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MINIREVIEWS

Fecal microbial transplant for the treatment of pediatric inflammatory bowel disease

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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 27 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; Crohn's disease; Ulcerative colitis

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* (*C. 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 findings from multicenter cohort studies, have 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*), and an 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 children may 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

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

FMT method	Resolution of symptoms	Studies/total patients analyzed
Upper gastrointestinal tract (Nasogastric/nasoduodenal/ nasojejunal) tube	77%	7/187
Enema	86%	6/264
Colonoscopy	90%	11/257
Upper gastrointestinal tract + colonoscopy	100%	1/27

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

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 rumen 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 *C. difficile*-induced pseudomembranous 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, 4 prospective case series, 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].

Table 2 Published pediatric fecal microbial transplant 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*[55], 2015	6-17	10	NG	90%
Wang *et al*[58], 2015	1	1	NJ	100%
Kelly *et al*[10], 2014	6-16	5	Not specified	89% (whole series)
Pierog *et al*[56], 2014	1-21	6	Colonoscopy	100%
Russell *et al*[57], 2014	1-21	10	NG (2); Colonoscopy (8)	90%
Walia *et al*[59], 2014	1-2	2	Colonoscopy	100%
Rubin *et al*[60], 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*[61], 2016. NG: Nasogastric; NJ: Nasojejunal; EGD: Esophagogastroduodenoscopy; FMT: Fecal microbial transplant.

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 *C. 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 89%-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].

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

Ref.	Fresh, *n*	Frozen, *n*	Fresh FMT resolution rate	Frozen/prepared FMT resolution rate
Hamilton *et al*[28], 2012	12	21	19/21	11/12
			90.5%	91.6%
Petrof *et al*[29], 2013	1	2	N/A	100%
			100%	100%
Lee *et al*[27], 2016	87 (PP)	91 (PP)	74/87, 85.1% (PP)	76/91, 83.5% (PP)
	111 (mITT)	108 (mITT)	78/111, 70.3% (mITT)	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).

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 preparation of FMT product[27]. Several studies have compared rates of clinical resolution in RCDI patients treated with fresh *vs* 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. A more recent study conducted by Lee *et al*[27] in 2016 compared response rates of RCDI patients treated with fresh *vs* frozen enemas, and broken down into two patient groups, those treated only with FMT (per-protocol) and those treated with concurrent antibiotics (modified intention-to-treat). 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 *vs* 75.0% in the frozen modified intention-to-treat 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. This may enhance FMT product standardization, and further reduce the risks of pathogen transmission between donor and recipient[27].

In 2013, a synthetic microbial microbial substitute described, consisting of 33 individually cultured isolates from a healthy donor using predefined ratios[29]. The solution was administered within a 24-h 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*[28] 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

Table 4 Published pediatric fecal microbial transplant case series for inflammatory bowel disease

Ref.	AGE (yr)	Diagnosis, *n*	FMT protocol	Clinical response criteria	Response rate (%)
Kunde *et al*[32], 2013	7-21	9, UC	Serial enemas for 5 d	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 wk	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.

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 three 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 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 studies suggest that serial treatment may be required to achieve an appreciable response in IBD patients, in contrast to single, or short-course, FMT administrations in the treatment of RCDI. This may

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

Ref.	Clinical outcome	Follow-up
Wang *et al*[62], 2014	Clinical remission (1/2: 1 mo, 3 mo); Clinical response (2/2: 1 wk)	3 mo
Kump *et al*[49], 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*[63], 2015	Mayo score: decreased from 5.80 ± 1.87 to 1.50 ± 1.35 ($P < 0.01$)	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*[64], 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*[65], 2015	Mayo score: 11 patients achieved reduction of score	1-7 mo
Cui *et al*[50], 2015	Clinical improvement and steroid-free remission: 8/14; Long-term remission: 4/14	3-18 mo
Damman *et al*[66], 2015	Clinical remission (1/6: 4 wk; 0/6: 3 mo); Worsening symptoms (6/6: 3 mo); Histology score improvement (5/6: 4 wk)	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*[49], 2013	Mayo score decrease > 3 points (5/9: 90 d); Sustained mucosal healing: 1/9; Failure to sustain clinical improvement: 4/9	1 mo
Landy *et al*[67], 2013	Clinical remission: 0/8; Improvement in Cleveland Global Quality of Life score: 0/8	1 mo

Adapted from Shi *et al*[48], 2016.

reflect the chronic nature of IBD, *vs* the acute changes that characterize secondary, infectious illnesses like *C. difficile* colitis.

Despite promising results, major drawbacks to these four pediatric 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 already believe in the therapeutic value of "natural" treatments. Further, inflammatory bowel disease has well-described associations between clinical symptoms, mucosal disease activity 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 pediatric case reports have been recently 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-mo 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 d, 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%

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 mL enema (8 g healthy donor stool) Administered weekly × 6 wk	500 mL nasoduodenal infusion (120 g 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.

(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 *vs* normal saline placebo enema. Nine 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 2/37 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 treatment arm achieved clinical and endoscopic remission, compared with 5/25 (20%) of the placebo arm; this 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 colon[40]. In contrast, Moayyedi *et al*[38] delivered infusions *via* rectal enemas, directly targeting the diseased colon. Second, Rossen *et al*[39] administered 2 enemas, *vs* 3 by Moayyedi *et al*[38]. This may suggest the necessity of administering a greater number of infusions in order to enable sufficient concentration of donor stool 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] were not. Moayyedi *et al*[38] observed a trend in greater response rates in patients concurrently taking immunosuppressant therapy (46% *vs* 15%), suggesting a potential synergistic role for FMT and immunosuppressant therapy 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*[44,45] 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,

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; 2 × weekly × 6 wk; 33-wk follow up
California, United States	NCT02291523	UC	7-2	Accepting volunteers	Colonoscopic	FMT, Saline Randomized Double Blinded	Patients on high-dose 5-ASA; 1 × colonoscopic administration; 12-mo follow up
Chongqing, China	NCT02335281	UC/CD	16-70	Not specified	Nasojejunal	FMT, Mesalazine Randomized Single Blinded	Single nasojejunal administration; 1-yr follow up
Texas, United States	NCT01947101	UC	12-20	Anonymous	Colonoscopic /Enema	FMT	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	Open Label FMT	Fresh stool sample; 1 ×, 1-h duration; 6-mo follow up
Michigan, United States	NCT01560819	UC/CD	7-21	Family member	Enema	Open Label FMT	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	Open Label FMT Open Label	Secondary treatment for antibiotic, corticosteroid failures; 3-yr 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-yr 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; CD: Crohn's disease.

patients appeared ready to consider FMT as a potential IBD treatment and were eager for FMT to become available[45].

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%)[46].

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 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 normal-saline placebo 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 and metagenomic profiling to evaluate changes in composition, diversity,

function and similarity to donor stool 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 *C. 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"[47]. 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[48,49]. The duration of these changes also varied. Approximately half of the 231 patients included in the meta-analysis maintained these changes for more than 2 mo. 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[50]. A 2015 study of 8 children receiving FMT for RCDI included 5 children with IBD. At 6 mo 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[22].

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/m^2 to 33 kg/m^2). 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[51,52].

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[32,53]. No directly associated infectious complications have been described in adult or pediatric FMT studies[36,54].

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.

REFERENCES

1 **Khoruts A**, Sadowsky MJ. Understanding the mechanisms of faecal microbiota transplantation. *Nat Rev Gastroenterol Hepatol* 2016; **13**: 508-516 [PMID: 27329806 DOI: 10.1038/nrgastro.2016.98]

2 **Haberman Y**, Tickle TL, Dexheimer PJ, Kim MO, Tang D, Karns R, Baldassano RN, Noe JD, Rosh J, Markowitz J, Heyman MB, Griffiths AM, Crandall WV, Mack DR, Baker SS, Huttenhower C, Keljo DJ, Hyams JS, Kugathasan S, Walters TD, Aronow B, Xavier RJ, Gevers D, Denson LA. Pediatric Crohn disease patients exhibit specific ileal transcriptome and microbiome signature. *J Clin Invest* 2014; **124**: 3617-3633 [PMID: 25003194 DOI: 10.1172/JCI75436]

3 **Gevers D**, Kugathasan S, Denson LA, Vázquez-Baeza Y, Van Treuren W, Ren B, Schwager E, Knights D, Song SJ, Yassour

M, Morgan XC, Kostic AD, Luo C, González A, McDonald D, Haberman Y, Walters T, Baker S, Rosh J, Stephens M, Heyman M, Markowitz J, Baldassano R, Griffiths A, Sylvester F, Mack D, Kim S, Crandall W, Hyams J, Huttenhower C, Knight R, Xavier RJ. The treatment-naive microbiome in new-onset Crohn's disease. *Cell Host Microbe* 2014; **15**: 382-392 [PMID: 24629344 DOI: 10.1016/j.chom.2014.02.005]

4 **Maslowski KM**, Vieira AT, Ng A, Kranich J, Sierro F, Yu D, Schilter HC, Rolph MS, Mackay F, Artis D, Xavier RJ, Teixeira MM, Mackay CR. Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. *Nature* 2009; **461**: 1282-1286 [PMID: 19865172 DOI: 10.1038/nature08530]

5 **Conte MP**, Schippa S, Zamboni I, Penta M, Chiarini F, Seganti L, Osborn J, Falconieri P, Borrelli O, Cucchiara S. Gut-associated bacterial microbiota in paediatric patients with inflammatory bowel disease. *Gut* 2006; **55**: 1760-1767 [PMID: 16648155 DOI: 10.1136/gut.2005.078824]

6 **Machiels K**, Joossens M, Sabino J, De Preter V, Arijs I, Eeckhaut V, Ballet V, Claes K, Van Immerseel F, Verbeke K, Ferrante M, Verhaegen J, Rutgeerts P, Vermeire S. A decrease of the butyrate-producing species Roseburia hominis and Faecalibacterium prausnitzii defines dysbiosis in patients with ulcerative colitis. *Gut* 2014; **63**: 1275-1283 [PMID: 24021287 DOI: 10.1136/gutjnl-2013-304833]

7 **Tedelind S**, Westberg F, Kjerrulf M, Vidal A. Anti-inflammatory properties of the short-chain fatty acids acetate and propionate: a study with relevance to inflammatory bowel disease. *World J Gastroenterol* 2007; **13**: 2826-2832 [PMID: 17569118 DOI: 10.3748/wjg.v13.i20.2826]

8 **Sekirov I**, Russell SL, Antunes LC, Finlay BB. Gut microbiota in health and disease. *Physiol Rev* 2010; **90**: 859-904 [PMID: 20664075 DOI: 10.1152/physrev.00045.2009]

9 **Putignani L**, Del Chierico F, Petrucca A, Vernocchi P, Dallapiccola B. The human gut microbiota: a dynamic interplay with the host from birth to senescence settled during childhood. *Pediatr Res* 2014; **76**: 2-10 [PMID: 24732106 DOI: 10.1038/pr.2014.49]

10 **Kelly CR**, Kahn S, Kashyap P, Laine L, Rubin D, Atreja A, Moore T, Wu G. Update on Fecal Microbiota Transplantation 2015: Indications, Methodologies, Mechanisms, and Outlook. *Gastroenterology* 2015; **149**: 223-237 [PMID: 25982290 DOI: 10.1053/j.gastro.2015.05.008]

11 **Lewin RA**. More on Merde. *Perspect Biol Med* 2001; **44**: 594-607 [PMID: 11600805 DOI: 10.1353/pbm.2001.0067]

12 **DePeters EJ**, George LW. Rumen transfaunation. *Immunol Lett* 2014; **162**: 69-76 [PMID: 25262872 DOI: 10.1016/j.imlet.2014.05009]

13 **Eiseman B**, Silen W, Bascom GS, KAUVAR AJ. Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis. *Surgery* 1958; **44**: 854-859 [PMID: 13592638]

14 **Konturek PC**, Haziri D, Brzozowski T, Hess T, Heyman S, Kwiecien S, Konturek SJ, Koziel J. Emerging role of fecal microbiota therapy in the treatment of gastrointestinal and extra-gastrointestinal diseases. *J Physiol Pharmacol* 2015; **66**: 483-491 [PMID: 26348073]

15 **Weil AA**, Hohmann EL. Fecal microbiota transplant: benefits and risks. *Open Forum Infect Dis* 2015; **2**: ofv005 [PMID: 26034756 DOI: 10.1093/ofid/ofv005]

16 **Schwan A**, Sjölin S, Trottestam U, Aronsson B. Relapsing Clostridium difficile enterocolitis cured by rectal infusion of normal faeces. *Scand J Infect Dis* 1984; **16**: 211-215 [PMID: 6740251 DOI: 10.1016/S0140-6736(83)90753-5]

17 **Drekonja D**, Reich J, Gezahegn S, Greer N, Shaukat A, MacDonald R, Rutks I, Wilt TJ. Fecal Microbiota Transplantation for Clostridium difficile Infection: A Systematic Review. *Ann Intern Med* 2015; **162**: 630-638 [PMID: 25938992 DOI: 10.7326/M14-2693]

18 **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**: 500-508 [PMID: 23511459 DOI: 10.1038/ajg.2013.59]

19 **Lee CH**, Belanger JE, Kassam Z, Smieja M, Higgins D, Broukhanski G, Kim PT. The outcome and long-term follow-up of 94 patients with recurrent and refractory Clostridium difficile infection using single to multiple fecal microbiota transplantation via retention enema. *Eur J Clin Microbiol Infect Dis* 2014; **33**: 1425-1428 [PMID: 24627239 DOI: 10.1007/s10096-014-2088-9]

20 **Kee VR**. Clostridium difficile infection in older adults: a review and update on its management. *Am J Geriatr Pharmacother* 2012; **10**: 14-24 [PMID: 22260856 DOI: 10.1016/j.amjopharm.2011.12.004]

21 **Kim J**, Smathers SA, Prasad P, Leckerman KH, Coffin S, Zaoutis T. Epidemiological features of Clostridium difficile-associated disease among inpatients at children's hospitals in the United States, 2001-2006. *Pediatrics* 2008; **122**: 1266-1270 [PMID: 19047244 DOI: 10.1542/peds.2008-0469]

22 **Hourigan SK**, Chen LA, Grigoryan Z, Laroche G, Weidner M, Sears CL, Oliva-Hemker M. Microbiome changes associated with sustained eradication of Clostridium difficile after single faecal microbiota transplantation in children with and without inflammatory bowel disease. *Aliment Pharmacol Ther* 2015; **42**: 741-752 [PMID: 26198180 DOI: 10.1111/apt.13326]

23 **Borody TJ**, Khoruts A. Fecal microbiota transplantation and emerging applications. *Nat Rev Gastroenterol Hepatol* 2011; **9**: 88-96 [PMID: 22183182 DOI: 10.1038/nrgastro.2011.244]

24 **Khoruts A**, Dicksved J, Jansson JK, Sadowsky MJ. Changes in the composition of the human fecal microbiome after bacteriotherapy for recurrent Clostridium difficile-associated diarrhea. *J Clin Gastroenterol* 2010; **44**: 354-360 [PMID: 20048681 DOI: 10.1097/MCG.0b013e3181c87e02]

25 **Girotra M**, Garg S, Anand R, Song Y, Dutta SK. Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection in the Elderly: Long-Term Outcomes and Microbiota Changes. *Dig Dis Sci* 2016; **61**: 3007-3015 [PMID: 27447476 DOI: 10.1007/s10620-016-4229-8]

26 **Angelberger S**, Reinisch W, Makristathis A, Lichtenberger C, Dejaco C, Papay P, Novacek G, Trauner M, Loy A, Berry D. Temporal bacterial community dynamics vary among ulcerative colitis patients after fecal microbiota transplantation. *Am J Gastroenterol* 2013; **108**: 1620-1630 [PMID: 24060759 DOI: 10.1038/ajg.2013.257]

27 **Lee CH**, Steiner T, Petrof EO, Smieja M, Roscoe D, Nematallah A, Weese JS, Collins S, Moayyedi P, Crowther M, Ropeleski MJ, Jayaratne P, Higgins D, Li Y, Rau NV, Kim PT. Frozen vs Fresh Fecal Microbiota Transplantation and Clinical Resolution of Diarrhea in Patients With Recurrent Clostridium difficile Infection: A Randomized Clinical Trial. *JAMA* 2016; **315**: 142-149 [PMID: 26757463 DOI: 10.1001/jama.2015.18098]

28 **Hamilton MJ**, Weingarden AR, Sadowsky MJ, Khoruts A. Standardized frozen preparation for transplantation of fecal microbiota for recurrent Clostridium difficile infection. *Am J Gastroenterol* 2012; **107**: 761-767 [PMID: 22290405 DOI: 10.1038/ajg.2011.482]

29 **Petrof EO**, Gloor GB, Vanner SJ, Weese SJ, Carter D, Daigneault MC, Brown EM, Schroeter K, Allen-Vercoe E. Stool substitute transplant therapy for the eradication of Clostridium difficile infection: 'RePOOPulating' the gut. *Microbiome* 2013; **1**: 3 [PMID: 24467987 DOI: 10.1186/2049-2618-1-3]

30 **Michail S**, Klonoff A. Review of fecal transplant in childhood gastrointestinal disorders. *Ann Pediatr Child Health* 2015; **3**: 1043

31 **Furuya-Kanamori L**, Doi SA, Paterson DL, Helms SK, Yakob L, McKenzie SJ, Garborg K, Emanuelsson F, Stollman N, Kronman MP, Clark J, Huber CA, Riley TV, Clements AC. Upper Versus Lower Gastrointestinal Delivery for Transplantation of Fecal Microbiota in Recurrent or Refractory Clostridium difficile Infection: A Collaborative Analysis of Individual Patient Data From 14 Studies. *J Clin Gastroenterol* 2016; Epub ahead of print [PMID: 26974758 DOI: 10.1097/MCG.0000000000000511]

32 **Kunde S**, Pham A, Bonczyk S, Crumb T, Duba M, Conrad H, Cloney D, Kugathasan S. Safety, tolerability, and clinical response after fecal transplantation in children and young adults with

ulcerative colitis. *J Pediatr Gastroenterol Nutr* 2013; **56**: 597-601 [PMID: 23542823 DOI: 10.1097/MPG.0b013e318292fa0d]
33 **Kellermayer R**, Nagy-Szakal D, Harris RA, Luna RA, Pitashny M, Schady D, Mir SA, Lopez ME, Gilger MA, Belmont J, Hollister EB, Versalovic J. Serial fecal microbiota transplantation alters mucosal gene expression in pediatric ulcerative colitis. *Am J Gastroenterol* 2015; **110**: 604-606 [PMID: 25853207 DOI: 10.1038/ajg.2015.19]
34 **Suskind DL**, Brittnacher MJ, Wahbeh G, Shaffer ML, Hayden HS, Qin X, Singh N, Damman CJ, Hager KR, Nielson H, Miller SI. Fecal microbial transplant effect on clinical outcomes and fecal microbiome in active Crohn's disease. *Inflamm Bowel Dis* 2015; **21**: 556-563 [PMID: 25647155 DOI: 10.1097/MB.0000000000000307]
35 **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**: 27-29 [PMID: 25162366 DOI: 10.1097/MPG.0000000000000544]
36 **Vandenplas Y**, Veereman G, van der Werff Ten Bosch J, Goossens A, Pierard D, Samsom JN, Escher JC. Fecal Microbial Transplantation in Early-Onset Colitis: Caution Advised. *J Pediatr Gastroenterol Nutr* 2015; **61**: e12-e14 [PMID: 24399213 DOI: 10.1097/MPG.0000000000000281]
37 **Shimizu H**, Arai K, Abe J, Nakabayashi K, Yoshioka T, Hosoi K, Kuroda M. Repeated fecal microbiota transplantation in a child with ulcerative colitis. *Pediatr Int* 2016; **58**: 781-785 [PMID: 27324973 DOI: 10.1111/ped.12967]
38 **Moayyedi P**, Surette MG, Kim PT, Libertucci J, Wolfe M, Onischi C, Armstrong D, Marshall JK, Kassam Z, Reinisch W, Lee CH. Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial. *Gastroenterology* 2015; **149**: 102-109.e6 [PMID: 25857665 DOI: 10.1053/j.gastro.2015.04.001]
39 **Rossen NG**, Fuentes S, van der Spek MJ, Tijssen JG, Hartman JH, Duflou A, Löwenberg M, van den Brink GR, Mathus-Vliegen EM, de Vos WM, Zoetendal EG, D'Haens GR, Ponsioen CY. Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis. *Gastroenterology* 2015; **149**: 110-118.e4 [PMID: 25836986 DOI: 10.1053/j.gastro.2015.03.045]
40 **Grinspan AM**, Kelly CR. Fecal Microbiota Transplantation for Ulcerative Colitis: Not Just Yet. *Gastroenterology* 2015; **149**: 15-18 [PMID: 26021232 DOI: 10.1053/j.gastro.2015.05.030]
41 Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat Clostridium Difficile Infection Not Responsive to Standard Therapies; Draft Guidance for Industry; Availability. Federal Register: The Daily Journal of the United States Government. National Archives and Records Administration, 2016
42 Guidance Document: Fecal microbiota therapy used in the treatment of Clostridium difficile infection not responsive to conventional therapies. Health Canada: Biologics, Radiopharmaceuticals and Genetic Therapies. Health Canada, 2015-2016
43 Power of Poop. Accessed 2016 Jul 31. Available from: URL: http://thepowerofpoop.com
44 **Kahn SA**, Young S, Rubin DT. Colonoscopic fecal microbiota transplant for recurrent Clostridium difficile infection in a child. *Am J Gastroenterol* 2012; **107**: 1930-1931 [PMID: 23211865 DOI: 10.1038/ajg.2012.351]
45 **Kahn S**, Vachon A, Rodriquez D, Goeppinger SR, Surma B, Marks J, Rubin DT. Patient perceptions of fecal transplantation for ulcerative colitis. *Inflamm Bowel Dis* 2013; **19**: 1506-1513 [PMID: 23624888 DOI: 10.1097/MIB.0b013e318281f520]
46 **Paramsothy S**, Borody TJ, Lin E, Finlayson S, Walsh AJ, Samuel D, van den Bogaerde J, Leong RW, Connor S, Ng W, Mitchell HM, Kaakoush N, Kamm MA. Donor Recruitment for Fecal Microbiota Transplantation. *Inflamm Bowel Dis* 2015; **21**: 1600-1606 [PMID: 26070003 DOI: 10.1097/MID.0000000000000405]
47 **Manichanh C**, Borruel N, Casellas F, Guarner F. The gut microbiota in IBD. *Nat Rev Gastroenterol Hepatol* 2012; **9**: 599-608 [PMID: 22907164 DOI: 10.1038/nrgastro.2012.152]
48 **Shi Y**, Dong Y, Huang W, Zhu D, Mao H, Su P. Fecal Microbiota Transplantation for Ulcerative Colitis: A Systematic Review and Meta-Analysis. *PLoS One* 2016; **11**: e0157259 [PMID: 27295210 DOI: 10.1371/journal.pone.0157259]
49 **Kump PK**, Gröchenig HP, Lackner S, Trajanoski S, Reicht G, Hoffmann KM, Deutschmann A, Wenzl HH, Petritsch W, Krejs GJ, Gorkiewicz G, Högenauer C. Alteration of intestinal dysbiosis by fecal microbiota transplantation does not induce remission in patients with chronic active ulcerative colitis. *Inflamm Bowel Dis* 2013; **19**: 2155-2165 [PMID: 23899544 DOI: 10.1097/MIB.0b013e31829ea325]
50 **Cui B**, Li P, Xu L, Zhao Y, Wang H, Peng Z, Xu H, Xiang J, He Z, Zhang T, Nie Y, Wu K, Fan D, Ji G, Zhang F. Step-up fecal microbiota transplantation strategy: a pilot study for steroid-dependent ulcerative colitis. *J Transl Med* 2015; **13**: 298 [PMID: 26363929 DOI: 10.1186/s12967-015-0646-2]
51 **Alang N**, Kelly CR. Weight gain after fecal microbial transplantation. *Open Forum Infect Dis* 2015; **2**: ofv004 [PMID: 26034755 DOI: 10.1093/ofid/ofv004]
52 **Ridaura VK**, Faith JJ, Rey FE, Cheng J, Duncan AE, Kau AL, Griffin NW, Lombard V, Henrissat B, Bain JR, Muehlbauer MJ, Ilkayeva O, Semenkovich CF, Funai K, Hayashi DK, Lyle BJ, Martini MC, Ursell LK, Clemente JC, Van Treuren W, Walters WA, Knight R, Newgard CB, Heath AC, Gordon JI. Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science* 2013; **341**: 1241214 [PMID: 24009397 DOI: 10.1126/science.1241214]
53 **Colman RJ**, Rubin DT. Fecal microbiota transplantation as therapy for inflammatory bowel disease: a systematic review and meta-analysis. *J Crohns Colitis* 2014; **8**: 1569-1581 [PMID: 25223604 DOI: 10.1016/j.crohns.2014.08.006]
54 **Brandt LJ**, Aroniadis OC, Mellow M, Kanatzar A, Kelly C, Park T, Stollman N, Rohlke F, Surawicz C. Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent Clostridium difficile infection. *Am J Gastroenterol* 2012; **107**: 1079-1087 [PMID: 22450732 DOI: 10.1038/ajg.2012.60]
55 **Kronman MP**, Nielson HJ, Adler AL, Giefer MJ, Wahbeh G, Singh N, Zerr DM, Suskind DL. Fecal microbiota transplantation via nasogastric tube for recurrent clostridium difficile infection in pediatric patients. *J Pediatr Gastroenterol Nutr* 2015; **60**: 23-26 [PMID: 25162365 DOI: 10.1097/MPG.0000000000000545]
56 **Pierog A**, Mencin A, Reilly NR. Fecal microbiota transplantation in children with recurrent Clostridium difficile infection. *Pediatr Infect Dis J* 2014; **33**: 1198-1200 [PMID: 24853539 DOI: 10.1097/INF.0000000000000419]
57 **Russell GH**, Kaplan JL, Youngster I, Baril-Dore M, Schindelar L, Hohmann E, Winter HS. Fecal transplant for recurrent Clostridium difficile infection in children with and without inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2014; **58**: 588-592 [PMID: 24792627 DOI: 10.1097/MPG.0000000000000283]
58 **Wang J**, Xiao Y, Lin K, Song F, Ge T, Zhang T. Pediatric severe pseudomembranous enteritis treated with fecal microbiota transplantation in a 13-month-old infant. *Biomed Rep* 2015; **3**: 173-175 [PMID: 25798243 DOI: 10.3892/br.2014.403]
59 **Walia R**, Garg S, Song Y, Girotra M, Cuffari C, Fricke WF, Dutta SK. 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**: 565-570 [PMID: 25023578 DOI: 10.1097/MPG.0000000000000495]
60 **Rubin TA**, Gessert CE, Aas J, Bakken JS. Fecal microbiome transplantation for recurrent Clostridium difficile infection: report on a case series. *Anaerobe* 2013; **19**: 22-26 [PMID: 23182843 DOI: 10.1016/j.anaerobe.2012.11.004]
61 **Hourigan SK**, Oliva-Hemker M. Fecal microbiota transplantation in children: a brief review. *Pediatr Res* 2016; **80**: 2-6 [PMID: 26982451 DOI: 10.1038/pr.2016.48]
62 **Wang M**, Wu KY, Ding YB, Wu J, Xiao KM, Li GQ, Wang NZ, Deng B. Preliminary clinical application of treating refractory inflammation bowel disease with fecal microbiota transplantation.

Zhonghua Xiaohua Neijiang Zazhi 2014; **31** [DOI: 10.3760/cma.j.issn.1007-5232.2014.03.011]

63 **Wei Y**, Zhu W, Gong J, Guo D, Gu L, Li N, Li J. Fecal Microbiota Transplantation Improves the Quality of Life in Patients with Inflammatory Bowel Disease. *Gastroenterol Res Pract* 2015; **2015**: 517597 [PMID: 26146498 DOI: 10.1155/2015/517597]

64 **Scaldaferri F**, Pecere S, Bruno G, Ianiro G, Laterza L, Gerardi V, Riccardo L Lopetuso, Schiavoni E, Bibbò S, Sterbini FP, Sanguinetti M, Masucci L, Gasbarrini A, Cammarota G. Tu1363 An Open-Label, Pilot Study to Assess Feasibility and Safety of Fecal Microbiota Transplantation in Patients With Mild-Moderate Ulcerative Colitis: Preliminary Results. *Gastroenterol* 2015: **148**: S-870 [DOI: 10.1016/S0016-5085(15)32950-4]

65 **Ren R**, Sun G, Yang Y, Peng L, Zhang X, Wang S, Dou Y, Zhang X, Wang Z, Bo X, Liu Q, Li W, Fan N, Ma X. [A pilot study of treating ulcerative colitis with fecal microbiota transplantation]. *Zhonghua Nei Ke Za Zhi* 2015; **54**: 411-415 [PMID: 26080819]

66 **Damman CJ**, Brittnacher MJ, Westerhoff M, Hayden HS, Radey M, Hager KR, Marquis SR, Miller SI, Zisman TL. Low Level Engraftment and Improvement following a Single Colonoscopic Administration of Fecal Microbiota to Patients with Ulcerative Colitis. *PLoS One* 2015; **10**: e0133925 [PMID: 26288277 DOI: 10.1371/journal.pone.0133925]

67 **Landy J**, Al-Hassi HO, Mann ER, Peake ST, McLaughlin SD, Perry-Woodford ZL, Ciclitira PJ, Nicholls J, Clark SK, Knight SC, Hart1 AL. A prospective controlled pilot study of fecal microbiota transplantation for chronic refractory pouchitis. *Gastroenterol* 2013; **144**: S897 [DOI: 10.1016/s0016-5085(13)63341-7]

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