Fecal microbiota transplantation in children: current concepts

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Purpose of review
Administration of fecal material into the gastrointestinal tract, termed fecal microbiota transplantation (FMT), is increasingly recognized as an effective treatment option for recurrent *Clostridium difficile* infection (RCDI). The impact of FMT on host microbial communities and subsequent disease states has also been explored in recent years for conditions as varied as inflammatory bowel disease especially ulcerative colitis, metabolic diseases, such as diabetes, graft-versus-host disease in hematopoietic stem cell transplant recipients, and autism and autism spectrum disorders. The purpose of this article is to review the evidence for FMT as a treatment option in various pediatric illnesses.

Recent findings
The rate of *C. difficile* infection is rising among children, and is associated with significant morbidity and disease, with recurrence in up to 20% of pediatric patients. Several randomized controlled trials evaluating the utility of FMT in RCDI in comparison to vancomycin have been published and demonstrate high rates of efficacy between 70 and 100%. In addition, the safety of FMT in the treatment of RCDI has been well described in the adult population, with several pediatric case series demonstrating similar rates of tolerability and adverse events. FMT in ulcerative colitis appears promising, especially with multiple infusions administered via the lower gastrointestinal tract. However, there are several limitations, including the lack of uniformity of protocols used, source of FMT, route of administration and the lack of standardization of concomitant therapies. The data on usage of FMT for other indications are preliminary and limited.

Summary
FMT is recognized as an effective treatment option for RCDI and is increasing sought by parents. Although limited, pediatric studies to date on the use of FMT for RCDI demonstrate similar efficacy rates as in the adult population. FMT has been proposed as a treatment option for an increasing number of pediatric conditions, and additional studies are needed to delineate the efficacy of FMT outside of RCDI, as well as its short and long-term impacts on human health.

Keywords
Clostridium difficile infection, fecal microbiota transplantation, graft versus host disease, inflammatory bowel disease, microbiome, multidrug-resistant organisms

INTRODUCTION

The human gut harbors an estimated 1000–1150 bacterial species responsible for a variety of functions ranging from the metabolism of carbohydrates, to the fermentation of indigestible food products, to the stimulation and regulation of the immune system [1,2]. Disturbances in the composition of microbial communities can lead to decreased gut diversity (dysbiosis), and has been associated with an array of neurologic, gastrointestinal, metabolic, oncologic, hepatic, cardiovascular, psychologic, respiratory and autoimmune disorders [3].

Gut dysbiosis is associated with an increased risk of colonization with microbial pathogens [4]. The role of dysbiosis is well documented in the pathogenesis of multiple disease states, including *Clostridioides difficile* infection (CDI), where the use

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KEY POINTS

- Recent insights into the composition and function of the human gut microbiome have highlighted its impact on the metabolic, immunologic and protective mechanisms of the human gastrointestinal tract.
- The loss of gut microbial diversity is associated with a number of disease states including CDI, GVHD following HSCT, gastrointestinal infection and IBD.
- FMT restores gut microbial diversity and has been shown to be an effective treatment for RCDI.
- FMT has been proposed as a treatment option for a number of other disease states, ranging from IBD, to MDRO colonization, to allergic colitis and autism spectrum disorder. However, data remain sparse at this time, and the efficacy of FMT in these settings is unclear.

of broad spectrum antibiotics has been identified as the most common associated risk factor for disease [5]. In addition, microbial signatures demonstrating decreased gut microbiota and phyla diversity have been shown to predispose individuals to CDI [6]. Among individuals with inflammatory bowel disease (IBD), polymorphisms responsible for the regulation of host bacterial responses, such as NOD2/CARD 15, have been identified, and associated with altered microbial immune responses and gut dysbiosis [7]. In genetically susceptible individuals, inappropriate immune responses to gut microbiota are considered key events in the pathogenesis of IBD, and may be exacerbated in such settings [8,9]. In postinfectious IBS, the severity of IBS was associated with a distinct fecal microbiota signature, characterized by reduced microbial diversity and a reduced prevalence of Methanobacteriales and Prevotella [10]. Similarly, polymorphisms in genes coding Toll-like receptor 9, interleukin-6 and CDH1 have been implicated in the pathogenesis of postinfectious IBS, with these polymorphisms likely to alter the gut–microbiome and host immune interactions [11].

Fecal microbiota transplantation (FMT) is a process by which fecal material is transferred from a healthy donor into the gastrointestinal tract of a recipient, in order to alter the microbial composition and ameliorate gut dysbiosis [12]. FMT is achieved by the administration of fecal material into the gastrointestinal tract via enema, colonoscopy, naso-gastric tube or as oral capsules. Transfer of human fecal product increases recipient fecal microbial biodiversity, alters microbiota community ratios (with increasing proportions of Anaerobes and decreasing proportions of Proteobacteria) and leads to increased short-chain fatty acid and secondary bile acid synthesis [13▪,14,15]. Such changes can persist up to 6 months following FMT [16].

FECAL MICROBIOTA TRANSPLANTATION: RISK, PRODUCT AND ADMINISTRATION

The administration of FMT product requires rigorous screening processes to minimize the risk of donor-derived infection (DDI). Although to date, no studies exist examining the impact of donor characteristics on FMT efficacy, and national donor screening guidelines are lacking, consensus recommendations from the Infectious Disease Society of America (IDSA), American Society for Gastrointestinal Endoscopy, North American Society for Pediatric Gastroenterology, Hepatology and Nutrition and American College of Gastroenterology employ a combination of screening questionnaires (to exclude-high risk donors), donor serologic testing for transmissible pathogens (e.g. syphilis and HIV) and donor stool tests to reduce the risk of DDI (e.g. stool enteric pathogen culture, CDI testing and Norovirus, Adenovirus) [17,18]. However, in the absence of specific regulatory guidelines from the US Food and Drug Administration (FDA), donor screening protocols often vary from institution to institution.

Human fecal product has been classified as a biological agent and drug, subject to regulation by the FDA. However, to date, no specific fecal product has been approved for use, and the use of FMT is considered investigational. Although current FDA guidance allows for the directed use of FMT for nonresponsive CDI without an investigational new drug (IND) permit, an IND application is required when FMT is used for research purposes, or to treat any other condition [19]. Although initial studies demonstrating the efficacy of FMT employed fresh-fecal product, subsequent studies have established the efficacy and noninferiority of frozen fecal product in the treatment of recurrent *Clostridium difficile* infection (RCDI) [20–23]. Additional products available for FMT include frozen encapsulated oral formulations, as well as synthetic microbial and metabolic microbial cocktails for use in targeted disease states [21]. In recent years, independent third-party stool banks have emerged as a source for frozen fecal product, leading to increased access of FMT to centers without the infrastructure in place for stool banking or donor screening. At our center, we exclusively employ frozen, prescreened FMT product obtained through a nonprofit stool bank.

In 2013, the FDA addressed regulatory concerns surrounding FMT practices and product by electing to practice enforcement discretion of standard IND regulations in the setting of CDI not responsive to

standard therapy. Since then, the FDA has released a series of nonbinding draft policy proposals on the use of human fecal products, the latest of which was released in 2016 [24▪]. No subsequent policies have been finalized to date.

FECAL MICROBIOTA TRANSPLANTATION: SAFETY

Although the long-term safety of FMT has not yet been established, serious adverse events (SAEs) are overall rare. In a systematic review of adverse events (AEs) associated with FMT among adults, Wang *et al.* [25] reported a total incidence of 28.5%, with the majority of these deemed to be mild to moderate; including abdominal discomfort, bloating, diarrhea, constipation and transient fever. In contrast, the incidence of SAEs, including death, infection, IBD relapse and CDI, was 2.0 and 6.1% for upper and lower gastrointestinal routes, respectively [25]. Among children, a multicenter retrospective cohort study of 335 pediatric patients receiving FMT for CDI demonstrated SAEs in 4.7% of individuals in the 3-month period following FMT [26▪].

Among immunocompromised hosts, FMT has been shown to be well tolerated in the setting of CDI, with clinical response and AE rates among adult solid organ transplant recipients, HIV-infected individuals and hematopoietic stem cell transplant (HSCT) recipients similar to that of the general population [27,28▪▪]. Among children, data on the safety of FMT among immunocompromised hosts are extremely sparse, with a single reported series of FMT in three pediatric HSCT recipients demonstrating no AEs, and a single report of cardiac allograft vasculopathy in a 3-year-old orthotopic heart transplant recipient 2 months after receiving FMT [29,30]. Thus, while the preponderance of studies to date suggests that FMT is safe and effective among immunocompromised individuals, additional studies are needed to characterize the safety and efficacy of FMT among immunocompromised children.

The Fecal Microbiota Transplant National Registry, a venture led by the American Gastroenterology Association and funded by the National Institutes of Health, aims to follow 4000 FMT recipients for up to 10 years and will provide robust real-world efficacy data as well as short and long-term safety outcomes (grant number 1R24A118629-01A1) [31].

FECAL MICROBIAL TRANSPLANT: INDICATIONS RECURRENT *CLOSTRIDIODES DIFFICILE* INFECTION

Clostridium difficile, more recently termed *Clostridioides difficile*, is a spore bearing gram positive anaerobic organism discovered in 1935, and is responsible for significant morbidity and mortality among children and adults [32]. Among children, the incidence of CDI has increased rapidly in recent years, with studies reporting an almost two-fold increase in pediatric CDI hospitalizations between 2001 and 2006, and a up to a 12.5-fold increase in overall CDI incidence per 100 000 children between 1991 and 2009 [29,30].

Risk factors for CDI include receipt of fluoroquinolones [odds ratio (OR), 17.04; 95% confidence interval (CI), 5.86–49.54] or nonquinolone antibiotics (OR, 2.23; 95% CI, 1.18–4.20) in the previous 4 weeks, solid organ transplant (OR, 8.09; 95% CI, 2.10–31.12) and the presence of gastrostomy or jejunostomy (G or J) tube (OR, 3.32; 95% CI 1.71–6.42) [33]. Diagnosis is often challenging because of high carrier rates for *Clostrdioides difficile* in children less than 2 years of age, in whom colonization rates can be as high as 33% [34,35▪▪]. Carrier rates are also increased in healthcare setting [36], where CDI is estimated to be responsible for as little as 5–10% of patients with diarrhea. Recurrence following CDI occurs in 11–20% of pediatric patients, and increases with subsequent infections [37,32].

Management of recurrent CDI is not well studied in children, with evidence mostly inferred from adult studies. Although antibiotics, such as vancomycin, fidoxomycin and rifaxmin, are recommended for initial recurrences, FMT is recommended for multiple recurrences. The accepted criteria for FMT for CDI include patients with more than three recurrences, two previous episodes requiring hospitalization, severe disease without response to anti-CDI therapy at 48 h or moderate CDI without response by 5 days [31].

Multiple reports have demonstrated the efficacy of FMT in the management of RCDI, including eight randomized controlled trials (RCTs) to date. Initial RCTs by Van Nood *et al.* [20] and Cammarota *et al.* [38] comparing vancomycin to FMT were both terminated early following interim analysis because of the significantly higher efficacy of FMT. The remaining studies have compared the efficacy of various forms of FMT delivery, including autologous vs. donor FMT (Kelly *et al.* [39], fresh vs. frozen FMT (Lee *et al.*) [23], capsule vs. colonoscopic delivery (Kao *et al.*) [40], low-dose vs. high-dose FMT (Allegretti *et al.*) [41], and nasogastric vs. colonoscopic delivery (Youngster *et al.*) [42]. In a recent randomized, open-label active comparative clinical trial between FMT, fidoxomicin and vancomycin for RCDI, Hvas *et al.* [43▪] reported 92% week 8 resolution of symptoms with FMT compared to 42% ($P = 0.002$) with fidaxomicin and 19% with vancomycin ($P = <0.001$). A recent systematic review of

seven RCTs examining the impact of FMT in RCDI showed an overall efficacy of 92% (95% CI 89–94%), with 88% (95% CI 82–94%) cure rate with upper gastrointestinal tract delivery and 95% (95% CI 92–97%) with lower gastrointestinal tract delivery [44]. Administering consecutive courses of FMT following the failure of first FMT also resulted in an incremental improvement.

Although RCTs evaluating the efficacy of FMT for RCDI are lacking in children, a recent multicenter retrospective cohort study by Nicholson *et al.* [26▪] reported the efficacy of FMT for recurrent CDI among 372 patients between the ages of 11 months and 23 years old, with 81% demonstrating resolution at 2 months following a single FMT and up to 86.6% demonstrating response with repeat FMT. Notably, 32% of patients in this cohort had IBD. In addition, multiple case series and reports demonstrate therapeutic success with FMT in pediatric RCDI, regardless of the mode of delivery, and despite a range of underlying conditions (including immunocompromised states including from IBD therapy) [27,45–50]. Among immunocompromised hosts with RCDI, FMT is less effective in IBD patients compared to patients without IBD (74.4 vs. 92.1%; $P = 0.0018$), and individuals with underlying immunodeficiency often require more than one FMT prior to remission. In a study by Khoruts *et al.* [51] approximately 25% of IBD patients reported a disease flare following FMT.

INFLAMMATORY BOWEL DISEASE

The microbiome is thought to play a central role in the pathogenesis of IBD, with dysbiosis noted in the majority of patients. As a result, FMT has been studied as a therapeutic option for the management of IBD, especially UC.

In a systematic review that included four RCTs and a total of 277 participants, Narula *et al.* [52] reported higher combined clinical and endoscopic remission at week 7 to week 12 after FMT compared with placebo [risk ratio for ulcerative colitis (UC) not in remission was 0.80; 95% CI: 0.71–0.89] with a number needed to treat of five (95% CI: 4–10). There was no statistically significant increase in SAEs with FMT compared with controls (risk ratio AE was 1.4; 95% CI: 0.55–3.58). In a meta-analysis of 24 cohort studies assessing 307 patients, Paramsothy *et al.* [53] reported a pooled clinical remission rate of 33% in UC after FMT. However, most patients included in these trials were on concomitant therapy with standard UC medications, and there was significant variation in methodology among studies. Overall, FMT in UC appears promising, especially with multiple infusions administered via the lower gastrointestinal tract. However, there are no studies looking at long-term efficacy/side-effects from FMT.

Among children, the evidence for FMT in pediatric IBD is limited to case series and individual reports. In a recent report of 10 children with IBD, clinical remission was noted in three of eight UC patients and two of two Crohn's disease (CD) patients after eight doses of FMT administered over a 2-week period [54]. In a prospective study, Goyal *et al.* [12] reported a clinical response in 57 and 28% at 1 and 6 months after a single FMT in 21 IBD patients. Although responders showed increase in diversity of microbiome 1-month post FMT, at 6 months these changes returned to baseline [12]. Several other reports have demonstrated similar efficacy and transient response [55,56].

FMT has also been evaluated in the management of pouchitis, with variable efficacy. In one open label study, sustained remission was observed in three out of five adults with chronic antibiotic-dependent pouchitis at 3 months following FMT [57]. However, an open labeled prospective study by Landy *et al.* [58] did not show clinical efficacy at 1 month after FMT for chronic pouchitis.

There are insufficient data on the role of FMT in CD management [50,53].

IRRITABLE BOWEL SYNDROME

FMT has also been explored as a therapeutic avenue for the management of functional gastrointestinal illness such as IBS and chronic idiopathic constipation. The data currently are limited to adult population and relatively small studies on slow-transit constipation [59,60] and IBS-diarrhea predominant [15,61]. The literature currently is insufficient to draw conclusions.

MULTIDRUG-RESISTANCE ORGANISMS

Infection with multidrug-resistant organisms (MDROs) is associated with increased rates of sepsis, treatment failure, prolonged hospital stay and mortality. Individuals colonized with MDRO pathogens are at elevated risk for MDRO infection, including bacteremia [62]. Intestinal microbiota communities have been implicated in the control of pathogen microbial gut colonization, and FMT has been successfully used in multiple reports to decolonize individuals with a spectrum of MDRO's, including vancomycin-resistant Enterococcus (VRE) and *Klebsiella pneumoniae* [63,64,65]. However, data regarding the overall efficacy of FMT in this setting remain limited, with no pediatric data currently available. In a prospective multicenter study of 17 MDRO colonized individuals, Dinh *et al.* [66] demonstrated

30–40% efficacy of FMT to eliminate carbapenemase-resistant Enterobactericiae and VRE 1 week following FMT. In contrast, Bilinski *et al.* [67] demonstrated the clearance in 15 of 20 (75%) individuals colonized with a variety of MDROs following FMT. Although FMT has been clearly demonstrated to restore gut biodiversity following antimicrobial exposures, additional studies are needed to assess the impact of this effect across multiple pathogens [68].

GRAFT VERSUS HOST DISEASE

Loss of gut microbial biodiversity following HSCT has been associated with CDI, bacteremia, graft versus host disease (GVHD), disease relapse and increased nonrelapse mortality [69,70]. FMT has been proposed as a mechanism to restore gut microbial diversity and decrease complications following HSCT, including GVHD [71▪▪,72]. In a prospective randomized trial of 25 allogeneic HSCT recipients with gut dysbiosis, Taur *et al.* [71▪▪] demonstrated the superior microbial diversity among individuals receiving autologous FMT, as compared to placebo. The potential role for FMT in the setting of acute gut GVHD was first demonstrated by Kakihana *et al.* [73] who reported the complete remission of steroid refractory acute gut GVHD in three out of four patients following FMT, with a partial remission in another. Subsequent studies have been limited to individual case reports and small series, but have further demonstrated the potential efficacy of FMT in the setting of refractory gut GVHD, whether administered via colonoscopy, oral capsule or naso-duodenal tube [74–76]. However, there are no pediatric data to date, and while the prospect of FMT for refractory gut GVHD remains promising, additional investigation is needed.

OTHER APPLICATIONS OF FMT

Potential therapeutic applications of FMT have been further explored in the treatment of a wide range of illnesses, including allergic colitis [77], behavioral and gastrointestinal manifestations of autism spectrum disorder [78], chronic fatigue syndrome [79], metabolic syndrome [80] and hepatic encephalopathy [81–83]. Synthetically tailored microbial cocktails are also under development for use in conditions, such as autoimmune disorders, and the promotion of gut resistance to pathogenic microbial invasion [84].

CONCLUSION

FMT is a safe and effective approach to improve gut dysbiosis associated with RCDI, as well as a number of other disease states. However, data on the efficacy of FMT in settings other than RCDI remain limited. Clinical applications and modes of delivery for FMT will continue to evolve as additional insight is gleaned on the role and mechanisms of the gut microbiota in disease. Future trends should focus on the longevity of changes following FMT, microbial community behaviors and cellular mechanisms by which microbiota exert auspicious effects, in order to refine more targeted and effective applications.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
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