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FECAL MICROBIOTA TRANSPLANTATION (OPENBIOME)

Background

Clostridium difficile infection (CDI) is traditionally treated with oral vancomycin or metronidazole, depending on severity. Metronidazole 500 mg given orally three times daily for 10-14 days is the treatment of choice for an initial episode of CDI that is mild to moderate in severity (Cohen, et al.). In patients with severe CDI, vancomycin 125 mg given orally four times daily for 10-14 days is the agent of choice. Severe, complicated cases of CDI are treated with oral vancomycin (PO 500 mg QID; Rectal: 500 mg/100 mL NS per rectum q6h) with or without IV metronidazole 500 mg IV q8h). The first recurrent episode of CDI is often treated with the same regimen as the initial episode depending on the presentation. Recurrences beyond this may be managed using alternative approaches including vancomycin or pulse regimens. UMHS manages CDI and recurrent CDI similarly to the management strategies outlined by the Infectious Disease Society of America (IDSA). Unfortunately, current antibiotic therapy does not often provide an adequate response in many patients and nearly 26% of patients will return with a recurrent C. difficile infection (rCDI) within 1-3 months (Zanella-Terrier, et al.). **The estimated efficacy for treatment of the first recurrence is 60% with antibiotic therapy and this rate decreases with subsequent recurrences (Youngster, et al).**

Research evaluating alternative treatment strategies for rCDIs is ongoing. **Clinicians are now more frequently using fecal microbiota transplantation (FMT) in these cases.** By transplanting fecal matter via lower or upper GI delivery from a healthy donor into the colon of patients with rCDI, the gut is able to restore microbiota diversity and develop resistance to colonization by C. difficile. FMT has been reported to have a cure rate as high as 90% with negligible side effects (Kelly, et al.). The lower route of delivery appears to be more efficacious than upper GI delivery (Kassam, et al). Stool donors are carefully screened and excluded based on criteria including antibiotic use in the previous 3 months, intestinal infections, irritable bowel disease (IBD), history of neoplasia, and presence of infectious diseases. Often, donors are family members or close friends. Some studies suggest that related donors are associated with a higher resolution of CDI than unrelated donors, 93% vs. 84%, respectively. However, the results of a meta-analysis indicated that there was no significant difference between outcomes from related and unrelated donors (Zanella-Terrier, et al.). **Furthermore, a randomized noninferiority trial conducted in patients with rCDI found that the use of frozen stool for FMT resulted in a rate of clinical resolution of diarrhea that was no worse than that obtained with fresh stool for FMT (per-protocol analysis revealing, 83.5% vs. 85.1%; difference, −1.6% [95% CI, −10.5% to ∞]) (Lee, et al.).**

The most robust efficacy data supporting the use of FMT exists for treatment of rCDI and refractory CDI. Limited data exists evaluating the efficacy of FMT in hospitalized patients and for indications outside of rCDI and refractory CDI. Although FMT now offers patients with rCDI a more efficacious treatment alternative, failure is still seen in up to 20% of patients (Kassam, et al). A recent risk factor analysis found the following as independent predictors of early failure after FMT: severe or severe/complicated, OR 5.95, $p < 0.00$, number of CDI-related hospitalization before FMT, OR 1.43, $p<0.001$, and inpatient FMT, OR 3.78, $p = 0.004$. Thus, use of FMT in these patient populations should be used with caution.

UMHS Experience

FMT has been utilized in patients with rCDI at UMHS with good success. In February 2016, UMHS changed methods by which FMTs are executed. The old process involved a donor, typically a related donor, who is responsible for collecting their stool the morning of the procedure, mixing it with saline, and blending it at home with a pre-purchased, single use blender to a milk-shake-like consistency before transporting it to the hospital in a zip lock plastic bag where the recipient will have the stool infused. This process was often a hindrance to the widespread use of FMT for treatment of rCDI cases, despite its evidence of efficacy. The new process utilizes product available from OpenBiome, a nonprofit organization that collects donor samples and develops various preparations that are ready-to-use. OpenBiome has a rigorous donor selection process that entails thorough screening questionnaires and testing of donors and donor stool in order to ensure safety. OpenBiome has a lower delivery microbiota preparation (via colonoscopy or enema), an upper delivery microbiota preparation (via an enteric naso-gastric tube), and an oral capsule formulation. OpenBiome was approved by UMHS P&T for restricted use in adult patients (18 years of age or older) with recurrent CDI in the outpatient setting.

Indications for Use

Consultation and approval by infectious diseases and gastroenterology must be obtained in patients with the following:

- Recurrent CDI (defined as having two or more episodes)
- CDI not responsive to standard therapies by day 5 assuming escalation of pharmacologic therapy has already been tried

Pharmacokinetics

No available information.

Adverse Reactions

Adverse events reported are transient and self-limiting and include fever, diarrhea, abdominal cramps, belching, nausea, and excessive flatulence. Other serious adverse events may occur but are likely related to the procedure include perforation and bleeding during colonoscopy or aspiration due to sedation. There is also a potential for transmission of infective pathogens, however this is rare due to the careful screening of donors. Long-term safety has not been established but concerns include the possible transmission of infectious agents or development of diseases (hepatitis C, HIV) or conditions linked to gut microbiota (obesity, diabetes, atherosclerosis, IBD, colon cancer, nonalcoholic fatty liver disease, IBS) as a result of FMT (Kelly, et al.).

Drug Interactions

Drug interactions have not been identified.

Medication Safety

REMS (Risk Evaluation Mitigation Strategy) Requirement	N/A
Pregnancy Category	No data available.
Black Box Warning	N/A
ISMP Medication Safety Concerns	Capsules must be kept frozen until time of administration. Capsules must be administered within 90 minutes of removal from freezer storage. If for any reason the capsules will not be administered to the patient, they must be returned to freeze storage within 10 minutes of removal or be discarded.
Hazardous Risk Assessment	Hazardous drug rating; detail any unusual handling/disposal guidelines, if applicable. (Attachment A)
Extravasation Potential	N/A
Latex	N/A
Do Not Crush	Oral capsules should not be opened or crushed.
Electronic Health Record Safety Assessment	Inclusion of criteria for use and approval process.
Miscellaneous Safety Concerns	Capsules are large and may be difficult to swallow. A swallow test should be performed using the placebo test capsules provided with each treatment to ensure the patient is not at risk of aspiration. Any patient at risk of aspiration is an absolute contraindication to capsules. Capsules must also be administered under direct supervision of a physician to reduce the risk of aspiration. Contraindications to Capsule G3: Severe-complicated CDI, dysphagia (oropharyngeal, esophageal, function, neuromuscular (e.g., Stroke, MS, ALS), history of aspiration, history of gastroparesis, allergies to glycerol, sodium chloride, hypromellose, gellan gum, titanium dioxide, or cocoa butter.

Study Results

Fecal microbiota transplantation has been shown to be superior compared to conventional antibiotic therapy. Please refer to Table 1 for an overview of key studies involving FMT.

Limited data exists evaluating the use of FMT in hospitalized patients. Please refer to Table 2 for an overview of select studies.

Dosage:

- Lower GI delivery: 250 mL
- Upper GI delivery: 30 mL
- Capsule G3 (concentrated formulation within a microbial emulsion matrix [MEM] technology to ensure long term physical integrity of the capsule while at the same time preserving the microbial contents). Dose: 30 capsules, swallowed consecutively in a single session. The capsules are size 00.
- Administration:
- Upper GI Delivery: 30 mL via naso-gastric (NG) tube. NG placement must be confirmed by radiograph or fluoroscopy prior to administration.
- Lower GI Delivery: 250 mL via colonoscopy or enema. A sigmoidoscopy can be performed in those unable to tolerate full colonoscopy. If delivered via enema, the 250 mL preparation must be transferred into an enema bag to be administered over 1 hour and retained for 1 hour.
- Capsule G3: capsules must be ingested within 90 minutes of removal from freezer storage

Note: The US Food and Drug Administration (FDA) declared in March 2013 that FMT falls within the definition of a biologic product and drug defined as a product intended for the use in diagnosis, cure, mitigation, treatment, or prevention of disease or is intended to affect the structure or function of the body, and is therefore regulated by the FDA. As there are currently no approved therapeutic indications for FMT, until recently, an investigational new drug (IND) application is required in order to administer FMT for the treatment of Clostridium difficile, or any other purpose. Due to the time consuming IND application process, physicians and scientists reasoned with the FDA that the IND requirement would adversely affect the availability of FMT for the treatment of individuals with CDI. The FDA agreed with these concerns and will not enforce the IND requirement of FMT for CDI as long as the following three criteria are met: (1) informed consent was obtained, (2) the patient is provided detailed information on the risks of the procedure, and (3) it is explained to the patient that FMT is an investigational therapy (FDA).

Storage Considerations

Preparations must be kept frozen and are stable for up to 6 months at -20ºC or up to 24 months at -80ºC. Packaging will assume storage in -20ºC and will be labeled with an expiration of 6 months after date of shipping. If the preparation is stored at -80ºC, it may be used within 24 months of the shipping date or 18 months past the expiration printed on the package (OpenBiome.org).

Recommendation

We recommend the addition of stool preparations from OpenBiome to both outpatient (formulations: lower GI, upper GI, and oral capsules) and inpatient (formulations: lower GI ONLY) formularies for restricted use in adult patients (18 years of age or older).

Recommended restriction criteria:

- Treatment INDICATIONS:
  - Recurrent CDI (defined as having two or more episodes)
  - CDI not responsive to standard therapies by day 5 assuming escalation of pharmacologic therapy has already been tried
- Treatment EXCLUSIONS:
  - Complicated CDI (defined as attributed hypotension or shock, ileus, megacolon, severe sepsis, peritonitis, and bowel perforation)
- Consultation and approval by infectious diseases must be obtained
- Consultation and approval by gastroenterology (if not primary team) must be obtained

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UNIVERSITY OF MICHIGAN

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MICHIGAN MEDICINE
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Table 1: Select Clinical Studies of Fecal Microbiota Transplantation for the Treatment of Recurrent or Refractory Clostridium difficile Infection

Title (abbreviated)/ Reference/ Funding	Study Design	Drug/Dosage Regimens	Study Parameters	Efficacy	Safety	Conclusion/ Comments
Duodenal FMT v. Conventional Vancomycin +/- Bowel Lavage in rCDI Els van Nood, et al. Funded by grants from the Netherlands Organization for Health Research and Development	R, OL In patients with rCDI	FMT: stool diluted in 500 mL NS and administered via ND-tube x 1 (n=17) Vancomycin alone: 500 mg QID x 14 days (n=13) Vancomycin +/- BL: Vancomycin 500 mg QID + BL on day 4 or 5 (n=13)	Primary outcomes: -cure without relapse within 10 weeks after starting therapy Secondary outcomes: -cure without relapse after 5 weeks -adverse events	Cure: 1st FMT: 13 of 16 pts **(81%)** FMT(overall) 15 of 16 pts (93.8%) Vancomycin alone: 4 of 13pts (31%) Vanco +BL: 3 of 13 pts (23%) Recurrence at 5 weeks: FMT: 1 of 16 (6%) Vanco alone: 8 of 13 (62%) Vanco + BL: 7 of 17 (54%) Overall Cure Rate Ratio: FMT vs. Vanco Alone: 3.05 99.9% CI 1.08-290.05 FMT vs. Vanco + BL: 4.05 99.9% CI 1.21-290.12 *Cure defined as absence of diarrhea or persistent diarrhea that could be explained by other causes with three consecutive negative stool tests for C. difficile toxin.	FMT adverse events: 94% diarrhea immediately post infusion 31% cramping 19% belching *Adverse reactions resolved within 3 hours in all patients	FMT is superior **(>81% cure rate)** compared to conventional vancomycin therapy with or without BL.
FMT using oral capsules for rCDI Hirsch, et al.	Single arm, OL in patients with rCDI	PPI the evening and morning prior to procedure. Morning of procedure, ingested 6-22 capsules with a mean mass of 2.3 g, estimated to contain $9.7x10^{10}$ viable bacteria at the time of initial production. (n=19)	Primary endpoint: Lasting resolution of CDI diarrhea assessed 90 days after the last FMT	Cure rate: 13 pts (68%) had resolution after a single FMT Overall cure rate of 89% *Cure defined as lasting resolution of CDI diarrhea, assessed 90 days after the last FMT	FMT was well tolerated, no distaste was reported, no respiratory distress or immediate discomfort, no infectious complications reported	FMT via oral capsules is effective, safe, and well tolerated in patients with rCDI.

FMT colonoscopy vs. conventional vancomycin therapy n=39 Cammarota et al. Funding in part by the Catholic University of Rome, Line D-1 research funding.	OL, RCT *Study was stopped after a 1 year interim analysis	Two groups: 1. Vancomycin 125 mg QID x 3 days, followed by bowel cleansing with 4L of macrogol on the last 1 or 2 days of abx, then FMT via colonoscopy. Repeated FMT every 3 days was permitted until resolution. (n=20) 2. Vancomycin 125 mg QID x 10 days, followed by a pulse regimen of 125-500 mg every 2-3 days x ≥3 weeks. (n=19)	Primary outcome: Diarrhea resolution 10 weeks after end of treatment course. Secondary endpoint: Toxin negative without rCDI 5 and 10 weeks after end of treatments	Cure (resolution of diarrhea): FMT: 13 of 20 (65%) were cured after first infusion Overall, 18 of 20 pts (90%) experienced resolution Vancomycin: Overall, 5 of 19 (26%) experienced resolution Overall Outcome analysis: 90% vs. 26%, p<0.0001. Overall cure rate: 25.2 (99.9% confidence interval 1.26-502.3). Secondary Endpoint: FMT: 18 of 20 (90%) were toxin negative Vancomycin: 3 of 19 (15%) were toxin negative after 10 weeks *Cure defined as the disappearance of diarrhea or persistent diarrhea explicable by other causes, with two negative stool tests for C. difficile toxin.	No significant adverse events were observed in either of the study groups. FMT: Diarrhea-94% Bloating & cramping-60% *all the symptoms resolved within 12 hours *No adverse events related to vancomycin regimen were reported.	At the 1 year interim analysis, FMT preceded by a 3-day vancomycin regimen showed significantly higher efficacy than standard 2 week vancomycin alone and so the study was stopped. FMT resulted in **>90% cure rate** with no significant adverse events.
FMT for rCDI comparing colonoscopic and NG-tube administration of unrelated frozen donor samples n=20 Youngster et al.	OL, RCT	Two groups: 1. FMT by colonoscopic administration with pre-bowel cleansing regimen of 4L PEG solution, followed by fecal preparation (n=10) 2. FMT by NGT delivery. (n=10)	Primary endpoint: resolution of diarrhea without relapse within 8 weeks Secondary endpoints: -Improvement in subjective well-being (using a standardized questionnaire) -Adverse Events	Of 20 patients in both study arms, 14 (70%) were cured after the first infusion 8 of 10 (80%) in the colonoscopy group vs. 6 of 10 (60%) in the NGT group, p=0.628 Overall, 18 of 20 (90%) were cured after subsequent FMTs. 10 of 10 (100%) in the colonoscopy group vs. 8 of 10 (80%) in the NGT group; p=0.53 Secondary endpoints: -Subjective well-being: was not significantly different among groups *Cure defined as resolution of diarrhea, which was defined as <3 bowel movements per 24 hours.	Adverse events: mild abdominal discomfort, transient fever	Infusion of unrelated frozen donor stool is effective in treating rCDI **(Overall cure rate >90% at 8 weeks)** NGT and colonoscopy are equally efficacious and suitable routes of administration.

Oral capsules frozen FMT for rCDI n=39 Youngster, et al. Funded by internal hospital division funds. Youngster received career support from Harvard Catalyst	OL, single-arm in patients with at least 3 episodes of CDI and failure of conventional therapy	Patients received 15 capsules on two consecutive days (n=20)	Primary endpoints: -safety (Grade 2 or worse) -Clinical resolution of diarrhea with no relapse at 8 weeks	Primary Endpoint: -No serious adverse events related to FMT -Resolution of diarrhea in 14 pts (70%; 95% CI, 47-85%) -Overall cure rate of 18 of 20 patients, 90% (95% CI, 68%-98%) *Cure defined as diarrhea resolution-symptom free and not receiving anti-CDI treatment at 8 weeks after time of inoculum.	Abdominal cramping and bloating, resolved within 72 hours	Frozen oral FMT capsules appears similar to cure rates seen with fresh samples in previous case studies. Oral FMT appears safe in patients with rCDI. **Overall cure rate of 90%**
Systematic Review Cammarota, et al.	Systematic Review, literature search using PubMed, SCOPUS, Web of Science, and the Cochrane Library	All human subjects with CDI treated with FMT in comparison with standard antibiotic therapy were included. 36 studies were included in the analysis, n=536 patients treated with FMT -Upper GI delivery (NG, ND, NJ tube) -Colonoscopy-preferred for many reasons can re-colonize entire bacteria, allows visualization of entire colon, can rule out other diseases (IBD), bowel cleansing can help eliminate remaining spores. -Retention enema	Primary endpoint: Resolution of diarrhea	Of those treated with FMT, 467 (87%) had resolution after the first FMT procedure. Rate of Efficacy by ROUTE: Stomach: 81% (87 pts cured) Duodenum/jejunum: 86% (84 cured) Cecum/ascending colon: 93% (183 pts cured) Distal colon: 84% (98 pts cured) *Cure defined as resolution of diarrhea	No adverse events were reported with the FMT procedures.	FMT procedure is safe Severe adverse events are uncommon FMT by any route is effective Overall, 467 of 536 pts **(87% were cured)** Colonoscopy route achieved higher response rate compared with other routes-(head to head comparisons have not been made).

Long-term follow up of rCDI n=77 Brandt, et al.	Long-term follow-up study on the use of colonoscopic FMT for rCDI from 5 medical centers in the US	Antibiotics until 2-3 days prior FMT, bowel preparation the day prior to FMT, and administered via colonoscopy	Primary outcomes: -Primary cure rate: resolution of diarrhea without recurrence within 90 days	-Cure occurred in 70 of 77 (91%) of patients *Cure defined as resolution of diarrhea symptoms without recurrence within 90 days	No definitive adverse effects noted.	Response to FMT is rapid, high response rate, and durable response.
FMT for rCDI, a retrospective review n=70 Mattila, et al.	Retrospective review of patients who underwent FMT by colonoscopy from Nov 2007-Feb 2010.	Patients with rCDI who were refractory to standard antibiotic therapy received FMT via colonoscopy as salvage therapy.	Symptom resolution	34 (100%) of patients with non-027 CDI had resolution of symptoms 32(89%) of patients with 027CDI had a favorable response.	No severe adverse events could be related to FMT.	66 of 70 patients (94%) recovered from rCDI. FMT is an effective treatment for rCDI. Other notes: ribotype 027 CDI is associated with more severe diarrhea and more recurrences.

Key: R= randomized, DB= double blind, PC= placebo controlled, Pb= placebo, OL=open-label, ND=naso-duodenal, NJ= naso-jejunal, abx= antibiotics, rCDI=recurrent *C. difficile* infection, BL= bowel lavage, FMT= fecal microbiota transplantation.

Table 2: Select Clinical Studies of Fecal Microbiota Transplantation for the Treatment of *Clostridium difficile* Infection in Hospitalized Patients

Title (abbreviated)/ Reference/ Funding	Study Design	Drug/Dosage Regimens	Study Parameters	Efficacy	Safety	Conclusion/ Comments
Early Fecal Transplantation by the Nasogastric Route n=61 (early transplant = 16) Lagier, et al.	Observational, single-arm	Early fecal transplantation at the primary infection using the nasogastric route (during first week after diagnosis) vs. antibiotics +/- tardive transplantation (performed after two relapses) Mild infection: metronidazole 500 mg TID then vancomycin 125 mg QID in cases of relapse/failure then fidaxomicin 200 mg BID Severe infection: metronidazole 500 mg TID and vancomycin 125 mg QID then then fidaxomicin 200 mg BID in cases of relapse/failure	Primary outcome: global mortality rate and one-month mortality following diagnosis	Early transplant vs. antibiotics +/- tardive transplant: Global mortality: 18.75% vs. 64.4%, p <0.01 Cox model, early transplantation was the only independent predictor of survival (HR 0.18, 95 CI 0.05–0.61, p=0.006)	one patient had uncontrollable nausea caused by the nasogastric tube, and one patient presented with acute cardiac insufficiency	*Clostridium difficile* ribotype 027
Predictors of Early Failure After Fecal Microbiota Transplantation N=328 Fischer, et al.	Retrospective, multi-center, cohort	FMT for recurrent (at least three episodes of CDI and failure of a 6- to 8-week vancomycin taper or pulse-dosed therapy or at least two episodes of CDI requiring hospitalization), severe (serum albumin concentration <3 g/dL and the presence of either of the following: abdominal tenderness or WBC >15,000 cells/mm^3), or severe-complicated CDI (admission	risk factors associated with FMT failure	Risk factors associated with FMT failure at 1 month after treatment in MV analysis: -severe or severe/complicated, OR 5.95, p <0.001 -number of CDI-related hospitalization before FMT, OR 1.43, p<0.001 -inpatient FMT, OR 3.78, p = 0.004	NR	Scoring system proposed

		to an intensive care unit for CDI, hypotension with or without the required use of vasopressors, fever ≥38.5 °C, ileus or significant abdominal distension, mental status changes, WBC >35,000 or <2000 cells/mm^3, serum lactate >2.2 mmol/L, and end-organ dysfunction)				
Long-term Follow-up of FMT for Severe and/or Complicated Clostridium difficile Infection N=17 (82% inpatient) Aroniadis, et al.	Multi-center, observational	FMT for severe and/or complicated CDI	cure rates and time to resolution of symptoms	Cure rates/time to resolution: -94.1% had diarrhea, which resolved in 75%; mean time to resolution = 5.7 d and improved in 25% -64.7% had abdominal pain, which resolved in 72.7%; mean time to resolution = 9.6 d and improved in 27.3% - 2 of 17 patients experienced early CDI recurrence (≤90 d) after FMT (primary cure rate, 88.2%) -In 1 patient, a second FMT resulted in cure (secondary cure rate, 94.1%) -Late CDI recurrence (≥90 d) was seen in 1 of 17 patients (5.9%) in association with antibiotics and was successfully treated with a repeat FMT	None	

Key: R= randomized, DB= double blind, PC= placebo controlled, Pb= placebo, OL=open-label, ND=naso-duodenal, NJ= naso-jejunal, abx= antibiotics, rCDI=récurrent *C. difficile* infection, BL= bowel lavage, FMT= fecal microbiota transplantation

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