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Review Article

Review of Fecal Transplant in Childhood Gastrointestinal Disorders

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Abstract

Fecal microbiota transplant (FMT) has been introduced several decades ago in an attempt to restore the gut microbial balance. FMT appears to be the most efficient method to effectively change and sustain the gut microbial composition. To this date there have been a great number of reports of success in eliminating recurrent Clostridium difficile infections and restoring the gut microbial profile to resemble that of the healthy donor. The new gut microbiome appears to be stable in the recipients for at least 24 weeks. The efficacy of this "relatively novel" intervention in this difficult to treat population is 90%. This is superior to any other therapeutic modality, yet effective when all other therapeutic avenues have failed. While over 300 cases have been described in the literature, it has been difficult for the pediatric scientific community to embrace this therapy as there are only sporadic reports in children. FMT has also been used to treat inflammatory bowel disease, especially ulcerative colitis. There have been a number of successful case reports in ulcerative colitis, to suggest control of disease activity and a cure in some cases. However, there has not been uniform success reported for the use of FMT, especially in severe cases recalcitrant to medical therapy. Therefore, there is a strong need to determine the safety and efficacy of FMT in future pediatric randomized controlled studies, especially in inflammatory bowel disease. This review describes the rationale for fecal transplant and provides an update on the current published studies.

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INTRODUCTION

Overview of the gut microbiome

The human gut hosts the largest microbial community harbored in our bodies. Its contribution towards our health and wellbeing is just beginning to be explored. Gastrointestinal infections, inflammatory bowel disease, obesity, and non-alcoholic fatty liver are just a few disorders that are directly

linked to an imbalance in the gut microbiome. So what exactly is the gut microbiome? It is a community of microorganisms living in a specified body space, in this case, the gut. The organisms interact with each other as well as with the gastrointestinal mucosa and the gut mucosal immune system. They can be bacterial, viral (virome) or fungal (fungome). They produce a host of metabolites also called the metabolome. The microbiome helps recycle non-digested carbohydrates and converts them into short chain fatty acids that contribute to a healthy colon and can be used as fuel for the colonocytes. Micronutrient synthesis, toxin elimination, gut development, maturation and angiogenesis and fortification of gut barrier and immune function are also important gut microbial accomplishments.

The role of the gut microbiome in Clostridium difficile infections

Clostridium edificial is an anaerobic spore-forming and toxin producing bacterium capable of causing colitis. The incidence of C. difficile infection (CDI) has alarmingly increased over the past several years [1-3] and the affected population has expanded to include those previously at low risk, such as children [4]. In a recent pediatric study[2], the incidence of CDI has increased 12.5 fold over the past 18 years, with severe CDI and death occurring in 9% and 1% of cases, respectively[5] (Figure 1). At least 20% of all the cases are recurrent in nature. Management of C. difficile infections has become progressively challenging due to the emergence of resistant strains which result in treatment failure with traditional antimicrobial therapy. The Centers for Disease Control (CDC) announced that, while most types of healthcare-associated infections are declining, C. difficile remains at historically high levels, causing diarrhea linked to 14,000 American deaths each year. Furthermore, the annual US financial burden associated with this infection is estimated to exceed $1.8 billion [6]. Therefore, there is an urgent medical and economical need to develop better therapies to reduce the recurrence of this infection.

The contribution of the gut micro biome in recurrent *C. edificial* is related to the fact that host susceptibility to infections is strongly dependent on the permissiveness of the intestinal microbiota to C. difficile colonization. It has long been documented that CDI occurs after antimicrobial therapy, which is known to perturb this delicate balance [7-10]. In one particular study, De La Cochetiere and colleagues evaluated the microbiota before antibiotic treatment and demonstrated differed profile between individuals who developed CDI, suggesting that some individuals have a permissive gut microbial influence on infection [11]. In other studies, a decreased microbial diversity was found to be associated with a high risk of recurrence [12,13]. Active infection has been characterized by a microbiome rich in facultative anaerobes and deficient in *Bifidobacteria* and *Bacteroides* [14,15]. In children, a microbiome rich in *Ruminococcus gnavus* and *Klebsiella pneumoniae* was permissive for *C. difficile* colonization and a microbiome abundant in *Bifidobacteria* was associated with colonization resistance [16]. Low levels of *Bifidobacteria* were seen in children with CDI [17]. Therefore, being able to reshape the gut microbiota could have a profound therapeutic effect.

The role of the gut microbiome in inflammatory bowel disease (IBD)

The imbalance or symbiosis of the enteric microbiota is now accepted as an important etiologic factor in the pathogenesis of human IBD and immune-mediated chronic experimental intestinal inflammation [18-22].Insights into genetic, immunologic, and microbial interactions have expanded with identification of immunological properties of individual species and groups of bacteria[23,24]. The contribution of the gut microbiome can be inferred from animals in germ-free environment which is protective against experimental colitis. In addition, increased gut permeability due to dysbiosis, is frequently seen in patients with IBD even during remission and, similarly, in their first-degree relatives [25]. This dysbiosis has also been confirmed in treatment-naive children in a recent study [26]. Moreover, anti-microbial antibodies targeting the gut microbiota can be recovered in the serum of IBD subjects even years before the diagnosis [27,28]. Furthermore, a number of genetic mutations seen in IBD relate to mucosal immunity and gut microbial recognition and autophagy [29]. Paneth cells, which are involved

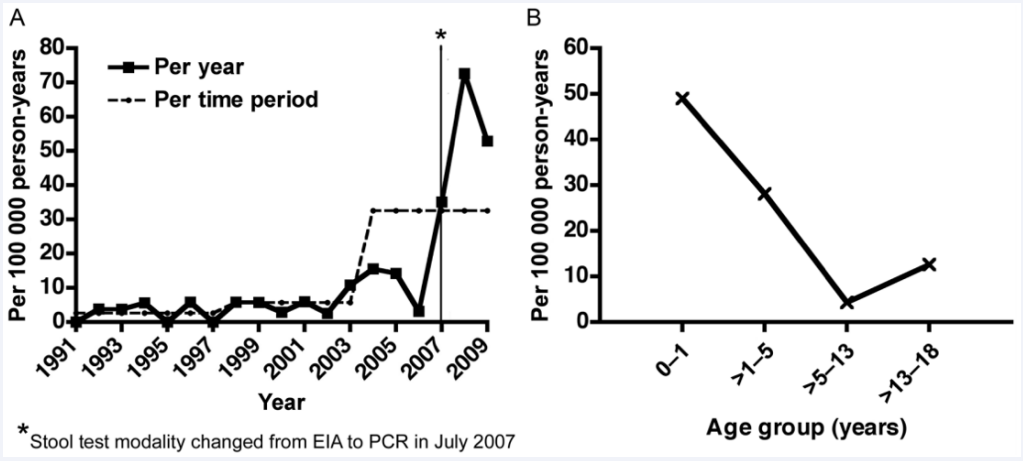

Figure 1 "Age and sex-adjusted overall incidence of C. difficile infection in children, 1991-2009." [Figure adapted from reference [2], with permission from publisher].

in the mucosal immunity targeting the microbiome, have been implicated in IBD pathogenesis[30]. Metagenetic analyses have shown a clear differing pattern of the fecal microbiome between IBD patients and healthy controls [31]. In Ulcerative Colitis (UC), dysbiosis can be seen even during remission, irrespective of the dysmotility seen during active disease suggesting that the dysbiosis can't be due to dysmotility but rather has a role in development of disease pathogenesis [32].

Ulcerative Colitis, an IBD disease entity, is characterized by chronic inflammation of the colon. It is an important pediatric disease since as many as 20-25% of all cases present during childhood. The incidence of the disease is constantly rising with an alarming 11 fold increase in pediatrics [33]. Early reports of the long-term survival in pediatric UC were gloomy with survival rates of 78, 58, 39 and 27 per cent at 10, 20, 30 and 43 years, respectively [34] and the risk of developing cancer at 20% per disease decade. With the advent of immunomodulation and biologic therapies, the outcome has become less dismal, but many children still develop severe disease [35,36], continue to require colectomy [37], and develop colon cancer later in life. Although there different medical options, [38] the first line treatment of mild to moderate disease remains 5-ASA. Unfortunately, there is a high failure rate with their use [39]. Higher efficacy therapies such as steroids, biologics and immunomodulators can be associated with significant side effects. Therefore, there is a great need for more effective and safer therapies.

Gut microbial changes in children with UC

Data from the author's laboratory show that children with UC have a gut microbiome that is deficient in many bacteria such as *Lactobacilli* and *Fecalibacteria*. More importantly, children responding to steroid therapy have a more diverse microbiome than non-responders, who require salvage medical therapy or colectomy (Figure 2) [40].

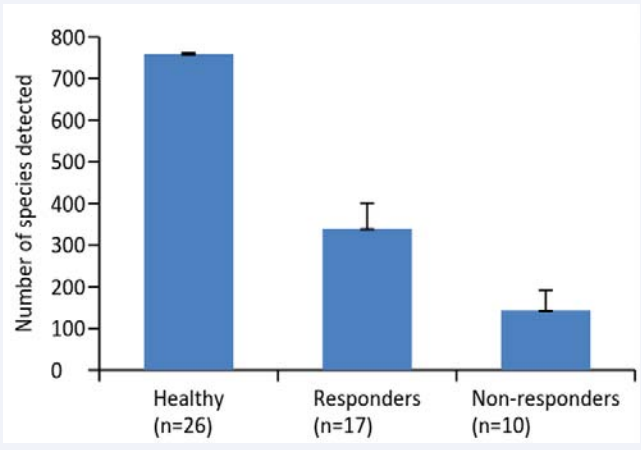

Figure 2 Number of species detected in healthy children and children with severe ulcerative colitis that (1) responded to steroids (Responders) and (2) those that failed to respond (Non-responders), values depicted as mean +SEM. Statistically significant differences are noted between responders and Non-responders (p=0.039). In addition, significant differences were also noted between healthy children and each of the two groups of ulcerative colitis (p<0.0001).

A deeper understanding of the etiological role of microbiota in the pathogenesis of IBD requires further comprehension of the factors that shape the gut microbiome and whether we can influence human disease outcomes in a durable fashion by altering the composition and function of the gut microbiota using therapeutic interventions, such as fecal transplant. Ultimately, these findings may influence clinical care through improved treatment, prevention, and minimizing the need for toxic therapies.

The gut micro biome in obesity and non-alcoholic fatty liver (NAFLD)

The incidence of obesity among children in the United States has increased three fold in the last few decades [41,42]. The obesity epidemic is paralleled by an increase of NAFLD in the pediatric population, affecting at least 3% of children and adolescents in the United States and Asia [43,44]. NAFLD is the most common cause of liver disease in children and adolescents in the United State [45]. The term NAFLD includes a spectrum of histological features from simple steatosis to inflammation with cellular injury to frank cirrhosis. Because the definitive diagnosis requires liver biopsy, which is not feasible in pediatric studies, increased serum aminotransferase levels and increased echogenicity on radiographic studies have been used as diagnostic tools [46]. Non-alcoholic steatohepatitis (NASH) can potentially progress to cirrhosis, liver failure, and hepatocellular carcinoma [47,48].

The pathophysiology of NAFLD remains unclear, but the gut microbiome is considered an important contributor. The human gastrointestinal tract houses a bacterial community that directs host digestion and energy homeostasis [49-51]. The "obese microbiota" is characterized by an increased capacity to harvest energy from the diet [52]. Studies on obese mice showed a 50% reduction in Bacteroidetes and an increase in Firmicutes by a comparable amount, demonstrating that "obesogenic microbiota" is distinct from "lean microbiota [53]". Comparable observations are noted in human studies. Microbiota of obese adults had fewer Bacteroidetes and more Firmicutes than lean controls, and the pattern was reversed with weight loss (figure 3) [54]. Another human study demonstrated that a 20% increase in Firmicutes and decrease in Bacteroidetes resulted in increased energy harvest, evidenced by decreased energy losses in the stool. In addition, increased abundance of Bacteroidetes correlated with loss of body weight. The authors suggested that the "manipulation of gut microbial communities could be another approach in the treatment of obesity"[55]. Recent studies support this notion and further demonstrate that microbiota can be transmissible and could prevent the development of obesity and obesity-associated metabolic phenotypes in experimental animals [56,57].

Therefore, it is not surprising that therapeutic interventions aiming at modifying the gut microbiome would be of therapeutic benefit. In general, this can be achieved through (Table 1). 1) antimicrobial therapy such as metronidazole and vancomycin, which can be effective in many cases of CDI [58], however, there are ever increasing reports of microbial resistance and recurrence. 2) Probiotics whose efficacy in CDI have yielded variable results but in general have not been proven very

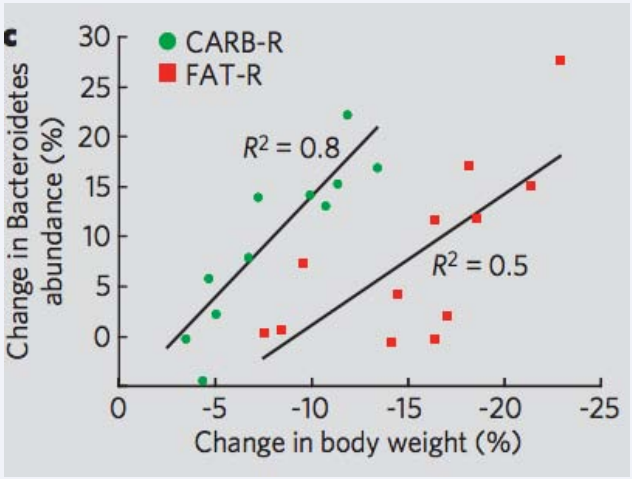

Figure 3 Change in Bacteroidetes Relative Abundance for Two Weight Loss Groups [Figure adapted from reference[54], with permission from publisher]. Correlation between body-weight loss and gut microbial ecology. Change in relative abundance of Bacteroidetes in subjects exceeding threshold of 2% weight loss for a carbohydrate-restricted diet (CARB-R) and 6% weight loss for a fat-restricted diet (FAT-R).

Table 1: Therapeutic interventions for modifying gut micro biome.

Method	Example
Antimicrobial Therapy	metronidazole, vancomycin
Probiotics	Saccharomyces boulardii
Fecal Microbial Transplantation	donor stool

efficacious [59]. Their use, as previously shown by the author and others, does not seem to alter the gut micro biome [60,61], and 3) Fecal microbial transplantation.

Fecal microbial transplant, even though unaesthetic, is perhaps the most powerful method for modifying the gut microbiome.

Fecal transplant

Definition and History: Fecal transplant is the process of transferring fecal microorganisms from healthy individuals into a recipient. Previous terms used to describe this process include stool transplant, fecal bacteriotherapy, fecal transfusion, human probiotic infusion, and fecal microbial therapy (FMT), which is becoming more widely used.

The concept of fecal transplant is not new. It is believed to have originated in China thousands of years ago. The Chinese healers offered patients 'Yellow soup' made of fecal matter and water to cure their diarrhea.

The first description of FMT was published in 1958 by Ben [62] and colleagues, a team of surgeons from Colorado, who treated four critically ill patients with fulminant pseudomembranous colitis using fecal enemas with great success. The first report of a successful fecal transplant for ulcerative colitis quickly followed in 1959 by Dr. Bennet who was the subject and the author[63]. Since then, there have been a large number of reports and clinical trials published in the literature, with a few exceptions; all had a similar theme, success!

Acceptance by pediatric patients: The acceptability of the concept of FMT transplant remains an issue, even though an intriguing report by Kahn et al., in which the authors investigated the opinion and view of patients and families towards fecal transplant, concluded that patients and parents of children with inflammatory bowel disease would readily consider fecal transplant and would be eager for it to become available[64]. The subject and family willingness to accept and undergo fecal microbial transplant for another indication such as CDI remains to be explored and is proposed in this study as will be described in experimental design.

The role of fecal transplant in specific clinical diseases

Clostridium difficile infection: Reported several decades ago for treating CDI [62], the use of fecal transplant is now supported by studies [65-71], including a NEJM controlled trial halted after interim analysis showed significant superiority of efficacy after fecal transplant [72]. A number of protocols have been utilized in the past, but a recently standardized method using colonoscopy and universal donors, yields the highest success rate[67]. Its safety and usefulness has also been documented in case reports of children as young as two years [73] and in immune compromised patients[74]. The degree of

Table 2: Summary of prior studies describing the use of FMT in ulcerative colitis.

No. subjects	Years of disease	Age (years)	Author	Outcome
6	5-15	25-42	Borody[88] 2003	Asymptomatic after 4 months, remission maintained 1-13 years later
10	0.6-8	8-18	Kunde[77] 2013	One subject could not retain enemas. Improvement in 6 of 9 remaining subjects by week 4.
1	11	48	Bennet[63] 1989	Colitis symptoms stopped after first week, maintained at 6 months
6	17-52	3-12	Kump 2013[78]	Subjects had moderate to severe disease not responding to multiple therapies prior to FMT. Initial improvement following FMT but no remission in any subject.
1	1.5	45	Borody[80] 1989	Stopped all therapy within days, asymptomatic 3 months later without therapy
5	1.3-9.7	22-51	Angelberger 2013[89]	Remission after 1 year in one subject, remaining subjects either experienced deterioration of symptoms or achieved no significant clinical improvements
1	13	51	Zainah 2012 [74]	Asymptomatic after 8 months, subject no longer required vancomycin
1	20	78	DeLeon 2013[85]	Symptoms persisted after 19 weeks, remission of UC required mesalamine

efficacy offered by this intervention is unmatched compared to any traditionally available therapy. A recent systematic review shows 90% efficacy in over three hundred patients[66].

INFLAMMATORY BOWEL DISEASE

Of all the sub entities of inflammatory bowel disease, UC is by far the most studied relative to fecal microbial transplant. The outcomes of the IBD studies have not been as bright as those for Clostridium difficile.

It is also becoming a more recognized therapy for UC [75]. In a recent review, nine small case series of FMT in IBD with variable quality have been identified, totaling 26 adult patients (18 subjects with UC) [76]. All patients, in whom symptoms were recorded, responded by 4 months and 15 subjects were in complete remission by 1 year. A total of 63% had endoscopic remission (3-36 months post FMT). A recent pediatric prospective pilot study of 9 children and young adults with mild to moderate UC were treated with FMT on 5 consecutive days [77]. Within one week 78% showed clinical response and 67% maintained clinical response after 1 month. However, not all studies show such positive outcome. A recent prospective study, even though showing initial improvement, failed to show complete remission. However, subjects had more severe disease and had failed to respond to multiple medical therapies including steroids, biologics and immunomodulators [78].

A number of case reports have described the use of FMT for treatment of UC [63,77-81]. The definition of successful outcome varied among reports. Five papers described 24 subjects with an average age of 28 years (SD=18.22), and an average duration of UC of 7.24 years (SD=6.21). Most subjects were adults except for the Kunde study. Eighteen out of 24 (78%) subjects had positive clinical outcomes with improvement of symptoms following FMT. No serious adverse events were noted but some subjects experienced short term abdominal cramping, bloating and fever. One pediatric subject could not retain FMT when administered by enemas. All authors concluded that FMT was a safe procedure in this patient population. A summary of prior studies describing the use of FMT in UC is outlined in (Table 2). While, the majority of the reported cases show improvement in colitis symptoms with some claims of cure of the disease, not all reports agree, with one negative study in adults. However, subjects had recalcitrant and severe disease that failed multiple medical therapies [78]. It is difficult to evaluate the true benefit of FMT as case report studies lack scientific rigor. We therefore propose a randomized controlled trial that would enable us to examine the true extent of the efficacy of FMT in treating UC and how it influences the intestinal milieu.

Safety of fecal microbial transplant: Many studies report safety of fecal microbial transplant, even in high-risk populations such as immunocompromised, elderly subjects, and young children [82-84].

Nevertheless, one question to consider is whether FMT in quiescent colitis can predispose subjects to a relapse in IBD symptoms [85]. Previous studies suggest that this is not a concern. In a prior adult study, subjects undergoing fecal transplant for Clostridium difficile and ulcerative colitis did not develop any relapse of their colitis symptoms [86]. Furthermore, a recent pediatric study utilizing FMT in ten children with recurrent Clostridium difficile infection and UC confirms this safety finding [87].

CLINICAL CONSIDERATIONS OF FECAL TRANSPLANT

Donor screening

Donor screening is critical to the safety and success of FMT. The universal donor should be negative for HIV, Hepatitis A, B and C, syphilis and have negative stool studies for culture, Ova and parasites, C. difficile (by PCR), Giardia, and Cryptosporidium in accordance with testing guidelines endorsed by the American Gastroenterological Association [90,91].

Donor selection

Donor choice is extremely important, and careful selection of donor has to be followed to maximize the benefit for the recipient. For example, relatives of subjects with IBD harbor a dysbiotic gut microbiome [92], rendering relatives unsuitable donors. Also, families or close acquaintances of children with C. difficile have a higher risk of exposure and infection with C. difficile [93], therefore, their gut microbiome may potentially be impacted by previous infection, colonization or prior therapy. Studies suggest that universal donors yield better outcomes than individual donors [67]. Donors with high body mass indexes are not appropriate donors as those individuals have dysbiotic microbiome and have harmful metabolites.

The age of the donor becomes important relative to pediatric studies. The author has provided published evidence that children, even in their adolescent years, have a distinct gut microbiome that is different from healthy adults [94]. Therefore, it would be best that the transplanted microbiome would be obtained from a donor in the same age group would so that it may closely resemble the subject's intended healthy microbiome.

Mode of transplant

Studies have utilized different delivery methods that include nasogastric tube, nasojejunal tube, enemas, colonoscopy and now we anxiously await a capsule form of the product. Delivery of FMT to the ileocecal area guarantees delivery of the transplanted microbiome to the entire colon, while rectal enemas are limited to the delivery of FMT to the rectum and left colon and therefore would limit their efficacy beyond those areas. It is also difficult for children in general, and especially children with severe colitis, to retain enemas when they have active disease due to frequent stooling and significant dysmotility secondary to rectal mucosal inflammation, which also explains the need for multiple administrations. In a pediatric study by Kunde et al, one out of ten children in the FMT study did not tolerate rectal enemas and the volume of enemas tolerated was only 165 ml [77]. Colonoscopic delivery of FMT would guarantee delivery of FMT to the entire colon and may eliminate the need for multiple applications. In addition, delivery of fecal microbiome to the upper GI tract (for example via nasogastric or nasojejunal tubes) is not desirable as it involves infusing metabolites that are specific to the colon that may become absorbed in the small bowel and may cause undesirable effects. FMT via nasogastric tube may pose a risk

for reflux of fecal material and possible aspiration. Finally, colonoscopic delivery of FMT yielded the best response in C. difficile colitis studies [66].

Dose of fecal transplant

Several quantities of stool transplant have been used in the past. The data suggest that doses of at least 50 grams of stool have better outcomes than lower doses.

Subject preparation

Traditionally subjects undergo cleanout and antimicrobial therapy targeting C. difficile, but it may not be necessary to use antimicrobial therapy for indications other than C. difficile, for example in UC.

Issues related to food allergies

Children who are highly sensitized to foods may develop anaphylactic reaction when in contact with antigens. The question then arises when such a child needs to undergo fecal transplant, can there be enough food antigen ingested by the donor that can trigger an anaphylactic reaction upon FMT?

Potential risks of FMT

Potential risks to subjects include potential side effects such as bloating, abdominal pain, changes in bowel habits. The likelihood of developing these side effects is rare as described in prior research studies of fecal transplant. In a systematic review of 317 cases, only 8 subjects (0.025%) had adverse events [66]. Among the adverse events, the following were noted: Upper gastrointestinal hemorrhage (n= 1) [95], Irritable Bowel Syndrome (IBS) symptoms (n= 4) [96], infectious IBS symptoms (n= 1) [68], constipation (n= 1) [97], and signs of irritable colon (n= 1) [98]. Transient fever immediately following FMT has also been reported in a recent study utilizing FMT in children with UC [77]. Furthermore, unforeseen infection risks as well as non-infection risks are also possible. The gut microbiome has been linked to the development of other disorders such as cancer, obesity and diabetes. A recent report suggests that FMT may transfer obesity [99].

Future directions

The future holds a lot of promise for the potential applications for FMT in obesity, NAFLD CDI, and IBD. A key question now arises: Could we manipulate the microbiota environment to treat or prevent obesity in humans especially children? Can FMT play a role in obesity or other conditions?

Can FMT play a role in IBS, which is a fairly common and difficult to treat disorder, has been shown to also result in a disturbed micro biome in children [100] . Many other disorders and diseases may prove to be associated with altered microbiomes and thus, may be potentially treated with FMT.

Future advancement in delivery of FMT will soon allow commercial use of a capsule form of FMT with desiccated microorganisms.

Do we need all the microorganisms or can we tailor them to a specific disease? For example, studies have shown that only 10 organisms can be helpful in eradicating CDI [101]. Would Bacteroides alone be sufficient to cure patients since they seem to be key organisms in this disease?[102].

Randomized, controlled trials will be necessary to further evaluate the answers to these questions and more closely evaluate this procedure.

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