

Encyclopedia of fecal microbiota transplantation: a review of effectiveness in the treatment of 85 diseases

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Abstract

Fecal microbiota transplantation (FMT) has been used as a core therapy for treating dysbiosis-related diseases by remodeling gut microbiota. The methodology and technology for improving FMT are stepping forward, mainly including washed microbiota transplantation (WMT), colonic transendoscopic enteral tubing (TET) for microbiota delivery, and purified Firmicutes spores from fecal matter. To improve the understanding of the clinical applications of FMT, we performed a systematic literature review on FMT published from 2011 to 2021. Here, we provided an overview of the reported clinical benefits of FMT, the methodology of processing FMT, the strategy of using FMT, and the regulations on FMT from a global perspective. A total of 782 studies were included for the final analysis. The present review profiled the effectiveness from all clinical FMT uses in 85 specific diseases as eight categories, including infections, gut diseases, microbiota–gut–liver axis, microbiota–gut–brain axis, metabolic diseases, oncology, hematological diseases, and other diseases. Although many further controlled trials will be needed, the dramatic increasing reports have shown the promising future of FMT for dysbiosis-related diseases in the gut or beyond the gut.

Keywords: Fecal microbiota transplant; Washed microbiota transplantation; Transendoscopic enteral tube; Spore; *Clostridioides difficile*; Methodology; Microbiota–gut–brain axis

Introduction

Humans have applied human fecal microbiota transplantation (FMT) to treat diseases for thousands of years in China.^[1,2] In ancient China (AD 300–400 years), Hong Ge as a doctor of traditional Chinese medicine described the details on using fecal suspension for the treatment of the serious conditions, such as food poisoning and fever.^[1,2] The ancient medical record of human FMT was confirmed by the following criteria^[2]: (1) the delivered materials are from human feces; (2) the administration route is the digestive tract; (3) the efficacy is caused by microbiota from the fresh fecal water or fermented fecal matter according to the modern medicine; (4) the recorded prescription, methods, indications, and efficacy in ancient literature are clear enough to be identified. Importantly, FMT has been used for refractory diseases by some elder-generation physicians in recent decades in China, indicating the sustained long tradition of using FMT from ancient to modern China.^[2]

The emerging refractory antibiotics related resistance in the post-antibiotics era has led physicians and scientists to revalue the role of FMT in modern medicine.^[3] FMT was reported as a highly effective treatment for pseudomembranous enterocolitis by Eiseman *et al*^[4] in 1958. The *Clostridioides difficile* infection (CDI) was later identified as the main pathogen of pseudomembranous colitis. Then, FMT as a well-established treatment for recurrent CDI has experienced a renaissance in recent years with great attention worldwide.^[5] In the last decade, a series of pilot studies on FMT, in conditions such as ulcerative colitis (UC), Crohn's disease (CD), epilepsy, autism, and recurrent urinary tract infections (UTIs), have revealed the potential effectiveness of FMT beyond CDI.^[6–13] In addition, the improved FMT methodology based on automated purification and washing process was named washed microbiota transplantation (WMT), which changed the preparation of fecal microbiota and the safety of transplantation.^[14,15] However, a complete understanding on how FMT cures or improves the

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patients and a general review of all FMT-treated diseases have not been undertaken.

We recently reviewed the global data on the safety of FMT from 2000 to 2020.^[16] FMT-related adverse events (AEs) were observed in 19% of FMT procedures with the most frequently reported FMT-related AEs being diarrhea (10%) and abdominal discomfort/pain/cramping (7%). FMT-related serious adverse events (SAEs), including infections and deaths, have been reported in 1.4% of patients who underwent FMT (0.99% microbiota-related SAEs). All reported FMT-related SAEs were in patients with mucosal barrier injury. In this review, we aimed to summarize the effectiveness of FMT for all conditions from 2011 to 2021, and discussed important medical progress of FMT from the perspective of medical history. The present review will assist physicians, researchers, patients, and health providers in general to arrive at a comprehensive understanding on FMT.

Methods

Our search terms were applied to medical publications and databases from EMBASE, MEDLINE, CNKI (database in Chinese), and Wanfang Data from (database in Chinese) January 1, 2011, to December 31, 2021. The search terms were derived from our previously published study.^[16] The inclusion criteria included: (1) studies referencing FMT for human subjects showing benefits with no limitation of age and gender; (2) article type: original full-text article, meeting abstracts, and letters to the editor on the clinical studies; (3) reports in English or Chinese. Exclusion criteria included: (1) duplicated reports; (2) non-original reports such as commentary, consensus, reviews, and meta-analysis; (3) publications in Chinese reporting on the same patients in an English article. The reports on pilot case study, high-quality real-world cohort study, and randomized controlled clinical trial (RCT) were cited and discussed.

Global Trend in the Benefits of FMT

A total of 14,539 records were identified in the search. After the exclusion, removal of duplication, screening and reviewing of full-text articles, we selected 782 searched studies for analysis in this review [Figure 1]. We divided all studies into eight main categories: infections, gut diseases, microbiota–gut–liver axis, microbiota–gut–brain axis, metabolic diseases, oncology, hematological diseases, and other diseases. Each category was further subdivided into specific diseases. A total of 85 diseases were shown in Figure 2. The number of treated cases using FMT for each disease were clarified as the following level: 1–10, 11–100, 101–1000, 1001–10,000, 10,000+. The baseline characteristics and main findings of high-quality clinical research (defined as any randomized clinical trial or any study with sample size ≥ 100 or the largest study on each disease with sample size ≥ 5) on the benefits of FMT were shown in Supplementary Table 1, <http://links.lww.com/CM9/B161>.

The global trend in the benefits from FMT was shown in Figure 3. The uses of FMT for infections and gut diseases were the most widely documented, followed by neuropsychological, hematological, and liver diseases.

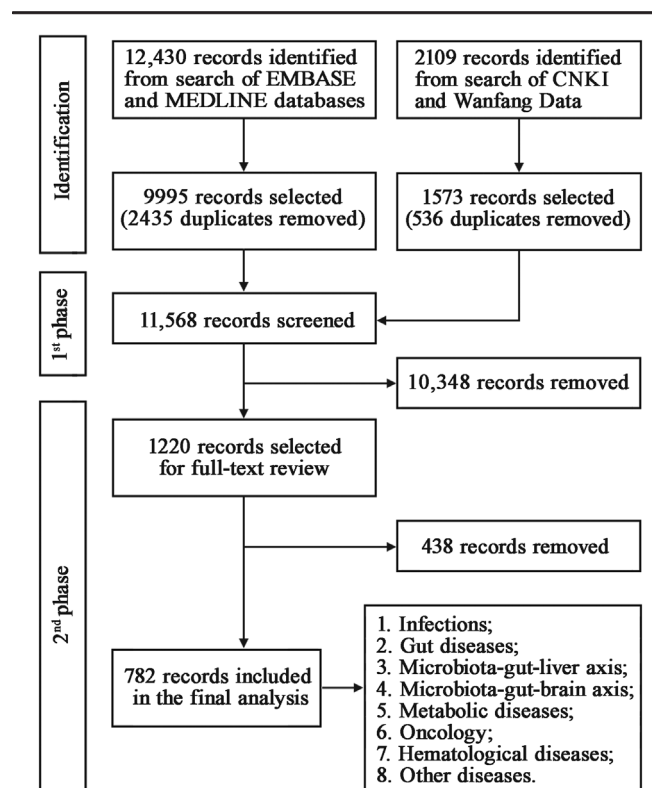


Figure 1: Flowchart of study selection.

Benefits from FMT

FMT and infections

Bacterial infections

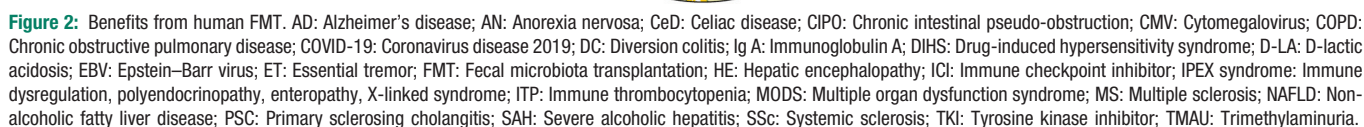
CDI

From 2011 to 2021, a total of over 10,000 patients with CDI have benefited from FMT globally. In 1983, Schwan *et al*^[17] documented the first cure of CDI by rectal infusion of feces using the patient's partner as a donor. Later in 2013, the first RCT by van Nood *et al*^[18] reported the infusion of donor feces was significantly more effective for the treatment of recurrent CDI than vancomycin. FMT has been expanded to treat CDI in the children, the elderly, and pregnant patients.^[19–21] In the most recent studies from Europe and Australia, the use of antibiotics as a pre-treatment has been unhelpful in most cases, highlighting the superiority of FMT treatments as an initial primary therapy.^[22]

Occasionally, CDI occurred with other diseases. Meighani *et al*^[23] found that the response to FMT and the rate of CDI relapse in patients with inflammatory bowel disease (IBD) were not statistically different compared to the rest of the cohort. A retrospective study found that overall cure rate of FMT for CDI was 91.3% at 3 months in solid organ transplantation patients.^[24] Notably, Elope and Rodriguez^[25] reported two cases of treating recurrent CDI in human immunodeficiency virus-infected individuals with FMT.

Multidrug-resistant organisms (MDROs)

Recently, at least 100 patients suffering from MDRO infection have benefited from FMT. In 2015, Crum-Cianflone *et al*^[26]



In 2013, Zhang *et al*^[30] first reported the successful treatment using a standardized FMT for a case of

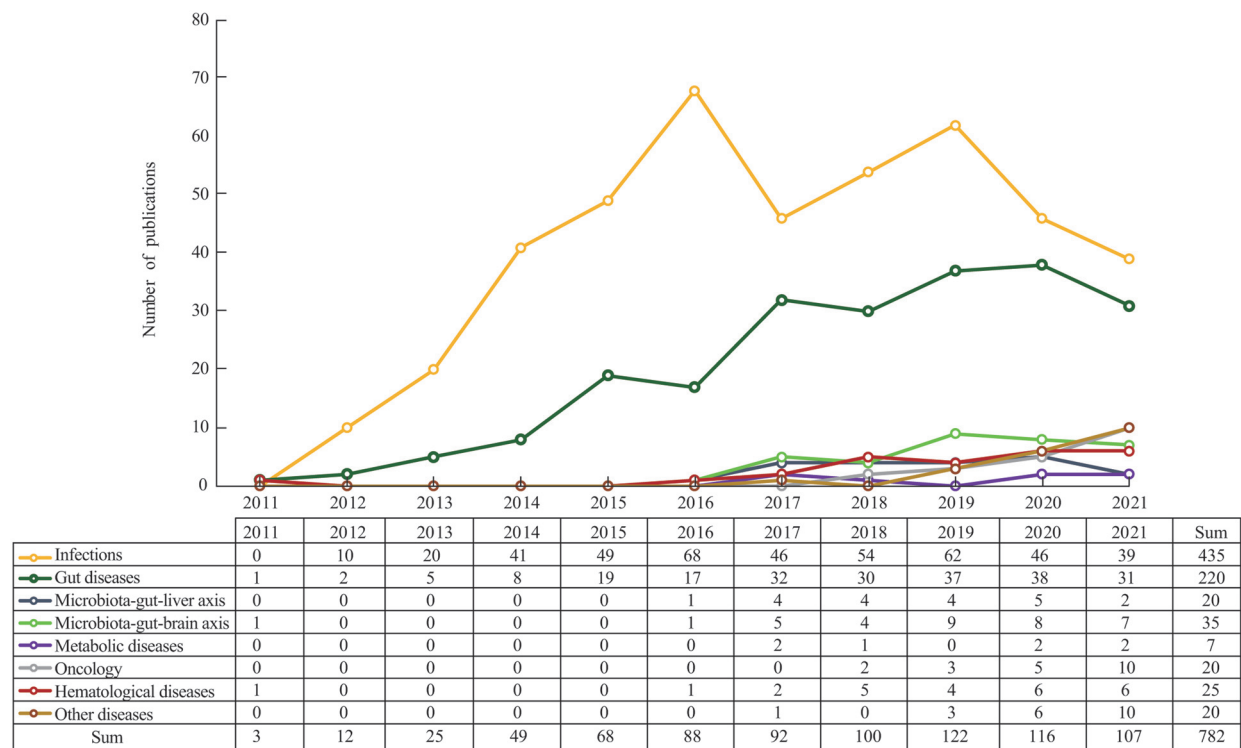


Figure 3: Global trend in the benefits from FMT. FMT: Fecal microbiota transplantation.

refractory CD complicated with intraperitoneal fistula. Moreover, a prospective study demonstrated that the overall eradication rate of *Helicobacter pylori* was 40.6% (13/32) by WMT.^[31] FMT also showed its efficacy in some extraintestinal infections such as pyogenic liver abscess, sepsis, and multiple organ dysfunction syndrome.^[32-34]

Viral infections

Hepatitis B

It is reported that >100 hepatitis B carriers had undergone FMT. In 2017, a clinical trial showed that in the FMT arm, all participants (3/3) achieved HBeAg clearance while none in the control arm did.^[35] Chauhan *et al*^[36] reported similar results. An open-label RCT demonstrated that FMT with tenofovir is superior to tenofovir alone in improving clinical outcomes in acute-on-chronic liver failure due to hepatitis B.^[37]

Coronavirus disease 2019 (COVID-19)

According to a case report, two patients diagnosed with COVID-19 showed negative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) stool testing 1 month after FMT.^[38]

Other viral infections

FMT appeared to be efficacious in norovirus infection and cytomegalovirus colitis.^[39,40]

Fungal infection

In one Chinese patient with UC and recurrent invasive infection of *Candida glabrata*, inflammatory markers rapidly

decreased after WMT via colonic transendoscopic enteral tubing (TET) within 1 week and repeated fecal fungal culture tests were negative during hospitalization and follow-up.^[41]

FMT and gut diseases

UC

Perhaps the earliest FMT carried out in 1988 treated UC successfully in one patient with over 20-year remission.^[42] Borody *et al*^[43] showed that 67.7% of UC patients (42/62) achieved complete clinical remission after FMT, and 24.2% of patients (15/62) achieved partial responses. Later in a randomized trial, his group showed FMT effectiveness in 27% *vs.* 8% in placebo.^[44] Costello *et al*'s^[8] RCT demonstrated that steroid-free remission was achieved in 12 of the 38 participants (32%) receiving pooled donor FMT compared with 3 of the 35 (9%) receiving autologous FMT. A recent double-blind RCT showed that repeated FMTs could induce and maintain clinical, endoscopic, and histologic remission in four (100%) UC patients.^[45] More than 1000 patients with UC have been treated with FMT globally between 2011 and 2021.

CD

Over 100 CD patients have benefited from FMT since the first successful case report of FMT in CD was published in 1989.^[42] In 2013, Zhang *et al*^[30] reported a patient with severe CD successfully treated using mid-gut FMT. In a retrospective study, the rate of clinical improvement and remission of CD at the first month after FMT was 86.7% (26/30) and 76.7% (23/30), respectively.^[9] According to Xiang *et al*'s^[10] study, 72.7% (101/139), 61.6% (90/146),

76% (19/25), and 70.6% (12/17) of CD patients achieved improvement in abdominal pain, diarrhea, hematochezia, and fever, respectively, at 1 month after FMT. An RCT also showed that the steroid-free clinical remission rate at 10 weeks and 24 weeks was 44.4% (4/9) and 33.3% (3/9) in the placebo group while 87.5% (7/8) and 50.0% (4/8) in FMT group.^[46]

Constipation

As early as 1989, a case with chronic constipation showed improvement after bowel-flora alteration.^[42] In total, over 1000 patients with slow transit constipation (STC) underwent FMT globally from 2011 to 2021. Tian *et al*^[47] carried out a randomized controlled trial, where FMT was significantly more effective (30% higher cure rate) for treatment of STC than conventional treatment.

Irritable bowel syndrome (IBS)

Almost 1000 patients with IBS have been treated with FMT. In Pinn *et al*'s^[48] study, 70% of the patients with IBS experienced resolution or improvement of symptoms after FMT. A double-blind RCT found that 36 of 55 (65%) participants receiving FMT *vs.* 12 of 28 (43%) receiving the placebo showed a response at 3 months.^[49] Another clinical trial also confirmed the efficacy of FMT for patients with IBS.^[50]

Pouchitis

In 2016, Fang *et al*^[51] reported successful treatment of chronic pouchitis utilizing FMT. According to Stallmach *et al*'s^[52] report, symptoms of chronic antibiotic-refractory pouchitis were resolved in four of five patients within 4 weeks after the last FMT. A pilot study showed that four of nine patients receiving FMT were in clinical remission at 30-day follow-up, and three patients remained in remission until a 6-month follow-up.^[53]

Other gut diseases

In 2014, FMT was first utilized in treating eosinophilic gastroenteritis and achieved a positive clinical response.^[54] According to a pilot study, symptoms of allergic colitis in 17 infants were relieved within 2 days of FMT, and no relapse was observed in the next 15 months.^[55] Clancy and Borody^[56] also showed that FMT could alleviate food intolerance symptoms. Several studies reported that the symptoms of diversion colitis improved after FMT.^[57,58] It is also reported that FMT had a positive therapeutic effect in treating microscopic colitis, collagenous colitis, and recurrent diverticulitis.^[59-61] Zheng *et al*^[62] reported that WMT reduced proton pump inhibitor dependency in non-erosive reflux disease.

In a case report, full recovery of duodenal villi and clinical symptoms of celiac disease after FMT was reported.^[63] Gastrointestinal symptoms of small intestinal bacterial overgrowth significantly improved after FMT in some reports.^[64,65] FMT had also been reported in effectively treating chronic intestinal pseudo-obstruction, gut fermentation syndrome, and D-lactic acidosis.^[66-68]

FMT and the microbiota-gut-liver axis

Hepatic encephalopathy (HE)

In 2016, Kao *et al*^[69] reported that the symptoms and examination indicators were improved in a patient with HE after receiving five weekly FMTs. One RCT showed that no FMT participant developed further HE whereas five patients in the standard of care group developed further HE.^[70] According to Mehta *et al*'s^[71] report, six patients with HE experienced sustained clinical response with single FMT treatment at post-treatment week 20.

Severe alcoholic hepatitis (SAH)

At least 100 SAH patients had received FMT recently. In 2017, Philips *et al*^[72] reported a steroid non-responder with SAH discharged home on the 10th day after FMT. In their following studies, they found that bilirubin, Child-Turcotte-Pugh (CTP), and Model for End-Stage Liver Disease (MELD) and MELD-sodium scores decreased significantly in the FMT group compared to the historical controls group.^[73] FMT showed a better outcome compared to steroid therapy for 90-day survival in SAH.^[74]

Non-alcoholic fatty liver disease (NAFLD)

Allogenic FMT in patients with NAFLD/metabolic dysfunction-associated fatty liver disease (MAFLD) was reported to help improve abnormal small intestinal permeability.^[75] In addition, Witjes *et al*^[76] observed a trend toward improved necro-inflammatory histology, and significant changes in the expression of hepatic genes involved in inflammation and lipid metabolism following allogenic FMT.

Cirrhosis

It was reported that FMT had improved CTP scores and led to a reduction in pro-inflammatory cytokines.^[77] A significant reduction was observed in plasma ammonia at day 30 post-FMT, with a trend toward an increase in ammonia in the placebo group.^[78]

Primary sclerosing cholangitis (PSC)

A case with PSC was afebrile and anicteric after the third and fourth session of FMT, respectively, and remained so up to 1 year.^[79] In a prospective study, three PSC patients experienced a $\geq 50\%$ decrease in alkaline phosphatase (ALP) levels after FMT.^[80]

Hepatic myelopathy

According to Sun *et al*'s^[81] report, the muscle strength of both legs in a case diagnosed with hepatic myelopathy was increased at various degrees after three FMTs.

FMT and the microbiota-gut-brain axis

Autism spectrum disorder (ASD)

It has been reported that over 100 cases with ASD had undergone FMT therapy from 2011 to 2021. Ward *et al*^[82] found that ASD symptoms were markedly

improved in half of the 8-year-old subjects. According to Kang *et al*'s^[12,83] study, behavioral ASD symptoms improved significantly and persisted 8 weeks and autism-related symptoms improved even more at a 2-year follow-up after FMT stopped.

Parkinson's disease (PD)

A case with PD successfully maintained daily unobstructed defecation until the end of follow-up and the tremor in the legs almost disappeared 1 week after FMT.^[84] Another study also reported motor, non-motor, and constipation scores were improved in 5/6 patients 4 weeks following the FMT.^[85]

Psychiatric disorders

Several studies reported that depression and anxiety symptoms in IBS patients were improved by FMT.^[86,87] In a case report, the patient with mental depression felt less sleepy, had a better appetite, and became more talkative and euphoric after FMT.^[88] Another case report also demonstrated the benefits of FMT in a patient with bipolar disorder.^[89] In addition, a few patients with alcohol use disorder and anorexia nervosa achieved some improvements from FMT.^[90,91]

Other neurological disorders

He *et al*^[11] firstly reported that the patient had no recurrence of epilepsy during the entire 20 months of follow-up after FMT in treating CD. Gunaratne *et al*^[92] also found that FMT reduced seizures. Moreover, several case studies reported improvement in Alzheimer's disease symptoms following FMT.^[93,94] FMT also showed its efficacy in chronic fatigue syndrome, multiple sclerosis, essential tremor, and Tourette syndrome.^[95-98]

FMT and metabolic diseases

Diabetes

In 2018, Cai *et al*^[99] firstly reported that the glycemic control was improved, with remarkable relief of the symptoms of painful diabetic neuropathy in particular after two infusions of FMTs. According to a prospective study, the insulin dose of the patients with brittle diabetes began to decrease from 1 week post-WMT, with the most significant decrease at 1 month post-WMT.^[100] One RCT also demonstrated that FMT halted a decline in endogenous insulin production in recently diagnosed patients with type 1 diabetes in 12 months after disease onset.^[101]

Obesity

In a retrospective study, the mean body mass index (BMI) of all the patients pre-transplant was 28.9 kg/m², and the mean BMI of all the patients 1–3 months post-FMT was 27.4 kg/m².^[102]

Metabolic syndrome

Allegretti *et al*^[103] observed a significant change in glucose area under the curve (AUC) at week 12, and in

the insulin AUC at week 6 in the FMT group compared to placebo.

Other metabolic diseases

A recent prospective study has proven that WMT was effective in reducing serum uric acid levels and improving gout symptoms in gout patients.^[104] FMT has shown its efficacy in trimethylaminuria.^[64]

FMT and oncology

Tumor

In a prospective study, FMT together with anti-programmed cell death protein-1 (anti-PD-1) provided clinical benefit in 6 of 15 melanoma patients.^[105] Baruch *et al*^[106] also found that FMT promoted response in immunotherapy-refractory melanoma patients. Moreover, an RCT showed that FMT from overweight or obese donors in cachectic patients with advanced gastroesophageal cancer could help to improve disease control rate at 12 weeks compared with the autologous group.^[107] The improvement of Good's syndrome by FMT was observed in one case.^[108]

Radiation enteritis (RE)

Ding *et al*^[109] for the first time reported that FMT brought the possibility to cure chronic refractory RE. WMT has been used a regular therapy for RE in few WMT centers in China. Patients with RE benefited from WMT with the improvement in diarrhea, rectal hemorrhage, abdominal/rectal pain, and fecal incontinence. The ongoing trials on WMT will essentially change the clinical management of RE.

Drug-associated colitis

Over 10 cases suffering from complications related to antitumor drugs have received FMT. FMT was utilized for the first time in immune checkpoint inhibitor-associated colitis and achieved encouraging results according to Wang *et al*'s^[110] report in 2018. Their subsequent study showed that endoscopic remission was achieved in 64% of the 11 patients who responded to FMT 4–8 weeks after FMT.^[111] FMT also showed its efficacy in the treatment of diarrhea induced by tyrosine-kinase inhibitors in patients with metastatic renal cell carcinoma.^[112]

FMT and hematological diseases

Graft-versus-host diseases (GVHD)

It has been reported that over 100 patients with GVHD had benefited from FMT. Kakihana *et al*^[113] conducted a pilot study in which all acute GVHD patients responded to FMT, with three complete responses and one partial response. Moreover, a pilot study by Qi *et al*^[114] showed that compared to those who did not receive FMT, patients achieved a higher progression-free survival after FMT. In an RCT study, more patients achieved clinical remission in the FMT group than in the control on days 14 and 21 after FMT.^[115]

Other hematological diseases

In 2011, Borody *et al*^[116] first reported a “cure” of the concomitant immune thrombocytopenia in a patient being treated with FMT for UC.

FMT and other diseases

FMT and skin diseases

Rebello *et al*^[117] reported incidental benefits of hair growth in two alopecia patients after FMT. Huang *et al*^[118] reported clinical efficacy of FMT treatment in adults with moderate-to-severe atopic dermatitis.

FMT and kidney diseases

Alleviation of refractory IgA nephropathy by intensive FMT was reported by Zhao *et al*^[119]. In an RCT, the patients who received FMT had less progression of chronic kidney disease at 6 months.^[120]

FMT and immune disorders

A recent RCT demonstrated that FMT reduced lower gastrointestinal symptoms of systemic sclerosis.^[121] One study reported resolution of the symptoms of allergic rhinitis and drug withdrawal of anti-histaminic drugs after seven sessions of FMT for UC.^[122] Dramatic improvement was reported in drug-induced hypersensitivity syndrome after FMT.^[123]

FMT and arthropathy

In a case report, FMT for CDI resulted in a decrease in psoriatic arthritis disease activity.^[124] Zeng *et al*^[125] showed that the disease activity index of rheumatoid arthritis dropped after FMT. A patient with axial arthritis also reported relief in his back pain and a reduction in morning stiffness after FMT.^[122]

FMT and other diseases

The blood pressure-lowering effect by WMT was observed in hypertensive patients, especially in those who underwent WMT via the lower gastrointestinal tract and in those not taking antihypertensive drugs.^[126] One patient with the chronic obstructive pulmonary disease was significantly relieved from the respiratory symptoms after WMT.^[127] In a prospective study, five individuals subjectively reported improved dry eye symptoms 3 months after FMT.^[128] Wu *et al*^[129] reported that the patient with immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome responded with remission of diarrhea after receiving FMT.

Methodology of FMT

Donor screening

Selecting an appropriate donor is vital to the success of FMT. Donors for FMT can be divided into two types, allogeneic donors and autologous donors, according to

the source of fecal matter.^[130] The allogeneic source is more commonly adopted than an autologous source because it can meet the requirement for one-to-many treatments.^[130] Moreover, it has demonstrated improved efficacy compared with an autologous source.^[130]

The strategy of screening healthy donors for FMT is the concept of exclusive methods. However, the recommended protocols varied among different guideline or consensus.^[131,132] The exclusion criteria for screening allogeneic donors can be listed into eight dimensions: age, physiology, pathology, psychology, veracity, time, living environment, and recipients. The guidance on donor screening of WMT, including questionnaire screening, interview screening, laboratory screening and monitoring screening, was coined in Nanjing consensus on WMT in 2019.^[15]

During the pandemic of SARS-CoV-2, specific recommendations have been released to reorganize the workflow of FMT to avoid the potential risk of the virus transmission through the FMT procedure.^[133] Briefly, these recommendations included the use of remote assessment of patients and donors whenever possible, the expansion of donor screening with questionnaires and laboratory testing aimed at excluding SARS-CoV-2 infection, and the application of specific safety measures during the endoscopic FMT procedure.

Preparation of fecal microbiota

The methods of laboratory preparation for FMT reported in the literature can be classified into manual FMT and WMT. The preparation of manual FMT was shown in Figure 4A. The dosage for delivering FMT mainly depends on the fecal weight, instead of the precise volume or amount of microbiota.^[131]

A newly improved methodology for FMT coined WMT is based on the automatic purification and washing process [Figure 4B].^[14] This method, originally designed on the concept of washed microbiota preparation, is based on the automatic microfiltration machine (GenFMTer, FMT Medical, Nanjing, China) and the following repeated centrifugation plus suspension with support from specific facilities.^[14,16] WMT has been used by multiple FMT centers in China since 2014.^[6,31,62,134] This progressive method permits the delivery of a precise dose of microbiota more possible.^[15]

Routes of delivering

The delivery methods for FMT/WMT can be grouped into the upper-gut, mid-gut, and lower-gut [Figure 4C].^[2,15,44,135] Gastroscopic-guided fecal transplants, as well as microbiota capsules, are direct ways to transplant into the upper-gut. Gastroscopic transplants can be guided as far as the small intestine beyond the second duodenal segment, defined as the mid-gut, via endoscopy, nasojejunal tube, mid-gut TET, small intestine stoma or percutaneous endoscopic gastro-jejunostomy (PEG-J). FMT can be also delivered to the lower-gut through colonoscopy, enema, distal ileum stoma, colostomy, and colonic TET. Among all delivering methods, colonic TET is perhaps the safest with the lowest rate of

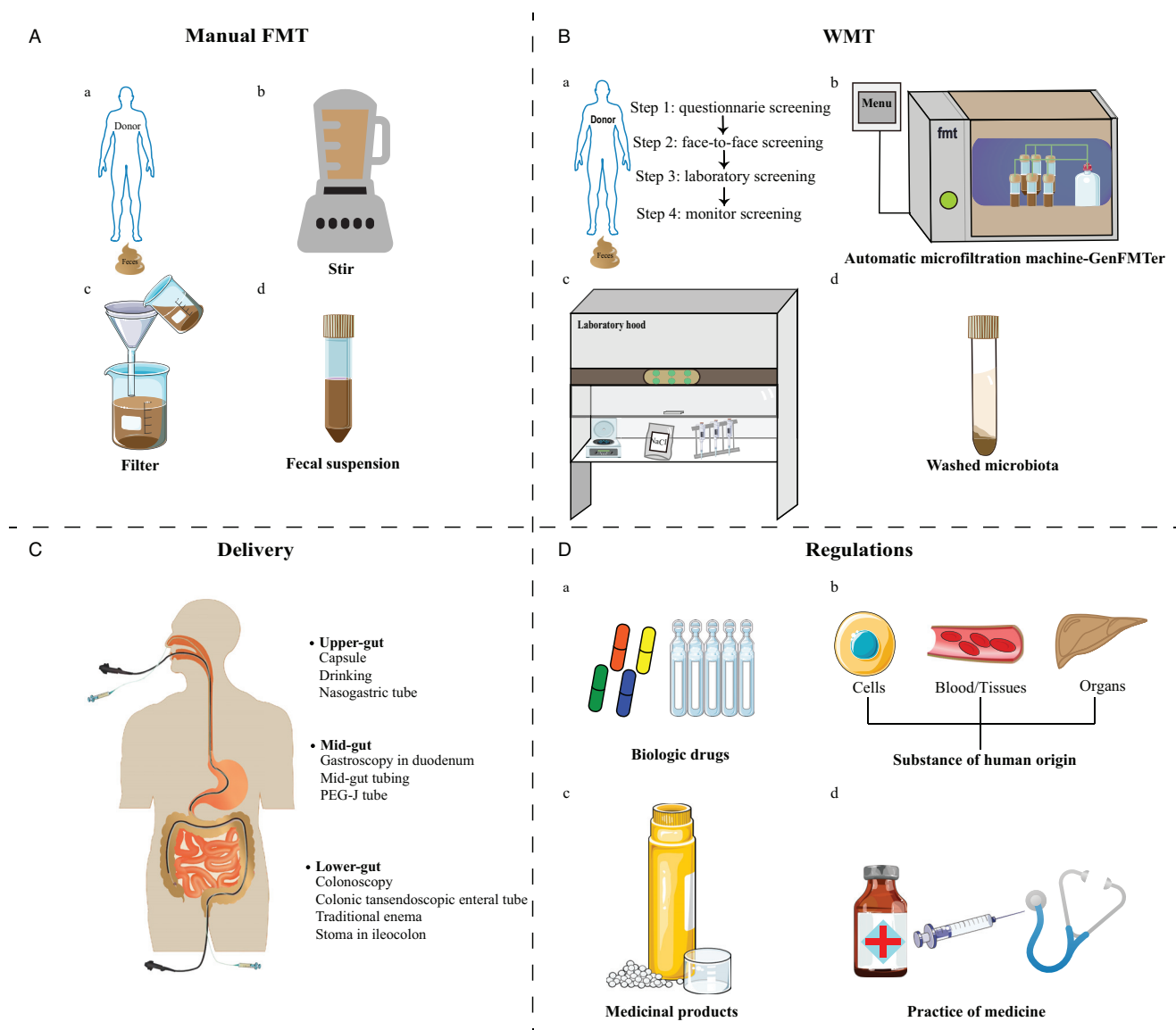


Figure 4: Methodology and regulations of FMT. (A) Manual preparation of fecal microbiota; (B) the process of WMT; (C) delivery of FMT/WMT; (D) the regulation policy of FMT/WMT. FMT: Fecal microbiota transplantation; PEG-J: Percutaneous endoscopic gastrojejunostomy; WMT: Washed microbiota transplantation.

delivery-related AEs according to a recent systematic review.^[16]

Colonic TET is the latest progress on FMT delivery. It was proven to be a safe and convenient procedure for multiple FMTs and colonic medication administration for patients aged over 7 years old.^[136] According to a survey, patients who had undergone FMT by TET were more likely to recommend FMT than patients who had not.^[137] Zhong *et al*^[138] also reported that colonic TET was a safe and convenient delivery method in children aged 3–7 years.

Treatment strategy using FMT

In 2015, Cui *et al*^[6] proposed a step-up FMT strategy for the steroid-dependent UC. Their pilot study demonstrated that 8 of 14 (57.1%) patients achieved clinical improvement and were able to discontinue steroids following step-up FMT.^[6] The step-up FMT strategy consists of three parts: step 1

refers to single FMT; step 2 refers to multi-FMTs (≥ 2); step 3 refers to the FMT combined with regular medication (such as steroids, cyclosporine, anti-tumor necrosis factor- α (anti-TNF- α) antibody, or exclusive enteral nutrition) after the failure of step 1 or step 2.^[2,139] This step-up FMT strategy can be considered for patients with refractory/severe infectious and immune-related diseases, especially when patients do not respond to single/multiple FMTs.

Increasing typical studies highlighted the necessity to formulate a treatment ladder with step 1, step 2, and step 3. In 2016, Kakhana *et al*^[113] reported multiple FMTs with steroids improved acute GVHD. In 2017, Fischer *et al*^[140] reported that sequential FMTs with interval antibiotics improved the outcome of treatment for patients with severe or severe-complicated CDI. In 2019, Ding *et al*^[7] reported that 74.3% (81/109) and 51.4% (56/109) of UC patients achieved clinical response at 1 month and 3 months after step-up FMT, respectively.

Regulatory agencies and FMT

The regulations on FMT vary from country or area worldwide. Overall, FMT can be placed into four categories: biological drug, human cell or tissue-based product, medicinal product, or practice of medicine [Figure 4D].^[15,141] Unfortunately, classification by national agencies has a significant impact on the direct availability of FMT products for patients. The main benefit of the biological regulatory paradigm is guaranteeing the safety and efficacy of FMT in any given disease. From Kraggsnaes *et al*'s^[142] view, a centralized, non-profit, blood and tissue transplant service was an ideal model to run a stool bank of high-quality FMT products and provide equivalent accessibility. Keller *et al*^[143] suggested that stool for FMT be classified as a transplant product and not as a drug. Australia and Switzerland's regulatory bodies have classified FMT as an investigational medicinal product, making FMT more widely accessible to patients.^[141] Regulatory authorities may choose to regulate stool under the discretion of the practicing doctor. Under this approach, all decisions relating to donor screening, material processing, and potentially decisions related to indication usage, are delegated to each patient's doctor and their doctor's supervisory institution.^[141] The policy on the use of FMT in China is the permitted medical therapy for CDI and many other diseases.^[144]

Although the treatment utility of FMT is generally on the rise, barriers remain to patient accessibility bolstered by complex regulatory affairs across jurisdictions. Concurrent international standardization in Good Manufacturing Practice (GMP) manufacturing for FMT products could also support the effectiveness and safety standards for FMT in line with other biological therapies and thus accelerate adoption in lagging countries.

Future Direction

The significance of the present review is to provide a comprehensive picture of many diseases with only small samples, for improving better understanding of FMT in the future. FMT has gained the great attention in the past decade in the world. All of those FMT-treated diseases can be named dysbiosis-related diseases, which essentially consist of three types of inflammation, including acute inflammation (CDI, etc.), chronic inflammation (chronic UC and CD, etc.), and chronic low-grade inflammation (type 2 diabetes, NAFLD, obesity, etc.). Accumulating studies have provided evidence for understanding the logic on treating CDI, UC, and CD by targeting gut microbiota.^[15,145] However, the treatment using FMT for chronic low-grade inflammation needs more larger sample size studies and RCT studies.

FMT technology is developing, which mainly involved the latest WMT and spores transplantation.^[14,146] The evidence linking clinical findings and animal experiments supports that WMT is safer, more precise and more quality-controllable method than the crude FMT by manual. WMT has been widely used as a legal medical therapy requiring hospital ethical approval in China for CDI and beyond, especially for those difficult and critical dysbiosis-

related diseases.^[15] The latest research revealed that washed preparation of fecal microbiota has changed the transplantation-related safety, quantitative method, and delivery.^[144] The purified Firmicutes spores from ethanol-treated donated stool were recently reported as an investigated new drug (SER-109) for the treatment of recurrent CDI in USA.^[146] This opens up a new development path of FMT for the pharmaceutical industry. However, there is a lack of head-to-head study of regular FMT/WMT *vs.* SER-109 for their use for diseases beyond CDI.

Conclusion

The current review aimed to create an encyclopedia of clinical FMT reports of benefits including case reports, case series reports, real-world studies, and RCT studies. Since FMT was formally named in 2011, a total of emerging 85 diseases treated by FMT have been reported. The number of studies on FMT/WMT has increased dramatically within the past decade. Integrated with our previous systematic review on FMT-related AEs from 2000 to 2020 worldwide, we profiled the back side and front side of FMT. Although many further controlled trials will be needed, the dramatic increasing in reports has shown the promising future of FMT for dysbiosis-related diseases in the gut or beyond the gut.

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Conflicts of interest

Zhang FM conceived the concept of GenFMTer, trans-endoscopic enteral tubing, and related devices. Borody TJ has a pecuniary interest in the Centre for Digestive Diseases, Finch Therapeutics, and Gioconda Ltd, and holds patents in the field of FMT and inflammatory bowel disease treatment. Other authors declare that they have no competing interests.

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