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UPDATES ON FECAL MICROBIOTA TRANSPLANTATION

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Abstract – Faecal microbiota transplantation continues to evolve. As we advance our understanding, we are finding novel uses of FMT which are reflected in the vast amount of research in the area. This year we discovered more about the mechanisms that help FMT work, as well as some interesting research into its potential therapeutic benefits. We have summarized the most important FMT updates within the last year in this review.

Keywords: Faecal microbiota transplantation, Gut microbiota, Clostridioides difficile infection, Metabolic syndrome, Inflammatory bowel disease, Irritable bowel syndrome.

INTRODUCTION

Faecal Microbiota Transplantation continues to evolve. As we advance our understanding, we are finding novel uses of FMT which are reflected in the vast amount of research in the area. This year we have discovered more about the mechanisms that help FMT work, as well as some interesting research into its potential therapeutic benefits. We have summarized the important FMT updates within the last year in this review.

GASTROINTESTINAL DISORDERS

Clostridioides Difficile Infection

One of the most successful approaches for recurrent *Clostridioides difficile* infection (rCDI) is faecal microbiota transplantation (FMT)[1]. This year saw further research highlighting its efficacy in treating CDI. Urbonas et al[2] confirmed that single fresh FMT *via* gastroscopy induced clinical remission in 80% of the patients pre-treated with omeprazole and vancomycin 500 mg four time a day for 5 days. They also demonstrate, in their cohort of 60 patients with rCDI, that performing multiple FMT in non-responders to initial infusion could enhance the overall efficacy (97.6% after a second infusion, 100% after a third infusion), with no evidence of higher risk of serious adverse events (SAEs).

An important step to assess the overall efficacy of FMT is to try and standardize how we prepare and deliver it, which may help us pool together resources and knowledge with much greater homogeneity. One important step in FMT for CDI was to assess the efficacy of different preparations of FMT. A meta-analysis of 12 case series and 3 RCTs recorded an efficacy rate for oral FMT capsules of 0.821 (95% confidence interval: 0.762-0.874), similar to FMT via colonoscopy[3]. A retrospective analysis showed significant superiority of single infusion of higher-volume fresh faecal filtrate (30-50 g) compared to single or multiple infusions of lower-volume frozen fecal preparation (22.7 g), 98.0% *vs.* 64.0% and 98% *vs.* 86% respectively[4]. Interestingly, Bestfater et al[5] tested the efficacy of bidirectional FMT (bFMT), the infusion of donor stools into the upper and lower gastrointestinal tract simultaneously. In their retrospective cohort, on the 90th day after the procedure, the group treated with bFMT did not experience any relapses. On the other hand, at the same time point, they recorded a recurrence rate of 18.8% (p=.010) for FMT *via* colonoscopy, 40.6% (p≤.000) for FMT via gastroscopy, and 28.1% (p=.001) for oral FMT capsules.

Next Generation Products

Beyond the classic FMT, in the last decade, several novel stool products have been identified and tested in CDI relapses and recurrences. Some of the studies published from April 2021 to April 2022 on this topic are summarised in Table 1.

Special Populations

Safety and efficacy of FMT in rCDI were demonstrated also in more fragile subgroups with special comorbidities.

FMT performed in 63 adults with cirrhosis (of which 24 with decompensated cirrhosis) showed similar efficacy as the general population after a single infusion of FMT *via* colonoscopy (85.7%). In this population, higher failure rates were correlated with decompensated cirrhosis assessed by the Child-Pugh score (100% *vs.* 37.7%; p<.001) and the use of non-CDI antibiotics (44.4% *vs.* 5.6%; p<.001)[11].

In patients with oncological comorbidities, FMT showed efficacy (84%) comparable to the general population in a recent retrospective study[12] and a single-centre, prospective observational study[13].

In the patients with Inflammatory Bowel Disease (IBD), the pooled cure rate of single FMT remained at 78% (CI 95%: 73%-83%; I^2=39%) and raised to 88% (95% CI: 81%-94%; I^2=73%) after multiple infusions, as reported by a novel meta-analysis encompassing 457 adults[14].

An old age was considered one of the principal predictors of FMT failure, along with IBD, severe CDI, incomplete bowel preparation, use of non-CDI antibiotics, and hospitalizations[15].

FMT for rCDI in patients aged ≥80 years was not significantly less effective than in the control group (18-79 years old), 78.9% *vs.* 89.7%, p= 0.29[16].

Mechanistic Studies

A lot of work has been done this year to understand the mechanisms to which FMT exerts its effects. One of the reasons underlying the success of FMT in rCDI is probably to be sought in the ability to dramatically increase bacterial diversity and richness. One such study employed metagenomic analysis[17] of recipients which revealed an increased presence of Firmicutes, Bacteroidetes, and Microviridae, a reduction of Proteobacteria and simultaneously they found that FMT caused a long-lasting increase in the abundance of *Faecalibacterium prausnitzii*[18].

Beyond understanding which species are present after success of FMT, a study looked to understand some of the metabolic changes that lead to the taxonomic shift witness after successful FMT. One such study[17] found that following FMT, there was inhibition of bacterial fluorobenzoate degradation and stimulating D-arginine and secondary bile acid biosynthesis, affected sporulation and toxin production by *C. difficile*[17].

TABLE 1. RECENT TRIALS ON "NEXT GENERATION PRODUCTS".

Next generation FMT products for CDI	Methods	Objectives	Results
Bacterial mixture of 12 bacterial strains, 5×10^{10} bacteria of each strain (Escherichia coli, MT-1108-1 Escherichia coli, MT-1109 Enterococcus cassiliflavus, Enterococcus gallinarum, Bacteroides thetaiotaomicron, Bacteroides ovatus, Bacteroides vulgatus, Clostridium bifermentans, Clostridium innocuum, Coprobacillus cateniformis, Lactobacillus rhamnosus, Lactobacillus gasserii) + 200 ml 0.9% saline for enema, strains (all sensitive to metronidazole and ampicillin) isolated from faeces of healthy donors[6].	• Prospective, open-label 3-arm, multicentre (Denmark) randomized controlled trial. • 96 participants with ≥ 1 CDI recurrences, divided into 3 groups, all received a pre-treatment with vancomycin 125 mg x 4 for 7-14 days • Group 1 (n = 31): after antibiotic therapy, they received rectal bacteriotherapy 1 enema daily for 3 consecutive days; group 2 (n = 34): after antibiotic therapy, they received FMT by enema once (with possible repetition for 2 or 3 infusions within 14 days); group 3 (n = 31): after vancomycin 125 mg x 4 daily for 14 days they received additional five weeks of tapering	• Evaluation of the safety and efficacy of the 3 therapeutic strategies in preventing recurrence within 90 days • Evaluation on 180-day all-cause mortality among the 3 groups	• Treatment success rates of 1-3 infusions of rectal FMT versus bacterial mixture: 76% *vs*. 52%, OR 3.0 (1.1-8.8), $p = 0.04$ • Treatment success rates of bacterial mixture *vs.* vancomycin was similar: 53% *vs*. 45% ($p = 0.61$). • The mortality rate of the 3 groups: 6% for the FMT group, 13% for bacteriotherapy group, and 23% for the vancomycin group.
RBX7455: orally capsules derived from a reduction and filtration of RBX2660, encapsulated (V-caps® enteric, Capsugel, a Lonza Company, Morristown, NJ, USA), room temperature-stable[7].	• Prospective, monocentric (US) phase I open-label trial • A total of 30 participants with ≥ 1 CDI recurrences treated by standard antibiotic therapy, divided equally into 3 groups receiving different dosages of RBX7455 • Group 1: 4 capsules x 4/daily for 4 days; Group 2: 4 capsules x 2/daily for 2 days; Group 3: 2 capsules x 2/daily for 2 days	• Evaluation of safety and efficacy of RBX7455 in preventing rCDI recurrence after 8 weeks, at different dosages • Evaluation of faecal microbiome before and for 6 months after treatment	• Treatment success rates: 90% for group 1, 80% for group 2, 100% for group 3 • 91% (88/97) of RBX2660 responders remained CDI occurrence-free after 24 weeks, and no SAEs related to treatment occurred • After 6 months responders' microbiomes showed an increased abundance of Bacteroides and Clostridia

CONTINUED

TABLE 1 *(CONTINUED)*. RECENT TRIALS ON "NEXT GENERATION PRODUCTS".

Next generation FMT products for CDI	Methods	Objectives	Results
Microbial Ecosystem Therapeutic 2 (MET-2): orally capsules contain 3.2×10^5 to 3.2×10^{11} CFU of 40 purified strains of lyophilized bacteria from a single healthy donor, but subsequently manufactured independently of donors[8].	• Prospective, single-group, monocentric (Canada) phase I open-label trial • 19 participants with mild to moderate C difficile infection and ≥ 1 CDI recurrences within 12 months of CDI treated by standard antibiotic therapy • Initial treatment with 10 capsules daily for 2 days, then 3 capsules daily for the following 8 days. If CDI within 40 days they received a rechallenge with 20 capsules daily for 2 days, then 3 capsules daily for the following 8 days	• Evaluation of the safety and efficacy of MET 2 in preventing recurrence after 40 days and after 130 days • Evaluation of quality of life before and after treatment (HRQoL)	• Treatment success rates: 79% after initial treatment, and 95% after 40 days from rechallenge in patients with recurrence within the first 40 days. 84% was the average treatment rate at day 130. • No SAEs related to the product occurred • After MET 2, alpha diversity in stool microbial composition was increased ($p = 1{\cdot}93 \times 10^{-6}$) • After MET 2 an improvement in HRQoL was recorded
RBX2660: a microbiota suspension, single-dose ready-to-use enema bag, consisting of 50 g of stool from healthy donor/150 mL + 0.9% saline/ polyethylene glycol 3350, containing ≥ 10^7 CFU/mL, stored frozen at ≤ –80°C for at least 45 days and stored at room temperature for up to 2 days before administration by enema[9].	• Prospective, multicenter (US and Canada), open-label Phase 2 trial • 146 participants with ≥ 2 CDI recurrences treated by standard antibiotic, therapy or ≥ 2 episodes of severe CDI requiring hospitalization • 2 doses of RBX2660 7 days apart • Comparison with a historical cohort treated with standard antibiotic therapy	• Compare treatment success (absence of CDI diarrhea without the need for retreatment for 8 weeks after completing study treatment) of RBX2660 to the historical control group • Evaluation of the safety profile of RBX2660, including adverse events and CDI occurrence through 24 months after treatment • Evaluation of faecal microbiome before and after treatment	• Treatment success rates (compared to historical controls): 78.9% *vs*. 30.7% ($p < 0.0001$; Chi-square test) • 91% (88/97) of RBX2660 responders remained CDI occurrence-free after 24 months, and no SAEs occurred • The faecal microbiota becomes more similar to RBX2660 also after 24 months

CONTINUED

TABLE 1 *(CONTINUED)*. RECENT TRIALS ON "NEXT GENERATION PRODUCTS".

Next generation FMT products for CDI	Methods	Objectives	Results
Bacterial mixture of 12 bacterial strains, 5×10^{10} bacteria of each strain (MT-1108-1 Escherichia coli, MT-1109 Enterococcus Cassiliflavus, Enterococcus gallinarum, Bacteroides thetaiotaomicron, Bacteroides ovatus, Bacteroides vulgatus, Clostridium bifermentans, Clostridium innocuum Coprobacillus cateniformis, Lactobacillus rhamnosus Lactobacillus rhamnosus Lactobacillus gasserii) + 200 ml 0.9% saline for enema, strains (all sensitive to metronidazole and ampicillin) isolated from faeces of healthy donors[10].	• Retrospective cohort study (Denmark) • 280 patients with recurrent or refractory CDI who had undergone FMT (n = 145) or RBT (n = 135)	• Evaluation, during the five years after the treatment of: risk of hospital admission, overall survival, risk of MDR; onset of predetermined diseases (cancer, diabetes mellitus, hypertension and inflammatory bowel disease)	• No differences were found in onset of any of the analysed diseases, in risk of MDR, survival (aHR 1.03; 95% CI 0.68-1.56, $p = 0.89$), risk of hospital admission (aHR 0.92; 95% CI 0.72-1.18, $p = 0.5$)

CFU: colony-forming unit; US, United States; CDI, clostridium difficile infection; FMT, faecal microbiota transplantation; HRQoL, C. difficile Health-Related Quality of Life Questionnaire; aHR, adjusted hazard ratio; CI, confidence interval; OR, Odds Ratio; SAEs, serious adverse events.

Further insights into the immunological methods through which FMT exerts its effects were advanced by a study which found that FMT seems to activate immune response by Th17 cells and by TcdB-specific T cell memory, increasing TCR (T-Cell Receptors) repertoire and not inducing merely a clonal expansion[19]. Furthermore, novel emerging molecular mechanisms appear to contribute to the efficacy of FMT that could restore systemic and intestinal microRNAs (miRNAs) production and sequentially activate cytoprotective cascade against *C. difficile* toxin B (TcdB)[20].

Side Effects

The other side of the coin is that FMT may have also collateral long-term effects, transferring potential pro-carcinogenic microorganisms. In a retrospective cohort of rCDI patients treated with FMT, Nooij et al[21] found the presence of Psk+ *E. Coli*, a strain able to produce a genotoxin peptide, in 27 of 49 recipients and 3 of 8 donors. Despite its currently unknown duration of colonization by pks+ *E. Coli*, psk+ donors could contribute to the persistence in the gut microbiota of the patients.

Severe CDI

The utility of FMT in severe or fulminant colitis has been investigated in many studies, but data remains of low quality. A recent meta-analysis[22] calculated an average cure rate of 61.3% (95% CI 43.2-78.0%), but 10.9% (95% CI 0.2-30.2%) of patients experienced SAEs, and the mortality rate was of 15.6% (95% CI 7.8-25.0%).

INFLAMMATORY BOWEL DISEASE

FMT is emerging as a promising treatment in IBD, mainly ulcerative colitis (UC). A network meta-analysis[23] compared FMT and other targeted pharmacotherapies in UC and showed that it is comparable with other agents in inducing clinical response, clinical remission, endoscopic remission, and safety. A randomized, double-blind, placebo-controlled trial evaluated the efficacy of oral lyophilized FMT for the treatment of active ulcerative colitis. Patient recruitment was stopped early because of the COVID-19 pandemic. After 8 weeks, 8 of 15 patients (53%) were in corticosteroid-free clinical remission, with endoscopic response or remission, against 15% in the placebo group (difference 38.3%, 95% CI 8.6-68.0; $p=0.027$)[24].

Despite the encouraging results, there is a paucity of data on the long-term durability and safety of FMT in UC. Seth et al[25] reported that in a cohort of 27 patients, who received 3 sessions of FMT through colonoscopy, corticosteroid and azathioprine-free clinical remission at week 24 was observed in 13 patients (48%). Ren et al[26] recruited 31 patients with active UC who received FMT at baseline and 2-3 months later, and during 4 years of follow-up, the relapse rate in the 12 remission patients was 33.33% within 1 year, and 58.3% within 4 years. Haifer et al[27] reported the long-term data of patients who received FMT followed by enema therapy for 8 weeks with a median follow-up of 66 months. The median time to disease relapse was 6 months in the 35 patients who achieved steroid-free clinical remission after FMT and, after 12 months, remission was observed in 12 patients (34.2% of patients in remission at study conclusion).

Another relevant area of interest is the identification of new parameters to maximize the effectiveness of FMT. The abundance of *Filobasidium spp.* in donor feces was correlated with clinical remission following FMT in UC patients[28]. Smith et al[29] tested the effect of antibiotic pretreatment, finding that 6 of 11 pre-treated patients experienced remission after 6 weeks *vs.* 2 of 11 non-pretreated patients, suggesting that it can contribute to microbiome engraftment and clinical effectiveness.

IBD patients are more exposed than the general population to CDI, and they can be effectively treated with FMT. Allegretti et al[30] evaluated the IBD-related outcomes after a single

FMT, showing that 11 out of 15 (73.3%) Crohn's disease (CD) patients had IBD improvement and 26.6% had no disease activity change. On the other hand, 22 out of 34 (62%) UC patients improved, 29.4% had no change, and 4% had a de novo flare.

Growing evidence suggests that FMT could be effective also for CD. The meta-analysis by Cheng et al[31] included 12 trials and showed that after FMT 0.62 (95% CI 0.48, 0.81) of CD patients achieved clinical remission and 0.79 (95% CI 0.71, 0.89) achieved clinical response, with no major adverse events. Moreover, FMT could be considered in CD patients with prior loss of response or intolerance to infliximab, achieving clinical response in 71.9% of patients and clinical remission in 62.5% of patients at six months, in a cohort of 32 patients[32].

In chronic pouchitis, a recent single-center, double-blinded, placebo-controlled trial evaluated FMT in 26 patients, finding that it was not effective[33]. Regarding diversion colitis, Tominaga et al[34] reported that in five patients treated with FMT, all patients achieved endoscopic remission (UCEIS score of 0 or 1) and symptomatic improvement.

IRRITABLE BOWEL SYNDROME

Intestinal dysbiosis is believed to be involved in the pathophysiology of irritable bowel syndrome (IBS), but the current literature shows conflicting results on the potential role of FMT in treating IBS.

A meta-analysis by Wu et al[35] included 7 RCTs comprising 472 patients and demonstrated that FMT was not associated with improvement in global symptoms in IBS at 12 weeks and at 1 year follow-up. The subgroup analyses showed that FMT could be effective when fresh stool is used and when it is administered *via* endoscopy. Several factors could influence the outcome of FMT in IBS: male sex and low fecal Alistipes levels are associated with a lower response to the treatment, while other factors, such as age, IBS duration, IBS subtype, and IBS symptoms were not associated[36]. Another study[37] found that patients affected by severe IBS symptoms have a higher response rate to FMT compared with those with moderate IBS symptoms.

An additional factor that could influence the effect of FMT is antibiotic pretreatment. Singh et al[38] evaluated the effect of a 7-day course with ciprofloxacin and metronidazole or rifaximin on bacterial engraftment in IBS-D patients who received FMT, showing that pretreatment significantly reduced bacterial engraftment, and observing no differences on clinical outcomes.

Anxiety and depression frequently co-occur in IBS population, plausibly through the gut-brain axis bidirectional communication. A recent study[39], in which 18 IBS-D patients with mild-modest anxiety and depression behaviors were recruited, showed that FMT could effectively alleviate the anxiety and depression behaviors.

Long-term clinical effects of FMT have been investigated in two studies[40,41] in the last year. El-Salhy et al[40] observed that between 77 patients who had responded to FMT after 3 months in a previous trial, most patients had maintained their response after 1 year. Moreover, after one year they improved abdominal symptoms, fatigue, and quality of life compared to 3 months after FMT. The retrospective study of Cui et al[41] confirmed the efficacy of FMT over a 5-year follow-up and observed that the treatment effect declines over time, suggesting that periodic treatment could be necessary.

Chronic Constipation

Chronic constipation is a prevalent gastrointestinal disorder, and an increasing number of studies are showing that intestinal motility and constipation are closely related to gut microbiota. A meta-analysis by Fang et al[42] included 5 randomized controlled trials and 409 patients and evaluated the joint efficacy of FMT and laxatives in the treatment of functional constipation. The authors showed that combined therapy of FMT and laxatives could improve stool frequency, stool consistency, the severity of constipation, and the quality of life, compared to laxatives alone. A retrospective cohort study by Yang et al[43] evaluated the effectiveness of FMT combined with biofeedback in mixed constipation, showing that the combination was

superior in terms of spontaneous bowel movements frequency (2.15 ± 1.05 *vs.* 3.61 ± 0.89 p = 0.0031), constipation symptoms and quality of life compared to biofeedback alone. The efficacy of FMT for treating functional constipation could be associated with the abundance of key bacteria, such as Fusicatenibacter and Paraprevotella[44].

METABOLIC DISEASES

Metabolic Syndrome

Gut microbiota plays an important role in the pathogenesis of metabolic syndrome, one of the greatest health epidemics in our society. A randomized double-blind, placebo-controlled trial tested the supplementation of high-fermentable (HF) or low-fermentable (LF) fibers, as an adjunct to FMT or alone to modulate metabolic outcomes. 70 patients were randomized into four groups: FMT-HF (n = 17), FMT-LF (n = 17), HF (n = 17), and LF (n = 19), and the primary outcome was the evaluation of changes in insulin sensitivity using the homeostatic model assessment (HOMA2-IR/IS). A significant improvement in HOMA2-IR has been observed in the FMT-LF group (3.16 ± 3.01 at 6 weeks *vs.* 3.77 ± 3.57 at baseline; p = 0.02), while there was no difference in the other groups[45]. A small trial randomized 24 patients affected by metabolic syndrome to receive FMT from a lean donor or autologous, in combination with a Mediterranean diet, but no synergistic beneficial metabolic effects on glucose metabolism were achieved[46]. Other retrospective studies found that FMT has an antihypertensive effect in hypertensive patients[47], and that is effective in reducing blood lipid levels[48].

Diabetes

In a nonblinded, single-arm trial, Ding et al[49] treated 17 patients affected by type 2 diabetes mellitus with FMT, with the primary endpoint of evaluating glycated hemoglobin changes. After 12 weeks the authors reported a significant decrease in glycated hemoglobin (from 7.565 ± 0.148 to 7.190 ± 0.210, p<0.01), blood glucose, uric acid, and an increase in postprandial C-peptide. Moreover, they suggested that the pre-treatment abundance of Rikenellaceae and Anaerotruncus could predict the clinical response to FMT. An open-label trial evaluated the health improvement of a new diet consisting of probiotics, prebiotics, and whole grains, alone or combined with FMT, in 13 patients affected by type 2 diabetes. After 90 days the authors observed that both diet and diet plus FMT were associated with weight loss and reduction in fasting blood glucose and glycated hemoglobin. Interestingly, weight loss was faster in the diet plus FMT group[50].

MALIGNANCIES, AND GRAFT VS. HOST DISEASE

Recent evidence[51] suggests that gut microbiota plays an important role in regulating different aspects of cancer cachexia. A double-blind randomized placebo-controlled trial enrolled 24 cachectic patients affected by metastatic gastroesophageal cancer, treated with allogenic FMT from healthy obese donors, or autologous FMT, before palliative chemotherapy. The twelve patients in the allogenic group did not improve the cachexia outcomes, but showed better disease control rate, overall survival, and progression-free survival compared to the autologous group[51].

A multicenter study[52] evaluated the effect of autologous fecal microbiota transplantation in 25 patients affected by acute myeloid leukemia treated with induction chemotherapy and antibiotics. Autologous FMT showed to be safe and effective in microbiota restoration after its disruption, as indicated by the richness and diversity indices after the procedure.

Acute, treatment-refractory, gastrointestinal graft-versus-host disease, is a life-threatening complication of allogeneic hematopoietic stem cell transplantation. In a prospective cohort study, the authors observed that 4 out of 9 patients affected by treatment-refractory

GI-GvHD responded to FMT, with a significant survival benefit ($p=0.017$). Moreover, they reported that the most important factor associated with FMT failure was the concomitant use of broad-spectrum antibiotics ($p=0.048$)[53].

In a clinical study by Zhao et al[54] the patients affected by grade IV steroid-refractory GI-GvHD were assigned to the FMT group (23 patients) or the control group (18 patients). Clinical remission was significantly higher in the FMT group at 14 and 21 days, and after 90 days the FMT group showed a better overall survival.

MULTIDRUG-RESISTANT ORGANISMS

Multidrug-Resistant Organisms (MDROs) are among the biggest concerns for public health systems globally and emerging evidence[55] is indicating FMT as a useful therapeutic tool since the gut microbiome could act as a reservoir.

By analysing 14 studies, FMT appears to be effective in 55.9% of the cases after 1 month (95% CI 0.42-0.74). Enterobacter hormechai, Klebsiella oxytoca, Citrobacter freundi, Acinetobacter baumanii, and Citrobacter koseri were the more susceptible MDROs (100% of decolonization after 1 month). Otherwise, Serratia marcescens was the organism with the lowest rate of response after FMT (33.3%)[56].

NEUROLOGICAL DISEASES

Parkinson's Disease

Alterations in gut microbiota (GM) and gastrointestinal symptoms may occur years before the classic onset of Parkinson's Disease (PD)[57].

Kuai et al[58] demonstrated that a single infusion of frozen FMT via colonoscopy increased community richness, and the procedure showed also improvements in the Unified Parkinson's Disease Rating Scale (UPDRS) score, the Non-Motion Symptom Questionnaire (NMSS), and the Wexner constipation score. These results were replicated by Segal et al[59], proving an improvement also after 24 weeks in terms of UPDRS-III score (from -13 to 7 points), NMSS scores (from -2 to -45 points), and Wexner score (from median 13.5 to median 9).

This data may suggest an influence of FMT not only on gastrointestinal symptoms but also on neurological symptoms, acting through the gut-brain axis.

Psychiatric Disorders

Increasing evidence highlight the role of the modulation of GM in the management of psychiatric disorders. After 8 weeks of oral assumption of MET-2 (Table 1), 12 patients with a previous diagnosis of major depressive disorder or generalized anxiety disorder, showed an improvement in Montgomery-Asberg Depression Rating Scale (MADRS) scores (from mean 19.00, SD 4.843 to mean 8.667, SD 8.732; $p=.002$) and in 7-item Generalized Anxiety Disorder scale (GAD-7) scores (from mean 13.58, SD 4.010 to mean 7.333, SD 6.583; $p=.03$)[60].

Autism

Autism spectrum disorders (ASD) are frequently associated with gastrointestinal (GI) disturbances, with a documented reduction of Bacteroidetes/Firmicutes[61].

In a cohort of 40 ASD children, both oral FMT capsules and FMT *via* colonoscopy induced a significant reduction in the abundance of Eubacterium coprostanoligenes, which was associated with decreased serum levels of serotonin and GABA and increased levels of dopamine. These changes correlated with an improvement of neurological and GI symptoms (evaluated through the Gastrointestinal Symptom Rating Scale (GSRS scores) for the following 8 weeks after the FMT procedure[62].

Alcohol Use Disorder

A growing number of studies are trying to discover the role of GM in alcohol use disorder (AUD) through an impaired gut-brain axis[63].

Recently, a phase 1 randomized trial by Bajaj et al[64] indicated that FMT *via* enema from selected donors with a higher abundance of Lachnospiraceae and Ruminococcaceae could be a safe therapeutic tool to reduce craving in patients with AUD-related cirrhosis.

After 15 days of treatment, craving decreased significantly in 90% of the 10 patients enrolled in the treatment group, in conjunction with an improvement in cognition and psychosocial quality of life (QoL). Moreover, FMT reduced serum IL-6 and lipopolysaccharide-binding protein (LBP) and increased microbial diversity with higher SCFA-producing taxa as *Ruminococcaceae*. After 6 months, the FMT group still showed fewer AUD-related serious adverse events (SAEs) compared to placebo groups (1 *vs.* 7, p=0.02).

MISCELLANEOUS

Psoriatic Arthritis

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis, frequently associated with a distinct gut microbial composition that could play a role in the pathogenesis[65].

Even though further investigations are needed to understand the efficacy of different FMT protocols, a recent RCT by Kragsnaes et al[66] failed to verify the beneficial effect of a single frozen FMT *via* gastroscopy on methotrexate failure rates and clinical scores after 26 weeks. FMT was found to be even inferior then placebo in this cohort of 31 patients with active PsA (≥3 swollen joints), showing a higher rate of treatment failure (60% *vs.* 19%) and lower Health Assessment Questionnaire Disability Index (HAQ-DI) scores (0.07 *vs.* 0.30; 95% CI 0.02 to 0.44; p=0.031).

Atopic Dermatitis

Current therapies for atopic dermatitis (AD) are still few, and novel promising therapies target the modulation of GM, because of its potential involvement in the regulation of host immune responses[67].

A recent cross-over study[68] demonstrated the efficacy of FMT capsules in reducing the average Scoring Atopic Dermatitis (SCORAD) (85.5 ± 8.4%, Wilcoxon p = .018) and weekly topical corticosteroids usage (90.5 ± 10.7%, Wilcoxon p = .008), at 8 weeks after the treatment phase.

Acute on Chronic Liver Failure

In cirrhosis, impaired equilibrium among gut bacterial communities could lead to acute liver decompensation, and different microbiota profiles may impact the decompensation rates[69].

Thus, Sharma et al[70] indagated the possible role of fresh FMT *via* a nasojejunal tube in the treatment of patients with alcohol-related acute-on-chronic liver failure.

Among 33 patients enrolled, 13 were assigned to FMT group and, after 28 days, this group showed, compared with standard of care arm, resolution of encephalopathy (100% *vs.* 57.14%, p = 0.11), resolution of ascites (100% *vs.* 40%, p = 0.04) and a better overall survival (100% *vs.* 60%, p = 0.01). At the same time point, FMT reduced serum IL1β by 21.39% (IQR -73.67 to 7.63) from the baseline.

Sustained and better response was also found after 90 days (53.84% *vs.* 25%, p = 0.02), and an analysis of adverse events found no difference in both groups[70], unlike a subsequent systematic review that recorded a SAEs rate of 3.6%[71].

Gout

Gout is an inflammatory arthritis caused by the deposition of monosodium urate crystals. In humans, the degradation of alimentary uric acid is supplied, at least in part, to intestinal bacteria, because of the absence of an intestinal uricase[72]. At the genus level, a novel metagenomic analysis found an increased abundance of Fusobacterium, Bacteroides and Prevotella, a reduction of the family of Enterobacteriaceae[73].

Hence, Xie et al[74] used washed microbiota transplantation (WMT), a micro-filtrated FMT to remove potentially harmful things, such as parasite eggs or fungi, in 11 patients with recurrent gout. FMT induced a reduction of duration time and decreased rates of acute flares ($p < 0.01$), together with lower levels of uric acid ($p = 0.031$), Lipopolysaccharides (LPS), and diamine oxidase (DAO).

CONCLUSIONS

This year has seen further mechanistic insights into what underpins the success of FMT and has also highlighted that FMT may be effective in a variety of health-related conditions. It is possible that in future years we will see further refinements to FMT which may improve efficacy, safety and utility in a variety of healthcare conditions.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Contributions

Writing - original draft preparation: M. Fiorani, L.E. Del Vecchio, J.P. Segal, G. Ianiro; Supervision and Conceptualization: G. Ianiro and J.P. Segal. All authors have read and agreed to the published version of the manuscript.

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