Faecal microbiota transplantation: applications and limitations in treating gastrointestinal disorders

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ABSTRACT

The process of stool transfer from healthy donors to the sick, known as faecal microbiota transplantation (FMT), has an ancient history. However, only recently researchers started investigating its applications in an evidence-based manner. Current knowledge of the microbiome, the concept of dysbiosis and results of preliminary research suggest that there is an association between gastrointestinal bacterial disruption and certain disorders. Researchers have studied the effects of FMT on various gastrointestinal and non-gastrointestinal diseases, but have been unable to precisely pinpoint specific bacterial strains responsible for the observed clinical improvement or futility of the process. The strongest available data support the efficacy of FMT in the treatment of recurrent *Clostridium difficile* infection with cure rates reported as high as 90% in clinical trials. The use of FMT in other conditions including inflammatory bowel disease, functional gastrointestinal disorders, obesity and metabolic syndrome is still controversial. Results from clinical studies are conflicting, which reflects the gap in our knowledge of the microbiome composition and function, and highlights the need for a more defined and personalised microbial isolation and transfer.

INTRODUCTION

The intestinal microbiota has long been recognised as partakers in human health and disease. In 400 B.C. Hippocrates stated that, '...death sits in the bowels...' and '...bad digestion is the root of all evil....'.¹ Faecal transfer from healthy donors to the sick in order to treat disease has been described in the ancient medical literature. In the 4th century in China, Ge Hong described the use of human faecal suspension by mouth for patients with food poisoning or severe diarrhoea. The first literary record of the application of faecal transplantation was reported in the Chinese handbook of emergency medicine 'Handy Therapy for Emergencies', and at that time it was considered a medical miracle that brought patients

back from the edge of death. Later in the 16th century, Li Shizhen described using fermented faecal solutions, fresh faecal suspensions, dry faeces, or infant faeces for treatment of severe diarrhoea, fever, pain, vomiting and constipation. Alternative medicine doctors labelled these products with unique names such as 'yellow soup' to avoid patients' repugnance. In the 17th century, faecal transplant was used in veterinary medicine orally and rectally, and was termed 'transfaunation'.² Much later, Bedouins recommended consumption of fresh, warm camel faeces as a remedy for bacterial dysentery, the efficacy of which was anecdotally confirmed by German soldiers in Africa during World War II.³

In modern medicine, the use of faecal enemas for the treatment of 'pseudomembranous colitis' was first reported in 1985 by the surgeon Eiseman.^{4 5} Over the last three decades, faecal transplant has received increased scrutiny after numerous studies proved that stool is a biologically active complex mixture of living organisms with therapeutic potential, and the intestinal microbiota was recognised as the biologically active component of stool.⁶ Thus, the process of stool transfer from a healthy donor to a person suffering from physical illness or symptoms is now termed faecal microbiota transplant (FMT).

The routes of administration of FMT have changed over the years with retention enemas being the most common route of administration in the 1980s. Subsequently, alternative routes were used including nasogastric (NG) tube instillation of the faecal material, administration during upper endoscopy and colonoscopy in 2000s and self-administered enemas in 2010. More recently, concentrated cryopreserved faecal-derived bacteria has emerged as a viable option that has shown promising results in the treatment of recurrent *Clostridium difficile* infection (RCDI).^{6 7} All delivery methods seem to be

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effective and there is no consensus on the best route of administration. Retention enemas are simple and cheap, but can be cumbersome to some patients. Stool delivery via NG tube is associated with discomfort and is unappealing to most patients. Endoscopic delivery especially via colonoscopy, although associated with the usual procedural risks and costs, is well tolerated and allows for the additional benefit of evaluating the colonic mucosa which can be helpful in ruling out competing pathology such as inflammatory bowel disease (IBD), and allows for endoscopic re-evaluation and comparison if a repeat FMT is necessary.

Present knowledge of the gut microbiome and its effect on disease state is in the development phase, and the use of FMT to treat gastrointestinal (GI) and non-GI illness is limited. Currently, the best evidence is in the treatment of RCDI, and the use of FMT in other conditions is considered investigational. This review will discuss our current knowledge on the use of FMT in various GI conditions and highlight key evidence and shortcomings in each area.

FMT IN THE TREATMENT OF *C. DIFFICILE*

RCDI is becoming an increasingly common healthcare problem, occurring in 19–45% of patients after successful treatment of the primary infection.^{8,9} The recurrence is usually due to reinfection with the same strain of *C. difficile*, or less commonly a new infection with a different strain. In some instances, the reinfection is likely due to the host's altered immune response, however it is largely attributed to the persistence of *C. difficile* spores, which are resistant to antibiotics, especially if the residual intestinal microbiota is disrupted and cannot restrain the infection.¹⁰

Several therapeutic modalities are available for RCDI. The treatment of the first and second recurrences mainly focuses on retreatment with the original antibiotic or switching to a different antibiotic with different dosing strategies. Antibiotics that have been shown to be effective for initial and RCDI include metronidazole, vancomycin and fidaxomicin. Clinical trials assessing the efficacy of immunologic therapy using pooled intravenous immunoglobulin (IVIG), and attempts to restore the damaged intestinal microbial milieu using probiotics have been less than ideal at best in treating RCDI.^{10–13} After the third recurrence, especially if pulse/tapered vancomycin regimen has been tried, FMT should be considered.¹⁴

The use of FMT for the treatment of 'pseudomembranous enterocolitis' dates back to 1958.^{4,5} In 1983, Schwan *et al*¹⁵ reported the first confirmed case of RCDI with 'prompt and complete normalization' of bowel function up to 9 months after treatment with FMT.⁵ Initially, FMT was administered by retention enemas. Later, faecal infusion was administered via NG/duodenal tube. Subsequently, other methods for administration of FMT have been successfully used including faecal

infusion via colonoscopy, self-administered enemas and more recently as enteric-coated capsules.¹⁶

Regardless of the route of administration, there is ample evidence supporting the fact that FMT is a highly effective and safe therapeutic option for RCDI.

The mean cure rate of FMT for RCDI based on case reports and case series is 90%.¹⁴ A recent systematic review of more than 500 cases treated with FMT demonstrated that 87% of patients experienced resolution of diarrhoea and no severe adverse events were reported.¹⁷ Two randomised clinical trials have assessed the efficacy of FMT for RCDI compared with vancomycin. Van Nood *et al* showed that 13 of the 16 patients (81%) with RCDI treated with nasoduodenal infusion of donor faeces (after an initial regimen of vancomycin for 4 days, followed by bowel lavage) had resolution of diarrhoea after the first infusion. Two of the three remaining patients had resolution of diarrhoea after a second infusion. No significant adverse events were observed, except for mild diarrhoea and abdominal cramping on the day of faecal infusion. In this study, the control groups (standard vancomycin regimen for 14 days and standard vancomycin regimen with bowel lavage) had a 31% and 23% resolution of diarrhoea, respectively ($p < 0.001$ for both groups compared with FMT group).¹⁸ In a more recent open-label, randomised clinical trial, Cammarota *et al* assessed the effect of FMT via colonoscopy in patients with RCDI compared with vancomycin. In the FMT group, patients received a 3-day course of vancomycin followed by faecal infusion via colonoscopy. Overall, 18 of the 20 patients (90%) in this group were cured compared with 26% ($p < 0.0001$) in the control group (standard regimen followed by a pulse regimen of vancomycin) concluding that FMT is significantly more effective than vancomycin in the treatment of RCDI. Additionally, 7 of the 20 patients in the FMT group were found to have pseudomembranous colitis (PMC) on colonoscopy. One patient received only one repeat infusion and another patient received two repeat infusions (with an interval of 1 week). Both patients later died from apparent *C. difficile*-related clinical complications and were considered as FMT failure in the intention to treat and per-protocol analyses. Therefore, they amended the protocol to treat any subsequent PMC with multiple faecal infusions repeated every 3 days until resolution of colitis is achieved. The remaining five patients with PMC received multiple faecal infusions repeated every 3 days until resolution of colitis was achieved (three patients received two infusions; one patient received three infusions and one patient underwent four infusions).

In contrast, none of the 13 patients without PMC required a repeat faecal infusion and all were cured with the initial infusion. This suggests that the presence of pseudomembranes makes the treatment of *C. difficile* more challenging and increases the likelihood of requiring repeat FMT. In this study, adverse events associated with faecal infusion were diarrhoea (94%), bloating and abdominal cramps (60%), all resolved within 12 h after

faecal infusion.¹⁹ Mandalia *et al*²⁰ also recently showed that FMT is as effective in immunocompromised patients as in non-immunocompromised patients with no significant difference in serious adverse events (SAEs). In summary, the evidence clearly suggests that FMT is safe and effective, and is an important therapeutic option for the treatment of RCDI.

FMT IN THE TREATMENT OF IBD

The exact pathogenesis of Crohn's disease (CD) and ulcerative colitis (UC) is not fully understood and is thought to be the result of the interplay of multiple factors. While genetic predisposition is well established in some patients with CD and UC, in the majority of cases no genetic association can be found. This could be due to a lack of genetic association in certain patients with IBD or due to limitations of genome-wide association studies to identify less common genetic variants associated with the development of IBD.²¹ However, it is clear that other environmental factors play a role in the pathogenesis of IBD. In the early 1900s, associations have been found between certain strains of bacteria and IBD.^{22–24} In the late 1900s, the recurrence of CD was noted postoperatively with restoration of faecal stream after ileal resection and ileocolonic anastomosis.^{25–26} It was also found that using antibiotics such as metronidazole following ileal resection was associated with decreased severity of early recurrence of CD in the neo-terminal ileum and delayed symptomatic recurrence.²⁷ Furthermore, certain genetic mutations seen in CD patients (NOD2, ATG16L1, FUT2 and others) can have significant effects on the composition of the intestinal microbial milieu.^{28–29} A variety of human and animal data support the hypothesis that IBD is a result of immune response to the faecal microbiota in genetically susceptible individuals. These immune responses may alter the microbiome leading to the loss of species complexity, particularly of protective microbes, resulting in disrupted microbiome homeostasis, a term referred to as dysbiosis.³⁰ It is not clear whether tissue damage results from an abnormal immune response to a normal microbiota or from a normal immune response against abnormal microbiota, and whether dysbiosis is a cause, or a result of IBD.²⁹ The conventional approach for treatment of IBD has been on targeting the inflammatory response. However, recent understanding of the microbiome, and the concept of dysbiosis and its potential role in the pathogenesis of IBD have made alternative treatment approaches such as FMT, an attractive field to explore.

The use of FMT from healthy donors as a means to overcome gut dysbiosis and restore microbiome homeostasis is not a new concept. In 1989 Dr Bennet, who was a UC patient himself, reported 6 months of clinical remission after self-administration of FMT by retention enema.³¹ However, until recently, the research on FMT in IBD has been sparse, mainly limited to case

reports.^{31–36} In a systematic review of FMT in patients with IBD, Anderson *et al* found that FMT lead to a reduction or a complete resolution of symptoms and cessation of IBD medications within 6 weeks in 76% of patients and 63% having no evidence of active disease 3–36 months after FMT. Outcome data extracted for 12/15 patients with comorbid *C. difficile* infection showed resolution of *C. difficile* in all patients and a marked reduction or a complete resolution of diarrhoea in 92% of the participants.³⁷ In another systematic review, the overall success rate of FMT in patients with IBD was 78.4%, and in patients with comorbid *C. difficile* infection, 90.5% achieved resolution of the infection with improved response rate to IBD medications.³⁸ These two systematic reviews lacked high-quality evidence for FMT efficacy in IBD as they predominantly included case reports/case series, and included patients with and without comorbid *C. difficile* infection. They also contained several methodological limitations that likely inflated the results and quantitative analysis was limited by the statistical limitations of the included studies. Colman and Rubin reviewed 18 studies with 119 patients. The review included nine prospective, uncontrolled cohort studies, eight retrospective case series/case reports and one randomised, placebo controlled trial of FMT in patients with UC. It excluded the studies that included *C. difficile* and other GI infections. Overall 45% of patients with IBD achieved clinical remission, however, the clinical remission rate dropped to 36.2% when case studies were excluded to minimise the risk of publication bias. Subgroup analysis revealed pooled estimates of clinical remission to be highest (64.1%) in young population (age 7–20 years), and in patients with CD with a response rate of 60.5%. Clinical remission in patients with UC was much lower at 22%, similar to the remission rate suggested by the study by Moayyedi *et al*.³⁹ Mucosal healing was described in a limited number of cohort studies and was observed in 75% of case study patients, but in only 3% from cohort studies. Safety analysis in this review suggests that FMT is generally tolerable and safe with no SAEs during short-term follow-up. Nonetheless, multiple studies reported fever, abdominal tenderness, fatigue, flatulence, vomiting, bloating, and diarrhoea after FMT.⁴⁰ Two recently published randomised clinical trials assessed the safety and efficacy of FMT in patients with UC. The first study was a phase II double-blind placebo-controlled trial involving patients with mild to moderately active UC randomised to receive FMT from healthy donors or autologous faecal administration. Faecal infusion was administered via nasoduodenal tube at the start of the study and 3 weeks later with the primary end point of clinical remission (simple clinical colitis activity index scores ≤ 2) combined with ≥ 1 -point decrease in the Mayo endoscopic score at week 12. Thirty-seven patients completed the primary end point assessment, and neither the intention-to-treat nor the per-protocol analyses showed a statistically significant difference in clinical remission

and endoscopic improvement between the two groups.^{41 42} The other study was a placebo-controlled, double-blind randomised trial involving 75 patients with active UC without infectious diarrhoea assigned to receive weekly FMT via enema (n=38) or water enema (placebo group)(n=37) for 6 weeks. The primary outcome was remission of UC (Mayo score ≤ 2 and complete mucosal healing) at week 7. Stool samples were sent for microbiome analysis before and during treatment. Remission was achieved in 24% of patients after FMT and 5% of the water enema group ($p=0.03$), with histologic resolution of inflammation in 78% of responders in the FMT group. Stool from patients receiving FMT had greater microbial diversity, compared with baseline, than that of patients in the water enema group. Factors significantly associated with greater success of FMT include a recent diagnosis of UC (≤ 1 year) and being on immunosuppressants at the time of FMT. No difference in SAEs between the two groups was noted.³⁹

Knowledge of FMT efficacy in IBD is still in its infancy. The initial results from clinical trials are mixed and limited, likely due to differences in patient populations among different studies, disease severity in participants, delivery mechanisms of FMT, FMT preparations and post-transplant follow-up.⁴³ However, this does not eliminate the potential role of FMT in the treatment of IBD. It is unclear why some patients with IBD respond so impressively after FMT while others fail to respond. It is clear however that FMT is not a 'one size fits all' and there appears to be many factors that play a role in the success of this modality in the treatment of IBD. The host genotype, duration of disease, whether antibiotic use was associated with disease onset, certain types of IBD-associated dysbiosis, and/or donor characteristics are all factors that could potentially determine the final outcome and need further studies and better understanding.^{41 44} Currently, the use of FMT in the IBD population is restricted to investigational settings and several large clinical trials on this topic are underway.

FMT IN THE MANAGEMENT OF FUNCTIONAL GI DISORDERS

Functional GI disorders (FGIDs) are a group of disorders characterised by a constellation of symptoms that are not explained by other pathologically based disorders.⁴⁵ Irritable bowel syndrome (IBS) is the most prevalent FGID, accounting for 10–20% of the population in developed countries^{46–48} and has a profound effect on the quality of life and healthcare expenditure.^{49 50} The etiology of IBS is not completely understood, and it is thought to be multifactorial with genetic and environmental factors leading to altered GI motility, visceral hypersensitivity and low-grade inflammation, along with alteration in the brain–gut axis and psychological disturbances; leading to the syndrome of abdominal pain and altered GI function.^{51 52} The role of microbiota in the pathogenesis of IBS has been an area of interest in

medical research. Perhaps one of the strongest indicators of the role of gut dysbiosis in IBS is the development of postinfectious IBS (PI-IBS) after acute gastroenteritis. Despite being associated with up to sevenfold increase in the development of IBS, acute gastroenteritis does not lead to PI-IBS in the majority of patients, thus other factors must play a role, such as female gender and possibly psychological disturbances.⁵³

There are different lines of evidence to support the association of IBS with a disturbed gut microbiome including differences in colonic microbiota between patients with IBS and age and gender-matched controls, the suggestion that small intestinal bacterial overgrowth may be more prevalent in IBS, and the possibility that the state of low-level immune activation described in IBS might be triggered or sustained by the microbiota.⁵⁴ Additional evidence includes the clinical benefits observed in response to interventions that are likely to alter the gut microbiome in patients with IBS including the use of prebiotics, probiotics and antibiotics, with the most evidence being in the use of antibiotics in the treatment of diarrhoea-predominant IBS (IBS-D).⁵⁵

The use of the non-absorbable antibiotic rifaximin has been shown, in TARGET 1 and 2 trials, to improve non-constipated IBS symptoms, and in cases of recurrence, retreatment with rifaximin leads to incremental quality of life improvement to the enduring improvements following the initial treatment with rifaximin which lead to approval of rifaximin for the treatment of IBS-D.^{56 57} Although the exact mechanism by which antibiotics can lead to relief of global IBS symptoms and bloating is not clear, it is thought that gross alterations in the gut microbiome or modulation of the behaviour of gut microbiota are the primary mechanisms involved.

Several studies have found altered gut microbiome in patients with IBS. Decreased microbial diversity has been a consistent finding in these studies, similar to findings in patients with *C. difficile*, IBD and obesity. However, the changes in microbiota composition are not consistent across studies, likely due to different study populations and different methodologies for sample preparation and analysis.^{42 58–61} Additionally, recent studies suggest that faecal microbiota in patients with IBS can be responsible for certain components of IBS, such as visceral hypersensitivity, GI transit and gut–brain axis.^{42 62–64}

Despite being highly successful in the treatment of RCDI, the use of FMT as a treatment modality in IBS has only recently been explored. A case series of 55 patients who underwent FMT via faecal enema for IBS and IBD reported a cure in 36%, symptom relief in 16%, and no response in 47%. The results were reported with no distinction between the two diseases.³² Another case series of 45 patients received FMT via colonoscopy followed by faecal enema the next day, and were followed for up to 19 months. Nearly 90% of the patients reported immediate relief in defaecation, bloating and abdominal pain, with 60% showing long-term

benefit.⁶⁵ A third study included 13 patients with refractory IBS (9 with IBS-D, 3 with IBS-C, 1 with IBS-M) which were followed for up to 18 months. FMT was administered via esophagogastroduodenoscopy (EGD). A total of 70% of patients reported symptomatic relief following FMT with improvement reported in abdominal pain (72%), dyspepsia (67%), bowel habits (56%), bloating (50%) and flatus (45%).^{66 67} Larger, well designed, randomised controlled trials are needed to determine the efficacy of FMT in IBS.

FMT AND OBESITY

The obesity epidemic and the rising incidence of the metabolic syndrome in the last decades, along with limited treatment options have lead researchers to investigate potential factors contributing to the development of obesity.⁴² The development of obesity is a complex process involving genetic and environmental factors. Studies have revealed profound changes in the composition and metabolic function of the gut microbiota of obese participants.^{68 69}

The exact mechanisms by which 'obese microbiota' influence obesity is still unclear, however, animal models have provided some insight on the process. Lean and obese mice have been found to have different gut microbiome, with increased capacity for energy harvest from the diet in obesity-associated gut microbiome. Mice colonised with the obesity-associated gut microbiota from obese mice exhibited a significantly greater percentage increase in body fat over a short period of time.⁷⁰

Ridaura *et al*⁷¹ showed that germ-free mice inoculated with microbiota from obese or lean human twins took on the microbiota characteristics of the donor and had an increase in adiposity or remained lean, respectively. They also identified that gut microbiota can break down and ferment dietary fibres into short-chain fatty acids (SCFAs) providing additional source of energy to the host. However, the SCFAs production was greater in lean mice compared with obese mice, suggesting that increased weight gain is not simply a result of increased energy harvest, but rather from SCFAs promoting leanness by inhibiting fat accumulation in adipose tissue, raising energy expenditure, and enhancing the production of hormones associated with feeling of satiety.^{71 72}

In humans, different gut bacterial composition has been found in obese participants compared with lean participants or patients after bariatric surgery.^{73–76} It is important to note that some of these studies did not account for diet as a confounding factor.

Recently, a double-blind, randomised controlled trial on participants with metabolic syndrome demonstrated that FMT from lean to obese participants resulted in improvement in peripheral insulin sensitivity and significant increase in gut microbial diversity.⁷⁷ To date, there are no clinical trials to assess the effect of FMT on weight change.

A case report of a female patient treated for RCDI reported unintentional rapid weight gain after FMT from an overweight donor who similarly experienced significant weight gain after FMT.⁷⁸ This raised the question of whether FMT can alter the recipient's weight, and possibly be used as a treatment option for obesity. A recent study (in an abstract form) examined changes in BMI in comparison to stool donors' BMI following a single FMT for RCDI and found no significant difference in recipients' BMI after FMT from lean, overweight or obese donors.⁷⁹

SAFETY OF FMT

FMT appears to be safe and well tolerated after faecal transplant with no SAEs during short-term follow-up.^{17 40} Most reported adverse events include 'IBS symptoms' of mild diarrhoea (up to 94%) and abdominal cramping on the day of infusion (31%) resolved within a few hours after FMT.^{18 19 80} Other reported adverse events after FMT include abdominal tenderness, fatigue, bloating and flatulence, nausea, rectal discomfort, headaches and sore throat (possibly due to FMT via NG tube).³⁸

It appears that most patients with IBD treated with FMT for RCDI tolerate the procedure well; however there appears to be a potential risk of precipitating a flare.

Whether this flare is related to FMT or as part of the natural course of IBD is not clear.²⁰

In a multicentre retrospective series by Kelly *et al*, a few patients with IBD were reported to experience 'IBD flare' after FMT (14%). However, patients with IBD did not experience a higher incidence of SAEs (11%) or adverse events (14%) compared with patient immunocompromised because of other conditions (18% SAEs; 16% AEs, $p \leq 0.3224$).⁸¹

Rossen *et al* assessed the efficacy and safety of FMT in 37 patients with UC in a double-blind randomised trial, and observed mild adverse events in the majority of patients (64%), including transient borborygmus (49%), increased stool frequency (34%), vomiting in 2 patients and transient fever in 2 patients. Most adverse events disappeared spontaneously within 2 days. No infectious complications were observed. Four SAEs occurred, but were not related to FMT itself.⁴¹

It has been observed that some patients develop self-limited fever and temporary elevation of CRP and IL-6 following FMT, but were considered non-significant, as patients did not deteriorate.^{82 83}

Deaths have been reported following FMT, but were not related to FMT, rather were due to the chronic progressive comorbid illnesses of the patients who received FMT.⁸¹

Gut microbiome is thought to be associated with many GI and non-GI conditions including diabetes, metabolic syndrome, obesity, colon cancer and many others. Just as FMT is being explored in its utility to alter certain conditions, the opposite could be true. At least theoretically, FMT from a donor with certain disease phenotype could

potentially transmit the disease to the recipient. Data on long-term safety of FMT is lacking.

A long-term follow-up study by Brandt *et al*, where they contacted 77 patients who had colonoscopic FMT for RCDI ≥ 3 months before the study. Patients were asked to complete a questionnaire that solicited pre-FMT, post-FMT and donor data. A total of 4 of the 77 patients reported a new medical condition after FMT including peripheral neuropathy, Sjogren's disease, idiopathic thrombocytopenic purpura and rheumatoid arthritis. A total of 7 of the 77 patients were deceased at the time of the study. Causes of death included metastatic colon cancer (present before FMT), metastatic ovarian cancer, pneumonia (secondary to non-enteric organism), myocardial infarction, stroke, sepsis in a patient with long-standing CD 5 months after FMT, and one patient died while on hospice care from unknown cause.⁸⁴ None of these causes seemed to be related to FMT.

Larger long-term follow-up studies are needed to identify potential long-term adverse events that would have an impact on the process of donor selection for FMT.

POTENTIAL FUTURE APPLICATIONS

FMT is currently being investigated for its utility in other conditions, such as hepatic encephalopathy, fatty liver disease, type 2 diabetes mellitus, metabolic syndrome and other conditions. This is still in the experimental phase and clinical trials are underway exploring FMT usefulness in these areas.

CONCLUSION

FMT safety and efficacy data in the treatment of RCDI is compelling and FMT should be the standard of care for patients who fail conventional antibiotic courses for the treatment of RCDI. It remains an interesting and promising option for patients with IBD. Perhaps, we will be able to better select patients for FMT yielding more positive outcomes. FMT in the treatment of other conditions is still in the experimental phase and needs more research to uncover any potential benefit.

As we achieve better understanding of the microbiome therapeutics, future developments will likely change faecal bacteriotherapy from a whole-stool transplant to a more refined and individualised approach that uses defined microbial ecosystems with precise mixtures of the microbes from stool needed to achieve specific clinical outcome.

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