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

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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[6] 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 colonicocytes, and indirectly, butyrate may inhibit inflammatory processes in the intestinal mucosa by suppressing cytokines, like interleukin-6[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[6,8]. 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
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 18\(^{\text{th}}\) 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 \textit{C. difficile}-induced pseudomembranous enterocolitis\(^{13}\). FMT continues to be best-described for the treatment of recurrent \textit{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 \textit{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 \textit{via} the lower gastrointestinal tract (colonoscopy, and/or retention enema)\(^{18}\).

A 2014 retrospective review by Lee \textit{et al}\(^{21}\) 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 \textit{C. difficile} infection throughout their 2-year follow-up period, and there were no reported adverse effects of FMT.

In contrast, conventional \textit{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 \textit{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\(^{26}\).

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**Table 1** Rates of clinical response after fecal microbial transplant for recurrent \textit{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 \textit{et al}\(^{23}\) 2015. FMT: Fecal microbial transplant.

**Table 2** Published pediatric fecal microbial transplant studies for recurrent \textit{Clostridium difficile} infection

| Ref | AGE (yr) | n | FMT route | Response rate |
|-----|----------|---|-----------|--------------|
| Hourigan \textit{et al}\(^{24}\), 2015 | 6-17 | 8 | Colonoscopy | 100% |
| Krommen \textit{et al}\(^{25}\), 2015 | 6-17 | 10 | NG | 90% |
| Wang \textit{et al}\(^{26}\), 2015 | 1 | 1 | NJ | 100% |
| Kelly \textit{et al}\(^{27}\), 2014 | 6-16 | 5 | Not specified | 89% (whole series) |
| Pierg et al\(^{28}\), 2014 | 1-21 | 6 | Colonoscopy | 100% |
| Russell \textit{et al}\(^{29}\), 2014 | 1-21 | 10 | NG (2); Colonoscopy | 90% |
| Walla et al\(^{30}\), 2014 | 1-2 | 2 | Colonoscopy | 100% |
| Rubin \textit{et al}\(^{31}\), 2013 | 6-8 | 2 | NG (64); EGD (7); Gastrostomy (previously placed) | 50% |
| Kahn \textit{et al}\(^{32}\), 2012 | 1 | 1 | Colonoscopy | 100% |

Adapted from Hourigan \textit{et al}\(^{33}\), 2016. NG: Nasogastric; NJ: Nasojejunal; EGD: Esophagogastroduodenoscopy; FMT: Fecal microbial transplant.
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\(^\text{[27]}\). 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\(^\text{[27]}\) 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\(^\text{[27]}\) 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\(^\text{[27]}\).

In 2013, a synthetic microbial microbial substitute described, consisting of 33 individually cultured isolates from a healthy donor using predefined ratios\(^\text{[29]}\). 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\(^\text{[29]}\) (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\(^\text{[27]}\) 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\(^\text{[27]}\) 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\(^\text{[27]}\) administered a final volume of 50 mL, in comparison to Hamilton et al\(^\text{[28]}\) 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 colonscopic administration may coat the entire colon\cite{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\cite{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\cite{32}, serial enemas with supplementary colonoscopic administration\cite{33}, and nasogastric tube (NGT)\cite{34,35}.

The first published study, involved five enemas administrations in the treatment of RCDI. This may be partially degraded by gastric acid. This suggests that targeting FMT in ulcerative colitis. This suggests that targeting FMT injection, 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\cite{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\cite{33}. 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

| Ref. | AGE (yr) | Diagnosis, n | FMT protocol | Clinical response criteria | Response rate (%) |
|------|----------|--------------|--------------|---------------------------|-------------------|
| Kunde et al\cite{30}, 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) |
| Kellermayer et al\cite{30}, 2015 | 14-16 | 3, UC | Serial enemas and colonoscopy over 6-12 wk | PUCAI < 35 | 6/9 maintained response at 4 wk (67) |
| Suskind et al\cite{34,35}, 2015 | 12-19 | 9, CD | Single FMT via NGT | PCDAI < 10 | 3/3 withdrawal of all immunotherapy at 15 wk (100) |
| Suskind et al\cite{34,35}, 2015 | 13-16 | 4, UC | Single FMT via NGT | PUCAI < 10 | 5/9 maintained response at 6, and 12 wk (56) |

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

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Table 4 Published pediatric fecal microbial transplant case series for inflammatory bowel disease
reflected 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. 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 nasoduodenal tube. These interventions led to clinical improvement, and complete resolution of histopathologic changes 6-mo post FMT. 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. 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.

**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%
The strongest evidence for FMT in IBD comes from two recent randomized controlled trials (RCT) of FMT for adult UC, both published in 2015. The studies had several protocol differences, and produced disparate results. Moayyedi et al. 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. In contrast, Rossen et al. 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.

Rosen et al. 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. In contrast, Moayyedi et al. delivered infusions via rectal enemas, directly targeting the diseased colon. Second, Rossen et al. administered 2 enemas, vs 3 by Moayyedi et al. 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. Finally, Moayyedi et al. allowed patients in the study to continue taking anti-TNF medications, while patients in the study by Rossen et al. were not. Moayyedi et al. 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. Health Canada offers similar clinical trial pathways for RCDI patients. 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.

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. A 2012 qualitative study by Kahn et al. 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[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 (ClinicalTrials.gov: NCT02487238). Pediatric patients with active UC, or IBD-Undifferentiated (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 RNA and metagenomic profiling to evaluate changes in composition, diversity,

| Location | Diagnosis | FMT route | Intervention | Protocol |
|----------|-----------|-----------|--------------|----------|
| Hamilton, Canada | UC | Enema | Single Blinded | Retention enema; 2 × weekly × 6 wk; 33-wk follow up |
| California, United States | UC | Colonoscopic | Double Blinded | Patients on high-dose 5-ASA; 1 × colonoscopic administration; 12-mo follow up |
| Chongqing, China | UC/CD | Nasojejunal | Single Blinded | Single nasojejunal administration; 1-yr follow up |
| Texas, United States | UC | Colonoscopic | Enema | Colonic administration for first treatment; subsequent periodic treatments over 1-year with enema administration |
| Pennsylvania, United States | UC/CD | Colonoscopic | Open Label | Fresh stool sample; 1 ×, 1-h duration; 6-mo follow up |
| Michigan, United States | UC | Not specified | Open Label | 1-hour retention enema; daily × 5 d; 6-mo follow up |
| Jerusalem, Israel; Toronto, Canada; Helsinki, Finland; Rome, Italy; Krakow, Poland; Malaga, Spain | UC/CD | Not specified | Open Label | Secondary treatment for antibiotic, corticosteroid failures; 3-yr follow up |
| Michigan, United States | UC | Family member | Enema | Retention enema; Administered daily × 5 d; 6-mo follow up |
| Turku, Finland | UC | Anonymouse | Colonoscopic | Single colonoscopic administration; 1-yr follow up |
| Jiangsu, China Shaanxi, China | UC/CD | Nasogastric | Open Label | Single nasogastric administration; 12-mo follow up |
| Jiangsu, China Shaanxi, China | UC | Duodenal | Open Label | Fresh, or frozen FMT administered via gastroscope No prior biologic, immunomodulatory, corticosteroid therapy |
| Jiangsu, China | UC | Not specified | Not specified | No prior biologic, immunomodulatory, corticosteroid therapy |

UC: Ulcerative colitis; CD: Crohn's disease.

**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 | Intervention | Protocol |
|----------|--------------|-----------|----------|-------|-----------|--------------|----------|
| Hamilton, Canada | NCT02487238 | UC | 6-17 | Anonymous | Enema | Single Blinded | Retention enema; 2 × weekly × 6 wk; 33-wk follow up |
| California, United States | NCT02291523 | UC | 7-2 | Accepting volunteers | Colonoscopic | 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 | Single Blinded | Single nasojejunal administration; 1-yr follow up |
| Texas, United States | NCT01947101 | UC | 12-20 | Anonymous | Colonoscopic | Enema | Colonic 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 | Fresh stool sample; 1 ×, 1-h duration; 6-mo follow up |
| Michigan, United States | NCT01560819 | UC/CD | 7-21 | Family member | Enema | Open Label | 1-hour retention enema; daily × 5 d; 6-mo follow up |
| Jerusalem, Israel; Toronto, Canada; Helsinki, Finland; Rome, Italy; Krakow, Poland; Malaga, Spain | NCT02033408 | UC/CD | 2-75 | Not specified | Not specified | 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 | Open Label | Retention enema; Administered daily × 5 d; 6-mo follow up |
| Turku, Finland | NCT01961492 | UC | 1-75 | Anonymous | Colonoscopic | Open Label | Single colonoscopic administration; 1-yr follow up |
| Jiangsu, China Shaanxi, China | NCT01793831 | UC/CD | 10-70 | Not specified | Nasogastric | Open Label | Single nasogastric administration; 12-mo follow up |
| Jiangsu, China Shaanxi, China | NCT01790061 | UC | 10-70 | Not specified | Duodenal | Open Label | Fresh, or frozen FMT administered via gastroscope No prior biologic, immunomodulatory, corticosteroid therapy |
| Jiangsu, China | NCT02560727 | UC | 10-70 | Not specified | Colonoscopic | Not specified | No prior biologic, immunomodulatory, corticosteroid therapy |

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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/m² to 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[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, Korns 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...
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19 Lee CH, Belanger JE, Kassam Z, Smieja M, Higgins D, Brouchanski 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. J Clin Microbiol Infect Dis 2013; 3: 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.jampharm.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, Dickesvd 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.0b013e3181c7e602]

25 Giorota 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/s12928-016-4229-8]

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, Petroff EO, Smieja M, Roscoe D, Nematallah A, Weese JS, Collins S, Moayyedi P, Crowther M, Ropeleski MJ, Jayarattne 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 Petroff 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, Klomoff A. Review of fecal transplant in childhood gastrointestinal disorders. Ann Pediatr Child Health 2015; 5: 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: 26974558 DOI: 10.1097/MCG.0000000000000511]

32 Kunde S, Pham A, Bonczyk S, Crumb T, Duba M, Conrad H, Conley D, Kugathasan S. Safety, tolerability, and clinical response after fecal transplantation in children and young adults with...
Wang AY et al. Fecal transplant in pediatric colitis

effect on clinical outcomes and fecal microbiome in active Crohn’s disease. Inflamm Bowel Dis 2013; 19: 2155-2165 [PMID: 23899544 DOI: 10.1097/MIB.0b013e31829a325]

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/s12967-015-0466-2]

Alang N, Kelly CR. Weight gain after fecal microbiota transplantation. Open Forum Infect Dis 2015; 2: ofv004 [PMID: 26043755 DOI: 10.1093/ofid/ofv004]

Ridaura VK, Faith JJ, Rey FE, Cheng J, Duncan AE, Kau AL, De Filippo C, Ley RE, Backhed F, Matarese G, Renom N, Larripa D, Versalovic J, Satsangi J, Sasseville D, Bustamante J, Kinjo K, Pignoni F, Feldman AM, Borody TJ, Lin E, Finlayson S, Walsh AJ, Samuel BS, Henrissat B, Consortium 454 GS. Gut microbiome in health and disease. Gastroenterology 2011; 140: 1767-1780 [PMID: 21290195 DOI: 10.1053/j.gastro.2011.05.059]

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

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

Power of Poop. Accessed 2016 Jul 31. Available from: URL: http://powerofpoop.com

Kahn SA, Young S, Rubin DT. Colonicoscopic 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]

Kahn S, Vachon A, Rodriguez 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: 24624885 DOI: 10.1097/MIB.0b013e318281f20]

Paramsothy S, Borody TJ, Lin E, Finlayson S, Walsh AJ, Samuel D, van den Bogaerde J, Leong RW, Connor S, Ng W, Mitchell HM, Kaakoub N, Kamm MA. Donor Recruitment for Fecal Microbiota Transplantation. Inflamm Bowel Dis 2015; 21: 1600-1606 [PMID: 26070003 DOI: 10.1097/MIB.0000000000000405]

Manichanh C, Borrel N, Casellas F, Guiller F. The gut microbiota in IBD. Nat Rev Gastroenterol Hepatol 2012; 9: 599-608 [PMID: 22907164 DOI: 10.1038/nrgastro.2012.152]

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]

Kampf PK, Grotzbach JP, Lackner S, Trajanoski S, Reichert G, Hoffmann KM, Deutschmann A, Wenzl HH, Petritsch W, Krejs GJ, Kergiciewicz H, Hofgenuer 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.0b013e31829a325]

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/s12967-015-0466-2]

Alang N, Kelly CR. Weight gain after fecal microbiota transplantation. Open Forum Infect Dis 2015; 2: ofv004 [PMID: 26043755 DOI: 10.1093/ofid/ofv004]

Ridaura VK, Faith JJ, Rey FE, Cheng J, Duncan AE, Kau AL, Griffin NW, Lombard V, Henrierrat B, Bain JR, Muellbauer MI, Ilkayeva O, Semenkovich CF, Funai K, Hayashi DK, Lyle BJ, Martini MC, Ursell KL, Clemente JC, Van Treuren W, Walters WA, Knight R, Newgard CB, Heath AC, Gordon JL. Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science 2013; 341: 1241214 [DOI: 10.1126/science.1241214]

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: 25223664 DOI: 10.1016/j.crohns.2014.08.006]

Brant LJ, Aroniadis OC, Mellow M, Kanatzar A, Kelly C, Park T, Stollman N, Rohlke F, Surawicz C. Long-term follow-up of colonscopic fecal microbiota transplant for recurrent Clostridium difficile infection. Am J Gastroenterol 2012; 107: 1079-1087 [PMID: 22450732 DOI: 10.1038/ajg.2012.60]

Kronman MP, Nielson HH, Adler AL, Giefer MJ, Wahbeh G, Singh N, Zerr DM, Suskind DL. Fecal microbiota transplantation via nasogastric tube for recurrent clostridium difficile infection in children with and without inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2015; 60: 23-26 [PMID: 25162365 DOI: 10.1097/MPG.0000000000000545]

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: 24855339 DOI: 10.1097/INF.0000000000000419]

Russell GH, Kaplan JL, Youngster I, Baril-Dore M, Schindeler 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]

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]

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]

Rubin TA, Gessest 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]

Hourigan SK, Oliva-Hemker M. Fecal microbiota transplantation in children: a brief review. Pediatr Res 2016; 80: 2-6 [PMID: 26928451 DOI: 10.1016/pr.2016.14.068]

Wang M, Wu KY, Ding YB, Wu J, Xiao KM, Li QQ, 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]

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]

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]

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]

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]

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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