Fecal Microbiota Transplantation: Harnessing the Gut Microbiota to Treat Disease

Despite technical and regulatory questions, this procedure appears effective for treating patients with persistent Clostridium difficile infections

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Fecal microbiota transplantation (FMT) involves the transfer of consortia of bacteria from healthy individuals to patients with Clostridium difficile infection (CDI) or other conditions to promote recolonization with missing components of intestinal flora. FMT dates as far back as 4th-century China when human fecal suspensions were used to treat food poisoning and severe diarrhea and has been used in veterinary medicine to treat ruminal disorders at least as far back as the 17th century.

Contemporary use of FMT in humans traces to 1958 when Ben Eiseman, an American surgeon, used this procedure to treat four patients with pseudomembranous colitis. Since then, FMT, also known as stool transplant or fecal bacteriotherapy, has been used more and more often to treat patients with CDI. During the past decade, for example, CDI epidemics in the United States and Europe led to a steadily increased use of FMT.

Recurrence of CDI after a course of standard therapy, typically with metronidazole or vancomycin, is a common clinical problem. Though previously considered a “last resort” for patients with CDI, interest in FMT among physicians and researchers is surging, leading to increased numbers of publications and registered clinical trials. Its high efficacy in treating CDI symptoms is prompting some investigators to test whether FMT will prove useful for treating several other disorders associated with microbial dysbiosis, including inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), the metabolic syndrome, neurodevelopmental disorders, autoimmune diseases, and allergies.

In 2013, the FDA announced it was classifying fecal matter for FMT as both an investigational new drug (IND) and a biologic, requiring formal regulatory review of INDs before beginning clinical procedures (Microbe July 2013, p. 274). The agency later agreed to exercise enforcement discretion by waiving this IND requirement when FMT is used to treat CDI patients who fail to respond to standard therapies provided that their physician obtains adequate informed consent, including a signed statement that the use of FMT products to treat C. difficile is investigational and to hold discussions with patients about FMT risks. Well-designed and well-executed randomized trials are now needed to further define the role of FMT in these microbiota-related conditions.

FMT for Treating C. difficile Infections

Of 536 patients treated with FMT for C. difficile infection, 87% experienced clinical resolution with no serious adverse events, according to Antonio Gasbarrini of A. Gemelli University Hospital in Rome, Italy, and his collaborators in their review from 2014. Cumulative experience is based on data from case reports.

SUMMARY

Fecal microbiota transplantation (FMT) involves transfers of bacterial mixtures from healthy individuals to patients infected with Clostridium difficile or facing other medical conditions.

Despite evidence that FMT is safe and effective, randomized controlled trials are necessary to evaluate FMT more fully, to determine the optimal route for administering microbiota to patients, and to investigate other variables.

Criteria for choosing or excluding donors for FMT procedures are based mainly on medical histories and laboratory tests for infectious agents.

Diverse efforts seek to standardize the collection, storage, and formulation of donor FMT samples, including to develop alternative “defined microbiota ecosystems” to use instead of fecal materials.

FMT for Treating C. difficile Infections

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Separately, Els van Nood of the University of Amsterdam, Josbert Keller of the Academic Medical Center, both in Amsterdam, and their collaborators completed a randomized controlled trial in 2013. They infused donor feces into the duodenum of CDI patients, effectively resolving disease in 81% of those patients, compared to only 31% efficacy in another set of patients who instead received a standard course of vancomycin administered orally. Not only did FMT appear safe, with no serious adverse events, but the safety monitoring board halted the study early because it was deemed unethical to continue treating patients with the inferior antibiotic therapy.

Long-term follow-up of FMT patients is limited, according to Lawrence Brandt of Montefiore Medical Center in Bronx, New York, and his collaborators. In their follow-up study, 77 patients who were treated with FMT were followed for 10 years or less. Of these, four developed autoimmune diseases, rheumatoid arthritis, Sjögren’s syndrome, idiopathic thrombocytopenic purpura, or peripheral neuropathy, albeit without a clear relationship between the new disease and FMT.

Further randomized controlled trials are necessary to evaluate the efficacy of FMT, to determine the optimal route for administering microbiot to patients, and to investigate other

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**TABLE 1.**

**Donor Exclusion Criteria**

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<tr>
<th>Absolute Exclusion</th>
<th>Possible exclusion</th>
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<tbody>
<tr>
<td>Risk of infectious agent</td>
<td>Gastrointestinal comorbidities</td>
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<tr>
<td>Known HIV, Hepatitis B or C infections</td>
<td>History of inflammatory bowel disease</td>
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<tr>
<td>Known exposure to HIV or viral hepatitis (previous 12 months.)</td>
<td>History of irritable bowel syndrome, idiopathic chronic constipation, or chronic diarrhea</td>
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<tr>
<td>High-risk sexual behaviors</td>
<td>History of GI malignancy or known polyposis</td>
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<tr>
<td>Use of illicit drug</td>
<td>Major immunosuppressive medications</td>
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<tr>
<td>Tattoo or body piercing within 6 months</td>
<td>Systemic anti-neoplastic agents</td>
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<tr>
<td>Incarceration or history of incarceration</td>
<td>Metabolic syndrome</td>
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<tr>
<td>Current communicable disease</td>
<td>Systemic autoimmunity</td>
</tr>
<tr>
<td>Creutzfeldt-Jakob disease risk factors</td>
<td>Atopic diseases (asthma, eczema, eosinophilic GI disorders)</td>
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<tr>
<td>Travel (previous 6 months) to areas of endemic diarrheal illnesses or traveler’s diarrhea risk is high</td>
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variables, including safety data. Publication of a double-blind, randomized controlled trial is comparing FMT delivered via colonoscopy with a sham procedure in which a recipient’s own stool is delivered via colonoscopy is expected by the end of 2015.

Despite these uncertainties, many physicians now recommend using FMT to treat recurrent or relapsing CDI when there are at least three recurrences and standard therapy has failed; refractory CDI, meaning cases of moderate CDI that does not respond to standard therapy with vancomycin after at least a week; and severe CDI which does not respond to standard therapy after 48 hours, according to Brandt and his collaborators. In all cases, primary consideration must be given to the severity and pace of a patient’s CDI when deciding whether early use of FMT is appropriate.

Choosing and Preparing Donors for FMT Procedures

Criteria for choosing or excluding donors for FMT procedures are based on their medical histories and specific laboratory test procedures (Table 1). Although identifying whether a donor is “optimal” is not yet possible, several factors are worth considering. For example, intimate contacts such as spouses likely share other, non-CDI infectious risks with their respective recipients, theoretically minimizing the risk of transmitting additional infectious agents.

However, fecal material from unrelated healthy donors is being used successfully at clinical centers and appears effective in treating CDI. Thus, there may be advantages in using fecal material from unrelated, healthy, but rigorously screened donors for FMT clinical procedures. For example, the greater availability of this broadly defined, volunteer donor pool could facilitate FMT procedures. Further, insisting that donors be related to recipients may lead some family members to feel coerced, while in other cases, potential donors might be excluded because of diseases or other risk factors, leaving their sick family members without recourse.

Donors should be free of any disease or condition that might, even theoretically, be associated with or transmitted by gut microbiota. The physicians performing FMT assume responsibility for evaluating potential donors. The primary purpose of questioning the donor is to ensure that he or she is in good health, and that any risk factors for diseases transmissible by stool can be identified. The donor interview is especially important to identify such risks, particularly those for which there are no or no appropriately sensitive laboratory tests.

Those meeting eligibility criteria then undergo serologic and stool testing for pathogens (Table 2). Pathogen tests supported by current professional society guidelines includes for HIV, hepatitis viruses, and *Treponema pallidum* for syphilis, cultures for pathogens commonly identified in stool specimens, such toxin-producing *C. difficile*, and ova and parasite tests. More rigorous testing may be advisable when donors have a history of residing in or traveling to tropical countries where such diseases are prevalent or in cases where the recipients are immunocompromised.

Protocols for Donors, Recipients and FMT Clinical Teams

Physicians who are using experimental FMT protocols to treat CDI patients agree on follow-
ing several additional criteria as prudent. For instance, donors should avoid eating foods to which recipients are allergic for about 5 days prior to a procedure. Donors also are asked to notify the practitioner if they develop any one of several symptoms of an acute infection, including fevers, diarrhea, and vomiting between screening and donation. A gentle osmotic laxative may be used the night before the procedure and before the donor collects a stool sample of 50 to 100 g the morning of the procedure.

Antibiotic treatment of CDI patients with vancomycin typically continues until 1 to 3 days prior to the procedure. Recipients are typically asked to undergo a bowel cleansing preparation regardless of how the FMT will be administered and, optionally, to be treated with an antidiarrheal product such as loperamide prior to the procedure, which may aid in retaining the transplanted material. If FMT is to be delivered by nasogastric or nasointestinal tube, a proton-pump inhibitor may be administered to the recipient to prevent gastric acid from damaging or inactivating the donor microbiota.

To preserve microbiota for near-term use, samples should be kept in airtight containers on ice or room temperature but not frozen, and then samples should be used for FMT within 6 hours of being collected, if possible. Whole stool is then diluted and homogenized to make it easier to administer. Although the choice of diluents differs among practitioners, either preservative-free normal saline or sterile water is most commonly used. Household blenders, hand mixers, or simply shaking of the stool with diluents is effective. Diluted samples may be filtered to remove particulate matter using gauze pads or a strainer. Because stool is considered a level 2 biohazard, one may consider conducting these mixing procedures within a laboratory hood. Those who handle and mix fecal transfusion material should wear fluid-resistant gowns, gloves, and masks with goggles or another type of eye shield.

Frozen, encapsulated FMT samples also are being evaluated for safety and efficacy, according to Elizabeth L. Hohmann of Massachusetts General Hospital (MGH) in Boston and her collaborators. Of 20 recurrent CDI patients treated with frozen FMT capsules, 90% of them responded and there were no serious adverse events, they report.

Although the ideal volume for sample instillation into recipients is not established, 25–50-ml samples are typical for the upper gastrointestinal (GI) tract and larger volumes of 250–500 ml, for the lower GI. Whether these routes or others will prove best for administering FMT is not known and may vary with the needs and status of individual patients. Means used to administer FMT include fecal suspensions given via nasogastric and nasointestinal tubes, through a colonoscope, or as retention enemas. Delivery to lower rather than the higher GI tract leads to better CDI eradication rates, note Gasbarrini, and his collaborators. However, the nasogastric route appeared to be as effective as colonoscopic administration in a more recent, open-label pilot study, according to Hohmann and her collaborators at MGH in Boston.

Challenges before FMT Is Used More Widely

Despite good efficacy data, ease of administration, and lack of effective alternatives for many patients, FMT procedures still are not widely available. Challenges include questions regarding safety, about donor materials, and regulatory issues.

Although FMT appears safe for recipients, prospective and long-term data are lacking. Moreover, although the procedure is well tolerated, there are case reports of fevers, bacteremia, and flare-ups of inflammatory bowel disease after FMT. For example, among 80 immunocompromised patients with recurrent, refractory, or severe CDI, 12 patients (15%) treated with FMT had a serious adverse event within 12 weeks, with most of these events being unrelated to FMT, according to our multicenter retrospective analysis. Of the two deaths, one was the result of aspiration during sedation for FMT administered via colonoscopy. Importantly, however, there were no infections related to FMT, although other adverse reactions included self-limited diarrhea and ulcerative colitis flare ups. Concerns over transferring microbiota are not limited to potential infections among recipients, but include transmission of microorganisms which may increase risk for other conditions such as obesity and IBD.

Meanwhile, some patients face difficulties identifying suitable healthy donors, and, even if one is found, screening protocols may be
cumbersome leading to further delays from laboratory testing before treatment. Relying on fresh fecal material presents obvious logistical difficulties. Lastly, the FMT regulatory landscape is rapidly changing, and how long the recent FDA policy of enforcement discretion will remain in effect is not known.

**Evolving Concepts in FMT**

In the near future, individual physicians may no longer need to identify FMT donors or rely on fresh stool. Stool banks, such as the nonprofit OpenBiome in Medford, Mass., are centralizing donor screening and stool processing procedures, supplying physicians researchers who are either using FMT to treat individual patients or are conducting FMT clinical trials. Meanwhile, several for-profit companies also are supplying physicians and researchers with minimally modified stool preparations for testing in clinical trials. Alternative, defined microbiota ecosystems, in which the several species that are responsible for FMT therapeutic effects are being isolated, and several of these mixtures have proved effective in animal and human clinical trials. Ultimately, encapsulated formulations would be the most convenient method of delivery to patient recipients.

Evidence supporting the use of FMT for the treatment of recurrent *C. difficile* infection continues to build. Innovative approaches to collecting and preparing samples, including stool banks and commercial preparations of mixed bacterial cultures, provide hope for streamlining these practices in the future. Although challenges remain and regulation is necessary, agencies must recognize the unusual nature of FMT and adapt their policies as microbial-based therapeutics emerge.

**Suggested Reading**


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