Pros and cons: Is faecal microbiota transplantation a safe and efficient treatment option for gut dysbiosis?

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Abstract
Faecal Microbiota Transplantation (FMT) is well established as an effective treatment for Clostridioides difficile infection (CDI), restoring gut microbiome diversity and function. The utility of FMT is currently being explored in relation to other immune-mediated pathologies, such as allergic disease, inflammatory bowel diseases and autoimmune diseases. Clinical trials in these areas are ongoing, and the altered gut microbiota (dysbiosis) that is often observed in these pathologies provides a rationale for the application of FMT to restore the microbiome. However, there is controversy on the risk-benefit ratio as it relates to the use of FMTs in pathologies other than CDI. In this Pro and Con article, we present the arguments for and against the use of FMT in immune-mediated pathologies, such as allergic disease. We further identify research gaps and recommend how these may be addressed in future studies.

KEYWORDS
allergic disease, allergy, Clostridioides difficile-infection, dysbiosis, efficacy, faecal microbiota transplantation, immune-mediated disease, microbiota, safety
1 | PRO—FAECAL MICROBIOTA TRANSPLANTATION (FMT) IS A SAFE AND EFFICIENT TREATMENT OPTION FOR GUT DYSBIOSIS

FMT is highly effective in managing *Clostridioides difficile* infections (CDI), likely by resolving aspects of the underlying dysbiosis (which may be defined as alteration in the composition and/or function of a microbial community thought to contribute to disease). National guidelines in many countries consider FMT an appropriate treatment strategy for CDI, and if microbiological recommendations are followed to screen for pathogens, the procedure is considered safe and few adverse events have been reported.

Gut microbiota dysbiosis is associated with a range of chronic diseases with an immunological aetiology, and the respective utility of FMT in their management is currently being explored. In inflammatory bowel disease (IBD), a systematic review, has reported a 36% [201/555] rate of clinical remission in ulcerative colitis, 50.5% [42/83] in Crohn’s disease, and 21.5% [5/23] in pouchitis, even though these conditions also have well described genetic risk factors. Thus, FMT is now considered a promising treatment for gut dysbiosis in a variety of clinical contexts, even if the associated disorder may have multi-factorial origins.

Epidemiological evidence suggests that gut microbiota dysbiosis predisposes towards the development of allergic disease. Factors that influence microbiological exposure and microbiome assembly, such as farming, urban-rural gradients, human migration and pet ownership, show a consistent connection to the development of allergic disease. In support of this link, culture-based, molecular and sequencing studies show dysbiosis in gut samples from infants who develop eczema and allergic disease. In murine models of allergic disease, rearing the pups of a murine asthma model in direct contact with *Firmicutes*, resulting in a reduced susceptibility to a Th2 immunological response. For instance, augmenting the diversity of the gut microbiota and the administration of beneficial microbes reduced in allergic infants have shown benefits in murine models of allergic disease.

Colonization of germ-free mice with bacterial strains and microbial consortia show that the gut microbiota promotes mucosal immunoregulatory suppression of the allergic response. For instance, rearing the pups of a murine asthma model in direct contact with soil increases the proportion of gut Bacteroidetes relative to *Firmicutes*, resulting in a reduced susceptibility to a Th2 immunological response. Researchers in Canada detected a dysbiosis, characterized by a decrease in taxa related to *Lachnospira, Veillonella, Faecalibacterium* and *Rothia*, in children at 3 month of age that preceded the later development of allergic wheeze. Early-life inoculation of these taxa into murine asthma models ameliorated airway inflammation, providing a proof-of-concept that a correction of dysbiotic patterns can result in therapeutic benefits.

In conclusion, gut microbiota dysbiosis may contribute to the development of allergic disease and other immune-mediated diseases, though these conditions also have well described genetic risk factors. Thus, FMT is now considered a promising treatment for gut dysbiosis predisposing towards the development of allergic disease. In support of this link, culture-based, molecular and sequencing studies show dysbiosis in gut samples from infants who develop eczema and allergic disease.

**BOX 1 Arguments for and against Faecal Microbiota Transplantation (FMT) interventions for patients with immune-mediated pathologies such as allergic disease**

**Pro—FMT is a safe and efficient treatment option for gut dysbiosis (Figure 1)**

- Altered microbiomes (dysbioses) are likely to contribute to the pathophysiology of several chronic diseases, providing a rationale to design interventions based on microbiome restoration for treatment and prevention.
- FMT has the potential to redress aspects of dysbioses, engraft health promoting microbes and/or expose the host temporarily to beneficial microbes.
- International guidelines recommend FMT after systemic antibiotic treatment for refractory diarrhoea-associated *C. difficile* infection (CDI).
- Many environmental risk factors for immune-mediated diseases (birth by caesarean section, antibiotics, urban living and industrialization) might contribute to pathology by disrupting the gut microbiota, providing a rationale for microbiome restoration through FMT.
- Experiments in animal models provide a rationale for FMTs. For example, augmenting the diversity of the gut microbiota and the administration of beneficial microbes reduced in allergic infants have shown benefits in murine models of allergic disease.

**Con—FMT is NOT a safe and efficient treatment option for gut dysbiosis (Figure 2)**

- For chronic immune-mediated conditions where there is uncertainty regarding the ecological factors that drive the dysbiosis, the timeline of its development and its causal contribution to disease, the rationale to use FMT might be weak and the and risk-to-benefit ratio unfavourable.
- Our conceptual, mechanistic and ecological understanding of FMTs is poorly developed, making it first difficult to rationalize timing and dosing regimens, and second unclear whether so-called dysbioses can be corrected.
- It may be detrimental to expose the immune system of patients that suffer from diseases characterized by pathologic immune responses (such as allergic disease, IBD and autoimmune diseases) to the allogenic strains of an FMT.
- There are safety concerns (both short- and long-term) regarding the exposure to infectious and non-infectious transmissible diseases, conveyance of un-intended characteristics of the donor microbiome that might predispose to chronic diseases, and the potential risks of antibiotic pre-treatment.
and microbiome augmentation through FMT has substantial potential for the prevention and treatment of these disorders (Box 1 and Figure 1). Studies are beginning to apply FMTs as personalized strategies (within a framework of precision medicine) in that both donor and recipient microbiome features are considered when selecting donor-recipient pairs (see Box 2). The challenge is now to understand which microbiome characteristics protect the individual host and design suitable, safe and personalized FMT therapies as translational interventions.

2 | CON—FMT IS NOT A SAFE AND EFFICIENT TREATMENT OPTION FOR GUT DYSBIOSIS

While we have a good conceptual and mechanistic understanding for why FMTs work and are likely safe for CDI, critical information for other pathologies is missing (Figure 2). These gaps of knowledge question the use of FMTs and relate to causality, mechanisms, ecology, timing and dosing, and safety.

For CDI, gut microbiota dysbiosis is likely a causal contributor to disease as it permits the overgrowth of the pathogen, making it a "broken microbiome condition". Such causal inferences are lacking for other pathologies, and microbiome alteration might just be a consequence or bystanders of a certain disease (a "broken host condition"). Corrections of altered microbiomes will be beneficial only if the alterations are causal or contributory to the disease and might even be detrimental if the microbiome alteration is a compensatory beneficial response. The absence of causal inferences for microbiome dysbioses in the aetiology of chronic diseases and a lack of information on the time frame in which pathologic triggers occur are serious limitations for the application of FMTs. Even if the dysbiosis would be causal, the pathologic events might occur years before the onset of disease, and FMTs may have to be applied prophylactically.

**FIGURE 1** The pro argument for FMT in immune-mediated pathologies. Hypothesized biological processes that underlie the beneficial effects of FMTs.
BOX 2  Research gaps and recommendations for future research

Research gaps

- The causal role of the gut microbiota, the time windows in which the microbiome contributes to pathologies, and the microbiome features that constitute causal components have not been established for chronic immune-mediated diseases.
- The basic principles that underlie the mechanisms by which the gut microbiome contributes to chronic diseases, and by which FMTs work, are poorly understood for pathologies other than C. difficile infection.
- Knowledge on efficacy and safety is lacking to establish risk-to-benefit ratios.
- The ecological processes that shape the recipient’s microbiome after a FMT are poorly understood.
- Effective timing and dosing regimens, and the potential role of adjuncts such as antibiotic treatments and nutritional strategies, have not been established.
- Microbiome signatures that can be used to personalize FMTs, be it in patients as a criterion for the use of FMT, to define appropriate donors or to select donor-recipient pairs, have not been identified and validated to date.

Recommendations for future research

- Basic studies are needed that focus on establishing causality for microbiome ‘dysbioses’ in human pathologies, and the time windows in which they contribute to pathophysiology. Studies need to be carefully designed to control for possible confounders, such as mode of delivery, dietary intake, age of assessment and clinical practices (e.g. antibiotics).
- Adequately powered clinical trials are needed to determine efficacy of FMTs in different human pathologies across representative patient groups, with several years of follow-up to examine stability of response, short-, and long-term safety.
- Trials are needed that compare specific timing and dosing regimens assessing clinically relevant patient outcomes.
- At this early stage of understanding, hypothesis-free, machine learning and predictive modelling approaches could be applied to identify microbiome features in the recipient and donor that predict the usefulness, outcomes and safety of FMTs, with the goal to develop them into biomarkers to personalize decisions and treatments.
- Research should be informed by ecological theory to develop a conceptual understanding of how the recipients’ microbiomes re-assemble after FMT, and if and how this process can be predicted using host, microbiome and environmental factors.

FMT represents a promising paradigm for treating conditions where the microbiome and gut dysbiosis makes a manifest contribution to pathophysiology (Box 1 and Figure 1). However, in chronic conditions where there is uncertainty regarding the ecological factors that drive the dysbiosis, the timeline of its development, and its causal contribution to disease, the rationale to use FMT might be weak and the risk-to-benefit ratio unfavourable (Box 1 and Figure 2). We list the research gaps for the use of FMT in immune-mediated pathologies and recommendations on how to address them in future research in Box 2.
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CONFLICT OF INTEREST
Both authors declare no conflict of interest pertaining to this manuscript.

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