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Chapter

Is a Fecal Microbiota Transplant Useful for Treating Inflammatory Bowel Disease?

Andra-Iulia Suceveanu, Andrada Dumitru, Marilena Musat, Claudia Voinea, Felix Voinea, Irinel Parepa, Anca Pantea Stoian, Laura Mazilu and Adrian Paul Suceveanu

Abstract

Ulcerative colitis and Crohn's disease represent the major groups of idiopathic disorders in inflammatory bowel disease (IBD). The etiology includes environmental factors, genetic factors, and immune responses. The pathogenesis is diversified; however, no guaranteed curative therapeutic regimen has been developed so far. This review contains information related to pathophysiology and current treatment options for IBD. It is known that IBD is caused by tissue-disruptive inflammatory reactions of the gut wall; that is why downregulation of the immune responses allows the healing of the damaged mucosa and allows the resetting of the physiological functions of the gut back to normal. The main treatment options are still corticosteroids, immunomodulators, antibiotics, probiotics, and a series of new agents. Their effects include modulation of cytokines, neutrophil-derived factors, adhesion molecules, and reactive oxygen/nitrogen metabolites. The monoclonal antitumor necrosis factor as infliximab recombinant anti-inflammatory cytokines or related gene therapy is also used nowadays. Still, the fecal microbiota transplantation (FMT) is considered to revolutionize the therapy in IBD, considering the abnormal inflammatory response due to the complicated relationship between microbiota and the immune system. It is imperative to mention the critical role dysbiosis may have in the pathogenesis of IBDs. This review summarizes the available literature concerning the efficacy of FMT in IBDs.

Keywords: inflammatory bowel disease, microbiota, fecal transplant

1. Introduction

The current manuscript represents an overview of literature reflecting the concern of gastroenterology physicians regarding the usefulness of fecal microbiota transplant as an appropriate and successful therapy in difficult to treat IBD patients. Inflammatory bowel disease (IBD) is a relapsing, remitting, and chronic disease that causes significant morbidity. The etiology of IBD is still unclear. The phenotype, the progression, and their development are multifactorial with environment and genetics. Nowadays, studies are confirming that the microbial influence in the

pathogenesis of IBD is increasing; this fact results from an inappropriate immune response towards components of the commensal microbiota. In IBD, the diversity of luminal microbiota is reduced. *Firmicutes* (bifidobacteria, lactobacillus, and *Faecalibacterium prausnitzii*) are especially decreased. On the opposite side, the mucosal adherent bacteria are increased [1, 2].

Both ulcerative colitis and Crohn's disease share many common features like bloody stools, diarrhea, fever, and abdominal pain, but each of them also has unique features. There are many differences between the two entities, the most important being the depth of involvement in the bowel wall and their location. Crohn's disease results in transmural ulceration of any portion of the gastrointestinal tract, but it affects most often the colon and terminal ileum; at the opposite side, ulcerative colitis affects the rectum, but it may extend beyond the sigmoid and into the sigmoid or include the entire colon into the cecum [1–3].

2. Inflammatory bowel diseases

2.1 Etiology and pathophysiology

The etiology of IBD is not fully elucidated, but it seems that it often occurs in genetically susceptible individuals after an inappropriate immune response to the microbiota; so, the key to the pathogenesis of IBD is represented by the intestinal immune system. Typically, the gut epithelium prevents antigen or bacteria entry into the circulation by sealed intracellular junctions. In IBDs, because of the inflammation or the loss of the primary barrier function, these intracellular junctions are defective. The Goblet cells produce mucus as an additional protective mechanism [4].

Crohn's disease is a patchy inflammatory disease affecting any part of the digestive tract, from the mouth to the anus and perianal area. Ulcerative colitis is a disease of continuity involving the rectum and colon in a centripetal manner and associating extraintestinal involvement of the skin, bones, or eyes [5].

2.2 Histopathology

In the active form of IBD, the microscopic evaluation reveals the infiltration of lamina propria with a mix of macrophages, dendritic cells, neutrophils, and natural killer T cells. Because of the increased activation and number of these cells, there is also an increasing level of cytokines, interleukin 1b, tumor necrosis factor-alpha, and interleukin 23-TH 17 [6–8].

2.3 Clinical manifestations

Patients with ulcerative colitis describe tenesmus, abdominal pain, and a sensation of incomplete evacuation. Still, the most upsetting symptom is represented by bloody diarrhea with or without mucus. The physical exam reveals predominantly left upper or left lower quadrant abdominal pain [1].

Patients with Crohn's disease have different clinical manifestations, depending on the region of gastrointestinal involvement. Symptoms like right lower quadrant pain, non-bloody diarrhea, and weight loss are the most common in Crohn's disease [9].

2.4 Diagnosis

When diagnosing IBD, the clinician has to combine inflammatory laboratory markers, clinical findings, endoscopic biopsies, and imaging findings. The guiding

laboratory tests are represented by leukocytosis, microcytic anemia, thrombocytosis, and elevated levels of C-reactive protein and erythrocyte sedimentation rate [10–12].

The imagistic methods that are useful when diagnosing IBD or assessing complications are ultrasound, magnetic resonance imaging (e.g., rectal fistulas), and computed tomography (e.g., perforation or bowel obstruction). But to confirm a diagnosis of IBD biopsies obtained via colonoscopy or esophagogastroduodenoscopy is necessarily needed [12, 13].

2.5 Options of treatment

There are many conventional and novel drug treatments that have proven efficacy in IBDs (aminosalicylates, steroids, biological therapies, and immunosuppressants). However, many patients become refractory to standard management of the disease, some of them presenting significant side effects that even require surgery. There are an increasing number of patients that live with mild active symptoms, despite medical treatment, having a poor quality of life [14–16].

The gastrointestinal microbiota has a dominant role in driving inflammation in IBD; that is why medications that manipulate the microbiota have been investigated (e.g., probiotics, prebiotics) with variable evidence of their efficacy [15, 16].

Alternative treatment in IBD management is fecal microbiota transplantation (FMT) consisting of the transfer of gut microbiota from a healthy donor, via infusion of a liquid stool suspension, to restore the intestinal microbiota of a diseased person. This therapy procedure was firstly documented in 1958 [17].

The reports concerning the patients that have been subjected to fecal microbiota transplantation had positive outcomes [18–20].

3. Microbiota

In humans, the gut microbiota varies across the digestive tract. There are relatively few bacterial species present in the stomach and small intestine, compared to the colon, which is the habitat of the highest microbial density—up to 10^{12} cells per gram of intestinal content. Ninety-nine percent of the bacteria are anaerobes, except the cecum, where aerobic bacteria achieve high frequencies [21].

Although many species in the human gut have not been studied because they cannot be cultured by the ways yet discovered, there are four dominant phyla: *Proteobacteria*, *Bacteroidetes*, *Actinobacteria*, and *Firmicutes*. Most bacteria belong to the genera *Bifidobacteria*, *Clostridium*, *Peptostreptococcus*, *Bacteroides*, *Peptococcus*, *Ruminococcus*, *Eubacterium*, and *Faecalibacterium* [22, 23].

3.1 Normal functions

The gut microbiota is still intensively studied. Besides metabolizing indigestible food compounds, it stimulates the gut immune system, directly defending against pathogens. It has a substantial role in developing and maintaining the intestinal epithelium and inducing antibody production. Also, studies focused on its action in the gut-brain axis [23, 24].

3.1.1 Direct inhibition of pathogenic bacteria

The intestinal barrier provides protection against pathogenic invasion through many defense mechanisms, including butyrate and other metabolically protective products, the commensal bacteria competitively preventing pathogenic bacteria's

colonization. Disruption of intestinal barrier function may cause local or even systemic immune over-response, afferent vagus nerve activation, neuroinflammation, and mast cell degranulation. Furthermore, some species of the commensal bacteria, like *Lactobacillus plantarum*, binds and stimulates the Toll-like receptor 2 (TLR2) in the intestinal epithelium, thus maintaining epithelial integrity [24–26].

3.1.2 Development of the immune system

The human intestinal flora develops in the first 2 years after birth, when the intestinal epithelium and mucosal barrier evolve in a tolerant and even in a supportive manner. Particularly, goblet cells—the ones producing the mucosa—proliferate, resulting in a thickening of the mucosa layer in which commensal bacteria may anchor and feed but cannot penetrate. Furthermore, the gut-associated lymphoid tissue, which is part of the gut epithelium, has a role in detecting and reacting to pathogens, being tolerant of commensal species and its metabolites and digestive products of food [26–29].

Cytokines stimulate the immune system to produce inflammation to protect itself, which may decrease the immune response to control homeostasis and favor healing after injuries. There is some bacterial species in the intestinal flora which seems to drive the production of selective cytokines by the immune system, such as *Bacteroides fragilis* and *Clostridium* species, which may induce an anti-inflammatory response, although some segmented filamentous bacteria cause the production of inflammatory cytokines [29, 30].

Another function of the intestinal flora is driving the immune system to produce antibodies. Thus, B cells switch class to IgA in another way, normally needing activation from T helper cells. Intestinal epithelial cells induce NF- κ B signaling, which causes the secretion of further signaling molecules. These interact with B cells and induce the switching class to IgA—an important type of antibody because it keeps healthy a mucosal environment by eliminating the microorganisms that cause inflammatory responses [24, 25].

Gut flora can produce metabolites that can affect cells in the immune system, such as short-chain fatty acids produced through fermentation, and can induce an increased production of eosinophils, neutrophils, and basophils, which are components of the innate immune system and have a role in limiting the infection's spreading [26].

3.1.3 Metabolism

The intestinal flora is essential for digestion through some enzymes that the human body does not possess to break down polysaccharides. Carbohydrates are turned into short-chain fatty acids by saccharolytic fermentation, including acetic acid, propionic acid, and butyric acid, used by the host cells as a source of energy and nutrients. Also, gut flora facilitates the absorption of minerals—magnesium, calcium, iron—and synthesizes vitamins, biotin and folate [27].

3.1.4 Microbiome-gut-brain axis

The microbiome-gut-brain axis includes the central nervous system and the neuroendocrine and neuroimmune systems, hypothalamic–pituitary–adrenal axis, sympathetic and parasympathetic arms of the autonomic nervous system, the enteric nervous system, the vagus nerve, and the intestinal microbiota [28].

The term refers to the biochemical signaling between the central nervous system and the gastrointestinal tract [29].

3.2 Dysbiosis

Dysbiosis represents microbial imbalance or maladaptation that can be caused by many triggers, such as antibiotic treatments, alcohol abuse, or inappropriate diet. Also, microorganisms present in the digestive tract may contribute to inflammatory disorders, or specific metabolites influence some signaling pathways leading to obesity and colon cancer. Additionally, sepsis may occur in cases of breaking down of the intestinal epithelium with the invasion of flora components into host's compartments [30, 31].

4. Fecal microbiota transplant (FMT)

4.1 General considerations

The new key in treating dysbiosis is the fecal microbiota transplant, which restores colonic microflora. It involves the transplantation of fecal bacteria from a healthy individual by colonoscopy, enema, orogastric tube, or orally by capsules containing freeze-dried material. FMT has been used in treating *Clostridium difficile* infection and experimentally in inflammatory bowel disease, irritable bowel syndrome, constipation, and some neurological conditions, like multiple sclerosis and Parkinson's disease [32].

The size of samples has to range from 30 to 100 grams of fecal material for the treatment to be effective. The fresh stool is needed to increase the viability of bacteria, and samples are prepared within 6–8 hours, diluted with 2.5–5 times the sample's volume with normal saline, sterile water, or 4% milk [32, 33].

The donor selection is strict and involves screening of medical history, screening for chronic diseases, and laboratory testing for pathogenic gastrointestinal infections [33].

However, clinical trials report cases of important adverse events after fecal microbiota transplant, such as gram-negative bacteremia combined with aspiration pneumonia or even toxic megacolon. Adverse events are the reason why the FDA decided to expand donor-stool screening by including tests for human T-lymphotropic virus, norovirus, and extended-spectrum beta-lactamase-producing microorganisms. Also, to minimize the risk of infection, clinicians should forget the “one size fits all” approach and consider the risks and benefits for each individual, especially in cases of immunocompromised patients [34–36].

The process of choosing donors include four stages as follows: stage 1, eliminating overweight (body mass index >30) patients, smokers, and those unable to donate periodically; stage 2, eliminating donors with microbiome-associated conditions, such as metabolic, gastrointestinal, autoimmune, allergic, atopic, neurologic, and psychiatric; stage 3, stool and nasal screening, involving tests for antibiotic-resistant bacteria; and stage 4, blood tests [35, 36].

We can conclude that healthy donors are hard to find. Thus clinicians should continue improving donor screening to reduce drug-resistant microorganisms transmission, and research should focus on the benefits and the risks involved in fecal microbiota transplant [37].

4.2 FMT in inflammatory bowel disease

It is mandatory to mention the important role that dysbiosis may have in the pathogenesis of inflammatory bowel disease, considering the abnormal inflammatory response resulted from the complex relationship between microbiota and the

immune system. This feature is the reason why ongoing research carries so much interest in correcting dysbiosis using fecal microbiota transplantation [37, 38].

FMT can reduce IBD's severity by increasing the production of short-chain fatty acids (butyrate); this way, the bowel permeability is reduced, and the integrity of the gut epithelium is maintained. Also, inhibiting the production of inflammatory elements, leukocyte adhesion, and the activity of T cells, FMT may restore the immune system [38].

In patients with ulcerative colitis and Crohn's disease, preliminary clinical studies showed a long-term follow-up clinical remission maintained, even endoscopic and histologic remission in a few other cases. A meta-analysis of nine studies showed a remission rate of 36.2%. Still, the results depend on some factors like age (higher remission in younger patients with ages between 7 and 20 years old), route of administration (naso-jejunal tube, enema, colonoscopy), and dose and preparation of donor feces. Also, it seems like fecal microbiota transplant is more effective in Crohn's disease than in ulcerative colitis with remission rates of 60.5 and 22%, respectively. On the other hand, a study involving 15 patients with steroid-dependent ulcerative colitis who received fecal microbiota transplant through colonoscopy showed a long-term maintained remission in 57% of cases [38–40].

Because of the lack of uniformity regarding the treatment protocols and the delivery method, it is hard to offer a solid conclusion referring to the safety and efficacy of fecal microbiota transplant in inflammatory bowel disease. If compared with the results collected in cases of recurrent *Clostridium difficile* infection (remission in about 90%), these results may look discouraging. Still, we have to keep in mind that the inflammatory bowel disease's pathogenesis is not purely driven by dysbiosis as it happens in *Clostridium difficile* infection. Following this direction, we need more randomized controlled placebo studies to clarify the role of fecal microbiota transplant in inflammatory bowel disease [40–42].

4.3 Potential adverse effects of FMT

These can be classified into short-term and long-term side effects [19].

Short-term side effects are related to the delivery method. They may include mild fever, flatulence, constipation, diarrhea, vomiting, and abdominal discomfort, but all of these usually resolve in a few weeks. In cases when FMT was administered through the naso-jejunal tube, patients presented with high fever and the rise of the C-reactive protein. When using colonoscopy, there have been reported cases of perforation, bleeding, and symptoms related to anesthesia [43].

Due to the lack of research, there are few data collected about the dominant concern regarding the safety of fecal microbiota transplant—long-term side effects. We can speculate a considerable risk for chronic diseases, involving obesity, diabetes, colon cancer, and atherosclerosis, due to the alteration of intestinal microbiota [43, 44].

5. Conclusions

Inflammatory bowel diseases are chronic, relapsing intestinal disorders, with pathogenesis not fully elucidated. Treatment disappointments are still high, despite the availability of different therapeutic options. Patients' reduced compliance, the impoverished life of quality, and the increased economic, sanitary, and social burden worldwide are still unresolved issues. For that reason, research must continue to identify more information about the intestinal microbiota, metabolic pathways, and

microbial genes. A moving target may be the identification and isolation of an active component of the microbiota that could be the new target of therapies for inflammatory bowel diseases [44–45].

Conflict of interest

All authors declare “no conflict of interest.”

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Author details

Andra-Iulia Suceveanu^{1*}, Andrada Dumitru¹, Marilena Musat¹, Claudia Voinea¹, Felix Voinea¹, Irinel Parepa¹, Anca Pantea Stoian², Laura Mazilu¹ and Adrian Paul Suceveanu¹

1 Faculty of Medicine, Ovidius University, Constanta, Romania

2 University of Medicine and Pharmacy Carol Davila, Bucharest, Romania

*Address all correspondence to: andrasuceveanu@yahoo.com

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