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Fecal microbiota transplantation: lights and shadows of a new weapon against inflammatory bowel disease

Andrea Piccioni[1], Federico Rosa[2], Federica Manca[2], Davide Antonio Della Polla[1], Martina Petrucci[1], Benedetta Simeoni[1], Marcello Covino[1,2]

[1] Department of Emergency Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

[2] Facoltà di Medicina e Chirurgia, Università Cattolica del Sacro Cuore, Rome, Italy

Corresponding Author: Andrea Piccioni, MD; e-mail: andrea.piccioni@policlinicogemelli.it

Orcid: 0000000157038737

ABSTRACT

Treatment of inflammatory bowel disease (IBD) remains one of the most critical public health issues, mostly due to its wide global prevalence and dramatic impact on patients' quality of life.
One of the many mechanisms implicated in the pathogenesis of this disease appears to be attributable to gut microbiota dysbiosis. For this reason, similar to what happened for *Clostridium difficile*, fecal microbiota transplantation is making its way as a possible new therapeutic weapon in the treatment of this disease.
In this article, we will discuss the strengths of this promising treatment, while also discussing the controversial aspects and concerns regarding one of the most innovative therapies of recent times.

KEYWORDS

GUT MICROBIOTA
INFLAMMATORY BOWEL DISEASE
FECAL MICROBIOTA TRANSPLANTATION
ULCERATIVE COLITIS
CROHN'S DISEASE
MICROBIOME

INTRODUCTION

In recent years, the gut microbiota has received considerable interest. Many studies have shown that gut microbiota plays a role in the pathogenesis of several chronic health conditions.
Gut microbiota's modification in composition and function causes significant dysfunction of intestinal permeability, digestion and metabolism, and it promotes immune response and pro-inflammatory state. This can trigger many diseases ranging from gastrointestinal and/or metabolic conditions to immunological and neuropsychiatric diseases[1].

Gut microbiota composition

Microbiota is composed of ten trillion diverse symbionts, 50 bacterial phyla, and about 100-1000 bacterial species colonizing the human gut. The cumulative genes of microbiota are known as the 'microbiome', which is 150 times larger than the human genome[2,3].
The human gut microbiota consists of several types of microbes, including bacteria, archaea, eukarya, viruses, and parasites. Among bacteria, there are seven predominant divisions: *Firmicutes, Bacteroidetes, Actinobacteria, Fusobacteria, Proteobacteria, Verrucomicrobia,* and *Cyanobacteria*[2].
More than 90% of the total population is composed of *Bacteroidetes* and *Firmicutes*. Under the phylum *Bacteroidetes*, most of the microbes belong to the genera of *Bacteroides* and *Prevotella*, and under the phylum *Firmicutes Clostridium*, *Eubacterium* and *Ruminococcus* are predominant[4].

Each gastrointestinal tract harbors distinct bacterial communities that vary in density and diversity because of the distinct gastrointestinal regions concerning different microenvironments due to its anatomical and functional characteristics, which can be the cause of selecting growth of specific microbiota[5].
The gastrointestinal microbiota composition may be affected by some environmental parameters, such as pH, oxygen levels/redox state, availability of nutrients, water activity, and temperature[6].
In the stomach, more than 65% of phylotypes originated from the mouth, bacteria such as *Veillonella, Lactobacillus,* and *Clostridium.* They were found to be acid-resistant[7,8].
The low pH of the gastric lumen limits the type of microbes that can live in that environment, selecting for acid-resistant bacterial populations. Previously, the stomach was thought to be sterile because of the bactericidal barrier, reflux of bile acids, the thickness of the mucus layer, and gastric peristalsis. In 1981, The Lancet reported a large number of acid-resistant bacteria in the stomach, such as *Streptococcus, Neisseria,* and *Lactobacillus*.
One year later, '*Campylobacter pyloridis*' was discovered by Robin Warren and Barry Marshall, and later, it was named *Helicobacter pylori (H. pylori)*. The presence of *H. pylori* affects the rest of the gastric microbiome, which can be a simple commensal species or a pathogen[9].
Blaser et al[10] were the first to propose the eradication in several gastric diseases.
The small intestine tract is characterized by a rapid luminal flow, secretion of bactericidal substances (e.g., bile acids), and plenty of oxygen. All these characteristics can limit bacterial diversity and density[11,12].
Firmicutes and *Actinobacteria* are the predominant phyla in the duodenum. The jejunum supports the growth of Gram-positive aerobes and facultative anaerobes (10^3-7 CFU/ml), including *Lactobacilli, Enterococci,* and *Streptococci*. In the transition to the ileum, the bacterial density reaches up to 10^9 CFU/ml with a predominance of aerobic species. In contrast, the distal part of the ileum close to the ileocecal valve is populated with anaerobes and Gram-negative organisms similar to the colon[13].
In the large intestine, the bacterial density reaches 1012 CFU/ml and is dominated by *Firmicutes* and *Bacteroidetes*. The large intestine is a predominant site of water absorption and fermentation of undigested food, also characterized by the slower transit of food and its anaerobic condition. So, the predominant species are anaerobes.
The colonic microbiota contributes to the digestion of undigested dietary ingredients, and the microbiota's metabolites are subsequently available for absorption by the colonic mucosa.
In terms of bacterial composition, the dominant microbes are *Bacteroides, Bifidobacterium, Streptococcus, Enterobacteriaceae, Enterococcus, Clostridium, Lactobacillus, and Ruminococcus*[8].
Plus, there are two types of microbes composing gut microbiota: the autochthonous, also known as indigenous, and the allochthonous or transient microorganisms.
In this context, only a relatively small number of opportunistic pathogens are considered to be members of the gut microbiota, residing unperturbed within the enteric host microbiota and becoming a health threat to the host only when the gut ecosystem is disturbed, and the gut microbiota homeostasis becomes disrupted[14,15].
Recent developments in technologies about genome sequencing, and bioinformatics enables researchers to explore the microbiota and its functions at a more detailed level than ever before. Evidence suggests that a part of the microbiota is conserved, and the other one is a dynamic microbiota. As well as its variation in different gastrointestinal tracts, it can vary from infants to elderly, primitives to modern human beings, and modify its composition in different health conditions.

From infants to elderly

The shaping and multiplication of gut microbiome start at birth, while the modification of their composition depends mainly on various genetic, nutritional, and environmental factors.
The development of gut microbiota in infants constitutes a dynamic process, in which positive and negative interactions occur.
This process is influenced by various perinatal conditions, such as mode of delivery, diet, mother's age, metabolic status, type of feeding, lifestyle, and antibiotic use. These factors have been reported to impact the infant microbiota[16,17].

Overview of inflammatory bowel disease

Inflammatory bowel disease (IBD) is one of the major public health problems worldwide because of its increasing prevalence and the severe consequences on the lives of affected patients.
IBD mainly comprise two entities, ulcerative colitis (CU) and Crohn's disease (CD).
While ulcerative colitis affects the colon, Crohn's disease can affect any area of the gastrointestinal tract, from the mouth to the perianal area[18].
Very often, inflammatory bowel disease does not have

a predictable, linear course and can be considered a chronic, relapsing, and remitting disease[19].

The prevalence of IBD worldwide has been steadily increasing and has seen its incidence nearly double in less than 30 years, from 3.7 million cases in 1993 to 6.8 million in 2017[20].

Pathogenesis of IBD appears to be multifactorial in origin, and as in many other autoimmune diseases, environmental mechanisms seem to be involved over a genetic predisposition[21]. The mechanisms involved in the pathogenesis seem to be really multiple, and in addition to those already mentioned common to many autoimmune diseases, there are some peculiar to the gastrointestinal tract, such as a dysfunction of the mucosal barrier, alterations in the microbiota, a dysregulation of the immune system, and lifestyle[22].

Characteristic symptoms are abdominal pain, bloody diarrhea, and tenesmus, with significant effects on the patient's quality of life[23].

Ulcerative colitis is associated with other notable complications, such as the risk of colectomy[24], and an increased risk of developing colorectal cancer compared to the general population[25].

IBD can occur at any age, although the peak incidence has been found in the population between the ages of 15 and 30 years, although according to some authors, there is a second peak between the ages of 50 and 80 years[26]. Despite the many similarities between the two forms of inflammatory bowel disease, several aspects differentiate them.

Ulcerative colitis predominantly affects the male sex, while Crohn's disease affects the female, which is why hormonal mechanisms have also been hypothesized to be behind its pathogenesis[27].

Regarding environmental risk factors, the best-known difference between the two forms is exposure to cigarette smoke, which, as is well known, increases the risk of developing Crohn's disease, but is not associated with the onset of ulcerative colitis[28].

Regarding treatment, as both of these conditions are sustained by an autoimmune-type inflammatory mechanism, their therapy finds its cornerstone in the use of aminosalicylates (Sulfasalazine) and other types of 5-aminosalicylic acid (5-ASA) drugs, immunomodulators such as thiopurines (TPs), methotrexate (MTX), calcineurin inhibitors, and Janus Kinase (JAK) inhibitors, corticosteroids, and biologic drugs such as pro-inflammatory cytokine inhibitors and integrin antagonists[29].

Precisely because most currently approved therapies are immunosuppressive and linked to major side effects in the long run, new therapeutic strategies have been tried, for example, by going for microbiota manipulation.

The relationship between gut microbiota and IBD

In recent years, studies dedicated an important role of gut microbiota changes in the onset of IBD.

The gut microbiota seems to be the most important environmental factor involved in the development of inflammatory bowel disease[30]. Nevertheless, for some authors, the role of the microbiome in gut inflammation is still controversial as it could be considered either the cause or the consequence, or even both[31].

Differences in the composition of the gut microbiota in patients with IBD

According to some authors, in patients with Crohn's disease, the phylum *Firmicutes* seems to decrease, while that of *Proteobacteria*, such as *Enterobacteriaceae* and *Escherichia coli*, increases (Figure 1)[32].

In patients with Crohn's disease also, an increase in mucosal bacterial counts and a concomitant decrease in *Faecalibacterium prausnitzii*, a commensal microorganism with anti-inflammatory activity, was found[33].

Reduced levels of *Bacteroidetes* and a consistent decrease in microbial richness were also found in patients with active inflammation[34].

An intriguing theory starts from the assumption that inflammatory bowel disease is recognized as a disease with autoimmune genesis, and according to some authors, this exaggerated immune response may be toward the commensal microbiota, although no specific microorganism has been identified[21].

Knowledge of the gut microbiota for the development of new therapeutic strategies

As mentioned above, in inflammatory bowel disease, there seems to be dysbiosis with a decrease in *Firmicutes* such as *Bifidobacteria, Lactobacilli,* and *Faecalibacterium prausnitzii*[35].

Precisely, because *Firmicutes* are the microorganisms most involved in the production of short-chain fatty acids such as butyrate, a substrate with immunoregulatory properties, butyrate enemas have been attempted as a therapeutic weapon[36].

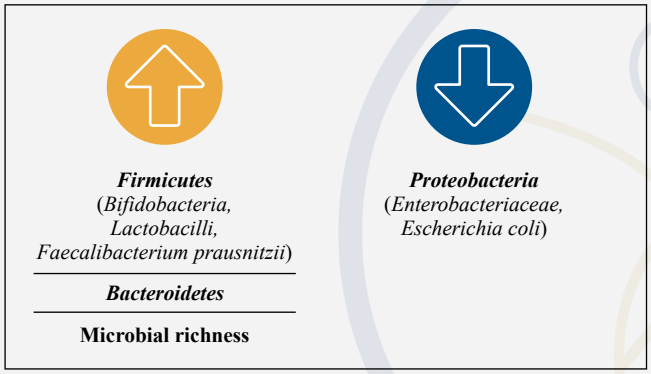
A fascinating avenue for manipulating the microbiota has been attempted through the use of prebiotics, probiotics, paraprobiotics, postbiotics, and synbiotics[37].

With prebiotics, an attempt is made to modify the microbiota through the diet, while with probiotics, beneficial bacteria are directly supplemented with the diet. The products that combine these two therapies are symbiotics instead.

Paraprobiotics are defined as non-viable, inactivated bacteria or their components, while postbiotics are products of bacterial metabolism or equal synthetic

products modulating the inflammatory and immune response[37].
This is also a promising field of study that deserves separate discussion because of its vastness.
The topic we will discuss, fecal microbiota transplantation, conceptually takes up the same idea as these treatments, with a quite different approach.
Fecal microbiota transplantation (FMT), is a treatment that manipulates the microbiota, now well established in the treatment of recurrent *Clostridium difficile* infection.
As we will see below, FMT represents one of the latest hot discussion topics regarding the increasingly well-known relationship between inflammatory bowel disease and microbiota[38].

Figure 1. Main alterations in the gut microbiota predisposing to the onset of IBD.



The experience of FMT in the treatment of *C. difficile* overgrowth

Therefore, based on the experience with the treatment of *C. difficile* overgrowth, FMT was tested as a possible therapeutic weapon for IBD. Dysbiosis is the condition underlying the onset of *C. difficile* overgrowth.
C. difficile is a gram-positive spore-forming bacillus present in 2-4% of healthy individuals[39]; this bacterium, harmless to many people, becomes responsible for such a severe infection when a dysbiosis in the microbiota comes to occur.
It is mainly the use of antibiotics that is the trigger that goes on to alter that delicate balance between the host and its commensal microbial flora, leading to colonization, uncontrolled growth, and toxin production until *C. difficile* overgrowth develops[39].
The treatment of *C. difficile* overgrowth, therefore, involves the use of antibiotics such as fidaxomicin, vancomycin, and metronidazole, but precisely because by now that delicate balance between microorganisms and host has been irreparably compromised, the risk of recurrence is extremely high. In this case, FMT is a valid option[40], since it restores the balance of normal microbial flora, unlike antibiotic treatments, which can aggravate the intestinal dysbiosis that leads to the onset of *C. difficile* overgrowth[41].
We have previously seen how dysbiosis also underlies the onset of inflammatory bowel disease.
The first evidence of the use of FMT for the treatment of IBD was described in patients treated for the onset of *Clostridium difficile* overgrowth. In those patients, FMT emerged as a safe and effective treatment[41], while in a minority of patients, FMT acted as a trigger causing a flare of disease[39]. It is unclear yet why FMT may improve IBD activity in some patients and causes inflammation in others[42].

FMT

With FMT, we transplant healthy microbiota into patients with unhealthy gut microbiota composition; in this way, we reconstitute its normal physiological functions to treat the underlying disease. In other words, by using FMT, we reverse dysbiosis in the recipient's gut by providing the full spectrum of microorganisms belonging to the healthy donor.
We have already explained how FMT has become one of the approved pivotal therapies for the treatment of recurrent *C. difficile* overgrowth. However, despite its proven efficacy, FMT is often underutilized due to some difficulties, such as donor recruitment, route of administration, and stool handling[43].
According to a meta-analysis[44], the most effective way of administration appears to be through the lower gastrointestinal tract.
Combining FMT with the use of antibiotics has also been tried to increase its efficacy. Patients pretreated with antibiotics before FMT presented a higher clinical remission rate[45].
Interestingly, following FMT, increased intestinal microbial diversity was indeed found to mirror that of the donor[44]. On this view, it was noted that the greater the donor's microbial diversity and richness, the greater the success rate following FMT[33].
Regarding microbial composition, by performing analysis of fecal samples pre- and post-procedure, patients recovered after FMT showed higher concentrations of *Eubacterium hallii* and *Roseburia inulivorans* and increased biosynthesis of short-chain fatty acids and secondary bile acids.
Despite all these encouraging results, some obscure aspects remain to be clarified, such as the long-term efficacy of these therapies, the best route of administration, and a proper donor and recipient selection strategy[29].

Main evidence on the use of fecal microbiota transplantation in inflammatory bowel disease

As we can see in Table 1, the main evidence supporting the efficacy of FMT in the treatment of ulcerative colitis comes from very recent evidence, starting with a systematic review in 2012 and the very recent trials conducted since 2015.

Regarding more in-depth features, we defer reading the individual studies.

To summarize the main features, these trials still had a low number of participants (the maximum number was reached in Paramsoty's 85), fecal transplantation was in some cases by nasoduodenal tube, in others by colonoscopy or enema, and in some cases, the feces came from a single donor, while in others from multiple donors. In each case, the endpoint was disease remission.

Thus, it becomes evident that a uniform validated protocol needs to be found for future studies to decrease variability.

Regarding some aspects still to be clarified, there are some concerning donor selection and the mode of stool administration.

Most of the evidence on FMT concerns ulcerative colitis, so we also point out two systematic reviews, both from 2021, published on the use of fecal microbiota transplantation for Crohn's disease, in which its therapeutic potential is confirmed.

Table 1. Timeline of the main evidence on the use of fecal microbiota transplantation in inflammatory bowel disease.

Characteristics of the study	Authors and year
Systematic review on IBD	Anderson et al (2012)[46]
Randomized Controlled Trial on CU	Moayyed et al (2015)[47]
Randomized Controlled Trial on CU	Rossen et al (2015)[48]
Systematic review and meta-analysis on CU	Shi Y et al (2016)[49]
Randomized Controlled Trial on CU	Paramsothy et al (2017)[50]
Randomized Controlled Trial on CU	Costello et al (2019)[51]
Systematic review on CD	Fehily et al (2021)[52]
Systematic review and meta-analysis on CD	Cheng et al (2021)[53]
Systematic review and meta-analysis on CU	Wei et al (2022)[54]
Systematic review and meta-analysis on CU	Huang et al (2022)[55]

FINAL CONSIDERATIONS

FMT is now a recognized potential therapeutic weapon for the treatment of IBD, although several aspects remain to be clarified (Table 2).

Table 2. Main topics of debate on the use of fecal microbiota transplantation for the treatment of IBD.

Aspects to clarify
Mode of administration
Donor selection
Pre-treatment with antibiotics
Safety
Treatment duration
Long-term effectiveness

The most credited pathogenetic mechanisms for its success are related to increasing microbial diversity[56] and rebalancing dysbiosis, thus reducing the well-known pro-inflammatory state.

For all these reasons, we agree with Quraishi's view[57] about the needing for a more personalized approach based on precision medicine. Interestingly, this has been fully understood by a group of researchers who have looked at predictive biomarkers of donor and recipient response to FMT in patients with ulcerative colitis[58].

Research is more alive than ever on this topic; in fact, we report a recent study of a small group of patients pretreated with antibiotics who were then given FMT orally, with encouraging results[59].

Although some authors have recently commented on the ineffectiveness of long-term treatment[60], there is still no unanimity on this aspect, so further studies are certainly needed.

One aspect that should definitely be taken into consideration is the safety of this procedure. With FMT, the aim is to rebalance the dysbiosis underlying the onset of inflammatory bowel disease, but one of the risks of this procedure is then to transfer pathogenic microorganisms into a patient who is very often taking immunosuppressive therapies, thus facing devastating consequences.

For this reason, the choice of the donor is extremely important, as is the careful selection of the recipient. Regarding the side effects of this procedure, those most commonly encountered were disease flares[39]. In a recent meta-analysis, the overall risk of worsening IBD was estimated to be 14%. This worsening is associated with fecal administration through the lower gastrointestinal tract, although not all authors agree on this[61].

Concerning mortality, we cite a very recent systematic review looking at adverse events over 20 years[62].

This work found that most adverse effects occurred within one month after FMT, which is then suggested as a cut-off for short- and long-term complications. Anyway, the mortality rate was extremely low (0.13%), most of which occurred due to aspiration pneumonia. This complication was also associated with patients undergoing upper gastrointestinal FMT, so specific arrangements could be considered to prevent it.

National registries are also active about complications, and the most cited are American (AGA) or Chinese (CMTS).

The American Registry collects data from 4,000 patients over a 10-year period, while the Chinese one shows the real-time incidence of adverse events on the website.

With these new tools, we can definitely monitor the safety of this procedure.

Regarding dysbiosis associated with the onset of IBD, a decrease in *Bacteroidetes* and a predominance of *Proteobacteria* were found (Figure 2)[63].

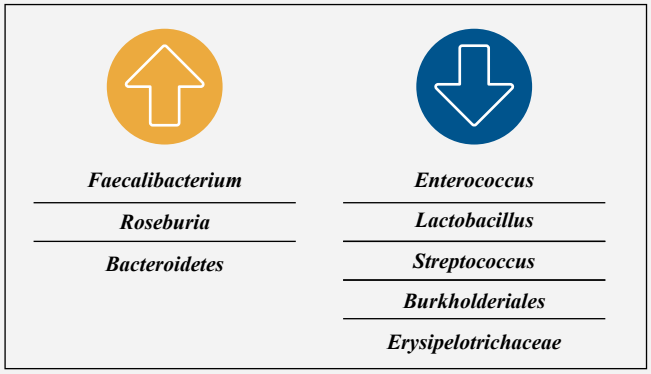
In addition, some important phyla such as *Firmicutes* and *Bacteroidetes* appear to be reduced in diversity, while an increase in *Veillonellaceae, Enterobacteriaceae, Pasteurellaceae,* and *Fusobacteriaceae,* and a decrease in *Erysipelotrichales, Bacteroidales,* and *Clostridiales* have been correlated with disease activity[56].

Following the procedure, an increase in IBD-protective bacteria, such as *Faecalibacterium* and *Roseburia,* and a decrease in those correlated with IBD worsening, such as *Enterococcus, Lactobacillus, and Streptococcus*, as well as groups of *Burkholderiales* and *Erysipelotrichaceae* was found[63].

Instead, according to some authors, one of the key aspects of the success of FMT seems to be precisely the recovery of *Bacteroidetes*[64,65].

Despite those observations, some limitations still occur about the real role of FMT in IBD. Issues such as long-term efficacy, heterogeneity of current trials, way of administration, and donor selection, are not well recognized. Therefore, it is crucial to restart from those open issues to clarify the therapeutic role of FMT in IBD.

Figure 2. Major changes in the gut microbiota resulting from FMT.



Conflict of Interest

The authors declare that they have no conflict of interest.

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