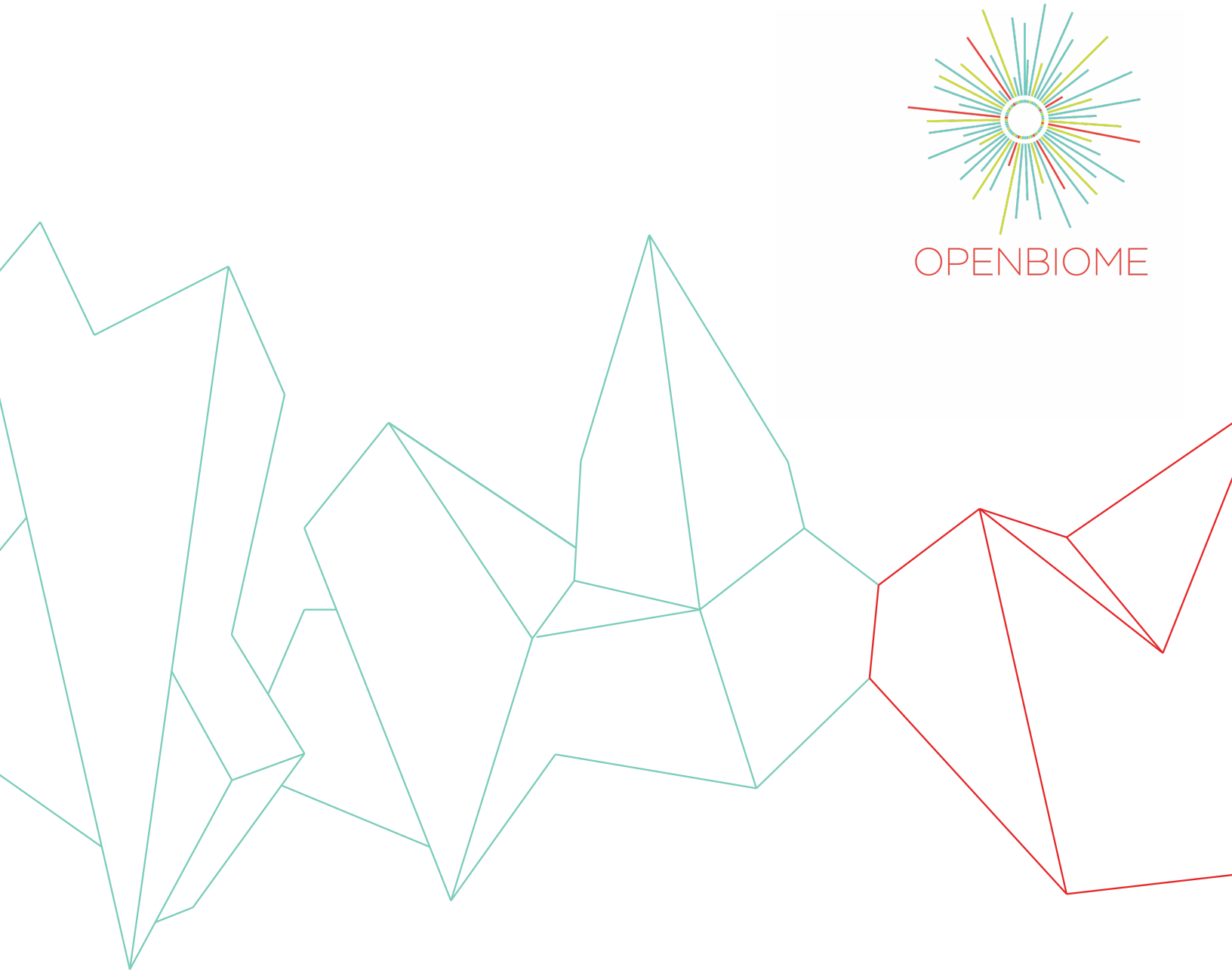

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Current Evidence on the Safety of Fecal Microbiota Transplantation (FMT) for *C. difficile* infection

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Abstract

In this paper, we provide an overview on the safety of FMT and important points to consider about the procedure. The perspectives presented here draw from the general safety of FMT sourced from universal stool banks (like OpenBiome) and hospital-based stool banks.

This paper is aimed at physicians and healthcare professionals caring for patients being considered for FMT as well as patients themselves. The information reviewed here will help ensure that patients are fully informed of the safety profile of FMT and potential risks associated with the procedure before undergoing treatment.

Disclaimer: *The guidance presented here are general principles drawn from the experience and medical opinions of OpenBiome's Clinical team. Physicians should use their own discretion when evaluating their patients and consider each patient's unique medical needs.*

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Introduction

C. difficile infection (CDI) carries high morbidity and mortality with 462,100 cases in the US annually.[1] In the past decade, Fecal Microbiota Transplantation (FMT) has developed from a fringe medical practice to the standard of care for recurrent CDI. FMT is recommended by the Infectious Disease Society of America, American College of Gastroenterology, and the British Gastroenterological Society for patients who have failed antibiotic therapy.[2–4]

Despite the widespread uptake of FMT into standard of care for CDI, FMT remains an investigational drug and the treatment carries risks that should be considered and clearly communicated in a fully informed conversation with your patient.

More information on the informed consent process—including discussing the potential risks and benefits of FMT with patients—can be found in our "Steps to Take Before and After Fecal Microbiota Transplantation."

The overall short-term safety profile of safely screened FMT appears good. However, it is crticial to evaluate the risks, benefits and alternatives in the context of your patient's unique comorbidities and goals of care. Some patient groups, including immunocompromised patients, are at higher risk of adverse events.

What are the risks of FMT?

Common, mild side effects

Mild side effects that are commonly reported include transient diarrhea, abdominal cramps/discomfort and nausea, fever, bloating, belching, vomiting, borborygmus, constipation, and excess flatulence. These symptoms are usually self-limiting and of short duration. These symptoms are also commonly associated with the delivery modality (eg, colonoscopy or upper endoscopy) independent of FMT.

Infection

Key to patient safety in FMT is rigorous donor screening. Although FMT material should have been screened for common enteric pathogens and antibiotic-resistant bacteria, there is a risk of transmission of known and unknown infectious organisms contained in the donor stool. Such infectious disease transmission could lead to post-FMT infections including diarrha, sepsis, and fatal adverse events.

A report of extended-spectrum beta-lactamase (ESBL) producing *E. coli* bacteremia following FMT highlighted the importance of ensuring that risks are adequately understood.[5] Importantly, in this case the donor FMT stool was not screened for ESBL.

More recently, a case was reported from OpenBiome of tranmission of Shiga-toxin producing *E. coli* (STEC) confirmed on genomic sequencing and strain tracking comparing donor and patient samples.[6] In this case, although the donor FMT was screened through conventional Shiga toxin EIA with reflex to culture, highly sensitive PCR-based detection subsequently identified STEC in the donor sample. This highlights that donor screening methods may not necersarily guarentee the absence of enteropathogens in stool. A full description of the case and investigation can be found in the report published in *Clinical Infectious Diseases*.[6]

Other cases reported in the literature include cytomegalovirus (CMV) colitis, influenza B transmission, and non-CDI diarrhea (eg, norovirus) however these cases were deemed not related or not evaluable.[7]

Therefore, even in the context of rigorously screened stool with donors evaluated for infectious disease risk factors there remains a potential risk of infectious disease transmission.

Gastrointestinal symptoms

Abdominal pain, appendicitis, peritonitis and diverticulitis have been reported as possibly related to FMT in cases reported in the peer-reviewed literature.[7–11] There is a theoretical risk of small intestinal bacterial overgrowth when FMT is delivered into the upper gastrointestinal tract, however, there have been no reported cases to date.

In those with underlying inflammatory bowel disease (IBD), flares have been reported in retrospective studies in which FMT was performed for CDI, with reports as high as 30%.[12] However, evidence—reviewed below— suggest that IBD worsening is likely to be primarily driven by underlying CDI rather than FMT.

Patients with IBD experiencing CDI are more likely to experience a flare independent of FMT. In a prospective cohort of FMT patients receiving OpenBiome FMP with comorbid

IBD, there were no flares related to FMT were observed among Crohn's Disease or ulcerative colitis patient cohorts.[13] Among the Crohn's Disease cohort, 73.3% (11/15) had IBD improvement, and 4 (26.6%) had no disease activity change. Among the ulcerative colitis cohort, 62% (22/34) had IBD improvement, 29.4% (11/34) had no change and 4% (1/34) experienced a de novo flare.

In systematic reviews and metanalyses of randomized controlled trials evaluating FMT for the treatment of IBD, there have been no observed significant differences in rates of worsening IBD disease activity between treatment and control groups.[14,15] Across 4 randomized controlled trials, FMT was associated with significant improvement in clinical remission of ulcerative colitis compared to placebo.[14] These data suggest that IBD worsening is likely to be primarily driven by underlying CDI rather than FMT.

Nevertheless, the risk of worsening of IBD should be discussed with your patients; however, if the patient has active IBD at the time of FMT their IBD will likely still be active afterward and further treatment plans should be discussed.

Allergy and anaphylaxis

While no cases of allergy or anaphylaxis have been reported in the literature, patients should be screened for food allergies before FMT. If the patient reports a severe food allergy or anaphylaxis, a patient should be evaluated by an allergist to confirm the allergy if there is clinical uncertainty, or if confirmed one may consider using material from a patient-selected donor, who has abstained from the offending allergen.

Autoimmune conditions

Rheumatoid arthritis, Sjogren syndrome, peripheral neuropathy, and idiopathic thrombocytopenic purpura have all been reported in the peer-reviewed literature as possibly related to FMT in a case series.[16] There remains a paucity of long-term prospective follow-up evaluating the emergence of autoimmune conditions post-FMT. However, there are two retrospective series evaluating the long-term effects following FMT. A Finnish cohort study did not detect any increased risk of autoimmune diseases compared to a standard of care (SOC), with mean follow up 3.8 years.[17] Another cohort from the United States (n=208) with mean 2.8 years of follow-up identified two cases of psoriatic arthritis and one case of mastocytosis.[18]

Obesity

A single case-report of new-onset obesity post-FMT from an overweight donor garnered significant media attention in 2015.[19] However, while weight change could be a *potential* risk of FMT, a more thorough analysis of 173 patients who received FMT using material from overweight, obese and normal weight donors revealed no significant weight changes post FMT compared to their pre-CDI weight regardless of donor weight.[20]

Other non-communicable diseases

There is a theoretical risk of developing diseases that may be related to donor gut microbiota. These include neurologic disorders, psychiatric conditions and malignancy. Persons with these known conditions should be excluded from donating stool, although a theoretical risk of acquiring these conditions and other unknown microbiome-mediated diseases after FMT remains.

There is a paucity of data on the long-term safety outcomes of FMT. Therefore, a critical point to cover during your discussion is to ensure the patient fully understands that the long-term safety of FMT remains unknown. Of the available data, the long-term safety profile of FMT appears favorable; however, few prospective studies have followed up patients beyond 6 months.[16,21,22] This lack of data is especially relevant for counselling pediatric patients.

The American Gastroenterological Association (AGA) has initiated a prospective FMT registry that will follow patients for up to 10 years. This registry will generate valuable evidence on the long-term effects of FMT. To-date, the registry has reported outcomes on 259 patients undergoing treatment with follow up to (6) months [23]. Severe symptoms at one month included diarrhea (5 (2%)) and abdominal pain (4 (2%)); 5 (2%) had hospitalization considered by the investigator to be related or possibly related to FMT (urinary tract infection; cholangitis; diarrhea/abdominal pain/dehydration/ fever; IBD flare; perforation). Endoscopy-related complications occurred in 3 patients (1%: 1 perforation, 2 bleeding episodes). There were 2 (1%) new diagnoses of Irritable bowel syndrome post-FMT (potentially post-infectious IBS) and 2 (1%) new diagnoses of ulcertative colitis. *C. difficile,* especially in children, can often be a presenting hospitalization associated with a new diagnosis of inflammatory bowel diseases.

In a large Finnish cohort there was no significant increases in cases of diabetes, neurologic diseases, malignancy, or allergies in the FMT cohort compared to those who received SOC.[17] A cohort of 208 patients in the United States reported single cases of diabetes mellitus type 2, Alzheimer's dementia, new-onset anxiety disorder diagnosis

during the follow up period.[18] Recent findings following patients treated in a randomized controlled trial of FMT for CDI from 2008-2010 found no new-onset autoimmune, gastrointestinal, or malignant disorder during follow-up among 34 patients followed up for 10 years.[24] They also did not find any deterioration or amelioration of pre-existing medical conditions.

Procedure related risks

The chosen delivery modality carries risks independent of FMT material. There have been serious adverse events reported in the peer-reviewed literature associated with the FMT delivery procedure. These include aspiration after upper delivery of FMT and bowel perforation after colonoscopic delivery of FMT.[25,26] Risks related to the FMT procedure should be clearly discussed with the patient and the choice of delivery modality may depend on the patient or specific clinical situation.

Is FMT for *C. difficile* infection safe?

We are often asked whether FMT is safe. FMT is an investigational drug and therefore we cannot make a claim that it is safe. However, FMT is now standard of care for CDI and is recommended by the Infectious Disease Society of America, American College of Gastroenterology, and the British Gastroenterological Society for patients who have failed antibiotic therapy.[2–4]

Based on the evidence from multiple randomized controlled trials and the experience of OpenBiome from the use of FMT preparations in 38,839 CDI cases under enforcement discretion, 255 subjects in investigator-initiated studies, and 22 subjects in OpenBiome-sponsored trials the balance between anticipated efficacy/benefits and the safety risks indicate that FMT is favourable for the general population of patients with recurrent *C. difficile* infection not responsive to standard therapy.

These findings are supported by the prospective real-world cohorts such as the AGA registry as well as randomized controlled trials.[23,27]

Physicians should consider the risks, benefits and alternatives of FMT for their unique patient. The risks of FMT should be balanced against the benefits and alternatives to FMT (including bezlotuximab, continued antibiotic therapy or surgery). Thisi risk benefit assessment will vary depending on your patient's comorbidities and goals for treatment.

Some special patient populations to consider when evaluating the risks and benefits of FMT are described further below.

Special patient populations

Immunocompromised patients

Immunocompromised patients should receive further counseling pre-FMT given the potential increased risk of infection in this population. A multicenter retrospective study of immunocompromised patients receiving FMT to treat CDI did not report any infectious adverse events in this high-risk cohort. However, the case report of ESBL *E. coli* bacteremia post-FMT in 2 immunocompromised patients highlights the risk.[5] As mentioned, in this case, the donor used to provide the treatments associated with these cases, administered by a hospital-based stool bank, was not screened for ESBL. Nevertheless, patients should be counseled on the risk of colonization, translocation, and infection.

Patients who are immunosuppressed and at particularly high risk of CMV or Epstein-Barr virus (EBV) infection should be counseled about the potential for additional risk of viral infections post-FMT. To date, there have only been 2 documented cases of CMV colitis in the context of FMT and no cases of EBV infection. One case report of CMV colitis occurred in a patient performing at-home, or DIY, FMT for the treatment of ulcerative colitis (UC).[28] This patient did not have CDI and used unscreened stool sourced from their child. Another small study assigned UC patients to either treatment with stool from healthy donors or to a control group receiving autologous fecal microbiota.[29] One patient did get CMV; however, interestingly they were in the control group receiving their own autologous FMT. Despite the unique features of these cases limiting their generalizability, the risks of both CMV and EBV should be clearly communicated to CMV/EBV-negative immunocompromised patients and alternative treatment options should be considered.

Fulminant *C. difficile*

Fulminant CDI (previously referred to as severe, complicated CDI) presents a particular challenge characterized by elevated white cell counts, hypotension or shock, and megacolon progressing to bowel perforation, which may be reported as adverse events following FMT treatment non-response. These patients are also more likely to be elderly or have other co-morbidities that could increase their risk of both CDI and the potential risks of FMT.

Fulminant CDI is associated with a high mortality rate in those who fail to respond to antibiotic therapy. Colectomy is recommended for fulminant patients but still results in mortality rates close to 50%.[30] Even in patients who are discharged after subtotal colectomy for fulminant disease, long-term outcomes are poor with average survival time of 18 months.[30] Findings from small study of 48 patients treated with OpenBiome

FMT or managed with standard of care found a 77% decrease in odds for mortality (OR 0.23, 95% CI 0.06-0.97, p=.045).[31]

In a retrospective review of 430 hospitalizations for fulminant CDI, FMT reduced mortality from 21.3% to 9.1% (P = .015).[32] FMT may therefore offer a potential option for patients who are poor candidates for surgery. However, given the severity of disease and associated poor outcomes the occurrence of adverse events may be higher in this group.

Pediatrics

There is growing experience of FMT in pediatric populations in the context of rCDI. FMT is also recommended for the treatment of CDI not responsive to antibiotics in pediatric patients by NASGHAN for the treatment of CDI in pediatrics.[33]

Of five recent studies of FMT in paediatric CDI, Nicholson et al. included the largest cohort of patients age 11 months to 23 years [median age 10] (n=335) and observed an 87% cure rate.[34] There were six related AEs, of which four were a flare in patients with existing IBD, one developed diarrhea with dehydration and one aspirated after an upper GI delivery (procedure-related complication associated with upper GI delivery). There were no deaths.

While the short-term safety of FMT in pediatrics appears good there is a paucity of long-term follow-up data on outcomes for pediatric patients undergoing FMT.

Summary

In this paper, we covered the safety of FMT. Key to FMT safety is the rigorous donor screening and a considered approach to patient selection. The overall short-term safety profile of safely screened FMT appears good. However, it is crticial *to evaluate the risks, benefits and alternatives of your patient's unique comorbidities and goals of care*. Make sure you provide time to discuss these risks, benefits and alternatives with your patient including a paucity of long-term safety data.

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