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REVIEW ARTICLE

Faecal microbiota transplantation in children: A systematic review

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Abstract

Aim: Novel technologies offer insights into the potential role of the intestinal microbiota in human health and disease. Dysbiosis has been associated with several diseases, and it is thought to play a role in the pathogenesis of different gastrointestinal diseases. Faecal microbiota transplantation (FMT) is emerging as a method to modulate the gastrointestinal microbial ecosystem. While recurrent Clostridioides difficile infection is the recognised FMT indication, exploration of other therapeutic uses is ongoing.

Methods: Following PRISMA guidelines, we conducted a systematic review, extracting 583 articles from Embase and PubMed (index date to October 2022).

Results: The search yielded 58 studies for full review, with 50 included in the systematic review. Articles were categorised by FMT indication, study design, efficacy, adverse events, donor selection and administration route. FMT appears safe and effective for recurrent Clostridioides difficile infection, although severe adverse events are reported in children. However, there are currently insufficient data to support the use of FMT for other potential therapeutic indications (such as irritable or inflammatory bowel disease or obesity), beside the potential to decolonise multi-drug resistant organisms.

Conclusion: This underscores the need for randomised, controlled, prospective cohort studies in children to assess FMT effectiveness in diverse conditions and counteract publication bias.

KEYWORDS
children, clostridioides difficile, faecal microbiota transplantation, inflammatory bowel disease

1 | INTRODUCTION

The gastrointestinal tract is home to a complex ecosystem of the gut microbiome, including archaea, bacteria, viruses and fungi.[1] A disturbance in this ecosystem can give rise to intestinal dysbiosis, which describes the qualitative, quantitative and/or functional microbial alterations usually associated with disease status. This dysbiosis can, in turn, aggravate existing disorders or induce new diseases.[2] Faecal microbiota transplantation (FMT) has been used for centuries to solve acute gastrointestinal infections. More recently, it has been used to improve dysbiosis, in the hope to regain a healthy gut microbiome.[2,3]

Abbreviations: (r)CDI, (recurrent) Clostridioides difficile infection; BMI, body mass index; CD, Crohn's disease; FMT, faecal microbiota transplantation; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; MDR(O), multi drug resistant organisms; RCT, randomised-controlled-trial; SCFA, short chain fatty acids; UC, ulcerative colitis.

During the last decades, knowledge in the field of microbiota is rapidly expanding.[1] Nevertheless, many hurdles still need to be overcome before translating these findings into therapeutic applications, such as FMT. Currently, the only recognised indication for FMT is recurrent *Clostridioides difficile* infection (rCDI).[4] However, FMT has been considered as a potential treatment in other conditions where dysbiosis is implicated in the disease pathogenesis. The role of FMT in patients with inflammatory bowel disease (IBD) or irritable bowel syndrome (IBS) is under active discussion due to conflicting success rates.[2] In addition, FMT has been used as an innovative attempt to treat a broad range of other disease modalities beyond the gastrointestinal tract, such as hepatic encephalopathy, obesity, metabolic syndrome towards neurologic and neuropsychiatric diseases, among others.[2] Nevertheless, a causal link between dysbiosis and these diseases remains difficult to establish.[2] Regarding FMT in children, there is a paucity of available data and treatment indications are more limited.

In FMT, stools will be transferred from a presumed healthy individual with a diverse microbiome to the patient. However, in children, there is no detailed consensus on the route of administration, donor selection and FMT preparation. Donor selection is maybe even more crucial in children who have a dynamic, developing microbiome that correlates with the development of the immune system and other physiological functions.[5] In comparison, adults have a more stable gut microbiome with a different proportion of gut phyla and lower interpersonal variation.[5] Finally, FMT is considered to be well tolerated.[6] However, the risk of triggering an invasive intestinal infection or bacterial translocation remains an important safety concern. Depending on underlying diseases, this risk could be potentially even greater. Therefore, the aims of this systematic review were to assess efficacy, side effects and donor selection for FMT in children for the different indications.

Key notes

- The aim of this systematic review is to study different indications, safety profile and future directions for faecal microbiota transplantation (FMT) for different disorders in children.
- While FMT shows safety and efficacy in treating recurrent Clostridioides difficile infection, limited data hinders its application for other conditions.
- The study highlights the necessity for rigorous, prospective cohort studies to ascertain FMT's effectiveness in diverse paediatric health conditions beyond its established use.

2 | METHODS

2.1 | Exclusion and inclusion criteria

FMT was defined as the administration of faeces-derived matter and microorganisms from a donor to a recipient with the intent of affecting the gut microbiome of the recipient. Only studies reporting on the clinical efficacy and/or safety of FMT in children (<18 years) written in Dutch or English were included. Case series or cohort studies were included. Animal models were excluded, as well as surveys and opinion pieces. The publication with the most complete data set was selected, if there were multiple reports related to the same patient group.

2.2 | Literature review

A systematic literature search was performed according to the PRISMA guidelines (Figure S1). We performed a search on Embase and PubMed using the following terms: ('faecal microbiota transplantation') AND ('child' OR 'paediatrics' OR 'Adolescent' OR 'Infant') from the index date to October 4, 2022. All articles were reviewed by two reviewers independently, initially by title and abstract, then by full text to define eligibility. Duplicates were removed using Endnote. References from relevant literature were also searched to detect studies that may have been missed by previous searches. In addition, the ClinicalTrials.gov registry was consulted, specifically to identify any unpublished data related to the outcomes included in this article to address potential publication bias.

Studies eligible for our systematic review were then further categorised based on indications of the FMT, study design, efficacy, adverse events, donor selection and route of administration. After reviewing the articles, a meta-analysis was deemed not possible due to the large heterogeneity in follow-up time and techniques (based on the route of administration, donor selection and FMT preparation) for each indication separately.

3 | RESULTS

3.1 | Indications and efficacy

3.1.1 | Recurrent Clostridioides difficile (rCDI)

The main indication of FMT in children is rCDI. *Clostridioides difficile*, a spore-forming Gram-positive bacillus, is one of the leading causes of healthcare-acquired diarrhoea in both children and adults.[4] The clinical manifestations can range from asymptomatic carriage, especially in young children, to fulminant colitis, severe sepsis and death. Reinfection or first relapse is seen in 20%–30% of patients, with a higher risk of recurrence after subsequent infections. Risk factors for rCDI include antibiotic use, proton pump inhibitors, chemotherapy, immunosuppressive drugs, prior hospitalisation, recent gastrointestinal surgery and underlying diseases

such as IBD or the presence of a tracheostomy or a gastrostomy tube.[4]

The use of FMT is well established as part of the treatment algorithm for rCDI proposed by a joint decision of the North American and European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN and ESPGHAN). They advise FMT as a treatment option for rCDI in case of (I) relapse within 8 weeks after treatment of at least two episodes of severe CDI requiring hospitalisation or three episodes of mild to moderate CDI after failure of vancomycin with a six-to-eight-week taper. Also, in the case of (II) moderate CDI with no response to standard therapy after more than 1 week (including vancomycin). Finally, in the case of (III) severe disease unresponsive after 48 h of standard therapy.[4]

The management of rCDI is mostly inferred from the excellent success rate of FMT in adult studies.[7] Although randomised controlled trials (RCTs) evaluating the efficacy of FMT for rCDI are lacking in children, this systematic review found 538 reported cases (see Table 1).[5,8–25] The average overall efficacy in this systematic review after one or more FMTs was 85%, with a follow-up range between 44 days and 4 years. Studies with longer follow-up reported a lower success rate. These results were mostly driven by a large multicentre, retrospective study of 335 paediatric and young adult patients with rCDI, showing an efficacy of 81% after a single and 87% after repeated FMTs.[12] This is similar to previous reports by Chen et al. in 2017, which described 45 patients with an effectiveness ratio of 89% and a relapse rate of 4% over time.[26] When assessing the efficacy of FMT, the underlying diseases can play a crucial role. Brumbaugh et al. reported an excellent outcome in otherwise healthy children (success rate of 93% after 3 months). However, efficacy dropped to 54% and 75% in children with IBD or another underlying comorbidity, respectively.[8] In this systematic review, at least 184/517 (35.6%) had IBD or a different concomitant disorder.

3.1.2 | Inflammatory bowel disease (IBD)

IBD is a collective term for chronic inflammatory disorders of the intestine such as Crohn's disease (CD) and ulcerative colitis (UC), with a relapsing-remitting course necessitating long-term medical therapy.[27] For decades, humans have attempted to modulate the gut microbiota through antibiotics and nutritional therapies as an alternative treatment for IBD, even before the era of microbiome research.[27] Nutritional therapy with exclusive enteral nutrition is the first choice of treatment for inducing remission in paediatric CD.[27] Compared to individuals with a healthy gut microbiome, patients with IBD have a less diverse microbiota with a reduced abundance of *Firmicutes* and *Bacteroidetes* and a relative increase in opportunistic pathogenic bacteria.[28,29] A decrease in short chain fatty acids (SCFA), which are necessary for the normal functioning of colonocytes, has been described in IBD patients. It is hypothesised that this reduction of SCFA, such as butyrate, is caused by intestinal dysbiosis and might contribute to the pathogenesis of UC, as these SCFA have anti-inflammatory properties (e.g. stimulation of IL-10 production).[28] Therefore, the potential role of FMT as a treatment for patients with UC has been explored; however, conflicting data has led to uncertainty about its efficacy in patients with UC.[30–34]

In three RCTs, FMT was beneficial in adults with UC, where donor-treated UC patients had a significantly higher steroid-free remission rate than sham-treated patients (32%, 24% and 27% in the active group vs. 9%, 5% and 8% in the placebo group, respectively).[30–32] However, the primary endpoint was not met in the RCT of Rossen et al. (30% vs. 20%)[33] and two recent RCTs were stopped early for futility. The RESTORE-UC (ClinicalTrials.gov identifier: NCT03110289) used pre-selected stool donors (super donor, unpublished data) for the FMT, and in the CRAFT UC study, patients were randomised to FMT or a UC diet or a combination of both.[34] In addition, researchers have been less successful in demonstrating this effect in CD patients.[35,36] Only recently, the first pilot RCT has been published, showing in 17 adult CD patients no significant benefit of FMT over sham transplantation based on steroid-free clinical remission.[37] Significant differences in terms of endoscopic activity and CRP level were seen after FMT, but the lower baseline endoscopic disease activity score in the sham group limits the generalisation of these data.[37] Therefore, the benefit of FMT in CD patients' needs to be confirmed in a larger population (ClinicalTrials.gov identifier: NCT02097797), as there is currently insufficient data to support FMT in CD patients.

Data on children are even scarcer. A systematic review with meta-analysis from 2018, including 67 paediatric IBD patients (47 UC and 20 CD) from nine different studies, was limited to case reports and case series.[3] The meta-analysis showed that the pooled proportion of clinical remission rates was 10% for paediatric UC patients and 45% for paediatric CD patients. However, this meta-analysis compiled two studies where the same patient group overlapped, resulting in duplicating the efficacy data in both studies (so 12 UC and 4 CD patients should be excluded from this study).[38,39] Since then, only 11 additional patients with IBD have been described in the literature, resulting in a total of 62 paediatric patients in our systematic review. The overall average efficacy in this systematic review was a 48% and 58% response rate and a 28% and 58% remission rate in UC and CD patients, respectively (see Table 2).[29,38,40–49] The possible discrepancy in FMT effectiveness between paediatric and adult CD patients may be explained by the fact that children with CD are more likely to have colonic involvement in comparison to adults.[3] However, these data must be interpreted carefully due to the small sample size and the lack of a sham-treated control group, making it challenging to differentiate between improvements attributed to FMT and those that would have occurred naturally over time. Additional well-designed, controlled studies of FMT in children are needed. Therefore, we wait eagerly for the results of the coming trials on the effects of FMT in paediatric CD and UC patients (ClinicalTrials.gov identifiers: NCT03378167, NCT05321758 and NCT05321745 for CD and NCT02487238, NCT02291523 and NCT05679622 for UC).

TABLE 1 Faecal microbiota transplantation in (recurrent) Clostridioides difficile infection.

Ref.	Delivery method	Underlying disease	*N*	Donor	Results	Efficacy (%)	Follow-up
5	Colonoscopy ($n=14$) Nasojejunal ($n=1$)	Healthy, IBD	12	Unrelated adult	12/12	100%	>3 months
8	Nasogastric	Healthy, concomitant disorders, IBD	42	Unrelated adult	32/42	Pooled efficacy 76% (94% healthy, 54% IBD 75% concomitant disease)	3 months
9	Colonoscopy	Healthy	9	Related/unrelated adult	9/9	100%	24 weeks
10	Colonoscopy	Healthy, IBD	8	Related adult	8/8	100%	6 months
11	Upper/lower GI tract	Unknown	11	Related/unrelated	11/11 (after one or more FMT)	100%	9–36 months
12	Upper/lower GI tract	Healthy, IBD	335	Unknown	271/335 (after 1 FMT) 290/335 (after 1 or 2 FMT)	87%	At least 2 months
13	Upper/lower GI tract	Healthy, immunocompromised	10	Unrelated adult	10/10 (after 1 or 2 FMT)	100%	10 weeks
14	Upper/lower GI tract	Healthy, concomitant disorders, ibd	34	Related Adult/child	25/34	74%	12 weeks
15	Colonoscopy	Unknown	11	Related/unrelated adult	11/11	100%	10–20 weeks
16	Upper/lower GI tract	HSCT	3	Related/unrelated adult	1/3	33%	1 year
17	Colonoscopy	Healthy, IBD	8	Unrelated adult	8/8	100%	10–20 weeks
18	Colonoscopy	IBD	8	Related/ Unrelated adult	6/8 (after 60 days) 4/8 (after 6 months and 1 or 2 FMT)	50%	6 months
19	Nasogastric nasojejunal	Healthy, tumour, IBD, neurologic	10	Related adult	9/10	90%	44 days
20	Colonoscopy	Healthy, concomitant disorders, IBD	6	Related adult	6/6	100%	Unknown
21	Upper/lower GI tract	Healthy, IBD	10	Related adult	9/10	90%	1 month–4 years
22	Upper/lower GI tract	Healthy, concomitant disorders, IBD	12	Related adult	10/12	83%	2 months
23	Colonoscopy	Unknown	5	Unknown	Unknown paediatric data	Pooled efficacy 78%	12 weeks
24	Colonoscopy	Premature birth	2	Related adult	2/2	100%	4 months
25	Upper GI tract	Unknown	2	Related adult	1/2	50%	2 months

Abbreviations: FMT: faecal microbiota transplantation; GI: gastrointestinal; HSCT: hematopoietic stem cell transplant; IBD: inflammatory bowel disease; N: number.

TABLE 2 Faecal microbiota transplantation in inflammatory bowel disease.

Ref.	Delivery method	Donor	Duration course	Follow-up	Indica-tion	Participants	Efficacy (%)
29	Nasogastric	Related adult	Unknown	12 wk.	CD	9	7/9 (=78%) remission rate after 2 wk. 5/9 (=56%) remission rate after 12 wk.
38	Colonoscopy + duodenal or jejunal	Related/unrelated adult/child	Unknown	Unknown	IBD	21	12/21 (=57%) response rate after 1 mo. 6/21 (=28%) response rate after 6 mo. 4/21 (=17%) remission rate after 6 mo.
					CD	7	5/7 (=71%) response rate after 1 mo. 3/7 (=43%) response/remission rate after 6 mo.
					UC	14	7/14 (=50%) response rate after 1 mo. 3/14 (=22%) response rate after 6 mo. 1/14 (=7%) remission after 6 mo.
40	Duodenal	Unrelated adult	2 wk.	2 wk.	IBD	10	9/10 (=90%) response rate 5/10 (=50%) remission rate
					CD	2	2/2 (=100%) response/remission rate
					UC	8	7/8 (=88%) response rate 3/8 (=38%) remission rate
41	Colonoscopy + enema	Single not related donor	6–12 wk.	6 mo.	UC	3	3/3 (=100%) remission rate
42	Enema	Related adult	5 days	1 mo.	UC	10 (mild/moderate)	6/9 (=67%) response rate 3/9 (=33%) remission rate
43	Nasogastric	Unknown	1 day	12 wk.	UC	4	0/4 (=0%) response/remission rate
44	Colonoscopy	Father	1 day	16 wk.	UC	2	1/2 (=50%) remission rate
45	Colonoscopy	Healthy adult	1 day	90 days	UC	1 child	0/1 (=0%) response/remission rate
46	Nasogastric	Healthy child	1 day	30 days	UC	1 child	0/1 (=0%) response/remission rate
47	Nasogastric	Healthy adult	1 day	4 wk.	CD	1 child	1/1 (100%) remission rate (not defined)
48	Nasogastric	Healthy adult	1 day	3 mo.	CD	Unknown	Unknown paediatric data
49	Colonoscopy + nasoduodenal	Healthy child	Unknown	6 mo.	UC	1	1/1 (100%) remission

Note: Response was defined as a decrease on paediatric ulcerative colitis activity index (PUCAI) ≥ 20 points or a decrease on paediatric Crohn's disease activity index (PCDAI) ≥12.5 points. Remission is defined as a PUCAI or PCDAI ≤10.

Abbreviations: CD, Crohn's disease; GI, gastrointestinal; HSCT, haematopoietic stem cell transplant; IBD, inflammatory bowel disease; IBD, inflammatory bowel disease; mo., month; MT, faecal microbiota transplantation; *N*, number; UC, ulcerative colitis; wk., weeks.

3.1.3 | Dysbiosis after caesarean

Babies born after a caesarean section have a different microbiome than babies born vaginally, where this difference is still noticeable up to the age of 6 months. After caesarean delivery, there is especially a reduced number of *Bacteroides* and bifidobacteria.[50] Although causality remains to be demonstrated, this dysbiosis has been implicated in the development of several acute and chronic immune diseases.[50] There is also evidence supporting the prophylactic use of probiotic microbes in very preterm infants for the prevention of necrotising enterocolitis and late onset sepsis.[51] Therefore, Korpela et al. suggested that this dysbiosis could be corrected by orally transferring diluted maternal faeces during the first feeding of the aterm neonates. After 3 months of follow-up, the microbiome of the seven treated babies was more similar to those born vaginally than to children born by caesarean section.[50]

3.1.4 | Multi drug resistant (MDR) organisms (MDRO)

Antibiotic resistance is a growing problem worldwide, and the genes for this resistance are partly located in the intestinal microbiome.[9] FMT is proposed as a potential therapy to treat such patients, as it has been shown to reduce antibiotic resistance genes in the microbiome of patients with rCDI.[9]

The first successfully treated paediatric patient was a 14-year-old girl with hemophagocytic lymphohistiocytosis, experiencing recurrent carbapenemase (CP)-producing *Klebsiella pneumoniae* infections.[52] No recurrence occurred in the following 1.5 years after only one FMT.[52] A second 16-year-old girl with acute myelogenous leukaemia underwent two FMTs for vancomycin-resistant enterococci (VRE) and CP-producing bacteria colonisation, resulting in decolonisation of VRE and persistence of CP-producing bacteria, with no reported adverse event.[53] In addition, five patients with hematologic stem cell transplants who were colonised with MDR bacteria received FMT. Although, 4/5 patients that were decolonised after 1 week were all recolonised after 1 month.[54] Patients are currently being enrolled to investigate the impact of FMT in decolonising antibiotic-resistant bacteria in larger paediatric populations (ClinicalTrials.gov identifiers: NCT06156956, NCT04593368 and NCT02543866).

3.1.5 | Obesity

Obesity has reached epidemic proportions and is estimated to affect 1.9 billion adults worldwide.[55] There is evidence that the gut microbiota can have an effect on metabolism and the regulation of weight.[56] Dietary or bariatric surgery interventions also showed to, at least partially, improve intestinal dysbiosis together with weight reduction and metabolic amelioration.[56] In adults, a significant increase in insulin sensitivity was seen after FMT intervention.[57] Therefore, the therapeutic benefits of altering the gut microbiota by FMT were addressed by two randomised, placebo-controlled trials in children. The Gut bugs trial evaluated the effect of FMT on adolescent obesity with a body mass index (BMI) above 30 ($n=87$) but found no significant effect on BMI.[58] Nevertheless, a post-hoc analysis did show a greater resolution of metabolic syndrome in the treatment group.[58] The second RCT assessed weight changes in children with underlying CDI or UC who underwent an FMT ($n=20$). This study confirmed that there was no significant difference in BMI after a follow-up of 12 months after transplantation.[59]

3.1.6 | Allergic colitis

Cow's milk protein allergy is the leading cause of allergic colitis in infants. The prevalence is estimated between 1% and 3%.[60] The evolution is largely favourable, 50% of the diagnosed children can tolerate cow's milk again after 1 year.[60] Liu et al. showed a positive effect of FMT on infantile allergic colitis that was insufficiently responsive to amino-acid-based formula.[61] All 17 infants were asymptomatic after one or multiple FMTs and remained asymptomatic until follow-up at the age of 15 months. However, these results have to be interpreted with caution given the favourable natural evolution of cow's milk protein allergy.

3.1.7 | Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a disorder of gut-brain interaction where the exact aetiology has not been fully elucidated yet. There is a general consensus that visceral hypersensitivity, motility disturbances, altered mucosal permeability and immune activation, in combination with dysbiosis of the gut microbiota plays an important role in the pathogenesis of IBS.[62] RCTs in adults have failed to demonstrate a benefit of FMT over placebo.[62] Studies in children are not available at present, but children are currently being recruited for an upcoming trial on the effects of FMT in patients with IBS (ClinicalTrials.gov identifiers: NCT03074227 and NCT05753774). However, the literature to date is insufficient for drawing definitive conclusions.

3.2 | Microbiome

Studies have shown a significant difference in gut microbiome pre- and post-FMT.[10,11,33,38] These changes have been seen to return to baseline as soon as after 6 months.[38] This may suggest that there could be a potential advance of serial FMT administration in non rCDI-indications. Indirectly, donor engraftment can be seen as a useful marker to assess the success of the intervention as it is related to the shift of the composition of the intestinal microbiota of the recipient towards that of the donor. Overall, higher success rate after FMT is seen in patients with higher donor strain engraftment.[63] In addition,

controlling inflammation in the recipient intestine might also facilitate engraftment after FMT by decreasing host immune system to react on the newly transferred microbiota.[64] However, the exact mechanisms and dynamics controlling the engraftment of the transplant in the recipient are poorly understood. Potential drivers that could explain this variability include the disease indication for FMT (including genetics and inflammation status of the patient), the composition of the donor's and patient's gut microbiome at baseline (presence or abundance of single bacteria and the diversity), specific aspects of the FMT administration (e.g. preparation of faecal material, route of administration, amount of infused faeces) and environmental factors such as dietary habits of the recipient.[63,64] Studies should further explore these dynamics as well as uncover species-specific engraftment patterns and their association with clinical variables, in order to further increase the efficacy and to be more consistent over cohorts.

3.3 | Adverse events

Based on current evidence, side effects are usually not serious and self-limiting. However, every patient needs to be informed about the potential risks before the FMT administration, especially in immunocompromised patients where the risk is potentially greater.[6] In addition, as most studies were small and retrospective the risk of underreporting could also limits these findings. Most common side effects are abdominal pain, diarrhoea, vomiting, low-grade fever, flatulence and nausea besides the complications from endoscopy and/or sedation.[6] The same adverse effects have been reported in the studies included in this systematic review (see Table 3).[5,6,8,10–14,17–21,29,38,40,42,50,54,58,61] This resulted in an overall number of serious adverse events (SAE) in 21/662 patients (3%) of which five could be related to the FMT (0.7%). The presenting symptoms of these latter were a large amount of rectal bleeding, gastric stricture, vomiting with dehydration, aspiration pneumonia and sepsis.[6,12,64] One death was reported with FMT due to sepsis and liver failure 4 weeks after FMT in an immunocompromised patient.[6] In adults, five deaths have been reported with FMT due to toxic megacolon with sepsis, peritonitis, two from aspiration pneumonia and one from anaesthesia during the colonoscopy.[6] The FDA also warned of the risk of translocation with MDRO, as this resulted in one death among two immunocompromised adult patients who received investigational FMT.[65] Finally, the risk of developing an IBD flare as well as the long-term immunological effects of FMTs should be considered.[6]

3.4 | Donor selection and microbiome

3.4.1 | Current guidelines

For rCDI, the donor choice appears of minor importance, where there is no preference for either related or unrelated donors for FMT based on the current evidence.[4] Although one could expect that FMT from a spouse might reduce the risk of infection transmission due to shared environmental risk factors. In addition, the adaptive immune system of the gut might be more tolerant towards the microbiota from the donor, as they will likely be more similar between the recipient and his/her close relative.[4] Nevertheless, these theoretical advantages have not been confirmed in practice. Even so, unrelated donors may be more favourable in other diseases, such as IBD, where genetics play a contributing factor in the pathogenesis.[4]

Potential donors should be screened according to international consensus guidelines 3–4 weeks before donation.[4,66,67] The purpose of donor screening is to avoid the transmission of infectious agents. Usually, pre-existing questionnaires for blood donors are used, in addition to testing the donor blood for viral pathogens (human immunodeficiency virus (HIV), hepatitis and syphilis) and the stools for the presence of pathogens such as CD or *Helicobacter pylori* if the upper gastrointestinal route is used for FMT administration. More often, a more rigorous approach is used with the exclusion of donors with underlying medical disorders (such as IBD or IBS), chronic diarrhoea, regular hospital visits, underlying diseases and recent antibiotic use.[26,66,67]

After publication of the joint position paper of NASPGHAN and ESPGHAN on FMT in children,[4] the FDA warned of the risk of translocation with MDRO. Stricter screening criteria for donors were proposed, with screening for these MDRO in FMT donors and to excluded donors at high risk for colonisation with MDRO.[65–67]

3.4.2 | Donor selection for specific conditions

While acknowledging the current insufficiency of data to substantiate the use of FMT for therapeutic indications beyond rCDI, it is crucial to recognise the multifaceted nature of FMT efficacy. Numerous variables, such as donor microbial profiles, recipient inflammatory burden, microbial diversity, FMT preparation protocols and administration specifics, can significantly influence outcomes. Exploring FMT under specific donor conditions may unveil more favourable effects, emphasising the importance of nuanced considerations in assessing its therapeutic potential. Published observations suggest that donor composition may be even more important in non-rCDI indications. More specifically, the key to FMT success probably lies in the ability of the donor to restore the metabolic deficits in the recipients and thereby reset the gut homeostasis that is contributing to disease. A high donor bacterial diversity was associated with more favourable FMT efficacy in patients with IBD.[68]

The potential of a 'super-donor' for treating UC patients with FMT was first described in the RCT of Moayyedi et al.[31] Seven of the nine FMT responders received faeces-derived matter from the same donor that was enriched with the *Ruminococcaceae* and *Lachnospiraceae* families.[31] Treatment successes attributable to this donor were 39% (7/18) versus 10% (2/10) with other donors.[31] Since then, several studies have confirmed that a high diversity of the gut microbiota is crucial, including in children.[38,41] Goyal et al. investigated the microbiome of paediatric IBD patients after FMT.[38] They saw that clinical responders had more *Fusobacterium*, reduced microbial richness (or alfa-diversity) pre- and higher post-FMT.[38]

TABLE 3 Adverse events of faecal microbiota transplantation.

Ref.	Number of patients	SAE	AE	Symptoms
5	15	0	2/15	Haematochezia (due to IBD)
6	49, 114 FMT procedures	2/114	30/114 (19/49 patients)	SAE: haematochezia and gastric stricture with haematemesis AE: abdominal pain, diarrhoea, fever and vomiting (all self-limited)
8	42	0	6/42	Vomiting
10	8	0	2/8	Abdominal pain
11	11	0	4/11	Abdominal pain, diarrhoea, fever and vomiting
12	335	17/335	19/335	SAE: 2/17 related (aspiration pneumonia and admission for dehydration); 5/17 possible related; 10/17: not related
13	10	0	0	
14	34	0	8/34	Abdominal pain, diarrhoea and bloating
17	3	0	0	
18	8	0	1/8	Abdominal pain, fever (influenza positive after 2 days)
19	10	0	1/10	Emesis and mucus in stool
20	6	1/6	0	Appendicitis
21	10	0	5/10	Abdominal pain, diarrhoea, flatulence or bloating, emesis and bloody stools
29	9	0	Depending on symptoms	Abdominal pain (5/9), diarrhoea (4/9), flatulence (1/9) and bloating (5/9)
38	21	0	12/21	Abdominal pain, diarrhoea, flatulence or bloating, emesis and bloody stools
40	10	0	2/10	Vomiting or nausea
42	10	0	9/10	Abdominal pain, diarrhoea, bloating and fever (2/10 fever)
50	7	0	0	
54	5	1	0	Sepsis (patient with HSCT)
58	42	0	529 responses	Diarrhoea (10%), abdominal pain (7%), nausea or vomiting (4%), fever (2%) and bloody stools (0,4%)
61	17	0	0	

Abbreviations: AE, adverse event; HSCT, haematopoietic stem cell transplant; IBD, inflammatory bowel disease; SAE, severe adverse events.

Kellermayer et al. also demonstrated that the increased abundance of *Coprococcus* and *Lachnospiraceae* could have a beneficial effect on paediatric patients with UC.[41]

Donor selection will also depend on the underlying disorder. For IBS patients, donors with high abundances of *Bifidobacterium* are preferred.[69] However, for inflammatory conditions, such as IBD and metabolic syndrome, restoration of butyrate-producing taxa by key members within Clostridium clusters IV and XIVa has been associated with prolonged clinical remission in IBD after FMT therapy. Whereas abundance of *Streptococcus* species was associated with no response.[70] Also, for rCDI, selecting donors containing a high butyrate and balanced *Bacteroidetes/Firmicutes* microbiota showed promising results in a small prospective paediatric cohort study with a 100% success rate after 10 weeks.[13] Despite this existing knowledge, the quest for optimal donor-specific conditions remains ongoing.

3.5 | Administration

Several routes of administration have been described for FMTs through the upper and lower gastrointestinal tracts. The most common routes are via esophagogastroduodenoscopy, nasogastric, nasojejunal or nasoduodenal tube, or colonoscopy or enemas. More recently, oral capsules with concentrated faecal microbes are also being introduced for ease of administration. In this systematic review, the most common route of FMT delivery in the different studies was via the lower gastrointestinal tract (15 vs. 19 studies).

The mode of administration seems to have little impact on the overall efficacy in adult patients with rCDI.[71,72] FMT enemas, FMT duodenal infusions or oral FMT capsules all resulted in similar efficacy rates (70%–90%). Unfortunately, in children only a head-to-head comparison between a nasogastric tube and a gastrostomy tube was made, and not with enemas or colonoscopy.[8,14] There are two head-to-head studies that showed conflicting results, emphasising the need for further investigations in children. The feasibility of oral FMT in children was also retrospectively investigated by Youngster et al.[73] The patients (five paediatric and 175 adult patients) needed to take 30 capsules over a two-day period. Only the overall effectiveness and side effects of this procedure were mentioned and they were similar to previously described in the literature when using the more common routes, with an effectiveness of 82% after one treatment and 91% after two treatments.[73]

Although the optimal route of administration remains to be determined, this will also influence the side effects.[67] The disadvantages of FMT via the upper gastrointestinal tract are the risk of aspiration, potential discomfort during tube placement, and the inability to evaluate the colon mucosa and/or take issue samples. Bowel cleansing before FMT via colonoscopy can probably reduce the number of residual organisms and spores, but it is an invasive and expensive procedure.[71] In addition, in children, this procedure requires sedation or anaesthesia. FMT via enema is less invasive than colonoscopy, but the optimal location of the delivery of the FMT is still unclear, whether this should be given all in the cecum versus distal colon versus distributed throughout the colon.[67] Another key point to discuss is whether FMT can be given once or in multiple intensive doses. This will probably depend on the underlying disease as well as the initial patient's response and the sustained response to the treatment.[67] Further investigation is warranted on this topic.

Finally, there is no consensus over the optimal FMT preparation procedure.[66,67] This can be either processed banked stool frozen at −80°C or fresh stool collected within 24 h of administration.

4 | DISCUSSION

FMT is considered a rapidly emerging new therapy with currently more than 379 studies listed on ClinicalTrials.gov, implying that FMT has found its way in the scientific community.

FMT is considered a standard treatment for rCDI, as also proposed by the NASPGHAN and ESPGHAN consensus guidelines.[4] In this systematic review, data of 538 reported cases with FMT use in children with rCDI has been collected, showing the efficacy and safety of this procedure in children. Even so, intervention with FMT has reached far beyond its undisputed indication, rCDI. By analogy with rCDI, there is some promising data on decolonisation of MDRO by treating them with FMT.[52–54] This could be of interest in the future to help children with MDRO infections, which is an emerging problem.[9] But the list does not end there. Despite promising results for many other disorders, major drawbacks are the small sample sizes, open label study design with patients who believe in the therapeutic value of this 'natural' therapy that will be selected, lack of long-term follow-up, the heterogeneity of the different protocols limiting generalisability and the propensity for studies with positive results to be published. Therefore, more RCT studies in children are wanted, especially in children with other comorbidities such as IBD.

Based on this systematic review, the side effects were limited, but potentially higher in immunodeficient patients and IBD patients, including the risk of developing a flare.[6,12] In addition, the downstream consequences of altering the microbiota by FMT are poorly understood. Especially at such an early age in the development where changes in the microbiome have been associated with the development of autoimmune, metabolic and psychiatric diseases.[2] Furthermore, FMT predominantly targets microbiome modification in the colon, yet crucial immune system interactions occur primarily in the small intestine. To ensure the successful integration of these therapies, a careful understanding of the functional role of the gut microbiome in regulating not only mucosal but also systemic immunity is imperative. Finally, the knowledge of the bacterial microbiota is rapidly expanding over the last few years, but little is known about the viral or fungal composition in the gut.[1] Also, the idea that FMT aims to replace 'bad' bacteria with 'good or healthy' bacteria is overly simplistic. Ongoing discussions persist about defining what constitutes a healthy microbiome. Current studies have solely focused on associations or correlations, falling short of establishing a causal relationship between gut microbiota and treatment response or disease severity.

In children, there is an added risk associated with performing endoscopies under anaesthesia in this vulnerable group. Additionally, alternative FMT delivery methods, such as oral capsule administration, seems an attractive option for children,[73] but may not be feasible for young children, as the large capsules may be impossible for younger children to swallow. Enemas are often less tolerated in children with lower retention time. Therefore, different routes are being proposed. A colonic transendoscopic enteral tubing can, for instance, be used to limit the amount of sedatives/anaesthesia used to admit multiple FMTs by colonoscopy.[74] This probe is fixated with clips by colonoscopy, which can then be used until the clips fall out. In the future, a more personalised medicine would be appealing through the oral admission of laboratory-designed bacterial products based on the patient's needs.[75]

To increase the efficacy of FMT formulations, preparations should be refined to help standardise therapy and reduce variability in patient response, and even define super-donors.[67] Follow-up studies are necessary to see if we must change our donor/recipient selection for better/safer results based on elucidating which patient profile might benefit from FMTs and which donors are able to induce a good response in certain conditions based on the microbiome or other characteristics. In addition, the frequency of treatment cycles and the longstanding effects of them still warrant further research. For instance, 18 weeks after the FMT administration, the effect of insulin sensitivity and the gut microbiota composition disappeared back to the baseline composition.[57] Or even as soon as, 6 months after a FMT intervention in children with IBD, changes in gut microbiota disappeared.[10] This underscores the temporary nature of this FMT intervention.

Donors are already being screened for many pathogens to eliminate the risk of being passed on to their potentially immunocompromised host. But this might not be enough. The study by Drewes et al. shows that procarcinogenic bacteria such as Enterotoxigenic *Bacteroides fragilis*, *Fusobacterium nucleatum* and *E. coli colibactin* can also be passed on to their recipients.[15] However, it is not yet clear whether this is associated with a higher risk of developing colorectal tumours.

5 | CONCLUSION

This systematic review confirms that FMT seems to be a safe and effective treatment for rCDI, although severe adverse events have

been reported in children. Secondly, there are currently insufficient data to support the use of FMT for other potential therapeutic indications beside maybe for decolonization of MDRO. In addition, there is a potential high risk of publication bias where selective reporting of positive outcomes (for instance, as seen in IBD) will have skewed the overall understanding of this intervention, leading to an incomplete and potentially misleading picture. Therefore, there is a need for large RCTs that can demonstrate the effectiveness of FMT in these other conditions, also in children. To date, there are still many considerations to address when conducting FMT in paediatric patients, especially the uniformity of transplant protocols, route of administration, donor selection, frequency of treatment cycles and the longstanding effects.

AUTHOR CONTRIBUTIONS

Karen van Hoeve: Conceptualization; writing – review and editing; supervision; formal analysis; methodology; investigation. **Ella Lauwers:** Conceptualization; writing – original draft; investigation; methodology; formal analysis; data curation. **João Sabino:** Writing – review and editing; supervision. **Ilse Hoffman:** Writing – review and editing; supervision.

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CONFLICT OF INTEREST STATEMENT

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REFERENCES

1. Gilbert JA, Blaser MJ, Caporaso JG, Jansson JK, Lynch SV, Knight R. Current understanding of the human microbiome. Nat Med. 2018;24(4):392-400.
2. Gurram B, Sue P. Fecal microbiota transplantation in children: current concepts. Curr Opin Pediatr. 2019;31(5):623-9.
3. Fang H, Fu L, Wang J. Protocol for fecal microbiota transplantation in inflammatory bowel disease: a systematic review and meta-analysis. Biomed Res Int. 2018;2018:8941340.
4. Davidovics ZH, Michail S, Nicholson MR, et al. Fecal microbiota transplantation for recurrent Clostridium difficile infection and other conditions in children: a joint position paper from the north American Society for Pediatric Gastroenterology, Hepatology, and nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and nutrition. J Pediatr Gastroenterol Nutr. 2019;68(1):130-43.
5. Fareed S, Sarode N, Stewart FJ, et al. Applying fecal microbiota transplantation (FMT) to treat recurrent Clostridium difficile infections (rCDI) in children. PeerJ. 2018;6:e4663.
6. Zhang XY, Wang YZ, Li XL, et al. Safety of fecal microbiota transplantation in Chinese children: a single-center retrospective study. World J Clin Cases. 2018;6(16):1121-7.
7. Quraishi MN, Widlak M, Bhala N, et al. Systematic review with meta-analysis: the efficacy of faecal microbiota transplantation for the treatment of recurrent and refractory Clostridium difficile infection. Aliment Pharmacol Ther. 2017;46(5):479-93.
8. Brumbaugh DE, De Zoeten EF, Pyo-Twist A, et al. An Intragastric fecal microbiota transplantation program for treatment of recurrent Clostridium difficile in children is efficacious, safe, and inexpensive. J Pediatr. 2018;194:123-7.
9. Hourigan SK, Ahn M, Gibson KM, et al. Fecal transplant in children with Clostridioides difficile gives sustained reduction in antimicrobial resistance and potential pathogen burden. Open Forum Infect Dis. 2019;6(10):ofz379. doi:10.1093/ofid/ofz379
10. Hourigan SK, Chen LA, Grigoryan Z, et al. Microbiome Changes associated with sustained eradication of Clostridium difficile after fecal microbiota transplantation in children with and without inflammatory bowel disease. Aliment Pharmacol Ther. 2015;42(6):741-52.
11. Li X, Gao X, Hu H, et al. Clinical efficacy and microbiome Changes following fecal microbiota transplantation in children with recurrent clostridium difficile infection. Front Microbiol. 2018;9:2622.
12. Nicholson MR, Mitchell PD, Alexander E, et al. Efficacy of fecal microbiota transplantation for Clostridium difficile infection in children. Clin Gastroenterol Hepatol. 2020;18(3):612-9.
13. Barnes D, Ng K, Smits S, Sonnenburg J, Kassam Z, Park KT. Competitively selected donor fecal microbiota transplantation: butyrate concentration and diversity as measures of donor quality. J Pediatr Gastroenterol Nutr. 2018;67(2):185-7.
14. Zeky N. Inpatient and outpatient fecal microbiota transplant in pediatric patients with clostridium difficile infections. Pract Gastroenterol. 2020;44(7):38-46.
15. Drewes JL, Corona A, Sanchez U, et al. Transmission and clearance of potential procarcinogenic bacteria during fecal microbiota transplantation for recurrent Clostridioides difficile. JCI Insight. 2019;4(19):e130848.
16. Bluestone H, Kronman MP, Suskind DL. Fecal microbiota transplantation for recurrent Clostridium difficile infections in pediatric hematopoietic stem cell transplant recipients. Pediatr Infect Dis Soc. 2018;7(1):e6-e8.
17. Chen LA, Hourigan S, Radin A, et al. Bile Acid Composition Changes over 6 Months Following Fecal Microbiota Transplantation in Children with Recurrent C. difficile Infections: 2016 ACG presidential poster award. Am J Gastroenterol. 2016;111:S453-S454.
18. Cho S, Spencer E, Hirten R, Grinspan A, Dubinsky MC. Fecal microbiota transplant for recurrent Clostridium difficile infection in pediatric inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2019;68(3):343-7.
19. Kronman MP, Nielson HJ, Adler AL, et al. Fecal microbiota transplantation via nasogastric tube for recurrent clostridium difficile infection in pediatric patients. J Pediatr Gastroenterol Nutr. 2015;60(1):23-6.
20. Pierog A, Mencin A, Reilly NR. Fecal microbiota transplantation in children with recurrent Clostridium difficile infection. Pediatr Infect Dis J. 2014;33(11):1198-200.
21. Russell GH, Kaplan JL, Youngster I, et al. Fecal transplant for recurrent Clostridium difficile infection in children with and without inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2014;58(5):588-92.

22. Aldrich A, Argo T, Olivero R. Analysis of treatment outcomes for recurrent Clostridium difficile infections and fecal microbiota transplantation (FMT) in a pediatric hospital. Pediatr Infect Dis J. 2019;38(1):32-6.
23. Kelly CR, Ihunnah C, Fischer M, et al. Fecal microbiota transplant for treatment of Clostridium difficile infection in immunocompromised patients. Am J Gastroenterol. 2014;109(7):1065-71.
24. Walia R, Garg S, Song Y, et al. Efficacy of fecal microbiota transplantation in 2 children with recurrent Clostridium difficile infection and its impact on their growth and gut microbiome. J Pediatr Gastroenterol Nutr. 2014;59(5):565-70.
25. Rubin TA, Gessert CE, Aas J, Bakken JS. Fecal microbiome transplantation for recurrent Clostridium difficile infection: report on a case series. Anaerobe. 2013;19:22-6.
26. Chen B, Avinashi V, Dobson S. Fecal microbiota transplantation for recurrent Clostridium difficile infection in children. J Infect. 2017;74:S120-S127.
27. Wellens J, Vermeire S, Sabino J. Let food Be thy medicine—its role in Crohn's disease. Nutrients. 2021;13(3):832.
28. Caenepeel C, Sadat Seyed Tabib N, Vieira-Silva S, Vermeire S. Review article: how the intestinal microbiota may reflect disease activity and influence therapeutic outcome in inflammatory bowel disease. Aliment Pharmacol Ther. 2020;52(9):1453-68.
29. Suskind DL, Brittnacher MJ, Wahbeh G, et al. Fecal microbial transplant effect on clinical outcomes and fecal microbiome in active Crohn's disease. Inflamm Bowel Dis. 2015;21(3):556-63.
30. Costello SP, Hughes PA, Waters O, et al. Effect of fecal microbiota transplantation on 8-week remission in patients with ulcerative colitis. JAMA. 2019;321(2):156-64.
31. Moayyedi P, Surette MG, Kim PT, et al. Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a randomized controlled trial. Gastroenterology. 2015;149(1):102-9.
32. Paramsothy S, Kamm MA, Kaakoush NO, et al. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. Lancet. 2017;389(10075):1218-28.
33. Rossen NG, Fuentes S, van der Spek MJ, et al. Findings from a randomized controlled trial of fecal transplantation for patients with ulcerative colitis. Gastroenterology. 2015;149(1):110-8.
34. Sarbagili Shabat C, Scaldaferri F, Zittan E, et al. Use of Faecal transplantation with a novel diet for mild to moderate active ulcerative colitis: the CRAFT UC randomised controlled trial. J Crohns Colitis. 2021;16(3):369-78.
35. Paramsothy S, Paramsothy R, Rubin DT, et al. Faecal microbiota transplantation for inflammatory bowel disease: a systematic review and meta-analysis. J Crohns Colitis. 2017;11(10):1180-99.
36. Qazi T, Amaratunga T, Barnes EL, Fischer M, Kassam Z, Allegretti JR. The risk of inflammatory bowel disease flares after fecal microbiota transplantation: systematic review and meta-analysis. Gut Microbes. 2017;8(6):574-88.
37. Sokol H, Landman C, Seksik P, et al. Fecal microbiota transplantation to maintain remission in Crohn's disease: a pilot randomized controlled study. Microbiome. 2020;8(1):12.
38. Goyal A, Yeh A, Bush BR, et al. Safety, clinical response, and microbiome findings following fecal microbiota transplant in children with inflammatory bowel disease. Inflamm Bowel Dis. 2018;24(2):410-21.
39. Goyal A, Yeh A, Siebold L, et al. Clinical efficacy and microbiome findings following fecal microbiota transplant in children with refractory inflammatory bowel disease. Gastroenterology. 2017;152(5):S959.
40. Karolewska-Bochenek K, Grzesiowski P, Banaszkiewicz A, et al. A two-week fecal microbiota transplantation course in pediatric patients with inflammatory bowel disease. Adv Exp Med Biol. 2018;1047:81-7.
41. Kellermayer R, Nagy-Szakal D, Harris RA, et al. Serial fecal microbiota transplantation alters mucosal gene expression in pediatric ulcerative colitis. Am J Gastroenterol. 2015;110(4):604-6.
42. Kunde S, Pham A, Bonczyk S, et al. Safety, tolerability, and clinical response after fecal transplantation in children and young adults with ulcerative colitis. J Pediatr Gastroenterol Nutr. 2013;56(6):597-601.
43. Suskind DL, Singh N, Nielson H, Wahbeh G. Fecal microbial transplant via nasogastric tube for active pediatric ulcerative colitis. J Pediatr Gastroenterol Nutr. 2015;60(1):27-9.
44. Quagliariello A, Del Chierico F, Reddel S, et al. Fecal microbiota transplant in two ulcerative colitis pediatric cases: gut microbiota and clinical course correlations. Microorganisms. 2020;8(10):1486.
45. Kump PK, Gröchenig HP, Lackner S, et al. Alteration of intestinal Dysbiosis by fecal microbiota transplantation does not induce remission in patients with chronic active ulcerative colitis. Inflamm Bowel Dis. 2013;19(10):2155-65.
46. Cui B, Li P, Xu L, et al. Step-up fecal microbiota transplantation strategy: a pilot study for steroid-dependent ulcerative colitis. J Transl Med. 2015;13(1):298.
47. Wei Y, Zhu W, Gong J, et al. Fecal microbiota transplantation improves the quality of life in patients with inflammatory bowel disease. Gastroenterol Res Pract. 2015;2015:517597.
48. Cui B, Feng Q, Wang H, et al. Fecal microbiota transplantation through mid-gut for refractory Crohn's disease: safety, feasibility, and efficacy trial results. J Gastroenterol Hepatol. 2015;30(1):51-8.
49. Vandenplas Y, Veereman G, van der Werff ten Bosch J, et al. Fecal microbial transplantation in early-onset colitis: caution advised. J Pediatr Gastroenterol Nutr 2015;61(3):e12-e14.
50. Korpela K, Helve O, Kolho KL, et al. Maternal fecal microbiota transplantation in cesarean-born infants rapidly restores Normal gut microbial development: a proof-of-concept study. Cell. 2020;183(2):324-34.
51. Deshmukh M, Patole S. Prophylactic probiotic supplementation for preterm neonates—a systematic review and meta-analysis of nonrandomized studies. Adv Nutr. 2021;12(4):1411-23.
52. Freedman A, Eppes S. Use of stool transplant to clear fecal colonization with Carbapenem-resistant Enterobacteraciae (CRE): proof of concept. Open Forum Infect Dis. 2014;1:S65.
53. Battipaglia G, Malard F, Rubio MT, et al. Fecal microbiota transplantation before or after allogeneic hematopoietic transplantation in patients with hematologic malignancies carrying multidrug-resistance bacteria. Haematologica. 2019;104(8):1682-8.
54. Merli P, Putignani L, Ruggeri A, et al. Decolonization of multi-drug resistant bacteria by fecal microbiota transplantation in five pediatric patients before allogeneic hematopoietic stem cell transplantation: gut microbiota profiling, infectious and clinical outcomes. Haematologica. 2020;105(11):2686-90.
55. WHO. Obesity and Overweight. 2021. World Health Organization: WHO. Accessed September, 26 2022. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
56. Aron-Wisnewsky J, Prifti E, Belda E, et al. Major microbiota dysbiosis in severe obesity: fate after bariatric surgery. Gut. 2018;68(1):70-82.
57. Vrieze A, Van Nood E, Holleman F, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology. 2012;143(4):913-6.
58. Leong KSW, Jayasinghe TN, Wilson BC, et al. Effects of fecal microbiome transfer in adolescents with obesity. JAMA Netw Open. 2020;3(12):e2030415.
59. Xi D, Michail S. Fecal microbiota transplantation in children does not significantly Alter body mass index. Transl Pediatr. 2019;8(5):398-401.
60. Flom JD, Sicherer SH. Epidemiology of Cow's Milk allergy. Nutrients. 2019;11(5):1051.

61. Liu SX, Li YH, Dai WK, et al. Fecal microbiota transplantation induces remission of infantile allergic colitis through gut microbiota re-establishment. World J Gastroenterol. 2017;23(48):8570-81.
62. Myneedu K, Deoker A, Schmulson MJ, Bashashati M. Fecal microbiota transplantation in irritable bowel syndrome: a systematic review and meta-analysis. United European Gastroenterol J. 2019;7(8):1033-41.
63. Ianiro G, Punčochář M, Karcher N, et al. Variability of strain engraftment and predictability of microbiome composition after fecal microbiota transplantation across different diseases. Nat Med. 2022;28(9):1913-23.
64. Danne C, Rolhion N, Sokol H. Recipient factors in faecal microbiota transplantation: one stool does not fit all. Nat Rev Gastroenterol Hepatol. 2021;18(7):503-13.
65. Michail S, Nicholson M, Kahn S, Kellermayer R. Addendum for: fecal microbiota transplantation for recurrent Clostridium difficile infection and other conditions in children: a joint position paper from the north American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2020;70(3):404.
66. Cammarota G, Ianiro G, Kelly CR, et al. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. Gut. 2019;68(12):2111-21.
67. Cammarota G, Ianiro G, Tilg H, et al. European consensus conference on faecal microbiota transplantation in clinical practice. Gut. 2017;66(4):569-80.
68. Vermeire S, Joossens M, Verbeke K, et al. Donor species richness determines Faecal microbiota transplantation success in inflammatory bowel disease. J Crohns Colitis. 2015;10(4):387-94.
69. Mizuno S, Masaoka T, Naganuma M, et al. Bifidobacterium-rich fecal donor may Be a positive predictor for successful fecal microbiota transplantation in patients with irritable bowel syndrome. Digestion. 2017;96(1):29-38.
70. Paramsothy S, Nielsen S, Kamm MA, et al. Specific bacteria and metabolites associated with response to fecal microbiota transplantation in patients with ulcerative colitis. Gastroenterology. 2019;156(5):1440-54.
71. Kassam Z, Lee CH, Yuan Y, Hunt RH. Fecal microbiota transplantation for Clostridium difficile infection: systematic review and meta-analysis. Am J Gastroenterol. 2013;108(4):500-8.
72. Furuya-Kanamori L, Doi SAR, Paterson DL, et al. Upper versus lower gastrointestinal delivery for transplantation of fecal microbiota in recurrent or refractory Clostridium difficile infection. J Clin Gastroenterol. 2017;51(2):145-50.
73. Youngster I, Mahabamunuge J, Systrom HK, et al. Oral, frozen fecal microbiota transplant (FMT) capsules for recurrent Clostridium difficile infection. BMC Med. 2016;14(1):134.
74. Zhong M, Buch H, Wen Q, Long C, Cui B, Zhang F. Colonic Transendoscopic enteral tubing: route for a novel, safe, and convenient delivery of washed microbiota transplantation in children. Gastroenterol Res Pract. 2021;2021:6676962.
75. Hourigan SK, Oliva-Hemker M. Fecal microbiota transplantation in children: a brief review. Pediatr Res. 2016;80(1):2-6.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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