

LEADING ARTICLE

Fecal microbiota transplantation: Current status and challenges in China

Fecal microbiota transplantation (FMT) is used to reconstruct the microbiota of the gastrointestinal tract by taking fresh or frozen feces from a strictly screened healthy donor through *in vitro* medical preparation and transplanting it into the digestive tract of the recipients through various approaches.¹

FMT in China

As early as the Western Zhou Dynasty of China in about 10th century BC, "Prescription Collection of Fifty-two Diseases" recorded the use of "golden juice" to treat infectious diseases.² Afterward, in the "Prescription Collection of Emergency" edited by Dr. Ge Hong in the Eastern Jin Dynasty of China about 1700 years ago, FMT preparation called "yellow soup" was used to treat food poisoning and severe diarrhea. FMT appeared in English literature in 1958 when four patients with pseudomembranous colitis were treated with fecal enemas. In 1966, Luo *et al.*³ successfully treated two patients with pseudomembranous colitis using fecal enemas from Chinese healthy donors. In the last 5 years, FMT has gained popularity in China, mainly amongst Chinese gastroenterologists and pediatricians. At present, there are more than 10 Chinese tertiary hospitals conducting FMT clinical trials and related research in Beijing, Shanghai, Nanjing, Guangzhou, Xi'an, Tianjin, and Chongqing.

FMT perceptions of Chinese physicians and patients

The cognitive acceptance of physicians and patients has important influence on the implementation of FMT. In 2014, a survey showed that Chinese physicians, especially gastroenterologists, had good acceptance and understanding of FMT, but the biggest challenge that troubled physicians was the acceptability of the patients and the lack of clinical guidelines.⁴ In another survey conducted in 2017, 89% of the gastroenterologists interviewed believed that FMT was a promising treatment option for certain diseases and worthy of recommendation for its potential high efficacy. Clinicians who are not familiar with FMT are worried about issues like patient dignity and psychological impact. In addition, more than half of the interviewees (56.1%) were concerned about the abuse of home do it yourself (DIY) FMT because of unpredictable consequences.⁵

FMT clinical trials in China

As of 10 April 2018, 173 clinical trials of FMT were registered on the website of the Clinical Trial Registry (www.clinicaltrials.gov), of which 17 were on the Chinese Clinical Trial Registry (<http://www.chictr.org.cn>). Among them, there are 43 registered studies from the mainland and 4 from Hong Kong, China. The clinical trials involved inflammatory bowel disease (UC and CD), autism

spectrum disorder, tic disorder, type 2 diabetes, irritable bowel syndrome (IBS), *Clostridium difficile* infection (CDI), decompensated cirrhosis, pancreatitis, constipation, chronic intestinal pseudo, epilepsy, methicillin-resistant *Staphylococcus aureus* enterocolitis, acute graft versus host disease, and antimicrobial resistance colonization. A total of 3125 articles related to FMT were found on a search of PubMed, EMPASE, and CNKI databases. Among them, 478 articles (including 249 articles in Chinese) were published by Chinese authors. The Chinese studies showed that FMT had good efficacy for CDI treatment. This positive effect was reported in the treatment of inflammatory bowel disease (IBD),⁶ constipation, autism spectrum disorder,⁷ and tic disorder.⁸ In addition, the FMT also shows potential efficacy in the treatment of obesity, Parkinson's disease, chronic hepatitis B infection, radiation-induced toxicity, sepsis, eosinophilic gastroenteritis, epilepsy, and so on. However, many of these trials using FMT were cases or a series of case reports, and evidence-based medical results about FMT efficacy, safety, and underlying mechanisms are eagerly awaited.

FMT donor screening and transplantation

FMT donors require strict selection based on their medical history and family and personal history and must undergo necessary special and laboratory examinations.^{1,9} For asymptomatic gastrointestinal diseases, there has been no report on whether screening endoscopy is needed. However, it is necessary that FMT donors with asymptomatic lesions like polyps be excluded. Donor screening criteria need to be updated according to our understanding, and an unpublished study with endoscopy screening in donor providers is required.

Donor screening requires informed consent from donor volunteers and guardians of child donor candidates. Once a donor has been identified, their recent medical history and laboratory tests will be rechecked every 2 months and transplant samples from each transplantation procedure will be retained for subsequent review.

The transplant preparation of fecal microbiota includes sample collection, separation, and purification. Fecal collection can be carried out using disposable sterile sealing bags or commercial disposable aseptic containers. In China, FMT transplants are prepared with biosafety cabinets in the qualified laboratories, usually at tertiary hospitals, and DIY FMT by patients at home is not recommended. The preparation of FMT materials can be purified artificially or mechanically; FMT executants partially use the intelligent microorganism separation system (GenFMter, Nanjing FMT Medical Co., Ltd. China) and the automatic stool pretreatment system (HHL-FDGL-I, Suzhou Hailu Biotech Co., Suzhou, China) in China. As for fresh or frozen fecal microbiota products, the majority of Chinese teams do not use frozen

products and obtain the fresh transplants from donors within 2 h; frozen FMT products are only used to treat emergency CDI. There is FMT assistance at each hospital for requirements of emergency CDI control in Beijing, Nanjing, and Shanghai. The effectiveness of FMT with frozen products in non-CDI conditions has not been ascertained. A big challenge is in the efficacy, storage, and safety of the use of frozen FMTs.

FMT is currently implemented through four ways, the upper digestive tract (gastroscopy or nasal cavity tube), the lower intestine (colonoscopy, retention enema, and colonic tube), the upper combined the lower approach, and oral capsules. However, the best way to perform FMT is still unclear due to the lack of related comparative studies. Based on publications and our experiences of the FMT approaches, the patients' condition and their willingness must be considered. It is generally recommended that the lower approach is the first option of FMT therapy for colorectal diseases,⁶ and the combination of upper and lower approaches can be used to treat systemic disorders.^{7,8} Oral capsules of FMT are convenient, and there are a few clinical trials that need to be evaluated.

Biobanking FMT samples

FMT has promising potential effects on a variety of conditions. However, its therapeutic mechanism has not been understood. Samples related to FMT are the key link and should be taken from donors and recipients for further biological studies and necessary rechecks. The standardization of biobanking samples is a core issue of subsequent evaluation. A consensus on standardized biobanking samples of gut microbiome has been reached by Chinese experts from the mainland and Hong Kong, including ethics, sample collection, preparation, storage, and so on, which is suited for the processing of FMT samples.

Safety of FMT

In general, FMT is a safe, biological modality for short-term observation. Abdominal discomfort was mostly reported, and other common adverse effects include transient fever, diarrhea, constipation, abdominal colic, nausea, vomiting, and itching, as well as opportunistic infections such as the singular deformation bacterium, *Candida albicans*.⁶ The safety of FMT is related to implementation approaches, the severity of the disease, transplant methods, dosage, and so on.

The long-term adverse effects of FMT remain unknown. Following more and more results showing gut microbiota to be risky or to contain pathogens of certain diseases, such as *fusobacterium nucleatum*, a risk to colon cancer, the long-term safety of FMT and current donor screening program need to be questioned and investigated. With the present donor-screening criteria, it is difficult to predict whether or not the recipients will develop chronic diseases such as metabolic diseases, autoimmune diseases, IBD, IBS, and colorectal lesions.

Standardization of FMT

Currently, there is no standardization of FMT process, and the implementation of FMT varies at different sites. Like all clinical trials, the FMT requires ethical approval and clinical trial

registration.^{1,9} China has formed an FMT consensus expert group under the Committee of Gut Microbiota in Chinese Society of Gastroenterology since 2016. The expert group organizes an annual meeting on FMT issues and updates and has drafted a consensus involving FMT concept, donor screening, methods, Chinese cultural and ethics, supervision, and so on, which will be published in 2018.

A unified FMT registration system is needed, and it should be jointly constructed by multiple societies, such as the Chinese Society of Gastroenterology, the Chinese Association of Digestive Disease, and the Chinese Society of Pediatrics and National Health Administration.


Limitations of FMT

FMT basically depends on rare donors and their fresh feces, which intensively restricts the application of FMT, as the technology to keep fecal microbiota alive has not been perfected.¹⁰ In addition, it is unclear what microorganisms of FMT are effective to treat different conditions.

The indication, dose, frequency, interval, and follow-up time of FMT treatment need more clinical research and evidence. All of these issues, and issues not limited to these, are the key challenges and clinical concerns about FMT. The mechanism of FMT therapy is also complicated by challenges that need to be solved.

Perspective of FMT

FMT has a long history and has been indicated to be a great potential technology and therapy for many diseases. It is a promising area in which to develop new microbial therapies and products and precision diagnostic and therapeutic modalities. The challenges and mechanisms of FMT are worth being solved.

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