1 *NRGH Perspective*

2 **Title: Recipient factors in faecal microbiota transplantation: one stool does not fit all**

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Abstract:

Fecal microbiota transplantation is a promising therapy for chronic diseases associated with gut microbiota alterations. FMT cures 90% of recurrent *C. difficile* infections. However, in complex diseases, such as inflammatory bowel disease, irritable bowel syndrome and metabolic syndrome, its efficacy remains variable. It is accepted that donor selection and sample administration are key determinants of FMT success, and great effort has been made to standardize these procedures. However, little is known about recipient factors impacting FMT success and long-term clinical improvement. In this review, we discuss the effects of the recipient parameters on donor microbiota engraftment and clinical efficacy. Especially, emerging evidence supports that controlling the inflammation level in the recipient's intestine might facilitate engraftment by reducing host immune system pressure on the newly transferred microbiota. Deciphering FMT engraftment rules and developing novel therapeutic strategies are priorities to alleviate the burden of chronic diseases associated with an altered gut microbiota.

Introduction

The intestinal microbiota plays major roles in the maintenance of human health, including functions in nutrition, metabolism, immune development, and host defense. In healthy adults, it is dominated by Firmicutes and Bacteroidetes, with a minor representation of Proteobacteria, Actinobacteria, Fusobacteria and Verrucomicrobia. Other microorganisms present, such as viruses, archaea and fungi, are currently essential subjects of exploration. Despite a conserved "core" microbiota, each intestine harbors a unique assembly of diverse microbial communities. Both environmental and host factors shape microbiota composition, leading to considerable variability among individuals¹.

Numerous diseases are associated with alterations in gut microbiota composition and function, such as recurrent *Clostridioides difficile* infection (rCDI), inflammatory bowel diseases (IBDs), including Crohn's disease (CD) and ulcerative colitis (UC), irritable bowel syndrome (IBS), hepatic encephalopathy (HE), metabolic syndrome, and graft-versus-host disease (GvHD)². The common point of these alterations is a loss of diversity, with enrichment of some microorganisms and loss of others. Microbiota transfer experiments in mice suggest a causative role in these conditions³. Despite available treatments, there is still a significant unmet medical need for these diseases. In this context, new therapeutic strategies targeting the microbiota are currently being developed. Fecal microbiota transplantation (FMT) consists of the administration of fecal material from a healthy donor into the intestinal tract of a patient to induce therapeutic effects.

FMT has been used for centuries before randomized controlled trials (RCTs) proved its efficacy for treating rCDI in 90% of cases^{4,5}. More recently, positive therapeutic effects were also described in the induction of remission in UC⁶⁻⁹, with a modest success rate (24-32 vs 5-9% for placebo) compared to the results obtained for rCDI^{6,8,9}. Similarly, in CD, small case series, uncontrolled studies and a single pilot RCT suggest a beneficial effect of FMT¹⁰⁻¹⁵. In IBS, two out of five RCTs revealed significant symptom relief at three months in patients receiving FMT compared to that in patients receiving placebo (65 vs 43%¹⁶; 89.1 vs 23.6%¹⁷), together with changes in microbiota profiles^{16,18-20,17}. Moreover,

patients with GvHD positively respond to FMT, with an improvement in gastrointestinal symptoms and no adverse effects despite their severely immunocompromised status^{21–23}. FMT might also be effective in extraintestinal disorders, such as recurrent HE^{24,25}, metabolic disorders^{26,27} and autism^{28,29}.

Thus, FMT is a promising therapeutic strategy in various diseases associated with altered gut microbiota, and hundreds of RCTs are currently ongoing. However, the differences in the efficacy of FMT between rCDI and other disorders demonstrate that the gut microbiota is not the only actor in many complex diseases. The influence of host and environmental factors on the gut microbiota also takes place after FMT and might limit its efficacy in multifactorial diseases. In this review, we define the effects of host factors on the intestinal microbiota. We discuss recipient factors that play crucial roles in FMT success and identify possible avenues for progress in FMT therapies.

1- Microbiota manipulation by the host

1-1 Genetics impacts the microbiota

Genetics affect the intestinal microbiota composition (FIG. 1), as suggested by the higher similarity between the microbiotas of homozygotic twins than dizygotic twins³⁰. As the variability in human genomes and environmental influences makes it challenging to understand polymorphic mechanisms regulating the intestinal microbiota, mice have been a valuable tool in microbiota research. For example, defects in the nucleotide-binding oligomerization domain-containing protein 2 (*Nod2*) gene, which encodes a receptor for bacterial molecules^{31,32}, or in the inflammasome NOD-like receptor family pyrin domain containing 6 (*Nlrp6*) induce alterations in the gut microbiota composition³³. *Nod2*^{-/-} and *Nlrp6*^{-/-} mice exhibit increased susceptibility to colitis-associated cancer^{31,33}. This phenotype is transmissible to wild-type mice upon cohousing, indicating that an altered microbiota plays a direct role in disease development^{31,33}. Deletion of the caspase recruitment domain family member 9 (*Card9*) gene, encoding an adaptor protein, indicates that it is responsible for the modification of both

microbiota composition and function³⁴. Indeed, *Card9*^{-/-} mice exhibit a decrease in *Lactobacillus reuteri* abundance and have a reduced capacity to metabolize tryptophan into aryl hydrocarbon receptor (AhR) ligands, which leads to increased susceptibility to colitis³⁴.

Moreover, germ-free mice with different defects in innate (antimicrobial peptides, complement, pentraxins, and enzymes affecting microbial survival) and adaptive (MHC-dependent and MHC-independent) immunity shape the gut microbiota differently³⁵. Mice lacking the myeloid differentiation primary response 88 (*MyD88*) gene, encoding an essential signaling protein for both innate and adaptive immunity, or Toll-like receptor 5 (TLR5) also have an altered intestinal microbiota composition^{36,37}. RAG-deficient mice, which lack T and B cells, have a reduced intestinal microbiota diversity compared to that of controls³⁸, with outgrowth of the mucus-associated bacteria *Akkermansia muciniphila*³⁹. Moreover, these mice exhibit an increased interindividual variability of their microbial communities, suggesting that adaptive immunity contributes to stabilizing the gut microbiota⁴⁰.

Host genetics also influences the mycobiota. Some of the genes mentioned above are involved in fungal sensing, such as *Card9*, which controls intestinal fungal loads^{41,42}. In addition, the multiple interactions between bacteria and fungi suggest that variation in bacterial communities impacts fungal populations^{43,42,44}.

Altogether, these data highlight the role of immune and regulatory genes in shaping intestinal microbiota composition and function, with a direct impact on disease development risk.

In humans, the association of the intestinal taxa with several polymorphisms suggests that host genetics also impacts gut microbiota composition (Table 1). Heritability analyses have identified four genetic loci statistically associated with microbial taxa (*Rikenellaceae*, *Faecalibacterium*, *Lachnospira* and *Eubacterium*) in two cohorts from geographically and culturally different areas⁴⁵. Multiple genetic variants in innate immunity players (particularly C-type lectins) and vitamin D receptor were associated with intestinal microbiota composition and function, highlighting their role in gut homeostasis^{46,47}.

These studies provide clues for genetic effects on the microbiota composition in healthy individuals. However, a comparison of independent studies highlights the complexity of the genetic architecture underlying microbiota composition, with only little overlap among identified loci⁴⁸. Moreover, the effect of major disease-causing genetic defects on the human gut microbiota remains elusive, even though notable advances have been made in the context of IBD.

The role of the intestinal microbiota in IBD pathogenesis is now accepted^{49–52}. Beyond mouse studies on IBD susceptibility genes such as *Nod2* and *Card9*, interaction with genetic factors is being explored in humans (Table 1). Patients harboring autophagy-related 16-like 1 (ATG16L1) polymorphism show significant microbiota alterations, with increased abundances of *Fusobacteriaceae*⁵³ and *Enterobacteriaceae* and decreased amounts of *Clostridium* groups IV and XIVa⁴⁴. NOD2 variants are associated with decreased abundances of *Roseburia* and *Faecalibacterium prausnitzii*⁴⁷. Mathematical modeling proposes that the effect of NOD2 risk variants on IBD is partially mediated by decreased *F. prausnitzii* abundance⁵⁴. Moreover, the gut microbiota of IBD patients with CARD9 but not NOD2 or ATG16L1 risk alleles exhibits an impaired ability to metabolize tryptophan into AhR agonists, as observed in *Card9*^{-/-} mice³⁴. Furthermore, analysis of the microbiota composition of patients with rare monogenic primary immunodeficiency causing an IBD-like phenotype (chronic granulomatous disease, X-linked inhibitor of apoptosis defect and tetratricopeptide repeat domain 7A defect) showed gene-specific differences compared to healthy subjects and patients with conventional IBD⁵⁵.

Taken together, these data in mice and humans demonstrate that host genetics has an impact on gut microbiota composition and function. In the FMT context, it suggests that the genetics of the recipients should be taken into account.

1-2 Immunity affects the microbiota

Intestinal inflammation drastically modifies the gut environment and leads to changes in the gut microbiota through several mechanisms (FIG. 1). The released antimicrobial peptides sequester specific host-derived nutrients, including iron and zinc, and favor the growth of bacteria that are more

efficient at acquiring those nutrients, such as *Enterobacteriaceae*^{56–58}. The production of reactive oxygen and nitrogen species by host cells leads to the luminal generation of exogenous electron acceptors, which selectively enhances the growth of facultative anaerobic bacteria, especially *Enterobacteriaceae*^{59–61}. Unlike the obligate anaerobic Bacteroidia and Clostridia, *Enterobacteriaceae* are more likely to encode enzymes for nitrate respiration and thrive in this new metabolic niche. Thus, inflammation confers a fitness advantage to facultative anaerobes, possibly explaining the expansion of *Enterobacteriaceae* in the inflammatory setting⁵⁹.

Intestinal secretory IgA also regulates the composition and function of the gut microbiota in both humans and mice (FIG. 1). IgA coating affects microbial fitness through various effector functions, such as modulation of bacterial gene expression and metabolism, immune exclusion, enhanced antigen uptake, alteration of bacterial motility and niche occupancy, and neutralization of toxins or other secreted factors⁶².

Only a fraction of commensals, such as Proteobacteria and *A. muciniphila*, are coated by IgA *in vivo*, while most members are not⁶². Increased IgA coating of the intestinal microbiota is observed in humans with IBD and mouse colitis models^{63–65}. In humans, a high IgA coating identifies taxa associated with disease, such as proinflammatory bacteria in patients with IBD^{64,65}. Interestingly, some patients with IgA deficiency have an IBD-like phenotype^{66,67} and exhibit alterations in gut microbiota composition despite the compensatory secretion of microbiota-targeted IgM⁶⁸.

IgA-deficient mice exhibit increased abundances of Proteobacteria⁶⁹ and segmented filamentous bacteria (SFB)⁷⁰ and produce abnormal IgG responses to intestinal bacteria, suggesting exposure of their systemic immune system to microorganisms due to ineffective compartmentalization⁷¹. Similarly, mice lacking MyD88 in the T cell compartment fail to control mucosa-associated bacterial communities due to an abnormal IgA response⁷². This effect induces an increase in the abundances of mucolytic Proteobacteria and Firmicutes (*Ruminococcus*) and worsens colitis⁷². Naturally occurring polymorphisms in MHC genes, which control intestinal IgA phenotypes, result in differences in

microbiota composition between different lines of MHC-congenic mice and are sufficient to explain susceptibility to enteric infection⁷³.

Finally, IgA can modulate gene expression in *Bacteroides thetaiotaomicron*, a prominent commensal, facilitating functional symbiosis with Firmicutes and promoting homeostasis and protection from colitis⁷⁴. Thus, diversified and well-selected IgA repertoires might be essential not only to eliminate potentially harmful microorganisms but also to maintain diverse and balanced commensal communities.

Collectively, these results reveal a unique and nonredundant role for intestinal secretory IgA in shaping and stabilizing bacterial communities. In parallel with intestinal inflammatory status, the variability in IgA repertoires and the resulting dynamic immunoselection might play a role in the evolution of the gut microbiota following FMT.

2- Factors associated with FMT success

2-1 What is a successful FMT?

FMT success is primarily defined by a positive clinical response in the recipient, with the main objective being a long-term therapeutic effect. However, the shift in gut microbiota composition of the recipient toward that of the donor, corresponding to the engraftment of the donor microbiota, is also a useful marker *per se* to assess the success of the procedure. Indeed, engraftment success is often directly associated with clinical improvement. The first RCT investigating FMT effects in patients with rCDI revealed a major increase in microbial diversity of the recipient microbiota toward that of the donor⁴. Similarly, a larger proportion of fungal and bacterial OTUs from the donor microbiota, with more similar abundances, are transferred in responding rCDI patients than in patients not responding to treatment⁷⁵. In the same way, patients with IBD who respond to FMT demonstrate a significant shift in microbiota composition toward their donor's profile, whereas nonresponders do not^{6,13}. Typically,

changes in microbiota composition following FMT are associated with increased microbial diversity^{8,13}, which is much more pronounced in responders than in nonresponders^{13,76,77}. In addition to composition, metabolic functions of intestinal microbiota might also be crucial to restore, as metabolites are one of the primary modes by which the gut microbiota interacts with the host^{78,79}. For instance, the presence of bacterial taxa transforming primary to secondary bile acids is associated with resistance to *C. difficile* infection^{80–84}. Moreover, FMT restores the short-chain fatty acid (SCFA) and polyunsaturated fatty acid composition in patients with rCDI^{83,84}. Similarly, in UC, remission is associated with the restoration of SCFA biosynthesis pathways and secondary bile acid levels⁷⁷. In a case series, filtrated bacteria-free FMT was also able to alleviate rCDI symptoms, suggesting that bacterial molecules, metabolites, or bacteriophages mediate some of the FMT effects in the rCDI context⁸⁵. Bacteriophage transfer during FMT is also associated with rCDI symptom resolution⁸⁶, supporting that live bacteria are not the only players in FMT therapy. These data highlight that the transfer of a variety of microorganisms and microbial molecules with diverse engraftment patterns might be necessary to restore a homeostatic intestinal environment in the patient. In line with these findings, complete transfer of the donor microbiota is not required to resolve rCDI⁸².

Following FMT, some components of the transplanted microbiota engraft and combine with the remaining recipient microbiota to rebuild a new commensal community, a process that can take months to years to stabilize^{87,88}. Although many studies report long-term FMT impact^{6,86,25,89}, the effect can also be transient. This situation is the case in patients with metabolic syndrome for whom insulin sensitivity improvement was observed at week 6 post-FMT but was lost at week 18, in line with transient donor microbiota engraftment^{26,27,90}. Thus, long-term clinical improvement relies on the successful establishment and adaptation of the newly transferred microbiota to the specific rules governing its novel host habitat.

2-2 Donor selection and FMT protocol

To date, the exceptionally high success rate of FMT therapy in rCDI has not been observed for any other diseases. The heterogeneity of FMT efficacy from one disease to the other likely reflects differences regarding the importance of the gut microbiota in their respective pathogenesis. While rCDI is almost purely microbiota related, other diseases, such as IBD or metabolic syndrome, are much more complex and involve dysfunctional host-microbe interactions and immune and genetic factors⁹¹. In this context, discrepancies in FMT procedures make it even more challenging to compare independent studies. Various approaches have been chosen in terms of donor selection (related or unrelated donors), preparation of fecal material (fresh or frozen, aerobic or anaerobic), route of delivery (colonoscopy, upper endoscopy, nasointestinal tube, enema or capsule), intestinal preparation (antibiotics or colon cleansing), and dose and frequency of administration^{92,93}. Even with the same procedure, response to FMT is variable from one recipient to the next. Specificities of the donor material can partly explain these differential responses, with the emergence of the "superdonor" concept⁹⁴. The first study revealing a superdonor effect was an RCT evaluating FMT efficacy in UC, in which seven of the nine FMT responders received material from the same donor⁶.

Since then, several studies have confirmed that high donor bacterial diversity is crucial to restoring a stable commensal community in recipients and is one of the most significant factors influencing FMT efficacy in IBD^{76,95,77}. A high diversity of bacteriophage communities in donors is also associated with FMT success in rCDI⁹⁶. Donor microbiota composition also matters. Members of *Clostridium* clusters IV and XIVa in the *Ruminococcaceae* and *Lachnospiraceae* families were found to be enriched in the microbiota of a superdonor for UC⁶, and their enrichment was associated with a positive FMT outcome in several IBD studies^{7,8,97}. Similarly, high abundances of *A. muciniphila*, *Ruminococcaceae* members and *Bacteroides* species were more likely to induce remission in patients with UC, whereas a high amount of *Streptococcus* was associated with no response^{77,95}.

2-3 Recipient genetics and lifestyle

For rCDI, the long-term stability of the donor microbiota might not be crucial. FMT rapidly induces clearance of the pathogen and restoration of a commensal community, and a gradual drift away from the donor's microbiota profile due to the recipient selection pressures is unlikely to lead to disease recurrence if there are no further insults to the gut microbiota. By contrast, the sustainability of the donor microbiota in patients with chronic diseases, such as IBD or metabolic syndrome, may be much more determinant. As microbiota alterations contribute to disease progression, FMT is essential to provide the initial relief, with a likely need for subsequent FMT to maintain the effect.

Strong evidence supports the theory of donor-recipient compatibility, which depends not only on donor material specificities but also on recipient genetics and environment. Recipient genes and immunity, as well as diet and antibiotic exposures, impact FMT engraftment and long-term maintenance. In metabolic syndrome, engraftment failure observed 18 weeks after FMT could be due to particular immune responses and dietary habits²⁷. Along with variable FMT outcomes, colonization levels differ largely among recipients sharing the same donor⁹⁸, suggesting the existence of individual permissivity patterns regarding donor microbiota. In hematopoietic stem-cell transplantation recipients undergoing FMT for rCDI, the functional and taxonomic concordance between donor material and their own post-FMT microbiota diminished after one year, supporting that environmental and host factors are essential determinants in the long-term shaping of the transferred microbiota⁹⁰. Thus, aspects such as strain and species fitness and colonization resistance should be investigated in the context of microbiota resilience, genetic traits, immune responses and lifestyle of the recipient. Indeed, it is likely that complex ecological interactions and donor-recipient compatibilities underlie the success of FMT.

As genetic traits are inherent to the recipient and cannot be changed, FMT might be combined with modulation of immune responses and dietary intervention (see section 3). Furthermore, donor-recipient matching approaches could rely on screening of functional perturbations in recipient microbiota to identify a specific donor material enriched in the metabolic pathways that need to be

restored. Thus, FMT is not a "one stool fits all" strategy, especially in the context of complex chronic diseases involving genetic, immune and environmental factors.

2-4 Recipient clinical status

Although rarely discussed, the clinical status of the recipient before FMT is also a key element to consider (Table 2). Severe and complicated indications, inpatient status during FMT, and the number of previous CDI-related hospitalizations are strongly associated with early FMT failure⁹⁹. Patients who need repeated FMT for rCDI have higher intestinal inflammation than patients cured with one single FMT¹⁰⁰. rCDI patients with an active IBD requiring medication escalation have reduced FMT success, with no impact of other parameters, such as CDI recurrence¹⁰¹. In the context of IBD, it is also crucial to question the timing and extent of the disease before performing FMT. Is the recipient in flare or remission? Is the inflammation in a maintenance phase after successful immunosuppressive treatment? No published human trial is powered to assess the role of these factors in FMT success, but several elements converge to support this idea^{10,91}.

Whereas a randomized FMT study in UC patients demonstrated no effect of concomitant steroid therapy on remission⁸, two others suggest the opposite. One study shows that patients taking immunosuppressants tend to have a greater benefit from FMT⁶. In another RCT, the reduction in disease score following FMT was greatly increased in patients taking oral steroids at baseline⁹. Recently, we published the first RCT in CD, evaluating the role of FMT in patients who achieved clinical remission using corticosteroids. Failure to maintain remission was associated with microbiota factors at baseline and weaker control of clinical activity¹⁵. In multivariate analysis, FMT and Crohn's disease activity index (CDAI) score were the only independent parameters associated with maintenance of remission, with FMT dividing the risk of a flare by 8 and higher CDAI score (although below the remission threshold) increasing the risk by more than 20-fold (Table 3).

Donor-recipient incompatibilities leading to FMT failure may partly be due to an active immune response toward the transplanted microbiota. An immune screening approach was examined in an

FMT case study for UC to minimize FMT failure¹⁰². Patient-derived lymphoid cells isolated from a rectal biopsy were incubated with the intestinal microbiota of different donors. FMT, performed with the donor microbiota inducing the lowest production of proinflammatory cytokines, induced a remission¹⁰². In addition to the noncontrolled nature of this study, the time and costs involved by personalized approaches limit their implementation. Controlling the inflammation level in the recipient's intestine using immunosuppressants might be a simpler strategy.

2-5 Recipient microbiota composition

Following FMT, donor bacterial strains cohabit with those of the recipient. In metabolic syndrome, colonization success for a given strain is greater if another representative of the same species is also present in the recipient before FMT⁹⁸. In both rCDI and metabolic syndrome, bacterial abundance and taxonomic identity in both the donor and recipient before FMT are strong predictors of engraftment¹⁰³. Following FMT, the recipient microbiota contains a combination of recipient- and donor-derived as well as newly acquired species¹⁰³, suggesting that complex microbial interactions contribute to overall FMT engraftment. Thus, two recipients receiving the same donor microbiota will not show the same clinical outcome, as both recipient genetics and microbiota are idiosyncratic and determinant in FMT success.

In numerous human studies, both microbial diversity and the presence of specific species in the recipient microbiota impact FMT engraftment (Table 3). In UC, higher fecal and mucosal microbiota richness before FMT is associated with positive therapeutic outcomes^{8,77}, while *Fusobacterium* and *Sutterella* species are associated with FMT failure⁸. In CD, FMT failure is associated with enrichment in different members of Gammaproteobacteria, such as *Klebsiella*, *Actinobacillus*, and *Haemophilus*, in the recipient microbiota at baseline¹⁵. In metabolic syndrome, responders have lower fecal microbial diversity before FMT, with higher relative abundances of *Subdoligranulum variabile* and *Dorea* and lower relative abundances of *Eubacterium ventriosum* and *Ruminococcus torques* than

nonresponders²⁷. Patients with IBS responding to FMT have a higher baseline abundance of *Streptococcus* species and higher microbiota diversity than nonresponders¹⁰⁴.

In rCDI, a low abundance of fecal *Candida albicans*, both in recipients at baseline and in donors, correlates with a positive FMT outcome⁷⁵. In contrast, a high initial abundance of *C. albicans* was associated with increased FMT success in patients with UC, suggesting that high fungal abundance allows better bacterial engraftment in this context¹⁰⁵. In rCDI, a higher richness of the bacteriophage Caudovirales in the donor than in the recipient microbiota predicts a positive therapeutic outcome⁸⁶. Moreover, in UC, responders to FMT have a lower baseline relative abundance of Caudovirales bacteriophages than nonresponders¹⁰⁶. Similarly, low eukaryotic virus richness before FMT in patients with UC is associated with a clinical response¹⁰⁷. These data suggest that in addition to bacteria, fungi and both eukaryotic and prokaryotic viruses in the recipient microbiota play a role in the establishment of a novel commensal community after FMT and in therapeutic effects.

Altogether, these data demonstrate that the baseline recipient microbiota affects FMT clinical outcome, probably by influencing the success of donor microbiota engraftment and maintenance but also by directly contributing to the new microbial ecosystem. Thus, extensive analysis of bacterial, fungal and viral species in patients before transfer might provide a valuable biomarker for FMT success prediction.

3- Avenues for progress

3-1 Gut preparation for engraftment

Inadequate bowel preparation is associated with FMT failure in rCDI¹⁰⁸. Although it seems logical to clear ecological niches for the new microbiota before administering it, procedures for preparing the recipient (broad-spectrum antibiotics, colon cleansing with polyethylene glycol or no preparation) vary between studies, and the best approach remains to be identified (FIG. 2). Antibiotic usage is questionable, as they may induce deleterious side effects (particularly in IBD) and/or enrich

for antibiotic-resistant bacteria. Few clinical studies suggest that antibiotic pretreatment improves the clinical response rate of FMT in UC, but control arms are missing^{109,110}. Mouse study results are divergent, with one study demonstrating a positive impact of bowel cleansing prior to FMT¹¹¹, while another found no effect of lavage but a positive effect of antibiotics¹¹². Conversely, antibiotic pretreatment does not improve the overall engraftment of donor microbiota compared to that with lavage alone but does increase the engraftment of specific taxa, such as *Bifidobacterium*¹¹³. Thus, further well-designed RCTs are needed to determine the best approach to prepare the gut environment for engraftment.

3-2 Targeting recipient immunity

Modulation of immune responses within the new gut habitat could improve engraftment (FIG. 2). In IBD, control of disease activity using corticosteroids is associated with improved FMT efficacy^{6,9,15}. Indeed, a healthy microbiota can rapidly be altered by existing intestinal inflammation, thus limiting its potential therapeutic effect. Moreover, transferring a large number of microbes into an inflamed intestine with a disrupted epithelial barrier could be detrimental and both exacerbate inflammation and promote bacterial translocation. Thus, treatment with immunosuppressants in addition to FMT protocols might be useful to alleviate immune pressure on the newly transferred microbiota and avoid additional damage to the intestinal tissue.

Furthermore, human leukocyte antigen (HLA) and other genetic compatibility factors between donors and recipients might play a role in FMT efficacy. Indeed, FMT engraftment failure can be related to graft rejection, which corresponds to the immunologic destruction of transplanted tissues between two individuals of the same species differing at the MHC for that species (i.e., HLA in humans). HLAs are extremely polymorphic in different populations and determine the specificity of T cell responses against the intestinal microbiota. MHC-dependent mechanisms impact the microbiota composition in mice^{73,114}. In humans, specific HLA polymorphisms are associated with the microbiota composition and

with several common infections^{46,115,116}. Considering HLA as a matching factor for FMT should be investigated.

3-3 Dietary intervention

Environmental factors impacting the microbiota, particularly dietary habits, might play a significant role in FMT success (FIG. 2). Dietary interventions show promising results in CD^{117–119} and could help maintain an optimal ecosystem after transplantation in IBD and non-IBD contexts. Adopting a “microbiota-protecting” diet enriched in fibers to promote SCFA-producing bacteria and reduced in ultraprocessed food might be beneficial in the post-FMT setting. Further basic and clinical research studies are required to validate the integration of such approaches to FMT protocols.

Conclusions

FMT efficacy could be improved by carefully selecting donors, but the specific parameters for implementing selection criteria are still mostly unknown. Similarly, no consensus exists on the best procedure for each condition. Standardization of methods and development of stool banks will improve follow-up over the years and help to optimize donor-to-recipient microbiota transfer. However, the role of recipient factors in FMT success remains underestimated. The main drivers of donor material engraftment into the recipient's intestine include microbiota composition, genetics, inflammation status and environmental factors, such as diet. Additional interventions, alone or in combination, could potentiate FMT. Optimization of donor/recipient matching at both the genetic and microbiota levels could help minimize engraftment failure due to incompatibilities. Deciphering the best bowel preparation method is also crucial to promote remission. Furthermore, strategies to limit immune pressure toward the newly transferred microbiota could be powerful, such as the administration of immunosuppressants at least during the first stages after FMT in chronic inflammatory diseases. Finally, improved control of the recipient environment, especially via dietary

intervention, might improve FMT engraftment and maintenance and support long-term clinical remission.

Figure legends:

- Figure 1: Demonstrated effects of the host immune system on the intestinal microbiota composition and functions

Multiple host factors, including intestinal immunity, shape the bacterial, fungal and viral populations of the microbiota. **A.** Intestinal secretory immunoglobulin A (SIgA) eliminates potentially harmful microorganisms and stabilizes bacterial communities. **B.** Production of antimicrobial peptides (AMPs) favors the growth of *Enterobacteriaceae* by sequestering specific host-derived nutrients, including iron and zinc. **C.** Production of reactive oxygen and nitrogen species (ROS and RNS) by host cells leads to the luminal generation of exogenous electron acceptors, which selectively enhance the growth of facultative anaerobic bacteria, including *Enterobacteriaceae*. **D.** Finally, immune and regulatory proteins are essential to maintain a balanced composition and function of the microbiota, especially the ratio between Bacteroidetes and Firmicutes. Mutation of these genes is associated with alteration of the microbiota composition. NOD2, nucleotide-binding oligomerization domain-containing protein 2; ATG16L1, autophagy-related 16-like 1; NLRP6, NOD-like receptor family pyrin domain containing 6; VDR, vitamin D receptor; MyD88, myeloid differentiation primary response 88; TLR5, Toll-like receptor 5; CARD9, caspase recruitment domain family member 9; TTC7A, tetratricopeptide repeat domain 7A; XIAP, X-linked inhibitor of apoptosis; CGD, chronic granulomatous disease.

- Figure 2: Potential targets and strategies on the recipient side to improve FMT efficacy

The main drivers of donor material engraftment into the recipient's intestine include microbiota composition, genetics, inflammation status and environmental factors, such as dietary habits. Additional interventions before or after transplantation, alone or in combination, could help to improve FMT success. **A.** Optimization of donor/recipient matching at the genetic, immune and

microbiota levels could help minimize engraftment failure due to incompatibilities. **B.** Identifying the best bowel preparation method between antibiotics and bowel cleansing is also crucial to promote engraftment. **C.** Furthermore, strategies to limit immune pressure toward the newly transferred microbiota, such as the administration of immunosuppressants at least before and during the first stages after FMT in chronic inflammatory diseases could be a powerful method. **D.** Finally, improved control of the recipient environment, especially via dietary intervention, might improve FMT engraftment and maintenance and support long-term clinical remission.

Tables:

Table 1: Associations between host genetics and intestinal microbiota in healthy individuals and IBD patients

Study (year)	Gene	Association with microbiota composition or function
Healthy individuals (GWAS)		
Turpin et al. (2016) ⁴⁵	rs62171178 (near UBR3) rs1394174 (CNTN6) rs59846192 (DMRTB1) rs28473221 (SALL3)	Presence of <i>Rikenellaceae</i> Presence of <i>Faecalibacterium</i> Presence of <i>Lachnospira</i> Presence of <i>Eubacterium</i>
Bonder et al. (2016) ⁴⁶	CLEC4F–CD207 and CLEC4A–FAM90A1 (C-type lectin) HLA-B (human leukocyte antigen)	Intestinal homeostasis Microbiota composition
Wang et al. (2016) ⁴⁷	VDR (vitamin D receptor)	Overall microbial variation and individual taxa
Patients with IBD		
Frank et al. (2011) ¹²⁰	NOD2 (nucleotide-binding oligomerization domain-containing protein 2) in IBD ATG16L1 (inflammasome NOD-like receptor family pyrin domain containing 6) in IBD	Increased abundance of <i>Enterobacteriaceae</i> (Proteobacteria) and decreased abundance of Clostridium groups IV and XIVa (Firmicutes)
Knights et al. (2014) ¹²¹	NOD2 in IBD	Increased abundance of <i>Enterobacteriaceae</i>
Sadaghian Sadabad et al. (2015) ⁵³	ATG16L1 in CD	Increased abundance of <i>Fusobacteriaceae</i>
Lamas et al., (2016) ³⁴	CARD9 (caspase recruitment domain family member 9) in IBD	Impaired ability to metabolize tryptophan into AhR agonists
Aschard et al. (2019) ⁵⁴	NOD2 in IBD	Decreased abundance of the <i>Roseburia</i> genus and <i>Faecalibacterium prausnitzii</i>

IBD-like phenotype in Primary immunodeficiency		
Sokol et al. (2019) ⁵⁵	CGD (Chronic granulomatous disease) XIAP (X-linked inhibitor of apoptosis)	Increased abundance of <i>Ruminococcus gnavus</i> Increased abundance of disease-associated taxa from Proteobacteria, Firmicutes, Actinobacteria, and Fusobacteria
	TTC7A (Tetratricopeptide Repeat Domain 7A)	Presence of the pathogen <i>Lactococcus garvieae</i> Increased abundance of Proteobacteria, decreased abundance of the <i>Ruminococcaceae</i> family (notably the <i>Oscillospira</i> genera)

Table 2: Donor and recipient factors at baseline associated with FMT success

Condition	Donor microbiota composition	Recipient microbiota composition	Recipient clinical status
rCDI	- Low abundance of <i>Candida albicans</i> ⁷⁵ - High bacteriophage diversity ^{86,96}	- Low abundance of <i>Candida albicans</i> ⁷⁵ - Low relative abundance of Caudovirales bacteriophages ⁸⁶	- Low disease severity ^{99,108} - Low intestinal inflammation level (calprotectin) ¹⁰⁰ - Low number of disease recurrence ⁹⁹ - Adequate bowel preparation ¹⁰⁸ - No active associated IBD requiring medication escalation ¹⁰¹
UC	- High microbiota diversity ^{77,95} - Enrichment in members of Clostridium clusters IV and XIVa in the <i>Ruminococcaceae</i> and <i>Lachnospiraceae</i> families ^{6-8,97} - High relative abundance of <i>A. muciniphila</i> , <i>Ruminococcaceae</i> members and <i>Bacteroides</i> species ^{77,95} - Low amount of <i>Streptococcus</i> ^{77,95}	- High fecal and mucosal microbiota richness ^{8,77} - Absence of <i>Fusobacterium</i> and <i>Sutterella</i> ⁸ - High abundance of <i>C. albicans</i> ¹⁰⁵ - Low abundance of Caudovirales bacteriophages ¹⁰⁶ - Low eukaryotic virus richness ¹⁰⁷	- Immunosuppressant therapy, such as oral steroids ^{6,9}
CD	- High microbiota diversity ⁷⁶	- Low abundance in members of Gammaproteobacteria such as <i>Klebsiella</i> , <i>Actinobacillus</i> and <i>Haemophilus</i> ¹⁵	- Low disease activity ¹⁵
Metabolic syndrome	- High abundance of <i>Bifidobacterium</i> ¹²²	- Low relative microbial diversity ²⁷ - High abundance of <i>Subdoligranulum variabile</i> and <i>Dorea</i> ²⁷ - Low abundance of <i>Eubacterium ventriosum</i> and <i>Ruminococcus torques</i> ²⁷	N/A
IBS	N/A	- High relative microbiota diversity ¹⁰⁴	N/A

		- High relative abundance of <i>Streptococcus</i> ¹⁰⁴	
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Table 3: Factors associated with remission maintenance in the whole population of the study in univariate and multivariate analyses (from ¹⁵)

Factors	P value univariate	P value multivariate	OR (Odds Ratio)	95% CI (confidence interval)
FMT vs Sham	0.23	0.0295*	0.13	[0.009 – 0.82]
Age	0.60			
Gender	0.70			
Active smoking	0.53			
Montreal : L2 / L3	0.91			
Disease duration	0.26			
Hemoglobin	0.46			
Platelet count	0.55			
CRP	0.21	0.42		
Fecal Calprotectin	0.06	0.72		
Previous azathioprine treatment	0.28			
Previous anti-TNF therapy	0.39			
CDAI Score	0.03	0.018*	26.9	[1.8 – 645.7]
CDEIS Score	0.31			

CRP: C reactive protein; CDAI: Crohn's disease activity index; CDEIS: Crohn's disease endoscopic index of severity; TNF: Tumor Necrosis Factor; L2: colonic involvement only ; L3: ileo-colonic involvement.

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