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-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.

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). 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. The donated stool was manufactured into capsules without ESBL screening. In response, the FDA created a national alert and mandated additional screening for ESBLs. In addition to the short-term risk of infection transmission, a recent prospective registry study suggested that 4% of participants developed new infectious diseases between 1 and 6 months; some were related to FMT, but others were not.
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%). Fatal aspiration pneumonia was reported as a severe complication of FMT administered by a nasoduodenal tube. 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. 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.

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. 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.

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), 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. However, the transmission of live microorganisms to recipients with underlying illnesses presents a greater potential risk. 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. 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. 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). 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. Table 2 summarizes the safety of FMT in high-risk patients.
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. 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. 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 non-postponable 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. 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.

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.

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

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

REFERENCES

1. Wang S, Xu M, Wang W, et al. Systematic review: adverse events of fecal microbiota transplantation. PLoS One 2016;11:e0161174.
2. DeFilipp Z, Bloom PP, Torres Soto M, et al. Drug-resistant E. coli bacteremia transmitted by fecal microbiota transplant. N Engl J Med 2019;381:2043–2050.
3. Merrick B, Allen I, Masirah M Zain N, Forbes B, Shawcross DL, Gold-
enber SD. Regulation, risk and safety of faecal microbiota transplant. Infection Prevention in Practice 2020;2:100069.
4. Kelly CR, Yen EF, Grinspan AM, et al. Fecal microbiota transplantation is highly effective in real-world practice: initial results from the fmt national registry. Gastroenterology 2021;160:183-192.e3.
5. Bonovas S, Fiorino G, Lytras T, Nikolopoulos G, Peyrin-Biroulet L, Danese S. Systematic review with meta-analysis: use of 5-aminosalicylates and risk of colorectal neoplasia in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2017;45:1179–1192.
6. Baxter M, Ahmad T, Colville A, Sheridan R. Fatal aspiration pneumonia as a complication of fecal microbiota transplant. Clin Infect Dis 2015;61:136–137.
7. Furuya-Kanamori L, Doi SAR, Paterson DL, et al. Upper versus lower gastrointestinal delivery for transplantation of fecal microbiota in recurrent or refractory Clostridium difficile infection: a collaborative analysis of individual patient data from 14 studies. J Clin Gastroenterol 2017;51:145–150.
8. Gulati M, Singh SK, Corrie L, Kaur JP, Chandwani L. Delivery routes for faecal microbiota transplants: available, anticipated and aspired. Pharmacol Ther 2020;199:104954.
9. Smillie CS, Saj J, Gevers D, et al. Strain tracking reveals the determinants of bacterial engraftment in the human gut following fecal microbiota transplantation. Cell Host Microbe 2018;23:229-240.e5.
10. Moayyedi P, Surette MG, Kim PT, et al. Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a randomized controlled trial. Gastroenterology 2015;149:102-109.e6.
11. Paramsothy S, Kamm MA, Kaakoush NO, et al. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. Lancet 2017;389:1218–1228.
12. Brandt LJ, Aroniadis OC, Mellow M, et al. Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent Clostridium difficile infection. Am J Gastroenterol 2012;107:1079–1087.
13. Shogbesan O, Poudel DR, Victor S, et al. A systematic review of the efficacy and safety of faecal microbiota transplant for Clostridium difficile infection in immunocompromised patients. Can J Gastroenterol Hepatol 2018;2018:1394379.
14. Alrabaa S, Jariwala R, Zeitler K, Montero J. Fecal microbiota transplantation outcomes in immunocompetent and immunocompromised patients: a single-center experience. Transpl Infect Dis 2017;19.
15. Lin SC, Alonso CD, Moss AC. Fecal microbiota transplantation for recurrent Clostridium difficile infection in patients with solid organ transplants: an institutional experience and review of the literature. Transpl Infect Dis 2018;20:e12967.
16. Mullish BH, Quraishi MN, Segal JP, et al. The use of faecal microbiota transplant as treatment for recurrent or refractory Clostridium difficile infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. Gut 2018;67:1920–1941.
17. Luo Y, Tixier EN, Grinspan AM. Fecal microbiota transplantation for Clostridiodes difficile in high-risk older adults is associated with early recurrence. Dig Dis Sci 2020;65:3647–3651.
18. Imdad A, Nicholson MR, Tanner-Smith EE, et al. Fecal transplantation for treatment of inflammatory bowel disease. Cochrane Database Syst Rev 2018;11:CD012774.
19. Cheng Y-W, Phelps E, Ganapini V, et al. Fecal microbiota transplantation for the treatment of recurrent and severe Clostridium difficile infection in solid organ transplant recipients: a multicenter experience. Am J Transplant 2019;19:501–511.
20. Caldeira L de F, Borba HH, Tonin FS, Wiens A, Fernandez-Llimos F, Pontarolo R. Fecal microbiota transplantation in inflammatory bowel disease patients: a systematic review and meta-analysis. PLoS One 2020;15:e0238910.
21. Ianiro G, Mullish BH, Kelly CR, et al. Reorganisation of faecal microbiota transplant services during the COVID-19 pandemic. Gut 2020;69:1555–1563.
22. Ianiro G, Bibbo S, Masucci L, et al. Maintaining standard volumes, efficacy and safety, of fecal microbiota transplantation for C. difficile infection during the COVID-19 pandemic: a prospective cohort study. Dig Liver Dis 2020;52:1390–1395.