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**Fecal microbial transplant for the treatment of pediatric inflammatory bowel disease**

Wang AY *et al.* Fecal transplant in pediatric colitis

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**Abstract**

The role of fecal microbial transplant (FMT) in the treatment of pediatric gastrointestinal disease has become increasingly popular among pediatric practitioners, patients, and parents. The success of FMT for the treatment of recurrent *Clostridium difficile* infection (RCDI) has bolstered interest in its potential application to other disease states, such as inflammatory bowel disease (IBD). FMT has particular interest in pediatrics, given the concerns of patients and parents about rates of adverse events with existing therapeutic options, and the greater cumulative medication burden associated with childhood-onset disease. Published literature on the use of FMT in pediatrics is sparse. Only 45 pediatric patients treated for RCDI have been reported, and only 26 pediatric patients with pediatric IBD. The pediatric microbiome may uniquely respond to microbial-based therapies. This review will provide a comprehensive overview of fecal microbial transplant and its potential role in the treatment of pediatric inflammatory bowel disease. We will discuss the microbiome in pediatric inflammatory bowel disease, existing adult and pediatric literature on the use of FMT in IBD treatment, and pediatric FMT trials that are currently recruiting patients. This review will also discuss features of the microbiome that may be associated with host response in fecal transplant, and potential challenges and opportunities for the future of FMT in pediatric IBD treatment.

**Key words:** Inflammatory bowel disease; Microbiome; Microbiota; fecal microbial transplant; Pediatric; Ulcerative colitis; Crohn’s disease

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**Core tip:** There is growing interest in fecal microbial transplant (FMT) for the treatment of pediatric inflammatory bowel disease (IBD). The therapeutic potential of bacterial therapies is intriguing. FMT is effective for treating recurrent *Clostridium difficile* infection, distinct microbial signatures in IBD continue to be described, and patients are increasingly looking for therapeutic options with lower rates of morbidity. This review describes existing adult and pediatric literature on the role of FMT in IBD, features of the IBD microbiome that may be associated with response, current trials, and the potential challenges and opportunities for the future of FMT in pediatric IBD treatment.

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**INTRODUCTION**

Fecal microbial transplant (FMT) has garnered increasing attention over the past decade for its role in the treatment of recurrent *Clostridium difficile* infection (RCDI). While underlying mechanisms for how the inoculation of whole stool contents from healthy donors may prevent recurrent pseudomembranous colitis remain unknown, several hypotheses exist[1]. Advances in sequencing and bioinformatics technologies, international collaborations like the Human Genome Project, and seminal work by leading investigators, has increased our understanding of the importance of microbial diversity and “dysbiosis” in health and disease. Scientific interest in FMT has been paralleled by interest from the general public. The notion of “natural,” medication-free treatment options are enticing to patients. This interest has been accompanied by many questions, particularly regarding the use of FMT for other diseases that are characterized by disturbances in the microbiome.

A recently proposed use of FMT is for the treatment of inflammatory bowel disease (IBD). IBD is a chronic autoimmune gastrointestinal disorder that has been associated with disease-specific microbial signatures in the host. Several investigators have characterized specific alterations of the gut microbiota in ulcerative colitis (UC) and Crohn’s disease (CD), compared to healthy controls[2][3]. Patients with active IBD may have a relative depletion in anaerobic microbes, such as *Bacteroides vulgatus*, *Lachnospiraceae* (p: *Firmicutes*)*,* andan increase in *Proteobacteria* and *Bacillus* (p: *Firmicutes*)[4,5]. These microbial signatures of IBD have led to several hypotheses about the protective, and pathological roles of different resident intestinal bacterial species. Conte *et al*[5] have suggested that *B. vulgatus* may have a protective role against colitis, downregulating inflammation. Other studies have suggested that dysbiosis in IBD leads to decreased production of key short-chain fatty acids, such as butyric acid metabolized by *Faecalibacterium prausnitzii.* Directly, butyric acid and other short-chain fatty acids are key substrates absorbed by colonocytes, and indirectly, butyrate may inhibit inflammatory processes in the intestinal mucosa by suppressing cytokines, like interleukin-8[6,7]. These studies have attempted to define canonical “intestinal-microbial-immune axes,” supporting the hypothesis that IBD may occur secondary to an altered microbiome in a genetically, immunologically susceptible host[4,8]. This constant host-microbial cross-talk may thus be altered by the introduction of key bacterial species that are otherwise absent, or decreased as a consequence of active mucosal inflammation, in the IBD gut. While FMT would not provide targeted, species-specific inoculations, whole stool transplant would theoretically introduce a broad range of bacteria, including those that are theoretically “favorable” to the host.

Pediatric IBD, and the pediatric microbiome, have several unique features that suggest microbial-based therapies could be particularly effective. Crohn’s disease and ulcerative colitis typically have a much more aggressive course in the pediatric age group, suggesting that the pediatric IBD phenotype may have a pathophysiology that is distinct from adult-onset IBD. In pediatric IBD, the early age of onset makes the cumulative burden of medications, nutritional impairment, and surgery greater. Several standard IBD medication therapies have unique, age-specific toxicities in children. The overlap of pediatric chronic disease with critical periods of growth, bone accretion, and psychosocial development can make disease exacerbations disproportionately affect a child’s long-term outcome. The pediatric microbiome itself has key differences. The shorter latency of disease may offer a unique window to reverse an underlying state of “dysbiosis.” The pediatric microbiome may be more malleable than a fully defined adult microbiome, and the relatively immature immune system of childrenmay be more influenced by FMT[9].

Given these differences, it is important to describe the unique role of FMT in pediatric IBD. This review will briefly summarize proposed clinical applications for FMT, current literature supporting its use in adult and pediatric IBD, and the potential challenges and opportunities of FMT in the pediatric IBD population.

**HISTORY OF FECAL MICROBIAL TRANSPLANT**

The use of FMT was first described in 4th century Chinese medical literature for the treatment of food poisoning and severe diarrhea[10]. Reports from World War II described German soldiers of the Afrika Korps consuming fresh, warm camel feces for the treatment of bacterial dysentery[11]. The application of FMT has also been extrapolated to ruminant animals since the 18th century, with rumin transfaunation being used to repopulate microbial changes in ruminant animals after surgery[12].

FMT was first officially used for the treatment of gastrointestinal disease in 1958, when fecal enemas were used as an adjunct to treat *Clostridium difficile*-induced pseudomembraneous enterocolitis[13]. FMT continues to be best-described for the treatment of recurrent *C. difficile* infection, and most literature has focused on techniques and protocols to optimize its use for this indication. Several murine models have described reproducible changes in obesity, non-alcoholic fatty liver disease, primary sclerosing cholangitis, metabolic syndrome, and neuropsychiatric pathology with fecal microbial transplant[14][15]. These alternative indications have been best described in animal studies, but have offered some understanding of the dynamics of host-microbial cross-talk – both before, and after FMT.

**FMT FOR THE TREATMENT OF RECURRENT *CLOSTRIDIUM DIFFICILE* INFECTION**

In 1958, a small case series described FMT as an effective therapy for RCDI. 25 years passed before another publication described its use[16]. Currently, 3 randomized controlled trials, 2 prospective, and 27 retrospective case series have been reported, consistently demonstrating that FMT is more effective for the treatment of RCDI than antibiotics in adults. Summary data from these studies have reported between 77-100% resolution of symptoms without recurrence, depending on route of administration[17] (Table 1). A systematic review of 11 RCDI studies showed a cumulative clinical symptom resolution rate of 89.7% (245/273). The greatest clinical response was reported in patients treated *via* the lower gastrointestinal tract (colonoscopy, and/or retention enema)[18].

A 2014 retrospective review by Lee *et al*[19]assessed 94 patients treated for RCDI from 2008-2012. There was a 92% resolution in clinical symptoms in patients who received a combination of FMT and antibiotic therapy, no patients experienced another episode of *C. difficile* infection throughout their 2-year follow-up period, and there were no reported adverse effects of FMT.

In contrast, conventional *Clostridium difficile* antibiotic therapy, consisting of oral metronidazole and vancomycin, has symptom recurrence rates between 15%-25% respectively, and ≥ 50% in the elderly[20].

There have been no randomized controlled trials of FMT for pediatric RCDI. This is partly due to the significantly lower incidence of *C. difficile* colitis in the pediatric age group[21]. However, small case series have shown similar treatment success of FMT in pediatric RCDI as adults, with rates of remission between 90%-100% in children[22] (Table 2).

**FMT PREPARATION AND ADMINISTRATION TECHNIQUES**

A potential mechanism for the observed benefits of FMT in the treatment of IBD is its colonization of the recipient’s intestine with donor flora[23]. In RCDI, several studies have compared the microbiota composition pre- and post-FMT and have shown that fecal bacterial composition of the recipient was highly similar to that of the donor and was accompanied by resolution of symptoms[24,25]. In a small pilot study of FMT in adult IBD patients, previously undetected donor bacteria were detected in patients during and after FMT. However, the relative abundance of these bacteria, and persistence of these changes, was highly variable between patients and generally transient[26]. Change in clinical symptoms did not correlate with timing of when the host’s microbiome reverted back to resemble their pre-FMT state.

Given the unclear mechanism of action of FMT in IBD, the most effective method of preparation and administration of FMT continues to be investigated. In particular, the efficacy of FMT therapy using frozen samples in place of fresh fecal samples has been a topic of significant interest, both for its scientific merit, and to enhance the practicality of FMT in the clinical context. Preparation of fresh fecal matter poses significant challenges in terms of identifying appropriate donors, correlating the timing of donor sample collection and patient administration, processing samples on a case-by-case basis, short shelf-life, and repeat screening of donors, thereby making the process unpredictable, time-consuming, costly, and limited to clinics specifically equipped for the production of FMT[27]. Several studies have compared rates of clinical resolution in RCDI patients treated with fresh versus frozen FMT, and synthetic stool substitutes and revealed no significant difference in patient improvement of symptoms or risk of adverse events. A 2012 study performed by Hamilton *et al*[28] demonstrated a 92% resolution rate in RCDI *via* fresh material in comparison to 90% resolution in the frozen preparation. Furthermore, a more recent study conducted by Lee *et al[*27] in 2016 compared response rates of RCDI patients treated with fresh versus frozen enemas, and broken down into two patient groups, those treated only with FMT (per-protocol) and those treated with concurrent antibiotics (mITT). Clinical resolution was achieved in 85.1% in fresh *vs* 83.5% in the frozen per-protocol FMT group, and 70.3% in the fresh versus 75.0% in the frozen FMT group. These findings demonstrate that frozen FMT are equally effective in treating RCDI, and further, the potential to freeze collected donor samples enables lengthy screening processes to take place prior to administration, providing additional product safety, and reducing the risks of pathogen transmission between donor and recipient[27].

In 2013, a synthetic microbial substitute[29] was described, consisting of 33 individually cultured isolates from a healthy donor using predefined ratios. The solution was administered within a 24-hour period *via* colonoscopy. Two patients with RCDI received RePOOPulate, with both resuming normal bowel habits and remaining symptom-free for 6 mo. Followup microbiome analyses demonstrated that both patients’ microbiota maintained similarity to the RePOOPulate mixture up to 6 mo after the transplant, suggesting that some of the bacterial isolates in the treatment were stably colonizing the colon, in contrast to the temporary colonization often observed with commercial probiotics[29] (Table 3)

Despite a lack of statistical significance between fresh or frozen samples, a challenge still remains: thus far, a standardized mode of stool preparation has not been determined. The principle of FMT preparation remains the same, however there are major differences in method of stool mixing and concentration of fecal matter. The study by Hamilton *et al[*29] blended 50 g of stool in a commercial blender, diluted the mixture with bacteriostatic saline to 250 mL, and passed the mixture through a series of decreasing sieves to selectively filter out undigested food particles down to 0.25 mm. In contrast, Lee *et al*[27] used 100 g of fecal sample, manually emulsified the sample with a wooden spatula and drinking water to 300 mL, and filtered the mixture by gauze. Furthermore, Lee *et al*[27] administrated a final volume of 50 mL, in comparison to Hamilton *et al[*28] administration of approximately 250 mL. These differences in protocol including method of stool blending, final concentration of fecal matter, and volume delivered may have an important influence on the therapeutic results and patient response. Further research must be conducted in order to determine the most effective, standardized mode of frozen sample preparation.

In addition to a variety of methods of FMT preparation, several methods of FMT administration have been reported, including *via* nasogastric tube (NGT), nasojejunal tube (NJT), colonoscopy, enema, and orally ingested microbial capsules. Each route bypasses, and targets different areas of the small and large bowel. Rectal enemas deliver fecal product largely to the rectum and left colon, while colonoscopic administration may coat the entire colon[30]. In contrast, orally ingested capsules, NGT, and NJT FMT delivery may preferentially affect the proximal and mid small bowel.

There are several potential drawbacks of upper gastrointestinal tract FMT administration. Bacterial metabolites (such as short chain fatty acids) may be broken down in the small intestine, before being delivered to the colonocytes where they have greater impact. Bacteria in the upper gastrointestinal tract may be partially degraded by gastric acid. These factors may underlie the greater rates of effectiveness found with lower gastrointestinal tract administration[31].

**FECAL MICROBIAL TRANSPLANT FOR PEDIATRIC INFLAMMATORY BOWEL DISEASE**

Four case series have been published for the treatment of pediatric UC and CD using FMT (TABLE 4). Protocols varied between all studies, and two main routes of administration were used: serial enemas[32], serial enemas with supplementary colonoscopic administration[33], and nasogastric tube (NGT)[34,35].

The first published study, involved five enemas administered daily to 9 UC patients, ages 7-21. Outcomes included clinical improvement from baseline using PUCAI (Pediatric Ulcerative Colitis Activity Index) scores, at one-week, and one-month post-treatment. 6/9 patients maintained clinical response at their one-month follow-up assessment[32].

In 2015, two case series of FMT for CD and UC patients were published[34][35]. A single FMT infusion was administered *via* NGT to 4 UC, and 9 CD patients. No clinical response was seen in UC through NGT administration. In contrast, remission was induced in 7/9 CD patients within 2-wk post-treatment, with 5/9 maintaining remission at week 6 and week 12[34,35].

The most recent pediatric case series from 2015 included a cohort of pediatric UC patients treated with oral 5-ASA monotherapy, who received a combination of serial FMT enemas and colonoscopic infusions. 3 patients were included; 100% went into clinical remission at week 2, sustained clinical remission at week 4, and had complete withdrawal of immunotherapy at time of publication[33]. Within the limitations of this small case series, there was a correlation between the number of FMT administrations, and the duration of remission.

The pediatric literature for FMT remains limited, and conclusions are difficult to draw off such small sample sizes. Yet these studies illustrate several key observations. Fifty percent of the failed responses in CD patients treated with NGT was attributed to patients with strictly colonic Crohn’s disease. Therefore, tailoring modes of FMT delivery to individual patients’ disease location and targeting specific “hot spots” may influence patient response rates. This is akin to the application of topical therapies (5-ASA, corticosteroid enemas) to patients with primarily colonic, and left-sided disease in ulcerative colitis. This suggests that targeting FMT based solely on disease classification may not be applicable in all instances. This may also reflect the relative degradation of microbial material from gastric acid exposure during proximal upper gastrointestinal tract delivery techniques[35]. Further studies clarifying the impact of gastric acid suppression on FMT may further delineate this.

These studies also demonstrated that UC is best treated by targeting the colon directly with direct, *per rectal* therapy. The strongest response occurred in patients with colonoscopic FMT administration, potentially as a result of inoculating a larger colonic surface area. The translation of this practice to the clinical setting is challenging in most pediatric centers where general anesthesia is required for colonoscopy. This is particularly challenging if multiple FMT administrations are required to maximize efficacy.

Lastly, these results imply that serial enemas may be required to achieve an appreciable response in IBD patients, in contrast to single FMT administrations in the treatment of RCDI. This may reflect the chronic nature of IBD, versus the acute changes that characterize secondary, infectious illnesses like *C. difficile* colitis.

Despite promising results, major drawbacks to these four studies include small sample sizes and their open label study design. Studies of clinical response demand a blinded study protocol, particularly given that many patients who enrol in FMT studies are a self-selected group, who implicitly believe in the therapeutic value of “natural” treatments. Further, inflammatory bowel disease has established linkages between clinical symptoms, mucosal disease and underlying stressors; thus, patient bias may have a significant influence on self-reported PUCAI/PCDAI (Pediatric Crohn’s Disease Activity Index) scores when measuring clinical response. In addition, it is also important to note that success of FMT for IBD reflected in the aforementioned studies may reflect a propensity for studies with positive results to be published and unreported, unsuccessful studies may exist.

Two single-center case reports have been published showing marked clinical improvement in two patients with severe colitis. A 2015 case report describes a 4-month old female presenting with an early-onset colitis with UC-like phenotype[36]. The patient was refractory to treatment with azathioprine and corticosteroids, and did not respond to further treatment with probiotics, a trial of amino-acid based formula, or infliximab. 2 serial FMT infusions with anonymous donor stool were administered *via* colonoscope, and a subsequent 5 infusions *via* nasoduodenal tube. These interventions led to clinical improvement, and complete resolution of histopathologic changes 6-months post FMT[36]. A recent, 2016 case report describes an 11-year old female with corticosteroid-dependent UC who was unresponsive to treatment with 5-aminosalicylic acid and tacrolimus[37]. An initial FMT using her father’s donor stool was performed *via* colonoscopy, and subsequent daily FMTs *via* fecal retention enema over the next 4 days, followed by 11 additional FMTs *via* retention enema every 2 to 4 wk over 10 mo. The patient has remained in clinical remission at 40 wk post final FMT, and showed complete endoscopic healing[37].

**FECAL MICROBIAL TRANSPLANT FOR ADULT INFLAMMATORY BOWEL DISEASE**

Several retrospective and prospective case series have reported their experience of FMT in adult IBD. A hundred twenty seven IBD patients (15 cohort studies, and 8 case studies) have received FMT through clinical trials. Inclusion criteria and FMT administration protocols have varied across these studies making aggregate statistical data imprecise. However, between these 15 cohort studies, the pooled estimate of patients achieving clinical response was 66.1% (95%CI: 43.7%-83.0%) (Table 5).

The strongest evidence for FMT in IBD comes from two recent randomized controlled trials (RCT) of FMT for adult UC, both published in 2015[38,39]. The studies had several protocol differences, and produced disparate results. Moayyedi *et al[*38]demonstrated higher rates of UC remission in patients receiving FMT enema versus normal saline placebo enema. 9 out of 38 UC patients achieved remission (at week 7 a Mayo score ≤ 2, endoscopic Mayo score = 0) in the FMT treatment arm, compared to 2 out of 37 patients who received placebo[38]. In contrast, Rossen *et al[*39]did not show a statistically significant benefit of FMT administered *via* NDT (nasoduodenal tube) from anonymous donors compared to the placebo arm (autologous donor sample), on either clinical or endoscopic evaluation. Seven out of 23 (30%) of the active group achieved clinical and endoscopic remission, compared with 5 out of 25 (20%) controls; this results did not achieve statistical significance. Key differences between these studies include: timing of FMT administration, choice of control group, duration of treatment and follow-up across both studies (Table 6).

Rossen *et al[*39]administered FMT *via* NDT, which primarily targets the upper gastrointestinal tract and may result in degradation of bacteria and absorption of colon-specific metabolites within the small bowel, prior to reaching the primary site of inflammation: the colon[40]. In contrast, Moayyedi *et al*[38]delivered infusions *via* rectal enemas, directly into the diseased colon. Second, Rossen *et al[*39]administered 2 enemas, versus 3 by Moayyedi *et al[*38]*.* This may suggest the necessity of administering a greater number of infusions in order to enable sufficient engraftment of donor microflora to induce a response in the recipient[40]. Finally, Moayyedi *et al*[38] allowed patients in the study to continue taking anti-TNF medications, while patients in the study by Rossen *et al[*39] *w*ere not. Moayyedi *et al[*38]observed a trend in greater response rates in patients concurrently taking immunosuppressant therapy (46%) *vs* those who were not (15%), suggesting a potential synergistic role for FMT and immunosuppressants in IBD treatment.

Until study protocols can be better matched it remains difficult to draw direct comparisons between these studies, particularly while mechanistic differences in FMT delivery remain poorly understood.

**PERCEPTIONS OF FECAL MICROBIAL TRANSPLANT**

**The perception of fecal microbial transplant as a “natural” therapy has broad appeal for many patients, particularly where medications are proposed that have rare, but significant side effect profiles. Recently, the United States Food and Drug Administration instituted expedited regulatory approval pathways for clinicians to offer fecal microbial transplant to select patients with RCDI[41]. Health Canada offers similar clinical trial pathways for RCDI patients[42]. In both settings, FMT remains available only through approved clinical trials. Other proposed indications for FMT, such as for the treatment of inflammatory bowel diseases, follow traditional regulatory approval processes, and protocols must demonstrate minimum standards of safety screening including donor and fecal sampling for fecal and blood-borne pathogens. Despite these measures, long-term risks of FMT are poorly understood, and theoretical concerns of transmissible neuropsychiatric disorders, metabolic syndrome, and infectious disease remain[15].**

**Nevertheless, public interest in FMT has boomed. Widely available resources online describe do it yourself, home-based protocols for preparing and administering FMT. Several online blogs about FMT strongly endorse its benefits[43]. A 2012 qualitative study by Kahn *et al[*44]assessed the attitudes, interests and concerns of adult patients and parents of children with ulcerative colitis. Several parents of pediatric patients compared FMT to probiotics, and described their perception of FMT as “safe and beneficial.” There were concerns raised about the safety of using anonymous donors, but this same concern was not expressed when household (parent, sibling) donors were proposed, instead. Overall, patients appeared ready to consider FMT as a potential IBD treatment and were eager for FMT to become available[44]**

**In a recent study of perceptions of FMT amongst gastroenterologists, 90% of those surveyed would consider referring a patient for FMT, but 94% shared concerns about the lack of evidence (42%), adverse effects (26%), or lack of efficacy (10%)[45].**

Until more studies are conducted using clearly defined outcomes, delivery methods, and donor screening protocols, significant public interest and relative clinical reticence are both likely to persist. However, the demand for new treatment options, for a population of patients that remains difficult to manage, will certainly keep this area of research active.

**CURRENT TRIALS**

No randomized controlled trials of FMT for IBD in pediatrics have been published thus far. There are 12 pediatric studies currently registered on Clinicaltrials.gov, with three studies using anonymous donors, and three studies having a randomized, placebo-controlled protocol (Table 7). McMaster Children’s Hospital, in Hamilton, CANADA is running the first single-blinded, randomized controlled trial using non-household, anonymized donors; this is also the first pediatric FMT trial in Canada (CinicalTrials.gov: NCT02487238). Pediatric patients with active UC, or IBD-Unclassified (IBD-U) are being recruited to receive twice-weekly frozen- thawed retention enemas, for 6 wk, with a 6-mo follow-up period. Patients are randomized 1:1 to intervention or control arms, and clinical symptoms, serum inflammatory markers, and mucosal disease is monitored throughout the 33-wk period using PUCAI scoring, standard laboratory tests and fecal calprotectin. Fecal microbiota is characterized through 16s rRNA sequencing to evaluate changes in gut bacterial composition, diversity, and similarity to donor compositions over the course of treatment and follow-up periods. This trial may be the first pediatric RCT to demonstrate the effectiveness, and durability of FMT in IBD-U and UC treatment, and to establish a robust blinded RCT protocol to support future studies elsewhere.

**CHALLENGES AND OPPORTUNITIES OF FMT**

IBD is a multi-system, chronic disease with multiple genetic, immunologic and environmental risk factors. This is in stark contrast to *Clostridium difficile* colitis, an acute infectious gastrointestinal process in an otherwise healthy host. Underlying changes that may predate clinical manifestations are found in the intestinal microbial composition of CD and UC patients, but how these changes correlate with disease activity remains unclear, and underscores the broader challenge of defining the constituents of a “healthy microbiome”[46]. These challenges also reflect limitations with current microbial sequencing techniques, and the availability of sufficient deep-sequencing technologies and bioinformatics analysis. Numerous potential opportunities exist in the field of microbial therapeutics for industry and biotechnology, but until reproducible, clinically relevant effects can be demonstrated in human studies, applications of these therapeutics will be limited.

A 2016 meta-analysis of adult and pediatric studies of FMT for UC showed that responders may show alterations of their microbiota towards donor microbiota. These changes may be accentuated in patients with more favorable outcomes, but heterogeneity in clinical response persisted, even in patients with similar microbial community structures[47,48]. The duration of these changes also varied. Over half of the 231 patients included in the meta-analysis maintained these changes for more than 2 months. Overall, successful FMT in IBD may be associated with increases in recipient bacterial diversity and richness, but notable differences, and confounders have challenged this association. Antibiotics, and other treatments commonly used in IBD can exert independent, significant alterations on the intestinal microbiome that are unrelated to inflammation, or FMT treatment effects in UC[49]. A 2015 study of 8 children receiving FMT for RCDI included 5 children with IBD. At 6 months post FMT, microbiota profiles of patients with IBD returned closer to their pre-FMT baseline composition while those patients without IBD retained similarity to FMT donor stool. This suggests the IBD microbiome may involve a dysbiosis that is more resistant to change than the microbiome of an otherwise healthy individual.

**POTENTIAL RISKS AND SIDE EFFECTS OF FMT**

The long term risks of FMT are unknown. Animal models have described transmissibility of obesity, metabolic syndrome, and possible neuropsychiatric phenotypes through FMT[14,15]. A 2014 case report described a patient who used her daughter as a fecal transplant donor for treatment of RCDI, and developed obesity (BMI change from 26 kg/m2to 33 kg/m2). The patient’s 16 year-old daughter had a BMI at the time of stool donation between 85-97% for age. This was the first reported case of obesity developing after fecal microbial transplant in a clinical setting, a finding that has been well-described in animal models[50].

A previous study conducted on RCDI noted transient abdominal cramping, diarrhea, or nausea immediately upon FMT administration and throughout the 13-wk follow-up[27]. Furthermore, increased blood in the stool, and infections of the urinary and respiratory tract were noted weeks after treatment, however these results were deemed unrelated to the therapy[27]. A review of the pediatric experience of FMT for UC described no serious adverse events, and self-limited, mild to moderate adverse events (transient vomiting, mucoid stools, and transient fevers) reported[32,51]. No directly associated infectious complications have been described in adult or pediatric FMT studies[36,52].

**CONCLUSION**

The use of FMT as a therapeutic option for IBD in adults and children is an active and emerging area of research. Well-designed, pediatric randomized controlled trials are needed, and available safety data suggests fecal transplant has low rates of mild-moderate, short-term adverse effects. The existing literature on IBD therapeutics has disproportionately focused on medication therapies. Accounting for differences in methodologies, donors, and outcomes between studies, existing studies have shown therapeutic benefit of FMT in IBD care. As patients increasingly embrace “natural” therapies, it is time we dedicate the funding and resources that have traditionally gone towards multi-center RCTs on immune modulators and explore microbial therapeutics for IBD care.

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**Table 1 Rates of clinical response after first fecal microbial transplant for recurrent *Clostridium difficile* infection by fecal microbial transplant method**

|  |  |  |
| --- | --- | --- |
| FMT Method | Resolution of symptoms | Studies / Total studies analyzed (n/N) |
| Upper gastrointestinal tract (Nasogastric/nasoduodenal/nasojejunal) tube | 77% | 7/187 |
| Enema | 78% | 5/45 |
| Colonoscopy | 90% | 11/257 |
| Upper gastrointestinal tract + Colonoscopy | 100% | 1/27 |

Adapted fromDrekonja *et al*[17] 2015. FMT: Fecal microbial transplant.

**Table 2 Published pediatric fmt studies for recurrent *Clostridium difficile* infection**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Ref | AGE (yr) | *n* | FMT route | Response rate |
| Hourigan et al[22], 2015 | 6-17 | 8 | Colonoscopy | 100% |
| Kronman et al[53], 2015 | 1-13 | 10 | NG | 90% |
| Wang et al[56], 2015 | 1 | 1 | NJ | 100% |
| Kelly et al[10], 2014 | 6-16 | 5 | Not specified | 89% |
| Pierog et al[54], 2014 | 1-21 | 6 | Colonoscopy | 100% |
| Russell et al[55], 2014 | 1-19 | 10 | NG (2); Colonoscopy (8) | 90% |
| Walia et al[57], 2014 | 1-2 | 2 | Colonoscopy | 100% |
| Rubin et al[58], 2013 | 6-8 | 2 | NG (64); EGD (7); Gastrostomy (previously placed) (4) | 50% |
| Kahn et al[44], 2012 | 1 | 1 | Colonoscopy | 100% |

Adapted from Hourigan *et al*[59], 2016.NG: Nasogastric; NJ: Nasojejunal; EGD: Esophagogastroduodenoscopy; FMT: Fecal microbial transplant.

**Table 3 Rates of resolution of recurrent** ***Clostridium difficile* infection using fresh *vs* frozen fecal microbial transplant**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Ref. | *n* Fresh | *n* Frozen | Fresh FMT resolution rate | Frozen FMT resolution rate |
| Hamilton *et al*[28], 2012 | 12 | 21 | 19/21  90.5% | 11/12  91.6% |
| Petrof *et al*[29]*,* 2013 | 1 | 1 | 1/1  100% | 1/1  100% |
| Lee *et al*[27]*,* 2016 | 87 (PP)  111 (mITT) | 91 (PP)  108 (mITT) | 74/87, 85.1% (PP)  78/111, 70.3% (mITT) | 76/91, 83.5% (PP)  81/108, 75.0% (mITT) |

PP: per-protocol (patients received ≤ 2 same-modality FMT treatments with no *Clostridium difficile* infection (CDI) antibiotics administered between treatments, and no systemic antibiotics administered throughout study period; mITT: modified intention-to-treat protocol (randomized patients; (1) received ≥ 1 same-modality FMT treatment but required antibiotics for CDI between administrations; (2) received different modality FMT treatments and did not complete follow-up period; or (3) required systemic antibiotic therapy for other infections throughout study protocol).

**Table 4 Published pediatric fecal microbial transplant studies for inflammatory bowel disease**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Ref. | AGE (yr) | *n*, Diagnosis | FMT Protocol | Clinical response criteria | Response rate (%) |
| Kunde *et al*[32]*,* 2013 | 7-21 | 9, UC | Serial enemas for 5 days | Decrease in PUCAI by > 15 points after FMT | 7/9 clinical response at 1 wk (78)  6/9 maintained response at 4 wk (67) |
| Kellermayer *et al*[33], 2015 | 14-16 | 3, UC | Serial enemas and colonoscopy over 6-12 wks | PUCAI < 35 | 3/3 endoscopic remission at 2 wk (100)  3/3 histologic remission at 2 wk (100)  3/3 clinical response at 4 wk (100) 3/3 withdrawal of all immunotherapy at 15 wk (100) |
| Suskind *et al*[34]*,* 2015 | 12-19 | 9, CD | Single FMT  *via* NGT | PCDAI < 10 | 7/9 clinical response at 2 wk (78)  5/9 maintained response at 6, and 12 wk (56) |
| Suskind *et al*[35]*,* 2015 | 13-16 | 4, UC | Single FMT  *via* NGT | PUCAI < 10 | No clinical response (0)  No laboratory benefit |

FMT: Fecal microbial transplant; PCDAI: Pediatric Crohn’s Disease Activity Index; NGT: Nasogastric tube.

**Table 5 Study characteristics and outcomes of published cohort studies of fecal microbial transplant for inflammatory bowel disease**

|  |  |  |
| --- | --- | --- |
| Ref. | Clinical outcome | FOLLOW-UP |
| Wang et al[60], 2014 | Clinical remission (1/2: 1 mo, 3 mo);  Clinical response (2/2: 1 wk) | 3 mo |
| Kump et al[48], 2013 | Clinical remission (0/6: 90 d);  Clinical response (6/6: 2 wk; 4/6: stool frequency increased: 30 d; 2/6 sustained improvement: 90 d); Total colectomy (1/6), Total proctocolectomy (2/6) | 3 mo |
| Wei et al[61], 2015 | Mayo score: decreased from 5.80 ± 1.87 to 1.50 ± 1.35 (*P* < 0.01) | 1 mo |
| Karolewska-Bochenek et al[62], 2015 | Clinical improvement (PUCAI) (all patients)  Clinical remission (none) | 1 mo |
| Angelberger et al[26], 2013 | Clinical remission (0/5:12 wk);  Clinical response (1/5: 12 wk);  Further deterioration (2/5: 4 wk) | 3 mo |
| Scaldaferri et al[63], 2015 | Clinical remission (2/8: 2 wk; 2/8: 6 wk; 3/8: 12 wk);  Clinical response (2/8: 2 wk; 4/8: 6 wk; 4/8: 12 wk);  Endoscopic response (2/6) | 3 mo |
| Ren et al[64], 2015 | Mayo score: 11 patients achieved reduction of score | 1-7 mo |
| Cui et al[49], 2015 | Clinical improvement and steroid-free remission: 8/14;  Long-term remission: 4/14 | 3-18 mo |
| Damman et al[65], 2015 | Clinical remission (1/6: 4w; 0/6: 3m);  Worsening symptoms (6/6: 3m);  Histology score improvement (5/6: 4w) | Not reported |
| Borody et al[23], 2012 | Complete clinical remission: 42/62;  Partial response: 15/62; Failure: 5/62;  Normalization of mucosa: 8/21 | 3 mo |
| Kump et al[48], 2013 | Mayo score decrease > 3 points (5/9: 90d);  Sustained mucosal healing: 1/9;  Failure to sustain clinical improvement: 4/9 | 1 mo |
| Landy et al[66], 2013 | Clinical remission: 0/8;  Improvement in Cleveland Global Quality of Life score: 0/8 | 1 mo |

Adapted fromShi *et al*[47], 2016.

**Table 6 Study characteristics and outcomes of published randomized controlled trials of fecal microbial transplant for inflammatory bowel disease**

|  |  |  |
| --- | --- | --- |
| Group | Moayyedi *et al* (2015) | Rossen *et al* (2015) |
| n (active/placebo) | 75 (38/37) | 48 (23/25) |
| Population | Adult patients; Mild-moderate UC | Adult patients; Mild-moderate UC |
| Active Arm | 50 cc enema (8 g healthy donor stool)  Administered weekly × 6 wk | 500 cc nasoduodenal infusion (120g healthy donor stool)  Administered at week 0, 3 |
| Control Arm | Normal saline | Autologous FMT (patient’s stool) |
| Inclusion of Patients on Biologics | Yes, stable doses ≥ 12 wk | No |
| Primary Outcome | Clinical remission (partial Mayo endoscopic score < 3 and Mayo endo score = 0) at week 7  Clinical response (reduction in full Mayo score ≥ 3) | Remission (SCCAI ≤ 2 + ≥ 1pt reduction in Mayo endoscopic score) at week 12 |
| Results | 9/38 (24%) treated with FMT *vs* 2/37 (5%) controls (*P* = 0.03) | 7/23 (30%) treated with FMT *vs* 5/25 (20%) controls (*P* = 0.51) |

Adapted from Grinspan *et al*[40] 2015. SCCAI: Simplified Clinical Colitis Activity Index.

**Table 7 Clinical trials of fecal microbial transplant for pediatric inflammatory bowel disease (registered through clinicaltrials.gov)**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Location | Trial  number | Diagnosis | Age (yr) | Donor | FMT route | Interven-tion | Protocol |
| Hamilton,  Canada | NCT02487238 | UC | 6-17 | Anonymous | Enema | FMT, Saline  Randomized Single Blinded | Retention enema; 2x weekly x 6 wk; 33-wk follow up |
| California, United States | NCT02291523 | UC | 7-21 | Accepting volunteers | Colonoscopic | FMT, Saline  Randomized Double Blinded | Patients on high-dose 5-ASA; 1 × colonoscopic administration; 12-month follow up |
| Chongqing, China | NCT02335281 | UC/CD | 16-70 | *Not specified* | Nasojejunal | FMT, Mesalazine  Randomized Single Blinded | Single nasojejunal administration; 1-year follow up |
| Texas, United States | NCT01947101 | UC | 12-20 | Anonymous | Colonoscopic / Enema | FMT Open Label | Colonoscopic administration for first treatment; subsequent periodic treatments over 1-year with enema administration |
| Pennsylvania, United States | NCT02108821 | UC/CD | 2-22 | Family  member | Colonoscopic | FMT  Open Label | Fresh stool sample; 1 ×, 1-h duration; 6-mo follow up |
| Michigan, United States | NCT01560819 | UC/CD | 7-21 | Family  Member | Enema | FMT Open Label | 1-hour retention enema; daily × 5 d; 6-mo follow up |
| Jerusalem, Israel;  Toronto, Canada; Helsinki, Finland;  Napoli, Italy;  Rome, Italy;  Krakow, Poland;  Malaga, Spain | NCT02033408 | UC/CD | 2-75 | *Not specified* | *Not specified* | FMT  Open Label | Secondary treatment for antibiotic, corticosteroid failures; 3-year follow up |
| Michigan, United States | NCT01560819 | UC/CD | 7-21 | Family member/ Chosen by family | Enema | FMT  Open Label | Retention enema; Administered daily × 5 d; 6-mo follow up |
| Turku, Finland | NCT01961492 | UC | 1-75 | Anonymous | Colonoscopic | FMT  Open Label | Single colonoscopic administration; 1-year follow up |
| Jiangsu, China  Shaanxi, China | NCT01793831 | UC/CD | 10-70 | *Not specified* | Nasogastric | FMT  Open Label | Single nasogastric administration;12-mo follow up |
| Jiangsu, China  Shaanxi, China | NCT01790061 | UC | 10-70 | *Not specified* | Duodenal (gastroscopic) | FMT  Open Label | 1-mo follow up  Fresh, or frozen FMT administered *via* gastroscope  No prior biologic, immunomodulatory, corticosteroid therapy |
| Jiangsu, China | NCT02560727 | UC | 10-70 | *Not specified* | Colonoscopic | *Not specified* | 12-mo follow up  No prior biologic, immunomodulatory, corticosteroid therapy |

UC: Ulcerative colitis; Crohn’s disease.