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Fecal Microbiota Transplantation: Is It Safe?

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Fecal microbiota transplantation (FMT) is an accepted procedure for the management of recurrent *Clostridioides difficile* infections. FMT is generally considered safe and well-tolerated - even in high-risk patients. Most short-term risks are mild and known to be associated with delivery methods. Long-term side effects have not been established, and no signs of harm have been found to date. However, causality for several microbiome-associated diseases has to be established. Even though FMT is generally considered safe with strict donor screening, serious adverse events have been recently associated with the FMT product from the stool bank, where screening for multi-drug resistant organisms is not included in protocols. Here, we discuss the adverse events associated with FMT and safety issues. **Clin Endosc 2021;54:157-160**

Key Words: Adverse events; Fecal microbiota transplantation; Safety

INTRODUCTION

Fecal microbiota transplantation (FMT) is an accepted procedure for managing recurrent *Clostridioides difficile* infection (CDI). FMT is generally considered safe and well-tolerated - even in high-risk patients. Most short-term risks are mild and known to be associated with delivery methods. Long-term side effects have not been established, and no signs of harm have been found to date. However, causality for several microbiome-disease associations should be established.

In this review, we discuss the adverse events associated with FMT, as well as its safety, based on clinical studies and systematic reviews on treatment for CDI.

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ADVERSE EVENTS ASSOCIATED WITH FMT

FMT is usually considered safe, and the common side effects are minor adverse events, including transient diarrhea, abdominal cramps or pain, low-grade fever, bloating, flatulence, and constipation (Table 1).[1] However, we should consider the possible uncommon severe side effects following FMT.

Adverse events related to stool bank

Among the adverse events, the risk of infection transmission after FMT has been a concern, especially after an Food and Drug Administration (FDA) report of two cases of extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* (*E. coli*) infection (one death) and six cases of Shiga toxin-producing *E. coli* infection (two subsequent deaths), probably transmitted through the donor stool.[2] The donated stool was manufactured into capsules without ESBL screening. In response, the FDA created a national alert and mandated additional screening for ESBLs.[3] In addition to the short-term risk of infection transmission, a recent prospective registry study[4] suggested that 4% of participants developed new infectious diseases between 1 and 6 months; some were related to FMT, but others were not.

Table 1. Adverse Events in Patients who Underwent Fecal Microbiota Transplantation

Short-term adverse events	Long-term adverse events
Bloating/Spasm	Obesity
Gaseousness	Immune-mediated disorders
Diarrhea	Immune thrombocytopenia
Irregular bowel habit	Rheumatoid arthritis
Irritable bowel syndrome	Inflammatory bowel disease
Constipation	Irritable bowel syndrome
Abdominal pain, tenderness	
Fever	
Nausea	
Aggravation of inflammatory bowel disease	
Gram negative bacteremia	
Bowel perforation	
Belching	
Death	
Hematochezia	

Adverse events related to delivery routes

The delivery method of FMT is another concern related to adverse events. Most short-term risks are attributable to the delivery method rather than FMT itself. A systematic review suggested that FMT treatment via the upper gastrointestinal route was associated with higher incidence rates of adverse events (43.9%) than FMT treatment via the lower gastrointestinal tract (20.6%).[5] Fatal aspiration pneumonia was reported as a severe complication of FMT administered by a nasoduodenal tube.[6] However, there was no general agreement on the better route for the administration of FMT. Even though there is no need for bowel cleaning when administering FMT via the nasoduodenal or nasojejunal route, clinicians need to consider the increased risk of aspiration pneumonia or pneumonitis, especially in patients with neurologic problems or bedridden patients. Moreover, lower gastrointestinal delivery of FMT is known to be more effective in patients with recurrent CDI.[7] Therefore, the optimum route should be selected based on the nature and intensity of the disease, the patient's age and preference, hospitalization, donor selection, psychological and economic status of the patients, and the need for subsequent FMTs.[8]

Long-term adverse events associated with donor microbe engraftment

Previous studies suggested the long-term effect of donor microbe engraftment, including host susceptibility to diseases, including obesity and immune-mediated disorders, such as immune thrombocytopenia, rheumatoid arthritis, and inflammatory bowel disease.[9-12] In a prospective registry, two patients were newly diagnosed with irritable bowel syndrome, and two patients were newly diagnosed with ulcerative colitis, among the 156 participants who underwent a 6-month follow-up after FMT.[4]

SAFETY ISSUE IN HIGH-RISK PATIENTS

The safety of FMT in high-risk patients has not been established, as almost all FMT trials excluded those patients. A recent systematic review of 44 studies on FMT for CDI showed an 88% treatment success rate in 303 immunocompromised patients (almost all patients used immunosuppressive medication),[13] of which 2 patients died, 2 patients had colectomies, 5 patients had treatment-related infections, and 10 patients were subsequently hospitalized. Based on the findings of that study, FMT in immunocompromised patients seems to have comparable safety to that in immunocompetent patients.[13] However, the transmission of live microorganisms to recipients with underlying illnesses presents a greater potential risk.[14,15] For example, clinicians should consider the possible transmission of the Epstein-Barr virus and cytomegalovirus from donors in immunosuppressed FMT recipients, for which recent guidelines recommend additional donor screening.[16] Several risks are mitigated by implementing a careful selection and screening process for prospective donors. Luo et al. suggested a higher incidence of adverse events in high-risk patients, including immunocompromised patients, patients with inflammatory bowel disease (IBD), and patients with fulminant colitis.[17] Particularly, clinicians should consider the risk of IBD flare-ups in patients with IBD. Another systematic review of FMT for the treatment of IBD showed bothersome serious side effects: 7% of FMT participants, compared with 5% of controls, had severe adverse events (relative risk, 1.4; 95% confidence interval, 0.5-3.6).[18] However, this should be interpreted with caution, because the adverse event reports were not standardized. In solid-organ transplant recipients who underwent FMT for the treatment of CDI, adverse events occurred in 22.3%, and relatively mild adverse events, such as nausea, abdominal pain, diarrhea, and severe adverse events occurred in 3.2% of patients, suggesting that FMT is safe in solid-organ transplant recipients.[19] Table 2 summarizes the safety of FMT in high-risk patients.

Table 2. Safety of Fecal Microbiota Transplatation in High-Risk Patients

Participants	Article types	Adverse events
Immunocompromised host	Systematic review (303 patients)[13]	Deaths (*n*=2), Colectomy (*n*=2), Bacteremia or infection (*n*=5), hospitalization (*n*=10), unspecificed life threatening complication (*n*=7), flare-up of IBD (*n*=7)
Ulcerative colitis (mild to moderate)	Meta-analysis (4 studies, 277 patients)[18]	Serious adverse events: 7% of FMT participants vs. 5% of controls (RR, 1.4; 95% CI, 0.5-3.6)
	Meta-analysis (11 studies)[20]	Overall adverse events (95% CI): 36.9% (21.5–55.6)
Crohn's disease	Meta-analysis (3 studies)[20]	Overall adverse events (95% CI): 5.8% (1.2–23.5)
Solid-organ transplantation recipients	Retrospective study (94 patients)[19]	Overall FMT related adverse events: 22.3% Serious FMT related adverse events: 3.2%

CI, confidence interval; IBD, inflammatory bowel disease; FMT, fecal microbiota transplantation; RR, relative risk

SAFETY OF FMT IN THE CORONAVIRUS DISEASE 2019 ERA

With the outbreak of the coronavirus disease 2019 (COVID-19), several centers have decreased the volume of routine diagnostic or elective procedures to avoid potential transmission of the virus. Several studies have reported a longer excretion of severe acute respiratory syndrome coronavirus 2 through feces than through the nasopharyngeal route.[21] Therefore, several FMT centers and stool banks have suspended the active performance of FMT and the recruitment of FMT donors. Recently, the FDA recommended only FMT products generated from donated stool before December 2019.[21] However, FMT plays a major role in the management of recurrent CDI and cannot be postponed, especially in patients with life-threatening conditions. Therefore, during this COVID-19 pandemic, FMT should be considered a nonpostponable treatment modality, especially in patients with severe and/or recurrent CDI. A recent study demonstrated the possible application of FMT in patients with recurrent CDI during the COVID-19 pandemic by adopting specific changes in the workflow.[22] Recent guidelines have proposed a very strict workflow of stool donation, in which positivity of polymerase chain reaction for nasopharyngeal swabs, stool, and/or Immunoglobulin M serology should be an absolute contraindication for donation.[21]

HOW TO AVOID HARMFUL EFFECTS OF FMT

Even though FMT is generally considered safe, a severe adverse event has been reported to be associated with its product manufactured under a protocol that did not involve screening for multi-drug resistant organisms. Therefore, rigorous donor screening and testing should be mandated to minimize the risks of FMT, especially during the COVID-19 pandemic.

CONCLUSIONS

FMT is generally considered safe, and a recent study suggested that it is well-tolerated in high-risk patients. Rigorous donor screening and testing should be mandated to minimize the risk of FMT, especially during the COVID-19 pandemic.

Conflicts of Interest

The authors have no potential conflicts of interest.

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