Chapter

Safety and Potential Risks with Fecal Microbiota Transplantation

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Abstract

The therapeutic potential of Fecal Microbiota Transplantation (FMT) is greatly proved worldwide in the recent years. The use of FMT is now an accepted treatment modality and effective standard of care for some patients owing to its success in treating recurrent *Clostridium Difficile* Infection (rCDI). However, it is still evolving and longer term follow-up data regarding safety are required. Post-FMT serious adverse events (SAEs) have been varied between studies, however have included significant morbidity necessitating hospital admission and mortality in the follow-up period. The follow-up of FMT recipients should be long enough to completely establish efficacy/adverse events. Furthermore, it is recommended that FMT should be offered with caution to immunosuppressed patients, in whom FMT appears efficacious without significant additional adverse effects. In the wake of COVID-19 situation, stringent policies in screening the FMT donors have to be put forth to ensure patient safety. There is a need for high-quality, large, prospective, randomized controlled trials and long-term follow-up investigating screened donors and recipients to evaluate the long term safety and the risk–benefit profile of this promising therapy.

Keywords: safety, risks, fecal, microbiota, adverse events, COVID-19

1. Introduction

Owing to the success of Fecal Microbiota Transplantation (FMT) in treating various diseases, there's a growing demand for standardizing the preparation of fecal material, using accepted standards for the delivery, ensuring safety for the recipient, and monitoring long-term outcomes [1]. The most robust clinical evidence is driven by studies of FMT as a treatment for refractory or recurrent *Clostridium difficile* infection (CDI). Despite the progress in studying the FMT therapy in CDI, there are no prospective studies assessing the safety or efficacy of FMT in IBD. However, critics still have significant concerns regarding the acceptability of FMT, the ethical issues associated with risk and studying FMT in patients with severe disease [2]. Despite the enthusiasm regarding FMT research, the pertinent questions remain, apart from those addressing potential therapeutic indications. These comprise whether the TM could be whole flora extract or cultured TM, methods of administration, implantation success, and immunologic responses, as well as the long-term safety implications of altering the microbiota composition [3]. In the first clinical trial that assessed this treatment modality, FMT proved so superior to standard antibiotics that the study's data and safety monitoring board stopped enrollment early, concluding that it was unethical to hold back

the treatment from the members of the control group. However, it is crucial to understand that diseases that have been linked to the microbiome may surface years post the procedure. As such, there remains a requirement for more investigation of the safety profile of FMT in the extreme long term [4].

2. Safety concerns and the significance of donor screening protocol

FMT as a treatment modality is considered unique owing to the difficulty of its characterization and the simplicity of its production, and each of these characteristics raises special safety concerns. First, the complexity of the communities of microbes in stool and the variability across samples makes it challenging to guarantee the contents from one batch to another. Per se, ongoing monitoring with regards to the presence of possible pathogens is vital for maintaining a safe product and should either be considered part of the approved manufacturing process or a condition imposed on manufacturers. Second, even though there is little scope that patients will manufacture traditional small molecule therapies in their lavatories, processing stool for transplantation at a basic level needs very little training or equipment. Patient online forums comprise lengthy thorough instructions coupled with discussions regarding best practices for mixing stool in a low-cost blender and administering it through enema. There is a considerable risk of pathogen transmission from improperly screened and handled tool due to unsupervised, do-it-yourself procedures. Few healthy subjects would be considered eligible for stool donation for fecal transplantation. Only six per cent of prospective donors to OpenBiome clear the full screening process. This includes a thorough 109-item clinical evaluation administered by a nurse or physician, and 30 stool and blood screens. It is wise to be very cautious about screening for diseases that are potentially transmitted by the microbiome. For instance, investigators have notably linked the microbiome to diverse parameters such as obesity, metabolic syndrome, and behavior. Likewise, it is just as crucial to accumulate longitudinal safety data to identify any conditions that may be transmitted via stool of which we are unaware. Thus, taking into account the known and unknown risks that come with improper donor screening and inadequate patient follow-up, the ease with which patients may prepare and administer fecal transplants themselves without medical supervision, any regulatory outcome that results in restricted access by either limiting supply or significantly increasing the cost of therapy should be adopted very cautiously [4]. Hence, donor screening protocol is a crucial step. Preferred stool donors are healthy individuals without pre-existing disease or risk factors for disease. These individuals are recruited by stool banks and undergo a detailed screening process that includes a questionnaire to exclude those with disease, exposure to transmissible diseases, or behavioral risk factors for transmissible diseases. Disease exclusions comprise, but are not limited to, blood- or stool-borne infections, gastrointestinal disorders, malignancy, atopy, metabolic syndrome and autoimmune diseases. Individuals who have recently taken antibiotics or have traveled to areas with a high risk of traveler's diarrhea are excluded [5].

3. The gaps in understanding FMT safety risk

Many researchers state that FMT is "safe" based on a multitude of uncontrolled trials without a placebo control. Closer examination of adverse event (AE) reporting, however, recommends a need for caution on several grounds. Some of the factors that could be responsible for these gaps are potential under-reporting of

adverse events and the uncontrolled design of FMT trials [6]. In the largest FMT trial so far, 219 subjects (mean age, 73 years) were randomized to fresh or frozen FMT via enema. Six deaths (5.6%) occurred in the frozen FMT arm, and 11 deaths (11.7%) occurred in the fresh FMT arm; none were attributed by the investigators to FMT [7]. Although the CDI morbidity and mortality rates have been reported to be as high as 15%, it is difficult to understand which AEs may be treatment-related without the benefit of a placebo-controlled arm [6]. A few FMT proponents have debated that some patient subgroups, such as immunocompromised hosts, often do not qualify for placebo-controlled trials and need open access to FMT [8]. Still, implicit in this statement is the implication that FMT has been demonstrated to be efficacious and safe in this patient population when there are no controlled trials to support such assumptions. Furthermore, comparison of AE rates between 2 FMT products is useful [6]. In a randomized, double-blind, placebo-controlled phase 2B trial of a stool-derived microbiome drug product, RBX2660, 64% of recurrent CDI patients reported an AE; the distribution of these AEs was comparable by treatment arm (2 doses of placebo vs. 2 doses RBX2660 vs. 1 dose RBX2660/placebo) [9]. On the other hand, a stool bank (OpenBiome, Cambridge, MA, USA) reported 42 AEs in 2050 subjects who underwent FMT, for an event rate of 2%. Besides, none of the AEs was judged to be "definitely related to FMT". Attributing the dramatic differences in event rates to major differences in the products themselves is challenging, as both are stool-derived. The main differences seem to be the methodologies used in collection of AEs and reporting. In the randomized placebo-controlled phase 2b trial of RBX2660, AEs were systematically collected on a prospective basis and investigators were mandated to allocate causality [6]. On the contrary, OpenBiome asks clinicians to retrospectively report, and the stool bank portrays the association of the product to AEs rather than the clinicians [6, 10]. This kind of methodology is disposed to bias. There is a chance of retrospective reporting missing the links between infections and FMT if the patient is assessed by a different health care provider who does not recognize the temporal relationship [6]. Serial FMT Interventions with invasive procedures is another matter to worry about. A trial reported 90% efficacy in 20 subjects managed with FMT, although on delving into the article, it was found that the first-dose efficacy was only 65% [11]. In order to reach 90% efficacy, multiple infusions (2–4 per patient) were given. Repeat infusions through invasive techniques such as colonoscopy, should also be weighed in the risk/benefit analysis of any procedure, and first dose efficacy rates need to be reported with clarity [6].

4. Safety of FMT in *C. difficile* infections

Arguably the best example of harnessing the gut microbiota to manage a disease is the use of F) for the treatment of CDI, where the most convincing safety and efficacy data for use of FMT has shifted the treatment paradigm and revolutionized its management [12]. Most patients with CDI are aged and often with present with co-morbidities, but many other recipients of FMT are likely to be much younger. For such patients, the long-term consequences of gut microbiome manipulation have yet to be understood. There are, for instance, anecdotal reports of numerous changes that have occurred post FMT [13]. These include reversal of immune thrombocytopenic purpura and neurological symptom reversal in three patients with multiple sclerosis [14, 15]. In two patients, the resistant coliforms present before FMT were supplanted by ciprofloxacin-sensitive coliforms after FMT. FMT for refractory CDI lead to an apparent improvement in the related urinary organisms exhibiting 'significantly decreased drug resistance.' This was further supported

by two case reports using FMT to decolonize patients with multi-drug-resistant carbapenemase-producing strains of *Klebsiella pneumoniae*. Other researchers have observed improvement in pre-existing allergic sinusitis and arthritis. In a case series of patients with Crohn's disease treated with FMT, eight out of 11 patients noted relief of concomitant 'skin lesions', a phenomenon also observed in another group using FMT to treat ulcerative colitis where three cases demonstrated improvement in 'skin problems' as well as decreased insulin requirements in a diabetic patient. Furthermore, a case report has been published linking FMT to the development of obesity [13]. FMT for recurrent *C. difficile* possesses a good short-term safety record. Very few adverse effects are directly attributed to the procedure. Most reported adverse events have been self-limiting gastrointestinal symptoms comprising abdominal cramps, diarrhea and constipation, which resolved within one week. At least two deaths from aspiration pneumonia related to sedation administered at the time of FMT have been reported. At least one death from transmission of a multidrug resistant *Escherichia coli* organism has been reported, however the donor in this case had not been tested for this organism. However, these deaths are relatively less compared to the large number of FMTs performed [5]. A long-term follow-up study by Brandt et al., patients who had colonoscopic FMT for RCDI≥3 months before the study were asked to completed a 36-item questionnaire that solicited pre-FMT, post-FMT and donor data. Out of 77, 4 patients reported a new medical condition after FMT including peripheral neuropathy, Sjogren's disease, idiopathic thrombocytopenic purpura and rheumatoid arthritis. A total of 7 of the 77 patients died at the time of the study. The causes of death were metastatic colon cancer (present before FMT), metastatic ovarian cancer, pneumonia (secondary to non-enteric organism), myocardial infarction, stroke, sepsis in a patient with longstanding CD 5 months after FMT, and one patient deceased while on hospice care from unknown cause. None of these causes seemed to be attributable to FMT [16, 17].

5. Safety of FMT in ulcerative colitis (UC)

UC, a major subtype of IBD, perhaps denotes one of the most robust potential indications for FMT after RCDI [18]. Rossen et al. evaluated the efficacy and safety of FMT in 37 patients with UC in a double-blind randomized trial, and noted mild adverse events in the majority of patients (64%), including transient borborygmus (49%), increased stool frequency (34%), vomiting in 2 patients and transient fever in 2 patients. Most adverse events resolved spontaneously within 2 days. There were no infectious complications observed. Four SAEs happened, but were not related to FMT itself. It has been noted that some patients develop self-limited fever and temporary elevation of CRP and IL-6 following FMT, but were considered non-significant, as patients did not show deterioration [16]. Fang et al. concluded that single fresh FMT is an effective and safe strategy to induce long-term remission in patients with active UC and could be expected to be an alternative induction therapy for recurrent UC, even primary UC. None of the patients suffered from other chronic diseases such as immune system diseases, non-alcoholic fatty liver disease and all patients demonstrated good tolerance to FMT treatment [18].

6. Safety of FMT in inflammatory bowel disease (IBD)

Owing to its success in treating rCDI, the use of FMT became rapidly accepted [1]. It appears that most patients with IBD managed with FMT for RCDI tolerate the procedure well; nevertheless, there appears to be a potential risk of precipitating a

flare. Whether this flare is related to FMT or as part of the natural course of IBD is ambiguous [16]. In a retrospective case series by Kelly et al., a few patients with IBD were reported to present with 'IBD flare' post FMT (14%). It is worth nothing that patients with IBD did not experience a higher incidence of SAEs (11%) or adverse events (14%) compared with patient immunocompromised due to other conditions (18% SAEs, 16% AEs, $p \leq 0.3224$) [19]. The definite mechanism of IBD flare post FMT is still ambiguous, although Quera et al. suggested that transient bacteremia may lead to an altered intestinal permeability, resulting in a flare [20]. In their open-label, single-center prospective trial, Goyal et al., concluded that a single FMT is relatively safe and can result in a short-term response in young patients with active IBD. Samples from responders had significantly increased Fusobacterium prior to FMT and showed more significant microbiome changes compared with non-responders after FMT [21]. Further research is needed to discern whether the abundance of Fusobacterium, an organism associated with numerous adverse health outcomes, has prognostic value in the setting of FMT for IBD [22].

7. Safety of FMT in immunocompromised patients

The safety of using live microorganisms in a treatment modality such as FMT remains unclear in certain patient groups—particularly, in severely immunosuppressed patients [23]. Few experts are concerned that there may be a greater risk for infection post FMT in patients with immunocompromised status. Kelly et al. examined FMT in 80 immunocompromised patients of CDI and observed that there were no infection events related to FMT while high cure rates of 78% following a single FMT were noted [20]. Among the different FMT delivery methods used, there were no observed differences in the proportion of adverse events [7, 24, 25]. Nevertheless, long-term immunologic effects of FMT is another matter of concern, but very little relevant data is available [20]. Numerous case reports have indicated that there might be some undetermined association between FMT and certain conditions, including peripheral neuropathy, idiopathic thrombocytopenic purpura, Sjogren's syndrome, and rheumatoid arthritis [17]. Presently, the definite periodicity and duration of follow-up post FMT for monitoring of long-term adverse events are not established. The European consensus proposed that the follow-up period post FMT in CDI patients should be minimum 8 weeks, and the contents of follow-up must comprise clinical and analytical information [26].

8. Adverse events reported in past clinical literature

Most clinical trials and systematic reviews demonstrated that some minor adverse events, like abdominal discomfort, diarrhea, constipation, and low-grade fever, were transiently observed post FMT, whereas uncommon severe side effects were often related to the possible complications of endoscopy and sedation [20, 27–29]. According to the past clinical literature, the two most common side effects of FMT observed are bloating and loose stools for the first 24 hours. These usually resolve soon thereafter and most patients usually have formed stool by 1–2 weeks. The clinicians do not recommend stool testing for resolution in those with formed stool, but is considered if 3 or more diarrhea stools per day occur post few weeks. It is crucial to note that the polymerase chain reaction test for *C. difficile* toxin may remain positive for 30 days after a successful treatment, which is another reason not to test asymptomatic patients who underwent FMT. An unclear presentation is abdominal cramping and intermittent frequent bowel movements occurring in a patient who

might be a carrier of *C. difficile* and who is a FMT recipient. These patients are most likely to have post-infectious IBS. Hence, the clinician should ideally be able to differentiate between post-infectious IBS and rCDI in order to avoid unnecessarily repetition of FMT [1]. In a systematic review by Marcella et al., FMT-related adverse events were summarized. (**Table 1**) Largely, 85 unique types of AEs were reported in 24% of FMT procedures (1347/5688) during or after FMT, including 6% (246/4241) of patients with SAEs [30].

Although FMT may seem "natural" and safe, possibly even "frugal," clinicians are concerned about the long-term effects that donors' intestinal microbes may have on patients receiving FMT [31]. For instance, the gut microbiota has been shown to be a possible transferrable agent of risk or phenotype in multiple disorders, including obesity, cardiovascular disease, and autoimmune disorders, such as type 1 diabetes [32, 33]. Furthermore, the gut microbiota has been found to interact with the central nervous system and to affect brain chemistry and behaviors [34]. Theoretically, FMT could bring about the transmission of anxiety and depression,

Adverse Events	**% of Patients Affected**
Diarrhea	10.00%
Abdominal discomfort, Cramping, Pain	7.35%
Nausea, Vomiting	3.31%
Excessive flatulence,	3.23%
Constipation	1.90%
Fever	1.71%
Fatigue, Malaise	1.32%
Fecal urgency	0.76%
Proctalgia	0.46%
Endoscopy-related respiratory difficulties	0.39%
Disease relapse	0.37%
Regurgitation Belching,	0.33%
Disease exacerbation	0.28%
Bloody Stool	0.21%
Sore throat, Rash, Skin erythema, Pruritus	0.14%
Anorectal discomfort, Headache	0.12%
Aspiration pneumonia, CMV infection, Rectal bleeding, Chills	0.11%
Bacteremia, Death	0.09%
Mucoid stool, Transient borborygmus	0.07%
Diverticulitis	0.05%
Peripheral Neuropathy, Norovirus gastroenteritis, Rhinorrhea, Herpes zoster, Decreased appetite, Dizziness, *C. perfringens* Infection	0.03%
Sjogren's disease, ITP, Rheumatoid arthritis, Minor mucosal tear during colonoscopy, Hematemesis, Chest distress, Testicular pain, Myasthenia gravis, Hot flashes, Allergic bronchitis, Dehydration, Rectal prolapse, Appendicitis, URTI, Pancreatitis, Stuffy nose, Depression, Anorexia, Soling of transplant, Vertigo	0.02%

Table 1.
FMT related adverse events [30].

autism, or neurological conditions, such as Parkinson's disease. However, most of these effects have only been observed in preclinical studies [32].

9. The different AEs report in randomized controlled trials (RCTs) and non-controlled studies

In a systematic review by Marcella et al., twenty studies of RCTs included 558 patients: 222 with IBS, 138 with UC, 70 with CDI and few patients with cirrhosis, constipation, obesity, autism spectrum disorder and hepatic encephalopathy. While in non-controlled studies, the most common indication was CDI followed by IBD. When compared to RCTs, non-controlled studies demonstrated a lower trend of FMT-related AEs rate. Nevertheless, all FMT-related SAEs were reported in non-controlled studies. This result should not be considered as a premise as patients with severe cases or immunocompromised were essentially excluded from RCT. Therefore, RCT results should not be referred to as the representative as a whole.

10. AEs in populations with different delivery route

The incidence of FMT-related AEs by route of delivery comprised colonic transendoscopic enteral tubing (TET) (6%), colonoscopy (15%), enema (26%), capsule (29%), midgut tube (29%) and gastroscopy (32%). Upon analysis, the incidence of FMT-related AEs was more common in patients who had FMT via the upper GI routes than lower GI routes (28.8% vs. 17.5%). This result is in conjunction with the incidence of FMT-related SAEs in upper and lower GI route (1.4% vs. 0.9%). Additionally, the SAEs that occurred in FMT recipients via gastroscopy and mid-gut tube were all delivery-related SAEs. This confers to a belief that patients likely experienced SAEs caused by invasive endoscope procedures rather than the microbiota-related SAEs for upper GI routes (except for capsule). On the contrary, for lower GI routes and capsule, a plethora of SAEs were microbiota-related. Kunde et al. outlined the tolerability of FMT in children with UC and intolerance with immediate leaking of enemas happened in one patient. Colonic TET was in recent times used as the delivery of washed microbiota for the elderly, adults and children to ensure the whole-colon administration of microbiota and to meet the patient's needs that required multiple FMTs [30]. AEs such as nausea (1%), pharynx discomfort (5%) and rhinorrhea (1%); and procedure-related: mild pharynx bleeding (1%), epistaxis (5%) and unplanned extubation (2%) were reported in a study comprising patients who underwent mid-gut TET [35]. Ekekezie et al. published a survey regarding do-it-yourself (DIY) FMT that consisted of 84 respondents [36]. The survey demonstrated that DIY FMT was most commonly used in IBD (35%) and IBS (29%) patients. AEs, such as abdominal pain, flatulence and bloating, changes in mood, fever, infection and hospitalization were reported in 12% of the participants. Self-administration of home FMT via enema was observed in two articles, which allowed eight patients to complete 11 courses of FMT in total. About 87.5% (7/8) of patients benefited from this. Three patients developed AEs, two patients had urinary tract infection post-FMT deemed to be not related to the FMT and one patient experienced severe bloody diarrhea, weakness, abdominal pain and weight loss several weeks post-FMT, which was due to CMV infection [30]. CMV is observed in up to one-third of IBD patients with the glucocorticoid-refractory disease [37]. Moreover, CMV may arise inadvertently from an unconventional method of home or self FMT preparation. Hence, there is a need for increased awareness around DIY-FMT and research around this phenomenon, which may leverage public health [30].

11. Informed consent

Informed consent usually presupposes three elements such as capacity to consent, voluntariness, and information [38]. It is not capacity to consent but inadequate information that may pose problems with regards to FMT [32]. In recurrent and refractory CDI cases, FMT could be considered in the "transition zone" between experimental research and standard of care [32, 39]. Even though innovative interventions are generally regulated less strictly than new drugs or biological products, their "experimental" nature does imply special ethical requirements for informed consent [32]. Despite the fact that there are no formal standards for the content of informed consent for "transition zone" interventions, it is usually accepted that such discussions should include the following components: the innovative nature of the procedure, the provider's experience with the procedure, the risk–benefit profile including unknown risks, the (lack of) evidence, and alternatives to the innovative intervention [32, 40].

12. Washed microbiota transplantation

The FMT procedure using washing process was coined as washed microbiota transplantation (WMT). FMT on the basis of washed microbiota preparation has been shown to reduce adverse events caused by traditional fecal suspension preparation and significantly improve the efficacy [41]. Population evidence demonstrated the washed microbiota preparation with microfiltration based on an automatic purification system followed by repeated centrifugation plus suspension for three times significantly decreased the adverse events related to FMT [42]. With the goal to improve the safety of FMT, studies regarding improved methodology of fecal microbiota preparation known as WMT continue to accrue in China since 2014. WMT is based on the principle of automatic filtration and washing process and the related delivery [30, 42, 43]. The improved safety of WMT was reinforced by the metagenomics next-generation sequencing and metabolomics analysis that demonstrated more types, amount of viruses, and pro-inflammatory mediators were washed out during the washing process [30].

13. FMT in the COVID-19 pandemic

Owing to the outbreak of COVID19, healthcare facilities have intensively decreased elective activities both to avoid potential transmission of the virus and to shift human and structural resources to the management of COVID-19 [44]. In the wake of COVID-19 situation, stringent policies in screening the FMT donors have to be put to ensure the patient safety [30]. Due to the potential risk of transmission of SARS-CoV-2 via Fecal Microbiota for Transplantation (FMT), FDA has determined that additional precautions are needed for any investigational use of FMT, whether under an Investigational New Drug Application (IND) on file with the FDA or under FDA's enforcement discretion policy. The following recommendation has been made by FDA. It has already notified all IND holders of the need for additional precautions namely:

No clinical use of FMT product manufactured from stool donated on or post December 1, 2019, until further screening and testing procedures and changes to the informed consent process are implemented for such stool donations as defined below:

1. Screening of stool donor, including an evaluation of whether, since December 1, 2019, the donor was diagnosed with laboratory-confirmed SARS-CoV-2 infection, experienced symptoms of COVID-19 not explained by another diagnosis, or was exposed to a suspected or confirmed case of COVID-19.

    ○ In any occurrences of suspected or confirmed SARS-CoV-2 infection or exposure as described above, exclusion of the donor from further donations is recommended. Also, it is recommended that there should not be any clinical use of any FMT product manufactured from stool donated by the affected donor beginning 4 weeks prior to the suspected or confirmed SARS-CoV-2 infection or exposure should be avoided.

2. Performing test of the stool donation or stool donor for SARS-CoV-2 virus or RNA.

    ○ Tests may include testing upper respiratory clinical specimens (e.g., nasal swabs) or other clinical specimens (e.g., rectal swabs or stool donations).

    ○ If SARS-CoV-2 is identified, exclusion of the donor from further donations is recommended. Also, it is recommended that there should not be any clinical use of any FMT product manufactured from stool donated by the affected donor beginning 4 weeks prior to the first positive test.

3. In the context of informed consent process, it is crucial to convey to the FMT recipient that healthy, asymptomatic stool donors may potentially be infected with SARS-CoV-2, explain the testing approach and other strategies used to alleviate the risk of SARS-CoV-2 transmission, and advise the FMT recipient of the limitations of testing and risk mitigation strategies [45].

In their position paper, Ianiro et al., depending on the available clinical evidence, the panel provided guidance on issues relating to the impact of COVID-19 on FMT, including selection of patient, selection and recruitment of donor, FMT procedures, patient follow-up and further research activities. Few feasible security measures have been proposed in this article so as to assure a safe cohabitation with COVID-19 in the near future. Following are the recommendations for every step of the FMT procedure to mitigate the potential risk of SARS-CoV-2 transmission:

Outpatient assessment:

Remote assessment (teleconsultation) is recommended.

If remote assessment not possible: Checkpoint at entrance (body temperature; patients must wear surgical mask; hand wash; no company admitted) is recommended.

COVID-19 screening (exposure and medical history, symptoms, laboratory analyses) is recommended.

If clinical suspect of COVID-19, nasopharyngeal swab must be carried out.

Inpatient assessment:

Exclusion of COVID-19 via tests. (nasopharyngeal swab, laboratory exams, if fever or respiratory distress conduct chest CT scan).

Isolation is recommended. (contact precautions and droplets in air).

If patient is COVID-19 positive:

- Dedicated COVID-19 wards and dedicated healthcare professionals recommended.

- Dedicated radiology and invasive procedures recommended.

- Assess the risk/benefit profile of FMT procedure.

Donor screening:

Remote evaluation (The screening could be done through teleconsultation).

Screening for COVID-19 (Details about exposure to confirmed cases, medical history, symptoms, if any).

Laboratory examinations are recommended (standard blood and stool tests plus nasopharyngeal swab and serology for SARS-CoV-2).

Donors who test positive must be excluded from donation and previously donated stool, up to 4 weeks before the occurrence of symptoms/COVID-19 diagnosis, should be discarded as initial clinical evidence proposes that SARS-CoV-2 is detected in stools up to 4 weeks post infection.

Sample donation:

A dedicated toilet at the stool bank should be reserved for collection of stool, and high-touch surface areas should be cleaned post each donation.

Repeat standard and COVID-19 screening interview is recommended for donors.

Checkpoint at the entrance (body temperature, subjects must wear surgical mask, hand wash, company forbidden) is recommended.

Direct stool testing for SARS-CoV-2 and/or common pathogens and quarantine approach as potential alternative is recommended.

Sample handling:

Stool sample transferred to laboratory by dedicated healthcare workers is recommended.

Retention of stool samples for 'look-back' testing is suggested.

Stool processing that conforms to local standard operating procedures and biosafety protocols; at minimum, biosafety level 2 is recommended.

FMT using endoscopic procedure:

- Patients undergoing outpatient elective endoscopic FMT should have temperature checked and be questioned about possible symptoms.

- Dedicated healthcare professionals for COVID-19 is recommended.

- Staff present in the endoscopic room must be protected for aerosol generating procedures.

- Patients need to wear surgical mask.

- Outpatient discharged post brief observation, medical and nurse staff report follow-up instructions to caregivers via teleconsultation.

Follow-up:

Follow-up visits should preferably take place via teleconsultation, outpatient visits should be limited to cases where in-presence assessment is mandatory [44].

14. Recommendations for future clinical trials

The safety of any investigational product is best understood with respect to a placebo-controlled trial with appropriate sample size with an adequate

follow-up period. A national FMT registry, supported by a grant to the American Gastroenterology Association from the National Institutes of Health, has been initiated to address the limited knowledge of the long-term risks of FMT [6]. This registry aims to collect the efficacy and safety data on 4000 patients who undergo FMT for up to 10 years to understand the long-term risks and benefits of FMT [30]. However, the study results will not be available for many years to come. The important reason for caution regarding potential long-term consequences of FMT is the ever-increasing list of diseases related to the microbiome [6, 46]. Clinicians should be aware of data limitations when counseling patients concerning any investigational therapy. The following recommendations could be made for future FMT based trials and for reporting of data to improve the fundamental understanding of FMT safety and efficacy:

Exclusive employment of toxin testing to ensure selection of patients with true recurrent CDI.

- Enrolment of subjects with acute-onset CDI.
- Consideration of key exclusion criteria such as long-term suppressive antibiotics for CDI.
- Reporting of the number of treatments required to achieve clinical resolution, as repeated FMT treatments carry procedural risks, depending on route of administration.
- Statistical interpretation should take into account loss to follow-up and other AEs that lead to treatment discontinuation, which are considered treatment failures in most clinical trials.
- Large double-blind, placebo-controlled trials are important for adequate evaluation of the efficacy and safety of any investigational intervention, including FMT. On the other hand, future comparator trials with vancomycin pulse-taper regimens should be considered to fully evaluate if FMT offers additional advantages over other recommended therapeutic approaches [6].

15. Concluding remarks

Over the last decade, much progress has been made studying FMT for the management of CDI, and there are multiple ongoing studies also assessing it as a therapy for other conditions. Nonetheless, there is still much to learn regarding the gut microbiome and its role in disease physiology and treatment. Both physicians and patients will benefit from a better understanding of the risks of FMT and delineated protocols to assess adverse events, complications, and follow-up. There is a need for high-quality, large, prospective, randomized controlled trials and long-term follow-up investigating screened donors and recipients to evaluate the long term safety and the risk–benefit profile of this promising therapy [47]. Furthermore, immunocompromised patients represent a special patient population, and designing a randomized controlled trial that addresses the safety and efficacy of FMT among these individuals will definitely be a welcoming step forward [48]. Mandatory stringent screening guidelines for stool donors are the need of the hour, even though screening cannot prevent unanticipated emerging infections [6]. The COVID-19 pandemic is challenging the healthcare systems globally, and it is reasonable to assume that it will be present also in the near future, compelling us to adjust

the overall clinical-procedural standards. Lastly, the development of investigational microbiome therapeutics with defined microbial consortia will provide greater confidence in drug purity, identity, and potency, in addition to risk mitigation for improved patient safety [6, 44].

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Conflict of interest

There are no conflicts of interest.

Notes/thanks/other declarations

There are no declarations.

Acronyms and abbreviations

FMT	fecal microbiota transplantation
rCDI	*clostridium difficile* infection
UC	ulcerative colitis
IBD	inflammatory bowel disease
WMT	washed microbiota transplantation
SAEs	serious adverse events
RCTs	randomized controlled trials
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TET	transendoscopic enteral tubing

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