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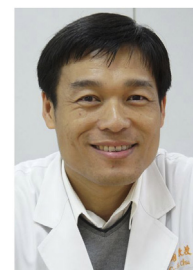
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Current and future applications of fecal microbiota transplantation for children

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ABSTRACT

Fecal microbiota transplantation (FMT) is a new and adequate route to modify the microbial ecosystem in gastrointestinal tract of the hosts. Intestinal microbiota is highly associated with human health and disease. According to the reports of human clinical trials or case series, the application of FMT ranged from *Clostridioides difficile* infection (CDI), inflammatory bowel disease (IBD), irritable bowel syndrome, refractory diarrhea, diabetes mellitus, metabolic syndrome, and even neurologic diseases, including Parkinson disease, and neuropsychiatric disorder (autism spectrum disorder, ASD). Although the current allowed indication of FMT is CDI in Taiwan, more application and development are expectable in the future. There is a relative rare data available for children in application of fecal microbiota transplantation. Thus, we review previous published research inspecting FMT in children, and address particular considerations when conducting FMT in pediatric patients.

Fecal microbiota transplantation (FMT) has been successfully applied in children for *Clostridioides difficile* infection (CDI), with the first reported publication in 2010 [1]. CDI is an illnesses where a decline in gut microbial diversity makes an overgrowth of *Clostridioides difficile* with an elevated risk of recurrent infection. According to this situation, FMT with healthy diverse microbiome to a recipient, has been applied to restore gut microbial diversity and successfully cure recurrent CDI [2]. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and European Society for

Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) published the first paper on the application of FMT for CDI in pediatric patients [3]. Most recently the NASPGHAN Special Interest Group conducted data collection on children with recurrent CDI from multiple sites around the USA and reported that FMT was successful in 272 of 336 (81%) patients after a single delivery [3]. The cumulative success rate approached 90% when the individuals who received a second FMT were included in the analysis. For analyzing the safety of FMT in 336 patients, the overall occurrence of serious adverse

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Table 1 Pediatric studies of fecal microbiota transplantation in patients with recurrent *Clostridium difficile* infection.

Author	Year of publication	Total number of patients	Age (years)	Delivery method	outcome	Follow up	Complication
Russell et al. [1]	2010	1	2	Nasogastric	Symptom resolution	6 months	None reported
Kahn et al. [26]	2012	1	1.5	Colonoscopy	Symptom resolution within 24 h	2 months	None reported
Rubin et al. [27]	2013	2	6, 8	Upper GI tract (exact route not described)	Symptom resolution in half (50%) of pediatric patients	2 months	None
Walia et al. [28]	2014	2	1.7, 2.5	Colonoscopy	Symptom resolution within 4–7 days	8–27 months	None reported
Pierog et al. [29]	2014	6	4–21	Colonoscopy	Not reported, but reported cure rate 100%	12 months	None reported
Kelly et al. [30]	2014	5	6.5–16	Colonoscopy	Not provided, but pooled efficacy was 78%	12 weeks	Not specified, no infectious complications
Russell et al. [31]	2014	10	2–19	Nasogastric or colonoscopic	9/10 (90%) had symptom resolution between 1 and 3 days	1 month to 4 years	None
Wang et al. [32]	2015	1	1.1	Nasojejunal	Symptom resolution and discharge within 5 days post-FMT	4 months	None reported
Kronman et al. [33]	2015	10	1.8–13.6	Nasogastric, nasoduodenal or nasojejunal	9/10 (90%) had symptom resolution	0.4 months–23 months	mucoid stools (1 patient)
Hourigan et al. [34]	2015	8	6–17	Colonoscopy	7/8 (88%) had symptom resolution within 1–3 days	6 months	Transient mild abdominal pain (2 patients)
Brumbaugh et al. [35]	2018	42	1–18	Nasogastric or gastrostomy	32/42 (76%) had symptom resolution	3 months	Vomiting within 24 h of the FMT (13%)
Aldrich et al. [36]	2019	12	1.1–22.8	Nasogastric, nasojejunal or colonoscopic	10/12 (83%) success	2 months	None reported
Nicholson et al. [37]	2020	335 ^a	3–15	colonoscopy	271/335 (81%) successful after a single FMT	2 months	(5.7%) Diarrhea
					86.6% successful after a first or repeated FMT		Abdominal pain bloating

^a A retrospective study of 335 patients, who underwent FMT at 18 pediatric centers, from February 1, 2004, to February 28, 2017.

Table 2 Pediatric studies of fecal microbiota transplantation in patients with inflammatory bowel disease.

Author	Year of publication	Age (years)	Number of patients	Route FMT	Outcome
Kinds et al. [40]	2013	7–21	10 with ulcerative colitis	Serial enemas	1 could not hold enema 7/9 had clinical response at 1 wk 6/9 maintained response at 1 mo No clinical or laboratory benefit
Suskind et al. [41]	2014	13–16	4 with ulcerative colitis	Single FMT via nasogastric tube	
Suskind et al. [42]	2015	12–19	9 with Crohn's disease	Single FMT via nasogastric tube	7/9 in remission at 2 wk 5/9 in remission at 6 and 12 wk
Kellermayer et al. [43]	2015	14–16	3 with ulcerative colitis	Colonoscopy and serial enemas	3/3 endoscopic and histologic remission at 2 wk 3/3 symptom free at 4 wk
Karolewska-Bochenek K et al. [44]	2018	10–17	10 patient 8 ulcerative colitis 2 Crohn's disease	nasal-duodenal tube or endoscope (stomach)	2 week interval 3/8 UC improved 2/2 CD improved
Brumbaugh et al. [35]	2018	1–18	13 patientsx 9 ulcerative colitis 4 Crohn's disease	nasogastric tube pre-existing gastrostomy tube	7/13 improved 4/9 UC improved 3/4 CD improved
Goyal et al. [45]	2018	8–21	21 patients 14 ulcerative colitis 7 Crohn's disease	Endoscope (distal duodenum) Colonoscopy (terminal ileum and right colon)	12/21 success 7/14 UC improved 5/7 CD improved
Moutinho et al. [46]	2019	17	One patient with ulcerative colitis	Colonoscopy 0, 8months	abdominal pain bloody diarrhea ↓ 8 times symptom decrease did not improve
Quagliariello et al. [47]	2020	15,16	2 patient with ulcerative colitis	Colonoscopy	1 success 1 moderate form there is probably need for multiple FMT administrations.

effects was only 5%. The most serious complications are aspiration pneumonia or worsening inflammatory bowel disease (IBD) symptoms following FMT procedure [3,4]. No death has been reported following FMT in pediatric patients.

FMT or the transfer of feces with an assumed healthy, and has been used in restoring microbiome diversity. The microbiota material is reached by the infusion of fecal contents into the intestinal tract via enema, colonoscopy, nasogastric tube, or nasojejunal tube, and as oral capsules. Pediatric patients, particular in very young age, have a rapidly developing intestinal microbiota which is associated with development of physiological functions and immune system, achieves the status of stabilization in the first few years of children [5,6], which differs from the gut microbiota of the elderly [7]. Further regular and longer-term analysis of gut microbiota changes which occur in pediatric patients with FMT is necessary. Immunological and metabolic responses are also necessary to better understand the potential impact of FMT in a growing child.

Fecal microbiota transplantation: recurrent or refractory *Clostridioides difficile* infection

Clostridioides difficile colonization results in clinical conditions ranging from asymptomatic carrier state to fulminant colitis. The disease course of *C. difficile*–associated diarrhea requires alteration of the colonic microflora, colonization by *C. difficile*,

and the release of enterotoxins from the toxigenic strains (such as toxin A and toxin B) [8,9].

This bacteria is a Gram positive, spore-forming, obligate anaerobic, toxin-producing bacillus and is acquired from the environment or by the fecal-oral route. The clinical manifestations of *C. difficile* infection (CDI) may be presented with diarrhea, bloody stool, abdominal pain, fever, flatulence, vomiting, or pseudomembranous colitis. The possible complications of severe *Clostridium difficile* colitis or enterocolitis may include electrolyte imbalance, volume depletion, hypoalbuminemia, toxic megacolon, bowel perforation, hypotension, sepsis, even death [10,11].

Basically, the first-line therapy for CDI are Vancomycin or Metronidazole. Disease of CDI relapse or recurrence is also a concern with both medications [12,9]. Fidaxomicin, a new class of macrocyclic antimicrobials against *C. difficile*, has been applied with greater efficacy in patients with recurrent *C. difficile* disease [9,13].

Fecal microbiota transplantation (FMT), may originate from ancient Chinese medicine [3,14]. The first reported application in modern times was for the treatment of severe refractory pseudomembranous colitis in 1958 [3,15]. Thereafter, especially over the last two decades, some retrospective or prospective studies in adult and pediatric patients describe 83%–100% cure rates by FMT for individuals with recurrent CDI [3,16].

Risk factors for pediatric CDI is using antibiotics (such as penicillin, cephalosporin, or fluoroquinolones) in the previous 4 weeks, the existence of gastrostomy or jejunostomy tube,

solid organ transplantation, recent surgery, malignancy, inflammatory bowel disease, and acid suppression [17–19]. Recurrence occurred at 11–20% of CDI in pediatric patients [20,21].

The antibiotics including vancomycin, rifaximin and fidoxomycin are recommended for first recurrence; whereas FMT are proposed for multiple recurrence. The indications for FMT in CDI include individuals with more than two recurrences, refractory disease without response to anti-CDI treatment at 48 h or moderate CDI without response by 5 days [22]. Randomized clinical trials [23,24] comparing vancomycin to FMT were both terminated early due to the significantly higher efficacy of FMT. A previous systematic review of seven randomized clinical trials for adult patients analyzing the impact of FMT in recurrence CDI revealed an overall efficacy of 92%. In this publication, there are about 88% cure rate with upper gastrointestinal tract approach and 95% with distal intestinal tract delivery including colonoscopy and enema [25].

Pediatric studies of FMT for recurrent or refractory CDI are listed as Table 1. The effectiveness of FMT was high, with some pediatric case series showing a 90–100% success rate in treating recurrent or refractory CDI.

In all children who received FMT, the common reported side effects of FMT include bloating, diarrhea, abdominal pain, constipation, vomiting and transient fever. The vomiting was usually a single, self-limited episode that did not require medical treatment. In the pediatric case series utilizing intragastric FMT procedure, Brumbaugh DE et al. reported only vomiting as post procedural complication (13%) in 42 children [35].

In general, FMT was safe and well tolerated. Only 5.7% reported minor adverse events (AEs) such as bloating, diarrhea, and pain and even fewer (5%) reported severe AEs [3]. The most serious complications involved aspiration pneumonia following upper GI delivery and worsening IBD symptoms requiring hospitalization following FMT [3,4]. No death has been reported following FMT in pediatric patients.

A farther follow-up visit at one-year post-FMT may be considered to evaluate for potential long-term adverse effects. These side effects may include fluctuations in weight, development of metabolic disease, and worsening course of underlying disease. Monitoring of late adverse effects and long-term effects of FMT is important. Long-term multicenter follow-up studies, which are currently in development, will help elucidate these potential complications [3].

Moreover, recent case report showed FMT cured the recurrent CDI in pediatric patients with heart transplant recipient [38] and hematopoietic stem cell transplant recipient [39].

Fecal microbiota transplantation: inflammatory bowel disease

In the pathogenesis of inflammatory bowel disease (IBD), gut microbiota with dysbiosis may play an essential role. Therefore, FMT has been studied as an option for therapeutic strategy of IBD. There are some clinical studies data for the management of IBD in children with FMT (as Table 2).

In pediatric population, the clinical data for fecal microbiota transplant in IBD is limited to some case reports and case series. Karolewska-Bochenek K et al. reported that FMT in ten children with IBD, using eight doses of fecal microbiota transfer administered over 2 weeks period. Clinical remission was found in 3 of 8 ulcerative colitis individuals and 2 of two children with Crohn's disease [44]. Besides, Goyal et al. [45] announced a clinical response in 57% and 28% at one and six months following a single fecal microbiota transplant in twenty-one pediatric patients with IBD. The responders revealed increase in diversity of gut microbiota at one month following the FMT [45].

In the previous published meta-analysis of adult clinical trials, 41 studies of ulcerative colitis and 11 studies of Crohn's disease were included, clinical remission in ulcerative colitis improved with increased number of FMT administration. There are lacking in data on the efficacy of FMT in Crohn's disease treatment [48].

Fecal microbiota transplantation: multidrug-resistant organisms

If the patients colonized with multidrug-resistant organisms (MDROs) are at raising risk for infection, such as bacteremia and sepsis. Gut microbiota communities may be incriminated in the control of pathogenic microbial intestinal colonization, and FMT has been successfully applied in several reports to decolonize the adult patients with a spectrum of MDRO's, such as *Klebsiella pneumoniae* and vancomycin-resistant *Enterococcus* (VRE) [49–51]. The efficacy of FMT in pediatric MDRO remain limited, but its future potential is expectable [51].

Fecal microbiota transplantation: graft versus host disease

Disturbances in the components of gut microbial ecosystems could result in decreasing intestinal diversity — dysbiosis. The above situation following hematopoietic stem cell transplantation (HSCT) has been associated with CDI, bacteremia, or graft versus host disease (GVHD). FMT has been suggested as a mechanism to restore intestinal bacterial diversity and reduce complications afterwards hematopoietic stem cell transplantation (HSCT), including GVHD [52,53]. In a randomized clinical trial of twenty-five allogeneic HSCT recipients with intestinal dysbiosis, Taur et al. [54] reported the superior bacterial diversity among the patients receiving autologous FMT, in which compared to placebo [54]. There are limited data of children to date, and while the application of FMT for refractory gut GVHD remains potentially, more investigation is necessary in the future.

Fecal microbiota transplantation: autism spectrum disorders

Autism spectrum disorder (ASD) is a neuropsychiatric disorder that affects daily behaviors and impaired communication with social interaction. In the children with ASD, many of

Table 3 Pediatric studies of fecal microbiota transplantation in autism spectrum disorder.

Author	Year of publication	Age (years)	Number of patients	Route FMT	Outcome
Kang et al. [56,57]	2017	7–16	18 with ASD	human fecal material; processed, frozen; administered orally or rectally	80% reduction in gastrointestinal symptoms and a slow but steady improvement in core ASD symptoms.
Zhao et al. [58]	2019	7–15	Autism Recruiting	FMT via colonoscopy and gastroscopy	the childhood autism rating scale (CARS) in the FMT group declined significantly which compared with the control group
Clinical trials [59] Location ^a	Actual Study Start Date	Age	Recruiting status	Route FMT	Outcome
NCT03426826 Children's Hospital Los Angeles, USA	2019	5–17	ASD Recruiting	FMT with Healthy Donor Stool into the jejunum through upper endoscopy	No results available
NCT04630847 ProgenaBiome, Ventura, California, USA,	2021	>2	ASD (based on DSM-V) Recruiting	colonoscopy	No results available
NCT04246398 Assaf-HarofehMC, Zerifin, Israel	2021	7–20	Children With Autism Not yet recruiting	Oral capsule	No results available
NCT04182633 Arizona State University, Tempe, Arizona, USA	2019	5–17	Children With Autism Recruiting	Intestinal microbiota (high dose for 2 days, then maintenance dose for 12 weeks)	No Results Available

^a Clinical [Trials.gov](https://clinicaltrials.gov) is a database of privately and publicly funded clinical studies conducted around the world. (<https://clinicaltrials.gov>).

them display gastrointestinal symptoms such as diarrhea, mushy stool, abdominal pain, and constipation, which may be associated with the intestinal microbiome [55]. The gut microbial-based interventions, including prebiotic, probiotic, and fecal microbiota transplant, could alter the intestinal microbiota and metabolic indicators, and improve behavioral symptoms and gastrointestinal symptoms among ASD individuals.

In a previous trial about autism spectrum disorder, a follow-up with the same 18 individuals trace two years after FMT treatment. Fecal microbiota transfer therapy for 1–2 days and 7–8 weeks of daily maintenance doses along with an acid suppressant, administered to children with ASD and chronic gastrointestinal symptoms. After 18 weeks follow-up observation period, Kang, et al. [56] reported an 80% reduction in gastrointestinal symptoms and a slow but steady improvement in core ASD symptoms. Two years after management, most individuals reported gastrointestinal symptoms remaining improved compared to the baseline. The improvement was on average 58% decrease in Gastrointestinal Symptom Rating Scale (GSRS) relative to baseline, and this result is similar to what they observed at the end of treatment. Kang et al. reported that they observed improvement in behaviors of autism related symptoms in most sub-categories [56,57].

In another study, Zhao et al. [58] reported that the childhood autism rating scale (CARS) in the FMT group declined significantly which compared with the control group. They also found that FMT therapy diminished the relative abundance of *Bacteroides fragilis* and persistently diverted the intestinal microbiota of autism individuals to a healthy state. Moreover, Kang et al. [57] reported that overall microbial

diversity and the abundance of *Bifidobacterium*, *Prevotella*, and *Desulfovibrio* increased following fecal microbiota transplantation and these changes persisted afterwards no treatment.

Pediatric studies or ongoing clinical trials of FMT for ASD are listed as Table 3. Intestinal microbiota could be a novel target for ASD individuals in the future. Unlike probiotic or prebiotic therapy, which only supplement some bacterial strains, FMT could ensure the transfer of more than hundreds of strains. In other hand, FMT could potentially be problematic, because of donors could transfer opportunistic pathogenic bacteria or infections to the recipients. Thus, researchers should properly screen fecal donors before donation to minimize the risk [55].

Fecal microbiota transplantation: comparison different dilivey method/route

Several reports have shown the efficacy of FMT in the treatment of clinical situation. Some studies seek to compare the efficacy of different forms of FMT delivery, including fresh vs. frozen fecal microbiota transplant. Lee et al. [60] reported that: in total 219 adult patients with recurrent or refractory CDI, the use of frozen FMT (n = 108) compared with fresh FMT (n = 111) did not result in worse proportion of clinical resolution of diarrhea. Another various form of FMT delivery, such as oral capsule and colonoscopic delivery was compared [61]. Among adults participants with recurrent CDI (n = 116), FMT via oral capsules (n = 57) was not inferior to delivery by colonoscopy (n = 59) for preventing recurrent CDI over 12 weeks.

Prevention of recurrent CDI after a single treatment was achieved in 96.2% in both group. Youngster et al. [62] investigated various form of FMT delivery, such as nasogastric vs. colonoscopic delivery. A total of 20 adult patients were enrolled, 10 in each group (colonoscopy vs nasogastric tube). Resolution of diarrhea was achieved in 14 patients (70%) after a single FMT (8 of 10 in the colonoscopy group and 6 of 10 in the nasogastric tube group).

Fecal microbiota transplantation: donor screen and specific consideration for safety

In our review, we found that most studies of FMT in pediatric patients have used an adult fecal donor. The intestinal microbiota of children may correlate with development of the physiological function and the immune reaction, which achieves a stable status in intestinal microbiota.

However, in adults, the development of autoimmune disorder and fast weight gain has been reported after FMT [63,64]. It is concerned that transplantation of an adult microbiome and related metabolites into a developing gut microbial ecosystem of a child may lead to accelerating of immune aging and expansion of immune related complications. Making use of age-matched donors, with a similar stage of intestinal microbial development, may address this concern in pediatric individuals and assures further investigation in a developing child.

Since June 2019, the Food and Drug Administration (FDA) released a safety alert after the events of beta-lactamase-producing *Escherichia coli* in two immunocompromised FMT recipients who may transfer from beta-lactamase *E. coli* positive donor [65].

According to this safety alert, additional donor screening for multidrug resistant microorganisms was recommended [66,67]. The presence of multidrug resistant microorganisms was the important cause for donor screening failure [68]. Moreover, as it became evident in 2020 that SARS-CoV-2 could be detected in the stool of infected individuals, additional FMT donor screening of SARS-CoV-2 was necessary for safety [69–71].

There are several limitations for usage of FMT in children, such as the source of donor feces. Adult or elder fecal donor may correlate with development of the aging physiological function and the immune reaction. The efficacy of fecal microbiota in age-matched donor or young age donor should be short and long term follow up. There is rare large scale FMT trial for children. Small case series and isolated case reports, however, indicate therapeutic success for FMT in pediatric recurrent CDI similar to adults [3]. Besides, uniformity of transplant protocols used, route of administration (oral, endoscopy, or enema), growth and development after FMT are lacking clinical data in children. The data on usage of FMT for children are preliminary and restricted [53]. More investigation of FMT in pediatric patients are necessary in the future.

Conclusion

FMT is an effective therapy for recurrent CDI in pediatric patients. For recurrent CDI, FMT seems to be safe and effective,

and also in the short term in IBD. For inflammatory bowel disease, multiple times of FMT may be necessary. In children who received FMT therapy, we suggest that longer follow up clinical course and comprehensive analysis of the effect on the intestinal microbiota and bacterial diversity of FMT in pediatric patients would help further to announce its efficacy and safety.

For treatment purpose, colonoscopic approach may be a favorable route to replace the majority gut microbiota of the recipient. In the future, FMT via colonoscopy may be gradually replaced by the oral consumption of laboratory-designed microbial products that reach similar successful treatment efficacy.

Conflicts of interest

The authors declare that they have no competing interests.

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