Review Article

Fecal microbiota transplantation: great potential with many challenges

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Abstract: In January of 2019, Samuel P. Costello and colleagues published a wonderfully executed, double blind placebo-controlled trial on fecal microbiota transplantation (FMT) versus autologous stool as placebo in mild to moderately active adult ulcerative colitis [UC: one type of inflammatory bowel disease (IBD)] patients. This review-commentary examines the current state of knowledge on human gut microbiome (live microbiota + their products and surrounding environment, i.e., fecal matter) and microbial therapeutics from a gastrointestinal (GI) clinician's standpoint. The varied forms of dysbiosis as the target of FMT, recipient donor and placebo considerations are also discussed in respect to randomized control trials in IBD [and the lack thereof in Crohn's disease (CD)] with this unconventional treatment modality.

Keywords: Fecal microbiota transplantation (FMT); ulcerative colitis (UC); Crohn's disease (CD); microbiome

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Introduction

In January of 2019, Samuel P. Costello and colleagues published a wonderfully executed, double blind placebo controlled trial on fecal microbiota transplantation (FMT) versus (*vs.*) autologous stool as placebo in mild to moderately active adult ulcerative colitis [UC: one type of inflammatory bowel disease (IBD)] patients (1). To appreciate the validity of this opinion, it is feasible to overview the current state of knowledge on the human gut microbiome (live microbiota + their products and surrounding environment, i.e., fecal matter) and microbial therapeutics from a gastrointestinal (GI) clinician's standpoint.

The gut microbiome: a difficult therapeutic target

The gut microbiome is perhaps one of the least understood "organ" in our body in spite of the exponentially increasing list of biomedical publications in the field. This controversy roots in part from our inability to conventionally culture most of the currently recognized members of the microbiome, which is most commonly defined by nucleic acid based sequencing methodologies (2). These methodologies are challenged by variation in sampling, handling, sequencing, annotation and bioinformatic analysis of biospecimens. Additionally, the fascinating environmental (including diet) responsiveness (3,4) and the complexity of the microorganisms involved (bacteria, bacteriophages and other viruses, fungi, and to lesser extent other unicellular organisms) adds to our inability to decipher critical questions about our microbiomes and their relationship to the currently common and emerging human diseases, especially based on cross-sectional (i.e., single time point; most of the microbiome studies to date) and not longitudinal studies (5). The increasing information about the gut microbiome and the augmented diagnostic sensitivity of laboratory testing for microorganisms has led to cumulating debates between commensal *vs.* pathogen, "good" *vs.* "bad" when considering human disease states in relationship to microbes and/or microbiota (6). A couple of outstanding examples for such debates, are *Clostridioides difficile* (*C. difficile*; formerly *Clostridium difficile*), and

Malassezia species (ssp.).

C. difficile is not only the most commonly detected pathogen in antibiotic associated diarrhea, but also an age dependent commensal in the human GI tract. It is more frequently found as a colonizer in several disease states, and in patients of healthcare facilities without symptoms of diarrhea than in healthy controls from the community (7-9). Therefore, in diseases that share the symptomatology (diarrhea in this case) with *C. difficile* infection, such as IBD, the detection of the organism during flares frequently presents as a major clinical conundrum (9,10).

Similar to *C. difficile*, the fungal *Malassezia* species are age dependent commensal colonizers of our skin with increasing abundance during childhood (11). Not surprisingly, while their pathogenic role is acknowledged in pityriasis versicolor and dandruff, their involvement in other skin disorders such as atopic dermatitis and psoriasis is of debate (12-14). The role of *Malassezia* beyond skin disorders and incidental cases of sepsis is even more questionable, especially in GI disease. Recent studies detected *Malassezia* in mucosal microbiomes associated with active pediatric granulomatous Crohn's disease (CD) (15), and in adult CD patients during medically induced remission who carried *CARD9* polymorphism (16). Yet, alive or dead (i.e., the diagnostic fragment of *Malassezia* ssp. DNA from disintegrated fungi may be selectively adherent to the GI mucosa of CD subset patients, for example), pathogen or commensal, good or bad, cause or effect, is yet unknown in respect to this fungal genus and CD.

While other single organisms [such as *Mycobacterium avium paratuberculosis* (MAP) in CD (17)] have been associated with common disorders, it is increasingly becoming recognized that the interactive network of an "abnormal" microbiome/microbiota is more likely to be at play in disease (18), CD again being a prime example (19). This abnormal state of a microbiome is designated as "dysbiosis" (18), which can associate with disease severity (19) and outcome (20,21). In the meantime, dysbiosis can be difficult to clearly define and varies by disease states (22), significantly influenced by geographically dependent socioeconomic environments (23). Similar to single GI pathogens, however, intense studies of dysbiosis have not brought us closer to understanding cause *vs.* effect in complex human disorders, such as IBD (24). Not surprisingly, the current state of microbial therapeutics defines FMT (the transfer of stool from a "healthy" individual to one with dysbiosis/disease) as the foremost effective (25). This conclusion is further supported by recent high quality trials on acute (transient/self-resolving) gastroenteritis, where single strain (26) or combination (27) probiotic candidates proved to be ineffective. Therefore, no matter how sophisticated explanations we make, the simple clinical reality is that we are treating challenging recurrent infections and complex human diseases similar to Ge Hong in the 4th century (28), albeit with advanced diagnostic and laboratory support, but also with increasing regulatory hindrance overshadowed by interests in capital gains (https://www.sciencenews.org/blog/scicurious/fecal-transplants-regulation).

FMT challenged by varying gut dysbioses

The trial of Samuel P. Costello and colleagues (1) is in full agreement with FMT being the most effective microbial therapeutic, one to be seriously studied in IBD, including UC. When we consider FMT for human disease, distinctions can be made between primary (none, or subtle host abnormalities, where the origin of dysbiosis can be clearly identified) and secondary (defined host pathology related) dysbiosis as the target, and acute/transient *vs.* recurrent/chronic within those categories (*Figure 1*). Obviously, the prime candidates for FMT/microbial therapeutics are the primary chronic dysbioses, such as recurrent *C. difficile* infection (rCDI) (7), malnutrition (NCT03087097 on clinicaltrials.gov), and antibiotic resistant bacterial strain carriage [as in the case of vancomycin resistant enterococcus (VRE) colonization (29)], for example. In respect to rCDI, a study on primary CDI comparing vancomycin therapy to FMT showed similar efficiency (30). On the contrary, there has been significant advantage of FMT shown over vancomycin (31) and even fidaxomicin (32) therapy in randomized controlled trials (RCTs) in rCDI. These findings indicate that advanced iatrogenic dysbiosis associated with recurrent antibiotic treatments for CDI (i.e., other microbes or the lack of microbes, sustaining or even augmenting *C. difficile* pathogenicity) is likely to play a role in the recurrence/chronicity of the infection. It is this advanced recurrent/chronic dysbiosis, which seems to be amenable to the complex microbial treatment of FMT by direct and indirect effects [direct effects: colonization from host; indirect effects: "enslapment" (33)/acceptance of non-donor, non-recipient ("newly detected") (34) microbes to reestablish a healthy community].

The question of FMT/microbial therapeutics becomes more problematic when considering secondary dysbioses

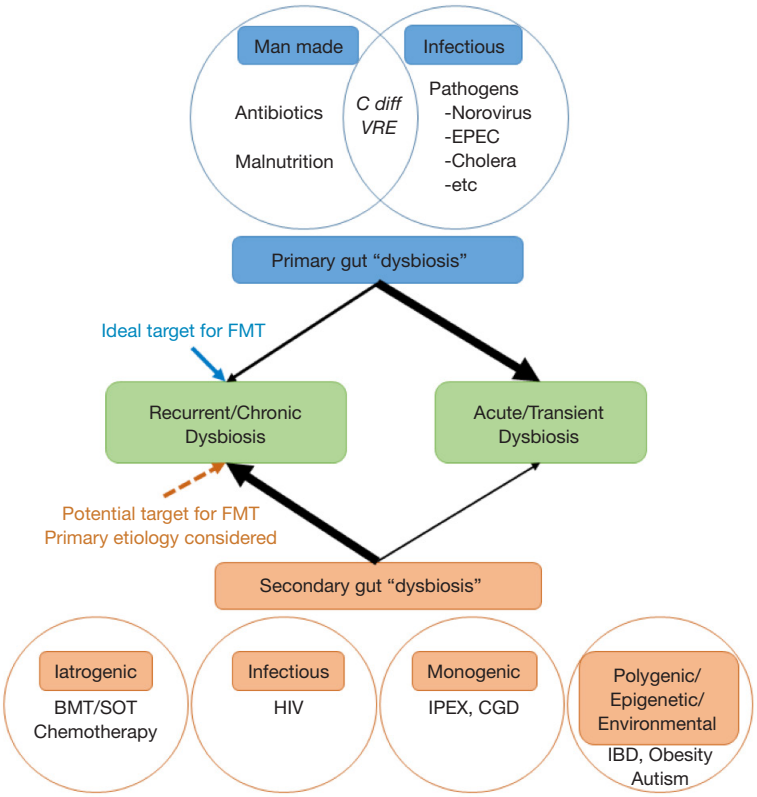

Figure 1 Arbitrary categorization of dysbiosis (i.e., altered microbiome composition in disease compared to healthy controls within the same socio-demographic and geographic region). Primary and secondary dysbioses are separated as acute/transient, or chronic/recurrent. Primary dysbioses are more commonly acute/transient as opposed to secondary dysbioses (depicted by arrow thickness). Each type of dysbiosis can be further separated. Note a few specific examples for these further subcategories. It is the primary chronic/recurrent dysbioses, which are the best targets for fecal microbiota transplantation (FMT) or defined microbial therapeutics. For the secondary dysbioses, underlying condition/disease based specific considerations have to be made for FMT. For further details see main text. BMT, bone marrow transplantation; *C. diff*, *Clostridioides difficile*; CGD, chronic granulomatous disease; EPEC, entero-pathogenic E. coli; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; SOT, solid organ transplantation; VRE, vancomycin resistant enterococcus.

(*Figure 1*). One can argue that FMT in secondary dysbioses will only be effective long term if persistently given (with questionable frequency), or if along with FMT, the primary cause of the dysbiosis is eliminated. In the latter respect, engraftment of donor organs and minimizing immunosuppression in organ transplant recipients, immune reconstitution in chemotherapy patients along with FMT may be fastest mode of resolving organ/tissue transplantation, or chemotherapeutic agent associated dysbioses. Similarly, gene editing based therapeutics for monogenic disorders, or remission of immune disruptive infections (such as HIV) along with FMT may serve as a curative solution for monogenic disorder, or mono-microbial infection related dysbioses in the future. The case becomes more challenging in polygenic/poly-epigenetic/environmentally-modulated diseases such as obesity (Allegretti JR, *et al.* Abstract 621. Presented at: Digestive Disease Week; May 18-21, 2019; San Diego), chronic constipation (35), irritable bowel syndrome (IBS) (36), autism (37), and IBD (see latter), just to name a few where FMT has been considered and/or performed (*Figure 1*). In most of these complex diseases, the key pathology is likely shared only by a subset of patients or is even unique to individuals (38), which arguably creates the biggest clinical challenge in current medicine. Our inability to identify the critical host pathology behind these disorders,

Table 1 Considerations for fecal microbiota transplantation trials in respect to recipient, donor, and placebo used (see text for details)

Recipient	Donor	Placebo
Age	Age	Artificial "stool"
Concomitant treatments	Screening	Normal saline/vehicle
Baseline disease	Microbiome ("super donor")	Only colon prep
Disease activity	Single *vs*. multi-donor	Autologous stool (handling)
Microbiome	–	–
Preconditioning	–	–
Frozen *vs*. fresh preparation	–	–
Route of FMT delivery	–	–
Amount of stool in FMT	–	–
Frequency and total number of FMT	–	–

FMT, fecal microbiota transplantation.

which orchestrates the associated dysbiosis hinders the potential for FMT to be curative. Perhaps obesity is the most straightforward in this respect, where in addition to strong genetic predisposition (39), addiction to eating is a clear culprit in the majority of the cases. Here, FMT [which alone delivers only transient effects (40)] along with dietary and behavioral modification or interventions (pharmaceutical or surgical) to decrease over-eating may be the fastest way towards resolution of morbid obesity and maintenance of lean weight, as already proposed in clinical trials (NCT03127696, NCT02346669, in clinicaltrials.gov). IBS, on the other hand, is a cluster of a biologically poorly defined group of diseases sharing clinical symptomatology by sub-classifications (such as diarrhea predominant, constipation predominant, etc.). Perhaps it is not surprising that a well-executed RCT, but in a relatively small population of mixed IBS patients (n=22 in FMT, n=23 in placebo groups) failed to show any benefits from FMT over placebo (36). Compared to IBS, IBD has more clearly defined biological distinctions resulting in CD and UC subtype delineations (41,42), making it a better target for FMT/microbial therapeutics.

Considering FMT for IBD

Dysbiosis in IBD is arguably primary or secondary (24). From our perspective, based on epidemiology and translational research findings, IBD dysbiosis is secondary; where genetic (43), and mostly prenatally (44) occurring epigenetic changes in the intestinal epithelium (45) modulate postnatal mucosal microbiome composition toward a pre-clinically susceptible pro-inflammatory state (46-48). Therefore, at least in the majority of the IBD cases, we predict that FMT cannot be curative, but could help to induce deep remission ["cure" (49)], serve as primary [monotherapy (50)] or secondary [combination (51)] therapy. Comprehensive reviews of the FMT literature in IBD indicate 23–33% clinical remission rates in UC from FMT, and 56–78% remission rates in CD (52). Making clear conclusions from these studies, however, is challenged by their uncontrolled nature, variation in recipient and donor selection, mode of delivery, preparation dose, treatment protocols and outcomes. This is true for the rarely performed RCTs, which for curious reasons have only been done in UC [namely 5 UC-FMT RCT trials to date (1,51,53-55)]. In the meantime, not only the reviews above, but observations on dysbiosis to be more significant in CD compared to UC (22,43), and mucosal microbiome correlations with severity (19) and type (i.e., granulomatous) (15) be more distinctive in CD than UC, would indicate CD to be a better target than UC for FMT.

When considering RCTs with FMT in IBD, one must examine the variables in recipients, donors, the preparation and delivery mode, as well as the placebo used (*Table 1*). Most information on these variables comes from the rCDI literature, since FMT is more commonly used there than in IBD. Therefore, many of the findings about such variables in rCDI may not be transferable to FMT in IBD, and will require more investigation. For the purposes of this review, rCDI and the RCTs on IBD are considered in regards to

the variables of FMT.

Gender variation in recipients and donors has rarely been observed to influence FMT outcomes. In one recent, relatively small (n=35) study, female adult patients were less likely to achieve primary cure for rCDI than male recipients (56). Although there is an age dependent maturation of the gut microbiome (9,44), recipient age has not been observed to significantly influence the outcomes (57), except from the prior small cohort on adult patients where older recipients (70 *vs.* 57 years) were less likely to respond (56). Nevertheless, most donor specific screens recommend age to be less than 45 when the recipients are children (i.e., in cases of large age difference between recipient and donor).

In respect to recipient (*Table 1*), concomitant medications and underlying disease states (see *Figure 1*) may affect outcomes beyond the scope of this review, but it is informative that in our recent large (n=335) retrospective pediatric study (where there are usually less confounders compared to adult recipients), even immunocompromised patients had similar outcomes from FMT targeting rCDI as non-immunocompromised patients did (57). As for FMT in IBD recipients, there was an inverse correlation between disease activity and FMT success in UC patients in the study of Paramsothy *et al.* (55), which is consistent with our unpublished results from a small pediatric case series. Recipients on concomitant steroid therapy at the time of FMT initiation also had poor outcomes compared to those on 5-ASA, immunomodulator, or biologic therapy (55).

In UC recipients, recent analyses indicated that those with decreased abundance of *Fusobacterium*, *Escherichia*, *Sutterella*, and *Prevotella* may have increased chance to positively respond to FMT. On the other hand, increased abundances of *Eubacterium hallii*, *Roseburia inulinivorans*, *Eggerthella* species and *Ruminococcus bromii* were the strongest positive predictors for this unconventional treatment method (58). As for other gut microbiome members beyond bacteria, recipient fungal (59) and bacteriophage (60) dysbiosis has been observed to influence FMT outcomes in rCDI. In IBD, such observations beyond bacteria have only been made on bacteriophages, where high abundance of *Caudovirales* was associated with lack of response to FMT in adult UC patients (61). The significance of these findings has yet to be determined, however, since causation in regards to bacteriophages in disease is just as difficult to prove as for bacteria. Due to the highly specialized, strain specific nature of bacteriophages, the diversity of those is strongly dependent upon bacterial diversity within a microbiome. Since prophage activation occurs upon host bacterial stress, increased phage abundance does not appear to be disease type specific. Increased *Caudovirales* abundance has been observed both in rCDI recipients (60) and UC recipients (61) less responsive to FMT. Since FMT has been observed to be less effective in UC patients with more intense mucosal inflammation (55), it is difficult to discern whether mucosal inflammation (augmented stress in select bacteria) induced increase in *Caudovirales* abundance or vice versa is the culprit. Recipient disease activity is likely to influence phage transfer between donors and recipients as well, since this process has been found to be limited in UC patients receiving FMT during medically induced remission (62). It is also unclear if prophage activation is good or bad in respect to overall bacterial community resilience/health (63), expanding the lack of our understanding between cause *vs.* effect, good *vs.* bad when it comes to the microbiome, including bacteriophages.

Preconditioning of recipients in rCDI appears to significantly impact outcomes as mentioned above (i.e., vancomycin preconditioning). As far as RCTs in IBD, none performed recipient preconditioning with antibiotics. In the meantime, uncontrolled trials did use antibiotic pre-treatment with good outcomes (64). RCTs are obviously needed to answer this question.

Frequency of FMT and length of therapy needed is also of question for IBD therapy. This will be discussed in the next chapter in the 5 UC RTCs published to date.

Another consideration is the preparation and delivery of donor stool when it comes to FMT. In rCDI, anaerobic *vs.* aerobic handling frozen *vs.* freshly processed fecal material use, or route of delivery (upper GI, colonoscopy, or enema) has not been observed to affect FMT outcomes [reviewed in (57)]. In children, however, our recent cohort study indicated that fresh donor preparation may be better than frozen, and colonoscopic delivery may be superior to other modalities (57). In the RCTs with FMT in UC, the single study with upper GI delivery of the fecal preparation failed (53), while in all other (4 total) studies using lower GI delivery, FMT was more effective than placebo. In these studies frozen *vs.* fresh [2 frozen successful (1,55), 2 fresh successful (51,54)] preparation did not seem to affect outcomes. Clearly, well designed controlled trials could answer these questions in the future.

It is also unclear, how much of donor stool needs to be transplanted for therapeutic success. The 5 RCTs in IBD used 8–120 g of stool per FMT treatment. Interestingly, the largest amount (120 g) of stool per FMT was delivered with

a nasoduodenal tube in the negative trial of Rossen *et al.* (53).

As for FMT donors (*Table 1*), microbiome richness has been indicated to aid success in IBD patients (65). In the meantime, it may not necessarily be the preparation richness per se that matters, rather than a single donor's unique microbiome composition, since one donor appeared to be superior over others in the large Australian RCT using multi-donor preparations (55), preceding that of Costello *et al.* Further, on the donor side, *Bacteroides* were beneficial in promoting FMT efficiency, and *Streptococcus* associated with lack of response in UC recipients (58). Actually, the existence of "super-donors" for FMT, influenced by donor genetics and diet has been proposed (66). Such super-donor state, however likely varies by recipient and the type of dysbiosis targeted. Interestingly, our recent findings in a mouse model system supported the therapeutic benefit of *Bacteroides*, and deleterious effects of *Streptococcus* for FMT in treating intestinal inflammation (67).

Lastly, in RCTs with FMT for IBD, one must pay attention to the placebo used as well (*Table 1*). Importantly, when it comes to the gut microbiome, even bowel preparation (68) can have significant impact, and supposedly inert substances such as normal saline can achieve therapeutic effects (69). If we consider stool a tissue/organ as opposed to a drug/biologic (which most of FMT supporter biomedical scientists agree upon), then in controlled trials one should not use the "placebo" designation in its conventional form. Placebo in this case should be the most similar, but inert tissue/organ compared to donor feces. Therefore, the biologically most meaningful "placebo" or control tissue is arguably autologous stool when it comes to FMT, being theoretically inert to the recipient (although processing and mode of delivery modifies its composition, but in a similar was as the donor stool, if appropriately controlled).

Advances and challenges from the Costello *et al.* FMT trial

With all the considerations above, let's further review the outstanding RCT performed by Costello *et al.* As already mentioned, this is the 4th RCT published in IBD, all in UC recipients. Moayyedi *et al.*, compared administration of weekly FMT versus water-enema for 6 consecutive weeks to recipients without bowel preparation (54). They found no difference in the primary outcome of clinical remission after 6 weeks. However, 16 of the 27 patients in the active arm reported subjective improvement, and were allowed to continue receiving weekly FMT for an additional 6–12 weeks. With the extended therapy, 33% of patients achieved clinical remission, reaching statistical significance over placebo. Additionally, patients with a less than 1-year history of UC responded better to FMT than those with a more prolonged disease course prior to the intervention (54). In contrast, the placebo controlled trial of Rossen *et al.* did not find a clinically significant benefit from FMT in adult UC patients (53). This protocol differed significantly from that of Moayyedi *et al.* by administering only 2 FMT treatments within 3 weeks by nasoduodenal delivery after bowel lavage, and by using autologous stool as placebo in the control group. These low intensity FMT trials were followed by the high intensity [40 FMTs (1 colonoscopy, 39 retention enemas) over 8 weeks] RCT of Paramsothy *et al.* (55), many findings of which (58) have been already discussed above.

Following the Paramsothy *et al.* RCT, Costello and colleagues made 2 major changes. They returned to a low intensity FMT protocol [3 FMTs (1 colonoscopy, 2 enemas) within 7 days], and used autologous stool as the placebo/control preparation (compared to the normal saline based artificial stool of Paramsothy *et al.*). Their results strongly indicate that a single or few FMTs over a short period of time may be effective for up to 2 months to alter the microbiome and sustain steroid free remission. This finding was further supported by the 5th RCT trial of FMT in UC from Sood *et al.* (51). Sood and colleagues randomized a select group of UC patients in whom FMT added to standard of care (SOC) induced remission. These patients during clinical and endoscopic remission were randomized to receive every 8-week colonoscopy delivered FMT (n=31) or colored normal saline as placebo (n=30) in addition to SOC up to 48 weeks (7 FMTs). At 48 weeks, significantly more patients were in endoscopic and histological remission in the FMT *vs.* the placebo arm (51).

There was no major consistency in respect to taxonomic or metabolomics prediction of success between Paramsothy *et al.* (55), and Costello *et al.* (1). As opposed to prior indications for microbiome richness increase to be important for FMT success (55,65), this outcome variable was not observed to be important by Costello and colleagues (1), consistent with our small scale uncontrolled study (50). Between Paramsothy *et al.* (58) and Costello *et al.* (1), there was taxonomic consistency only at the family level in respect to abundance increase of *Ruminococcaceae* and *Bacteroidaceae* in UC patients with steroid free remission after FMT.

Anaerobic handling of fecal material as performed by Costello *et al.* (1) may matter, but it was not done by Paramsothy and colleagues (55). Yet, there were similar steroid free remission outcomes between the 2 studies, although with a much more intense FMT regimen in the latter. If anaerobic handling matters, then Costello and colleagues should have treated the autologous stool (placebo) anaerobically as well (which they did not) to give the same chance for beneficial activity for the control/placebo tissue. This lack of identical handling between FMT and placebo may have positively biased their results toward FMT, since all the bacterial species associated with improvement in disease activity were anaerobic organisms in their study.

Altogether, the following conclusions for future RCTs in IBD, but truly only for UC, can be made:

- Patients with a shorter duration of disease, and those in endoscopic remission may be best candidates for FMT;
- Concurrent steroid therapy may decrease efficiency;
- Careful microbiome-based recipient selection (bacterial, phage, fungal, and metabolomics considerations) may be useful, but limited knowledge on the specifics for such selection exists currently;
- Recipient preconditioning (targeted elimination of particular microbes such as *Fusobacterium*, *Sutterella*, *Escherichia*, *Streptococcus*, for example) may enhance FMT efficiency;
- Single well selected donor ("super-donor": abundant *Bacteroides*, *Roseburia*, *Eubacterium*, *Ruminococcus*, but lack of *Streptococcus*) for each specific patient may be the safest and most effective for FMT practice;
- Lower GI delivery of FMT may be superior to the upper GI route;
- Anaerobic handling of stool may provide benefit;
- Single or a few FMTs every 2 months may be sufficient to maintain effects;
- Amount of stool and FMT volume is likely important (more the better?);
- Autologous stool is likely the best/physiologically most relevant placebo (but should be handled identical to donor FMT).

It needs to be highlighted that none of the IBD RCTs have examined FMT as monotherapy, but only as a steroid sparing agent, since steroid free remission was their common outcome measure, while all other immunotherapies were continued. Compared to such practice, most of the RCTs studying novel therapeutic agents in IBD only allow for steroids and 5-ASA preparations to be taken at patient recruitment. Outstanding examples are the OCTAVE trials on tofacitinib to treat adult UC, where beyond steroids, only oral 5-ASA was allowed to be taken (70). In the Sustain phase of the study, 45.7% of patients on 10 mg twice daily tofacitinib primary therapy had week 52 steroid free mucosal healing compared to 13.1% on placebo (32.6% effect size). In comparison, FMT as secondary therapy induced steroid free mucosal healing in 45.2% patients compared to 16.7% on placebo (28.5% effect size) at 48 weeks (51). Therefore, there is much to be done for optimizing FMT through sorely needed RCTs in IBD, and cautious enthusiasm is advised for GI colleagues when discussing this topic with interested patients.

The execution of well-designed, and well-powered RCTs with FMT is a significant challenge for lack of enthusiasm from the pharmaceutical sector. Yet, without such RCTs, it will be extremely difficult to create efficient microbial therapeutics not only for IBD, but other disorders as well. The work from Costello and colleagues strongly supports a bright future for microbiome-based treatments in IBD. We trust that not only governmental funding agencies and philanthropists, but also the private sector will recognize the importance of translational research on FMT in order to bring its potential to reality.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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