment. None of the adverse events observed in the trial were considered to be related to FMT.
Zhou et al (2020) completed a systematic review and meta-analysis and searched for studies to September 2019 evaluating the efficacy and safety of FMT, biological agents, and tofacitinib in patients with UC. Sixteen RCTs were identified (4 with FMT, 10 with biological agents, and 2 with tofacitinib). Compared with placebo, the clinical response was significantly higher with FMT (RR, 1.648; 95% CI, 1.253 to 2.034) as was clinical remission (RR, 2.486; 95% CI, 1.393 to 4.264). Indirect comparisons did not reveal any statistically significant differences between FMT and adalimumab, infliximab, golimumab, vedolizumab, or tofacitinib for either clinical response or clinical remission. The incidence of adverse events was also similar when comparing FMT to biologics or tofacitinib. Relevant limitations include is it is unclear whether excluding patients with severe disease is appropriate or matches the intended use profile, the type and quantity of vehicle used for the placebo group were not clearly defined, the rationale for clinically significant difference not provided, and there was not sufficient duration of time provided for harms as well as the investigators were not blinded to the treatment.

(2020) Li et al published the results of a prospective observational cohort study that included 202 patients with UC who underwent the first course of FMT at a single center in China between November 2012 to September 2018. Patients with mild, moderate, and severe active UC (Mayo score from 3 to 12) were included. Of the initial 202 patients, 122 patients who achieved clinical response at 1 month after the first course of FMT were included in the analysis for time of maintaining efficacy. Among these 122 patients, 22 patients had a sustained response without undergoing a second course of FMT until January 1, 2019 (the terminal point of follow-up), 77 patients had disease relapse before the second course of FMT, and 23 patients underwent consolidation therapy with a second course of FMT before disease relapse. The median follow-up was 25.5 months (interquartile range [IQR], 11.75 to 43 months). The median time of maintaining efficacy from the first course of FMT in 99 patients was 120 days (IQR, 45 to 180 days) and the median time of maintaining efficacy from the second course (i.e., consolidation) of FMT in 23 patients was 415 days (IQR, 255 to 780 days; p<.001). No new safety issues were reported in this study.

(2019) Costello et al published the results of a double-blind, placebo-controlled trial assessing whether high-intensity, short-duration, anaerobically prepared FMT could induce remission in patients with active UC (Costello, 2019). Patients with Mayo Clinic scores between three and ten and endoscopic subscores greater than or equal to two were enrolled. The primary outcome was steroid-free remission of UC, defined as a total Mayo Clinic score less than or equal to two with an endoscopic Mayo score of one or less at week eight. Steroid-free remission was reassessed at 12 months. Secondary outcomes included adverse events. Seventy-three patients were randomized to receive pooled donor stool (dFMT) (n=38) or autologous stool (aFMT) (n=35). There were three serious adverse events in the dFMT group (worsening colitis, CDI requiring colectomy, and one case of pneumonia) and two serious adverse events in the aFMT group (both worsening colitis).

(2019) Sood et al published results of a 48-week, small, single-center RCT in India evaluating maintenance FMT (n=31) versus placebo (n=30) in patients with UC receiving standard of care therapies who are in clinical remission after prior FMT sessions. The primary endpoint was the maintenance of steroid-free clinical remission (Mayo score ≤2 and all subscores ≤1) at week 48. Relapse occurred in 3 patients in the FMT group and 8 patients in the placebo group. There were no serious adverse events reported in this trial.

The same study also reported results of a 48-week RCT evaluating maintenance FMT (n=31) versus placebo (n=30) in patients with UC receiving standard of care therapies who are in clinical remission after prior FMT sessions. Maintenance of steroid-free clinical remission (Mayo score ≤2 and all subscores ≤1) was numerically higher in patients allocated to FMT (27 patients [87.1%]) versus placebo (20 patients [66.7%]), but the difference did not reach statistical significance (p=.111). A significantly higher number of patients with FMT versus placebo achieved endoscopic remission (58.1% vs. 26.7%; p=.026) and histological remission (45.2% vs. 16.7%; p=.033). Three patients receiving FMT (9.7%) and 8 patients on placebo (26.7%) relapsed.

(2017) Paramsothy et al completed a systematic review and meta-analysis by searched for studies to January 2017 evaluating the efficacy and/or safety of FMT use in treating IBD, distributed across 3 disease subtypes (UC, CD, and pouchitis). Fifty-three studies were selected and analyzed for this review (41 in UC, 11 in CD, 4 in pouchitis). Overall, 36% (201/555) of UC patients, 50.5% (42/83) of CD patients, and 21.5% (5/23) of pouchitis patients achieved the primary outcome of clinical remission. Pooled proportion achieving clinical remission was 33% among cohort studies, with a moderate risk of heterogeneity; among the 4 RCTs selected, there was a significant benefit in clinical remission (OR, 2.89; 95% CI, 1.36 to 6.13; p=.006), with moderate heterogeneity. Transient gastrointestinal complaints comprised most of the adverse events. Reviewers concluded that FMT appeared most promising in treating UC, and the use of FMT to treat CD should be interpreted cautiously, due to wide CIs.

(2014) Sha et al published a systematic review of observational data on FMT for the treatment of IBD. Reviewers identified reports of 111 IBD patients (UC and CD)

worldwide who received fecal transplants for IBD. All studies were case series. Remission was achieved in 87 (77.8%) of 111 IBD patients.

Section Summary: Inflammatory Bowel Disease
For individuals who have IBD who receive FMT, the evidence includes systematic reviews and RCTs. Two systematic reviews with meta-analysis concluded that FMT had shown promise in treating patients with UC, but 1 meta-analysis recommended caution about using FMT to treat patients with 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. 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. This current evidence is not sufficient to permit conclusions on the efficacy of FMT for UC. 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.

Irritable Bowel Syndrome

Clinical Context and Therapy Purpose
The purpose of a fecal transplant is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with irritable bowel syndrome (IBS).

The question addressed in this evidence review is: Does the use of a fecal transplant improve the net health outcome in patients with IBS?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with IBS. Irritable bowel syndrome is a gastrointestinal disordered marked by chronic abdominal pain with or without altered bowel movement patterns, in the absence of underlying damage or an identified cause. It is the most diagnosed gastrointestinal condition, accounting for approximately 30% of all gastroenterologist referrals. The clinical prevalence as estimated from population-based studies in North America is approximately 10 to 15%. While the pathophysiology of IBS remains uncertain, the complex ecology of the fecal transplant has led to speculation as to whether alterations in its composition could be associated with IBS.

Interventions
The therapy being considered is a fecal transplant .

Comparators
The following therapy is currently being used to treat IBS: standard of care. Standard of care may include lifestyle and dietary modifications, the establishment of a physical exercise program, and counseling to manage psychosocial factors. For patients with moderate to severe symptoms that impair quality of life, medication management with

various symptom-targeting supplements and/or pharmacologic agents (e.g., soluble fiber, polyethylene glycol, osmotic laxatives, lubiprostone, linaclotide, tegaserod, loperamide, cholestyramine, and others) may be considered. For patients with refractory symptoms despite adjunctive pharmacologic therapy, food allergy testing, behavior modification, and pharmacological management of psychiatric impairment may be considered.

Outcomes
The general outcomes of interest are symptoms, change in disease status, and treatment-related morbidity. Though not completely standardized, follow-up for IBS would typically occur in the months to years after starting treatment.

Due to the absence of a biologic disease marker, IBS is often difficult to diagnose in the clinical setting. Several symptoms-based criteria have been developed in an effort to standardize the diagnosis of IBS.

1. *The most widely used criteria are the Rome IV criteria, which define IBS as recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with 2 or more of the following criteria*:
    - Related to defecation, with an increase or improvement in pain
    - Associated with a change in stool frequency
    - Associated with a change in stool form (appearance).

2. The previous Rome III diagnostic criteria are less restrictive and are commonly featured in current studies on IBS. *The Rome III criteria define IBS as recurrent abdominal pain or discomfort, 3 days per month in the last 3 months (12 weeks), associated with 2 or more of the criteria below:*
    - Improvement with defecation
    - Onset associated with a change in stool frequency
    - Onset associated with a change in stool form (appearance).

    The Rome III criteria are fulfilled when symptoms have an <u>onset 6 months prior to diagnosis.</u>

3. Subtypes of IBS are based on patient-reported predominant bowel patterns on days with abnormal bowel movements and may utilize the Bristol stool form scale to record stool form and appearance. Irritable bowel syndrome subtypes defined for clinical practice include:
    - IBS with predominant constipation (IBS-C): abnormal bowel movements with predominant constipation (type 1 and 2 on the Bristol stool form scale)
    - IBS with predominant diarrhea (IBS-D): abnormal bowel movements with predominant diarrhea (type 6 and 7 on the Bristol stool form scale)
    - IBS with mixed bowel habits (IBS-M): >1/4 of abnormal bowel movements were constipation and >1/4 of abnormal bowel movements were diarrhea
    - IBS unclassified: patients meet diagnostic criteria for IBS but cannot accurately be categorized into 1 of the 3 main subtypes.

4. The Manning criteria is another diagnostic algorithm that may be used in the diagnosis of IBS, consisting of a questionnaire delivered to the patient by the treating clinician to establish the presence of typical symptoms. Positive diagnosis requires that 3 or more of the following symptoms are met:
    - Pain relieved with defecation
    - More frequent stools at the onset of pain
    - Looser stools at the onset of pain
    - Visible abdominal distention
    - Passage of mucus
    - Sensation of incomplete evacuation.

A validation study comparing the Manning criteria to a previous version of the Rome criteria found it to have less sensitivity but greater specificity in diagnosing IBS.

Measuring outcomes and severity of illness for patients with IBS can be challenging. The Rome Founding Working Team Report indicates that calculating severity in IBS is a complex matter, and is primarily determined by patient-reported symptoms, behaviors, and personal experience of illness. Severity must be understood through a broad integration of health-related quality of life, psychosocial factors, healthcare utilization behaviors, and burden of illness. Individual symptoms such as abdominal pain was considered important but insufficient determinants of IBS severity. Two validated severity measurement scales include the Functional Bowel Disorder Severity Index and the IBS Severity Scoring System (IBS-SSS).

- The Functional Bowel Disorder Severity Index assesses severity based on patient pain behaviors such as the presence and intensity of pain and the number of illness-related healthcare visits. Resultant scores categorize patients with mild (≤36), moderate (37-110), or severe (>110) IBS.
- The IBS-SSS evaluates the intensity of IBS symptoms during a 10-day period and includes assessments of abdominal pain, distension, stool frequency and consistency, and interference with patient quality of life, with each component graded via a visual analog scale. The IBS-SSS provides scores between 0 and 500 and categorizes patients as having mild (75-175), moderate (175-300), or severe (>300) IBS.

(2021) Madsen et al reported the results of a double-blind RCT evaluating the efficacy of FMT capsules (n=26) versus placebo capsules (n=25) in patients with moderate-to-severe IBS (IBS-SSS score ≥175 points). Both groups administered capsules for 12 days and patients were allowed to continue any concomitant IBS medications, including laxatives or agents for constipation. Patients tracked their symptoms in a diary and were followed for 6 months. The primary outcome was not specified, but investigators evaluated abdominal pain, stool frequency, and stool form. Subgroup analyses by IBS subtype were not performed. A noted limitation included a clinically significant difference was not prespecified for the primary outcome; safety outcomes were not reported.

(2020) Holvoet et al reported the results of a double-blind RCT evaluating the efficacy of FMT in patients with IBS-D or IBS-M and severe bloating (mean abdominal bloating

sub-score of ≥3). The intervention group (n=43) received donor FMT via the nasojejunal route and the control group (n=19) received autologous FMT placebo via the same route. A daily symptom diary was used to assess IBS-related symptoms and improvement in IBS symptoms at 12 weeks was the primary outcome of the trial. After a single FMT, more patients in the treatment group versus placebo reported efficacy for more than 1 year (21% vs. 5%). A second FMT reduced symptoms in 67% of patients with an initial response to donor stool, but not in patients with a prior non-response. Limitations of the study included a rationale for excluding individuals with IBS with constipation was not provided, FMT products were not prepared with a standard amount of autologous stool but placebo FMT products were not prepared with a standard amount of autologous stool, a primary outcome measure was not established, and a clinically significant difference was not prespecified for the primary outcome.

(2020) Lahtinen et al reported the results of a double-blind RCT evaluating the efficacy of FMT in patients with IBS. The intervention group (n=23) received donor FMT via colonoscopy and the control group (n=26) received autologous FMT placebo via the same route. Approximately 35% of patients experienced adverse events with no significant difference between groups. A limitation of the study was noted when the placebo FMT products were not prepared with a standard amount of autologous stool.

(2019) Ianiro et al performed a systematic review and meta-analysis to examine the efficacy of FMT as a treatment for IBS compared to either inactive placebo or autologous stool placebo. Five RCTs enrolling 267 patients were included for analysis. Only 7.8% of the included patients had IBS-C. After study data were pooled, 79 (50%) of 158 patients assigned to donor FMT failed to respond, whereas 56 (51.4%) of 109 assigned to placebo failed to respond. Further characteristics and results are summarized in Tables 6 and 7. Study outcomes were mixed by both routes of administration and assignment to treatment or placebo. When data from 3 RCTs utilizing autologous FMT as control groups were pooled, patients were more likely to experience an improvement in IBS symptoms with autologous FMT compared to donor FMT. While all studies utilized Rome III criteria for patient diagnosis and enrollment, not all studies utilized a validated IBS severity scoring system to quantify patient outcomes, limiting interpretation of results.

Section Summary: Irritable Bowel Syndrome
For individuals who have IBS who receive FMT, the evidence includes a systematic review and RCTs. 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 (ie, 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 used FMT delivered 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.

Miscellaneous Conditions

Clinical Context and Therapy Purpose
The purpose of a fecal transplant is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with pouchitis, constipation, multi-drug resistant organism (MDRO) infection, or metabolic syndrome.

The question addressed in this evidence review is: Does the use of a fecal transplant improve the net health outcome in patients with pouchitis, constipation, MDRO infection, or metabolic syndrome?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with pouchitis, constipation, MDRO infection, or metabolic syndrome.

Interventions
The therapy being considered is a fecal transplant.

Comparators
The following therapy is currently being used to treat pouchitis, constipation, MDRO infection, and metabolic syndrome: standard of care.

Outcomes
The general outcomes of interest are symptoms, change in disease status, and treatment-related morbidity. Though not completely standardized, follow-up for pouchitis, constipation, MDRO infection, or metabolic syndrome symptoms would typically occur in the months to years after starting treatment.

(Current through December 2021) Shen et al reported on UpToDate for the management of acute and chronic pouchitis that fecal microbiota transplantation is of no or uncertain benefit. (*Accessed January 2022*)

(2021) Bar-Yoseph et al completed a cohort study and evaluated FMT for carbapenemase- producing Enterobacteriaceae (CPE) eradication. A total of 15 patients who were CPE carriers were prospectively enrolled and received encapsulated FMT (15 capsules daily) for 2 days, of which 13 patients completed treatment. Eradication of CPE at 1 month (defined as 3 negative swab cultures plus negative polymerase chain reaction for carbapenemase gene) occurred in 9/13 patients (69.2%). The authors noted that the

quantity of Enterobacteriaceae decreased in post-FMT samples of the responders but increased among failures.

(2020) Seong et al completed a cohort study and evaluated FMT for patients colonized with CPE and/or vancomycin-resistant enterococci (VRE). A total of 35 patients were prospectively enrolled and underwent donor FMT via colonoscopy: 4 for CPE, 19 for VRE, and 12 for combined CPE and VRE. Within 1 year of receiving FMT, 24 (68.6%) patients were decolonized. Recolonization occurred in 9 patients at a median time of 55 days following FMT.

(2020) Cold et al completed a systematic review by evaluating FMT treatment in 69 patients with chronic pouchitis concluded that the use of FMT in this population requires further study before incorporation into clinical practice.

(2020) Proenca et al completed a systematic review and meta-analysis by searched for RCTs assessing the use of FMT in obese and metabolic syndrome patients. Six RCTs (N=154) were included in the meta-analysis, of which 5 studies assessed the role of FMT for metabolic syndrome in obesity and 1 assessed the role of FMT in obese patients without metabolic syndrome. Two to 6 weeks after intervention, patients in the FMT group had a lower mean concentration of glycated hemoglobin than the placebo group (mean difference [MD], -1.69 mmol/L; 95% CI, -2.81 to -0.56; p=.003) and higher mean high-density lipoprotein (HDL) cholesterol than the placebo group (MD, 0.09 mmol/L; 95% CI, 0.02 to 0.15; p=.008); the placebo group had lower mean low-density lipoprotein (LDL) cholesterol than the FMT group (MD, 0.19 mmol/L; 95% CI, 0.05 to 0.34; p=.008). Fasting glucose, triglycerides, and total cholesterol did not differ between groups after 2 to 6 weeks. At 12 weeks after treatment, there was no statistically significant difference between FMT and placebo for the following outcomes: concentration of glycated hemoglobin, fasting glucose, LDL cholesterol, HDL cholesterol, and triglycerides. The authors concluded that more data are needed before FMT can be applied in clinical practice as a treatment for metabolic syndrome.

(2019) Saha et al completed a systematic review by identified 21 studies (N=192) on FMT in preventing multi-drug resistant infections and/or its effect on MDRO colonization. Only 1 of the studies was a RCT (see Huttner et al summary under Randomized Controlled Trials), 7 were uncontrolled clinical trials, 2 were retrospective cohort studies, and 11 were case series or case reports. The MDRO eradication rate ranged from 0 to 100% using all included data; when excluding data from case series and case reports, the eradication rate ranged from 37.5% to 87.5%. No serious adverse events from FMT were reported. The authors concluded that more data are needed before FMT can be applied in clinical practice as a treatment for eradicating MDR colonization and preventing recurrent MDR infections

(2019) Huttner et al completed a RCT and evaluated the superiority of a 5-day course of antibiotic therapy followed by FMT (n=22) for the treatment of MDROs compared to no intervention (n=17). Patients with either extended-spectrum beta-lactamase-

producing Enterobacteriaceae and carbapenem-resistant Enterobacteriaceae (CRE) were enrolled. In the intention-to-treat analysis, 9/22 (41%) patients assigned to the intervention group were negative for both extended-spectrum beta-lactamase-Enterobacteriaceae and CRE compared to 5/17 (29%) patients in the no-intervention control arm at follow-up days 35 to 48. No superior benefit was observed with an odds ratio for decolonization success of 1.7 (95% CI, 0.4 to 6.4).

Section Summary: Miscellaneous Conditions
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. Systematic reviews of data from patients who received FMT for constipation, pouchitis, MDROs, 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.

Adverse Events
(2016) Wang et al published a systematic review of adverse events associated with FMT. Reviewers identified 50 publications (N=1089 FMT-treated patients). Of these, 831 patients were affected by CDI, 235 had IBD, and the remainder had miscellaneous indications. The overall incidence of adverse events in the studies was 28.5% (310/1089). Most reported adverse events were mild to moderate in severity and included abdominal cramping, flatulence, fever, and belching. A total of 9.2% (100/1089) of patients developed serious adverse events. Thirty-eight patients died. Reviewers attributed 1 death to be definitely related to FMT, 2 were possibly related, and 35 were unrelated. The definitely related death was due to aspiration during colonoscopy sedation, and the 2 possibly related deaths were associated with infections (due either to FMT or the patients' immunocompromised state). The incidence of severe infection was 2.5% (27/1089). Reviewers categorized 8 cases of severe infection as probably or possibly related to FMT; the other 19 cases were categorized as unrelated.

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 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 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.

Practice Guidelines and Position Statements

The American College of Gastroenterology (ACG)
(2021) The guideline for Clostridioides difficile infection (CDI) recommends the following:

- "We recommend patients experiencing their second or further recurrence of CDI be treated with FMT to prevent further recurrences (strong recommendation, moderate quality of evidence)."
- We recommend a repeat FMT for patients experiencing a recurrence of CDI within 8 weeks of an initial FMT session.
- We suggest fecal microbiota transplantation (FMT) be considered for patients with severe and fulminant CDI refractory to antibiotic therapy, particularly, when patients are deemed poor surgical candidates (strong recommendation, low quality of evidence)."
- "We recommend FMT be delivered through colonoscopy (strong recommendation, moderate quality of evidence) or capsules (strong recommendation, moderate quality of evidence) for treatment of CDI; we suggest delivery by enema if other methods are unavailable (conditional recommendation, low quality of evidence)."... (*Accessed January 2022*)

American Gastroenterological Association (AGA)
(2020) Clinical Practice Guidelines on the Management of Mild-to-Moderate Ulcerative Colitis

- In patients with mild–moderate ulcerative colitis (UC) without Clostridium difficile infection, the AGA guidelines does not reference fecal microbiota transplantation as a recommended treatment. (*Accessed January 2022*)

American Society of Colon and Rectal Surgeons
(2021) American Society of Colon and Rectal Surgeons (ASCRS) guideline for Clostridioides difficile Infection recommends the following:

- …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.
- Oral vancomycin or fidaxomicin is considered first line treatment for an initial CDI, whereas metronidazole alone is no longer considered appropriate first line
- treatment. (Strong recommendation based on high-quality evidence, 1A.)

- A prolonged course of vancomycin, adding bezlotoxumab or using fidaxomicin, is an acceptable therapy for recurrent or refractory CDI in stable patients. (Strong recommendation based on moderate-quality evidence, 1B.)
- "Conventional antibiotic treatment should be used for at least 2 recurrences (i.e., 3 CDI episodes) before offering fecal microbiota transplantation."
- Patients with recurrent or refractory CDI should typically be considered for fecal bacteriotherapy (eg, intestinal microbiota transplantation) if conventional measures, including appropriate antibiotic treatment, have failed. (Strong recommendation based on moderate-quality evidence, 1B.)
- "Third or Subsequent" CDI episode: "If FMT is available, then 10-day course of vancomycin followed by FMT."

(*Accessed January 2022*)

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

(2021) A focused update of the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) Guideline on Management for Clostridioides difficile infection (CDI) in Adults states the following:

- …patients with multiple recurrences of CDI who have failed to resolve their infection with standard of care antibiotic treatments are potential candidates for FMT. It was the opinion of guideline panelists to have patients try appropriate antibiotics for at least 2 recurrences (i.e., 3 CDI episodes) before FMT is considered. The optimal timing between multiple FMT sessions is not discussed in the guidelines. (*Accessed January 2022*)

(2018) The clinical practice guidelines for the diagnosis and treatment of clostridium difficile infection in adults and children.

- Recommended pharmacotherapy using vancomycin, fidaxomicin, and/or metronidazole depending on the episode and the severity of the C difficile.
- The guidelines strongly recommended fecal microbiota transplantation (FMT) as a treatment option for adults following an initial treatment of CDI and two recurrences (i.e., after three treated CDI episodes) that have been non-responsive to at least two regimens of antibiotics (i.e., various combinations of vancomycin, fidaxomicin, and/or metronidazole). Similar recommendations are made for children, but the strength of the recommendations is low, and the quality of evidence is low for pharmacotherapy and very low for FMT.
- The Societies recommendations for the treatment of C. difficile included the following:
    - Initial episodes, non-severe: oral vancomycin (VAN) 125 mg four times a day for ten days; OR oral fidaxomicin (FDX) 200 mg twice a day for ten days; OR if neither VAN or FDX are available, oral metronidazole 500 mg three times a day for ten days.
    - Initial episode, severe: oral VAN 125 mg, four time a day for ten days; OR FDX 200 mg twice a day for ten days

    - Initial episode, fulminant; 500 mg VAN oral or via NG tube four times a day. If ileus is present, consider rectal instillation of VAN. Intravenous metronidazole, 500 mg every eight hours, with VAN if ileus is present.
    - First recurrence: VAN 125 mg four times a day for ten days if metronidazole was used for initial episode; OR prolonged tapered and pulsed VAN regimen if a standard VAN regimen was used initially; OR FDX 200 mg twice a day for ten days if VAN was used for the initial episode.
    - Second or subsequent recurrence: VAN in tapered and pulsed regimen; OR oral VAN 125 mg four times a day for ten days followed by rifaximin 400 mg three times a day for 20 days; OR FDX 200mg twice a day for 10 days; OR fecal microbiota transplantation (IDSA, 2018). (*Accessed January 2022*)
- While the previous guidelines recommended metronidazole as the first-line therapy for initial cases of mild-to-moderate CDI and vancomycin for more severe cases, the new guidelines recommend either vancomycin or fidaxomicin (FDX) as the drug of choice for all initial episodes.
- Currently, the use of fecal capsules (oral administration) has been shown to be inferior to upper or lower gastrointestinal infusion (e.g., endoscopy, nasogastric tube, enema, colonoscopy).
- (2017) IDSA/SHEA guideline, a recurrent case occurs within 2 to 8 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.*

Regulatory Status
Food and Drug Administration (FDA)
The US Food and Drug Administration (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.

(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 the publication.

(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). Two immunocompromised individuals received investigational FMT and developed invasive infections caused by the transmission of extended-spectrum betalactamase-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

PRIOR APPROVAL

Not applicable.

POLICY

Medically Necessary: Clostridioides difficile

Fecal transplantation may be considered **medically necessary** in individuals when documentation supports **all of the following** criteria:

- The request is for treatment of Clostridioides difficile (previously known as Clostridium difficile) infection; **and**
- The individual has had one initial infection of Clostridioides difficile plus two recurrences (i.e., 3 episodes); **and**
- The Clostridioides difficile episodes are confirmed by a positive stool test; **and**
- The Clostridioides difficile episodes are refractory to antibiotic therapy including at least **one of the following** standard antibiotic regimens:
    - Tapered/pulsed vancomycin (VAN); **or**
    - Vancomycin (VAN) followed by Rifaximin; **or**
    - Fidaxomicin (FDX); **or**
    - Metronidazole; **or**
    - All of the above antibiotics are contraindicated or not tolerated as prescribed with supporting documentation; **and**
- The individual is not immunocompromised.

Investigational

Fecal transplantation is considered **investigational** when the criteria above have not been met and including but not limited to the following due to a lack of evidence demonstrating an impact on improved health outcomes:

- Irritable Bowel Syndrome (IBS)
- Inflammatory Bowel Disease (IBD)
  - Crohn Disease (CD)
  - Ulcerative Colitis (UC)
- Metabolic Syndrome
- Pouchitis
- Repeat fecal microbiota transplantation

Policy Guidelines

Note: There is a lack of consensus on the number of recurrences that warrants consideration of fecal microbiota transplantation (FMT). Wellmark's current medical policy follows the guidelines published by the American Society of Colon and Rectal Surgeons, Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA).

Definitions

Recurrent: Clostridioides (formerly Clostridium) difficile infection (CDI) is defined by complete abatement of CDI symptoms while on appropriate therapy, followed by reappearance of symptoms within two to eight weeks after treatment has been stopped.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 44705 Preparation of fecal microbiota for instillation, including assessment of donor specimen.
- 44799 Unlisted procedure, small intestine *(instillation of the specimen by nasogastric tube or enema)*
- G0455 Preparation with instillation of fecal microbiota by any method, including assessment of donor specimen.

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POLICY HISTORY

Date	Reason	Action
January 2022	Annual Review	Policy Revised
January 2021	Annual Review	Policy Revised
January 2020	Annual Review	Policy Revised
January 2019	Annual Review	Policy Revised
January 2018	Annual Review	Policy Revised
January 2017	Annual Review	Policy Revised
January 2016	Annual Review	Policy Revised
February 2015		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
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