



## REVIEW ARTICLE

# Inflammatory bowel disease: The role of commensal microbiome in immune regulation



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## KEYWORDS

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**Abstract** The incidence of inflammatory bowel disease (IBD) is increasing. Microbiome is one of the most important factors in its development and affects the different clinical outcomes of IBD patients depending on its composition and different alterations. We conducted a systematic review to discuss the association between microbiome and IBD in terms of immune regulation, and therapies that can modify microbiota. A comprehensive systematic literature search was performed through April 2020 in PubMed, Web of Science, the Cochrane Library, and clinicaltrials.gov. Inclusion criteria required IBD immune regulation and alternate therapeutics for IBD. This analysis helps explain the multifactorial origin of microbiome diversity including normal immune regulation, immune pathophysiology of IBD, and shows the evidence of several therapeutic targets to change microbiome in patients with IBD, such as prebiotics, probiotics, antibiotics, fecal microbiota transplant, and others.

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## PALABRAS CLAVE

Enfermedad inflamatoria intestinal;  
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Trasplante microbiota

**Enfermedad inflamatoria intestinal: el rol de microbioma comensal en la regulación inmune**

**Resumen** La incidencia en enfermedad inflamatoria intestinal (EII) va en aumento. El microbioma es uno de los factores más importantes en su desarrollo y afecta los diferentes escenarios clínicos en pacientes con EII dependiendo de su composición y diferentes alteraciones. Se realizó una revisión sistemática para discutir la asociación entre el microbioma y EII relacionado con inmunorregulación y las terapias que pueden modificar la microbiota. Se realizó una búsqueda

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en la literatura hasta abril de 2020 en Pubmed, Web of Science, Cochrane library y clinicaltrials.gov. La inclusión del material requiere EII, inmunorregulación y las terapias alternativas para EII. Este estudio ayuda a explicar el origen multifactorial de la diversidad del microbioma incluyendo la inmunorregulación normal, fisiopatología inmuno de EII y muestra la evidencia de diferentes blancos terapéuticos para cambiar el microbioma en pacientes con EII como prebióticos, probióticos, antibióticos, trasplante de materia fecal, entre otros.

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## Introduction

Inflammatory bowel disease (IBD) epidemiology has changed over time. There is an increase in prevalence and incidence in many countries. The reports of IBD epidemiology models forecasts that IBD prevalence will increase by 3% per year, rising in prevalence from 0.7% in 2018 to 1% by 2030.<sup>1</sup> IBD epidemiology is heterogeneous among different countries; however, regions with a lower prevalence such as Latin America, have had an increased incidence in the last decades, as in Brazil and Mexico.<sup>2,3</sup> Therefore, it is burdensome to establish an accurate incidence or prevalence in IBD worldwide but there is a trend toward an increase.

The changes in incidence have not been fully explained. IBD is recognized as a multifactorial disease that can affect the small or large intestine in many different ways. It is still difficult to establish a relationship of causality; however, there is enough rationale to presume that the synergy among environmental, genetic, and compositional changes in intestinal microbiome could predispose the development of IBD. Multiple environmental determinants, such as antibiotic use, breastfeeding, air pollution and other urban conditions, influence the risk of developing IBD and can alter the natural history of IBD from perinatal development to adulthood.<sup>4</sup> In terms of genetics, genetic and epigenetic changes were found in IBD that can trigger different disease phenotypes; e.g., severity and cancer propensity. This precision medicine information requires more aggressive surveillance and treatment in patients.<sup>5</sup> Moreover, there is an association between an altered microbiome in IBD called dysbiosis, which results in a different metagenomic and metabolomic profile, and different concentrations of metabolic compounds in feces.<sup>6</sup>

The purpose of this review is to summarize the current association between commensal microbiome and immune regulation in healthy individuals and IBD patients, and discuss the potential treatments related to modifications in the microbiome in human IBD.

## Methods

### Search strategies

We searched for articles published in PubMed, Web of Science, the Cochrane Library, and clinicaltrials.gov with the following MeSH terms for IBD and commensal

bacteria: "Microbiota", "Commensal", "Dysbiosis", "IBD", "Ulcerative colitis", "Crohn's disease", "Gastrointestinal immune". Then, the results were combined using "AND" with studies identified by other keywords such as "Ulcerative colitis", "Crohn's disease", "Prebiotics", "Probiotics", "Antibiotics", "Faecal microbiota transplant", "IBD therapy", "Meta-analysis". We enrolled all relevant data up to April 2020 by reviewing the titles and abstracts. The reference lists of relevant articles were also scrutinized.

### Data collection and quality assessment of studies

The methodological quality of the current study includes case reports, cohort studies, random clinical trials (RCTs) and reviews and meta-analysis. The risk of bias in the information included depends on the level of evidence according to the type of study.

### Normal immune regulation

The immunologic system is composed of innate and adaptive responses. In the latter are the classical Th1 and Th2 immune response theory where different production of cytokines with interferon- $\gamma$  (IFN- $\gamma$ ) for Th1 cells to attack intracellular organisms and interleukin (IL)-4, IL-5, and IL-13 for Th2 cells for parasitic infections. Another immunologic pathway with Th17 cells can raise IFN- $\gamma$  effects that are similar to Th1 response, but also target innate immunity through neutrophil activity and epithelial cells response.<sup>7</sup> The cytokine IL-23, an important component in the cascade of Th17 cells acts as an effector of T cell subsets and it is involved in many responses that cause inflammation. CD4+ Th17 are not found in the germ-free mouse intestines, showing that are generated according to microbiota and external stimuli. Some reports indicated that IL17A deficient mice caused increased colitis associated to high levels of IFN- $\gamma$  due to the lack of inhibition of Th1 cells pathway. After all the subsets of T cells are in a steady state, antigen presentation cells favor development of regulatory T cells (Tregs) that act to suppress inflammation by suppressing effector T cells.<sup>8</sup>

Intestinal epithelial cells (IECs) and mesenchymal are important as barrier function and host response to infection and tissue damage as well. IECs are not only a barrier but also the beginning of the innate immune response to tissue

damage; the balance of immune response is between NF- $\kappa$ B and STAT3 signaling pathways. Different cytokines induce activation, proliferation and inflammation-driven repair pathways in IECs including IL-6, IL-11, and IL-22 through STAT3 signals stimulation.<sup>9</sup> The mesenchymal cells underlying IECs in another important component in immune system. NOD2 activation through mesenchymal cells protects against enteric pathogens, and provides differentiation factors for IECs stem cells for repair.<sup>10</sup>

### Microbiota in immune-regulation

The gastrointestinal tract has an enriched number of microorganisms that interact with the immune system to produce certain types of signals depending on the entity involved. Different bacteria harbored in the intestine are well tolerated by the immune system because of the host genetic code or a response induced by bacteria; this process is called tolerogenic response.<sup>11</sup> The signal between the microbe and the host is reciprocal at several levels and is interconnected by a mutual regulation of development and homeostasis. The detection of disarrays in the components that are related in this interaction between microorganisms and intestinal environment is responsible for a cascade that triggers an inflammatory process. This inflammatory process ends in the abrupt increment of frequency of oncologic, liver, and immunoallergic processes, including IBD.<sup>12</sup>

The microbiome is not constant during the lifespan and changes with age. Every segment of the gastrointestinal tract influences the concentration and type of microbiome.<sup>13</sup> Microbiota diversity depends on diet as well. The type of diet influences the plasticity of microorganisms living in the gastrointestinal tract. A diet rich in animal products enhances bile tolerant bacteria (*Alistipes*, *Bilophila*, and *Bacteroides*) and depletes others that metabolize plants, such as Firmicutes.<sup>14</sup> The growth dynamics of microbiota is very diverse and includes all kingdoms of organisms, such as prokaryotes, eukaryotes and viruses. The introduction of specialized databases with metagenomics has consistently allowed the classification of more than 30 prokaryotic phyla, finding human eukaryotic microbiome as pathogens, commensals and beneficial organisms, and identifying bacteriophages that keeps the gut in healthy homeostasis.<sup>13</sup>

The role of different organisms as pathogenic or commensal is still an area of study. Some studies showed specific bacteria that help in several ways in mucin production, such as *Akkermansia muciniphila* which changes mucus characteristics that improves barrier function and affects homeostasis. Commensals, such as *Faecalibacterium prausnitzii* needs an environment enriched with mucin to colonize the intestine. Furthermore, different bacteria byproducts like butyrate, boosts the growth of commensal bacteria.<sup>15</sup> Likewise, a few fungal microbiota are considered mycobiota in the gastrointestinal tract; this includes *Candida*, *Saccharomyces*, *Penicillium*, and *Aspergillus*; however some data argue against fungal colonization and suggest that fungi are not common colonization flora. It is debated whether the fungal microbiota is able to colonize as commensals, like bacteria, or is external contamination from the mouth or diet.<sup>16</sup>

The progress of genetic profiling, including proteomics, metagenomics, and metabolomics, has contributed to the discovery of the composition of complex microbial communities of not only bacteria, but also many other microorganisms. This can help elucidate the change in microbiota as a cause of diseases.

### Pathogenesis in IBD

#### Immune-regulation in IBD

IBD is involved in the whole process of immune regulation including innate and adaptative mechanisms. The disease pathogenesis is multifactorial and complex through different immune abnormalities. Innate immunity involving neutrophils, monocytes, and macrophages respond to invading bacteria. These cells accumulate in inflamed intestines in UC and CD in the form of neutrophil-enriched crypt abscesses and granulomas, respectively. NOD2, which is the strongest predictor of CD, is associated with defects in innate immunity. Furthermore, TGF- $\beta$  is another regulator of intestinal inflammation which is impaired by the inhibition with molecules like SMAD 7.<sup>10</sup>

Dysfunctional Tregs activity, disrupt T and B cell activation and decreased innate immune system are implicated in auto-inflammatory responses. Th1, Th2, and Th17 cells subsets are arranged in different levels of the pathogenesis of IBD. The main signaling defects that lead to infantile IBD are IL-10 signaling. IL-10 has an important role in intestinal homeostasis, mice with IL-10 knock out develop colitis.<sup>10</sup> It is controversial the exact mechanism of Th17 cells in the pathogenesis of CD, however populations of CD4 T cells with CCR6+, IL-23R+, and CD 161+ are present in patients with IBD lesions. CD is associated with defects in autophagy, bacterial sensing, and excessive Th17 pathway activation.<sup>17</sup> In UC, genetic studies linked IL23 receptor and Th17 pathway to immune responses. IL-23 promotes survival of Th17 cells during inflammatory response; it increases cytokines such as granulocyte-macrophage colon stimulating factor and IFN- $\gamma$  and inhibits intestinal Tregs cells response. Another cytokine is IL-13 which excessive production is implicated in pathogenesis by the natural killer T cells, defects in epithelial barrier integrity and excessive Th17 pathway activation.<sup>7</sup>

Mesenchymal cells are involved in the pathogenesis of IBD and have implications in its treatment. IL-6 family cytokine Oncostatin M (OSM) and its receptor are increased in active CD and UC. Moreover, inflammatory monocytes and inflammation-associated fibroblasts (IAFs) are augmented in inflamed tissue of IBD patients. These types of cells intervene in medication resistance through OSM and its receptor pathways.<sup>10,18</sup>

Different recognized targets such as IL-1 receptor, anti-TNF, anti-IL-23, anti- $\alpha$ 4-integrin, and anti- $\alpha$ 4 $\beta$ 7 integrin have effective activity against IBD inflammatory response. Further investigation in IBD immunology to increase the success of these treatments and to find other therapies.

#### Microbiota in IBD

There are several hypotheses about homeostasis between microbiota, intestinal epithelia, and the immune system that is disrupted by an interaction of genetic and environmental factors, resulting in chronic inflammation. Data

showed that different IBD variants are likely mediated by a change in microbiota, and this change is influenced by a certain genetic background. A good example is the decreased population of *Faecalobacterium Prausnitzii* and *Roseburia* in patients with a NOD 2 mutation.<sup>19</sup> Moreover, the dysregulation of intestinal crypts in IBD can be secondary to cells variations. The change in mucosal barrier, identified as a loss in goblet cells in IBD patients, results in a reduction of antibacterial proteins, and it is still unclear if others cell modifications underly the event triggering the disease.<sup>20</sup>

Some bacteria contribute to immune responses in T cells as well as in IBD patients, affecting cytokine-cytokine receptor signalling, the interaction with epithelial cells, and the immune system. It was showed in experimental mice models that *Bacteroides fragilis* and capsular lipopolysaccharide A improved Th1/Th2 responses by regulating the secretion of TNF- $\alpha$  and IL-12, and inducing the production of Treg cells.<sup>21</sup> Other models in mice propose that several bacterial strains are NF- $\kappa$ B suppressors, suggesting that the microbiome is an extrinsic regulator of host immunity.<sup>22</sup> Another example is *Candidatus Arhromitis*, the segmented filamentous bacteria, where colonization of such bacteria promotes the maturation of the mucosal immune system preventing dysbiosis.<sup>23</sup>

The composition of the microbiota is altered in patients with IBD. These findings are associated with the increase in several pathogens and overall changes in the composition of microbiome compared to healthy controls, considering not only bacteria, but also fungi, viruses, and other organisms. *Phylum firmicutes* is commonly reduced in the stool of patients with Crohn's disease. Proteobacteria phylum are increased in patients with IBD compared to healthy patients.<sup>23</sup> Moreover, the biodiversity and composition of fungal microbiota is altered as well. A skewing of microbiota compared to healthy subjects was observed. There is an increase in *Basidiomycota/Ascomycota*, a decrease of *Saccharomyces*, and an increase proportion of *Candida albicans* compared to healthy controls.<sup>16</sup> Furthermore, metagenomics allows the analysis of viral particles isolated from samples. A change in bacteriophage composition in IBD was found, showing an increase in Caudovirales bacteriophages in ileal biopsy samples, which is correlated with a reduction in bacterial diversity.<sup>24</sup> This suggests that dysbiosis is part of the pathogenesis of IBD.

It is recognized that metabolites are different between IBD patients and non-IBD controls secondary to IBD microbiome. One hundred twenty two associations between metabolic diversity and specific microbiome were identified in IBD patients. Several computation methods provide a guidance to characterize the IBD microbiome and metabolome. The different variation patterns of disease phenotypes depends on the microbial taxonomic profile of every patient.<sup>6</sup> Deep sequencing technology progressively discloses the role of dysbiosis in IBD.

The role of diet in IBD and the alteration of the microbiota are at several levels and are demonstrated by an association in patients with low fibre intake and a risk of Crohn's disease caused by changes in the gut microbiota in susceptible individuals.<sup>25</sup> Increased dietary heme iron intake increases the ratio of gram-negative/gram-positive bacteria in mice.<sup>26</sup> Moreover, an increase in sulfite-reducing *Bilophila wadsworthia* induces colonic inflammation in mice

with an IL10-knockout.<sup>27</sup> Meanwhile, a Mediterranean diet, rich in fruits, vegetables, and red wine is associated with an increased diversity of the microbiome, especially *Faecalibacterium prausnitzii*, which is considered bacteria with anti-inflammatory properties.<sup>28</sup>

## Treatment

There are different ways in which bacteria and other microorganisms' changes can alter composition and functions in IBD. Conventional therapy with corticosteroids, immunomodulators, and biologic therapy might help induce remission; however, there are many alternatives to treat inflammation through modifications in the microbiome environment that further ameliorate dysbiosis.<sup>29</sup> It can be divided into traditional methods, methods under development, and novel hypotheses to configure microbiome. First, in the traditional methods the use of probiotics, prebiotics, antibiotics, and combinations of these are included. Thereafter, in the methods under development there are fecal microbiota transplant (FMT) and other novel hypotheses.

## Probiotics

The rationale behind probiotics is restoration of the microbial balance, modulation, mucosal protection, and induction of immune responses in IBD.<sup>30</sup> The study of probiotics in IBD has many outcomes and is broad. One meta-analysis showed a significant increase in remission rates in patients with active ulcerative colitis ( $p=0.01$ ) and the rate of remission rates was significantly higher in patients with active UC treated with concomitant probiotics. The probiotic called VSL#3 showed an increased remission rate in mild-to-moderately active UC compared to controls, and a relapse reduction rate in patients with pouchitis.<sup>31,32</sup>

Another recent meta-analysis including 18 trials revealed that probiotics had different effects in terms of remission in Crohn's disease. Some studies did not find a significant influence in Crohn's disease ( $p=0.07$ ); however, 3 trials in children with IBD showed the advantage of its use.<sup>33</sup> Mice models suggest that *Lactobacillus plantarum* CBT LP3 can be used as a potent immunomodulator with implications in IBD by decreasing intestinal permeability; however, this needs further confirmation.<sup>34</sup> No adverse effects were detected between probiotics and controls in UC treatment.<sup>31</sup> Current Cochrane studies do not favor the use of probiotics in CD; however, the last study needs an update with new information about probiotics in CD.<sup>35</sup>

## Prebiotics

Prebiotic formulations are food substances that are not digested in the human small bowel and increase selective growth of beneficial bacteria in the colon; a benefit that has not been fully explored in IBD. The basis of providing fiber and prebiotic oligosaccharides to increase the abundance of short-chain fatty acid commensal species is as a therapeutic target with immunoregulatory properties.<sup>23</sup> The nondigestible polymers of fructose (fructo-oligosaccharides,



FOS) are found naturally and fermented by bifidobacteria and lactobacilli.<sup>36</sup>

In mice models, it is suggested that colitis is diminished in subjects treated with prebiotics compared to untreated controls, and an increase in the abundance of *Bifidobacterium* spp, and a decrease of *Clostridium* cluster XI and *C. difficile* toxin gene expression are closely related to less chronic intestinal inflammation.<sup>37</sup> Another trial in mice showed that side chains of pectin not only increased the levels of prebiotic effects but also downregulated inflammatory cytokines (IL-6).<sup>38</sup> The clinical trial with more patients ( $n = 103$ ) demonstrated a lack of clinical benefit in using prebiotic supplementation in active Crohn's disease; however, this warrants further investigation in maintaining remission or other unexplored areas.

### Synbiotic

Probiotic therapy can be improved by adding a prebiotic; allowing a better substrate for bacterial growth. This combination is called synbiotic. A pilot study showed that combining a probiotic like *Bifidobacterium longum* and a prebiotic like inulin promotes short-term active clinical UC improvement and decreases inflammatory cytokines, such as  $\text{TNF}\alpha$  and IL1a.<sup>39</sup> Another study showed histological improvement and  $\text{TNF}\alpha$  levels in biopsies at 3 months<sup>40</sup> and that preparations composed of six probiotic strains, and a prebiotic of FOS resulted in decreased inflammatory markers in the synbiotic group. In terms of clinical, serologic, and endoscopic activity levels a statistically significant improvement of synbiotic versus placebo was shown.<sup>41</sup>

Newer data showed that a combination of *Lactobacillus* probiotics and prebiotics had a significant effect in remission only in patients with UC ( $p = 0.03$ ) and combination with *Saccharomyces boulardii*, *Lactobacillus*, and VSL#3 probiotics in CD could be potentially worthy.<sup>33</sup> However, information regarding synbiotic studies has a low number of patients and this precludes making assumptions.

### Antibiotics

Dysbiosis is an important cause of pathogenesis in IBD and its alteration with the use of antibiotics is a potential therapy; however, based on several studies, antibiotics play a role in the development of IBD by leading to dysbiosis and reducing bacterial diversity.<sup>42</sup> There is an upward trend of data in favor of antibiotic use for IBD flare-ups, and no association exists between the use of antibiotics and the development of IBD in early stages of life.<sup>43</sup>

Regarding active UC, data from meta-analyses suggest that antibiotic use maintain remission in 64% compared to placebo, 48%, favoring its use in UC.<sup>44</sup> However, the heterogeneity among studies showed that intravenous antibiotics in the long-term are not helpful in UC activity. Some other studies demonstrate that either antibiotic monotherapy or combinations help to achieve better clinical and endoscopic outcomes at 6 and 12 months.<sup>45</sup>

In CD, antibiotics are used in treating primary active disease in luminal disease, fistulizing disease, and septic complications such as abscesses or post-operative infections. Information from meta-analyses and Cochrane data

suggest that either luminal antibiotics or other type of antibiotics have a modest benefit against active CD and may not be clinically meaningful in the short-term or as maintenance of remission with a clinical endpoint at 52 weeks.<sup>46</sup> Moreover, the benefit of using antibiotics with immunomodulators or anti-TNF therapy in CD has little benefit in patients at high risk for recurrence, with weak supporting evidence and a need for further evaluation.<sup>47</sup>

The use of antibiotics in pouchitis, acute or chronic, has different managements depending on data. A meta-analysis shows that antibiotics induce remission with a rate of 74% in chronic pouchitis (95% CI: 56–93%,  $p < 0.001$ ). Another meta-analysis that included prevention and treatment of pouchitis showed good effectiveness of ciprofloxacin in acute and chronic pouchitis; however, with a low effectiveness of metronidazole. Furthermore, current data in terms of pouchitis prevention is inconclusive, powered studies are needed to determine its effectiveness.<sup>48</sup> In chronic pouchitis, antibiotic use promotes microbiome-associated resistant strains. This suggests that new schemes of antibiotic therapy and short-term antibiotic alternation should be used.<sup>49</sup>

### Fecal microbiota transplantation (FMT)

Fecal microbiota transplantation is a process in which a fecal suspension from a healthy individual is transferred to a recipient. This process was originally designed as part of the treatment of refractory *Clostridioides difficile*; however, there is robust information about its use in IBD including 9 meta-analyses, 4 RCT, and many cohort studies (Table 1).

The information among meta-analyses is heterogeneous due to the information included and the outcomes reviewed. Induction of remission of active UC with FMT was significantly more effective than placebo in the four published RCT with 28% in the FMT group versus 9% in placebo groups ( $p = 0.64$ ,  $I^2 = 0\%$ ). The latest meta-analysis including 4 RCT and 23 cohort studies, 21% of patient achieved clinical remission (CR) with a high risk of heterogeneity. FMT was associated with clinical improvement and endoscopic remission.<sup>50,51</sup> Moreover, FMT is associated with a significant increase in the mucosal gut of immunoregulatory cells and anti-inflammatory metabolism (increase of butanoate) and a reduction of Th17 proinflammatory pathways.<sup>52</sup>

The first meta-analysis regarding the success of CD in CR showed a pooled estimate of 60.5% ( $p = 0.05$ ;  $I^2 = 37\%$ ); however, a more recent meta-analysis showed a pooled portion of CR of 30% ( $p < 0.01$ ,  $I^2 = 75\%$ ) with moderate heterogeneity and lower than previous data.<sup>50,53</sup> The main limitation among studies with CD and FMT is the poor correlation between clinical and endoscopic outcomes and the lack of data in this topic due the low prevalence of CD; most information is from cohort studies and case reports.

When IBD patients are divided into subgroups according to disease severity, information shows that patients with moderate-severe disease from cohort studies could achieve more CR than those with mild-moderate disease; however, in RCT, all patients included had mild-moderate disease severity.<sup>50</sup>

One of the most important characteristics of FMT is its safety. Common adverse events related to patients treated with FMT included gastrointestinal system diarrhea (13%),

**Table 1** FMT for IBD reviews and meta-analysis.

Author/year	Studies	Number	Study of donors' microbiome	Study of donors' diet	Disease activity	Clinical	FMT route	Outcome	Adverse effects
Colman et al./2014 <sup>53</sup>	9 cohort studies + 8 case studies + 1 RCT	122 patients 79 UC; 39 CD, 4 IBD unclassified	No	No	23% mild/moderate 13% moderate–severe 16% severe	Refractory therapy 8% Active disease 44% Refractory pouchitis 4%	Single NJ tube/Colonoscopy/ Daily enemas/Gastroscopy	Overall CR 45% UC CR 22% (95% CI 10.4–40.8, $I^2 = 0\%$ ) CD CR 60% (95% CI 28.4–85.6, $p = 0.05$ , $I^2 = 37\%$ )	Fever, abdominal tenderness, diarrhea
Shi et al./2016 <sup>60</sup>	15 cohort studies + 8 case studies + 2 RCT	234 UC	No	No	NR	NR	Enema/Colonoscopy/ Gastroscopy/ Nasogastric tube/ Nasoduodenal tube/Endoscopic cecostomy	Overall CR 41.58% (95% CI 24.7–58.7, $I^2 = 36.5\%$ ) 65.2% Clinical response (95% CI 43.7–83, $I^2 = 40.2\%$ )	Fever, diarrhea, bloating, worsening colitis, urgent colectomy (placebo), rectal abscess, perforation, CMV, cervix carcinoma
Sun et al./2016 <sup>61</sup>	8 cohort studies + 1 case–control + 2 RCT	133 UC Adults + Children	No	No	Endoscopic scores	NR	Enema/NJ/Colonoscopy/ Gastroscopy	UC CR 30.4 (95% CI 22.6–30.4, $I^2 = 33\%$ )	Fever, diarrhea, abdominal cramping
Costello et al./2017 <sup>62</sup>	14 cohort studies + 4 RCT	168 UC	No	No	Mild–moderate majority of patients	NR	Nasogastric/ NJ/endoscopic duodenal, enema, colonoscopy or rectal tube	UC CR 28% (95% CI 1.82–7.39, $p > 0.01$ , $I^2 = 0\%$ )	Worsening colitis, small intestine CD, gastrointestinal complaints

Table 1 (Continued)

Author/year	Studies	Number	Study of donors' microbiome	Study of donors' diet	Disease activity	Clinical	FMT route	Outcome	Adverse effects
Paramsothy et al./2017 <sup>63</sup>	34 cohort studies + 14 case studies + 4 RCT	661 patients, 555 UC; 83 CD; 23 CD	No	No	53% mild/moderate 12% moderate/severe	8.4% active disease	Nasogastric/ Gastroscopy/ Colonoscopy/ Enema	UC CR 33% (95% CI 23–43, $p=0.01$ , $I^2=54\%$ ), CD CR 52% (95% CI = 40–64, $p=0.01$ , $I^2=58\%$ ), pouchitis CR 21.5%	Bloating, diarrhea, flatulence, abdominal pain, borborygmus, fever
Narula et al./2017 <sup>64</sup>	4 RCT	277 UC	No	No	100% mild/moderate	NR	Nasoduodenal/ Colonoscopy/ Enema	UC CR 42.1% (95% CI 3–17)	No statistical difference in adverse effects
Cao et al./2018 <sup>65</sup>	14 cohort studies + 4 RCT	446 UC	No	No	RCT 100% mild/moderate Cohorts NR	NR	Nasogastric/NJ/ endoscopic duodenal, enema, colonoscopy	UC CR 28.9 ( $p0.59$ , $I^2=0\%$ ) Clinical response 46.1%	NR
Fang et al./2018 <sup>50</sup>	23 cohort studies + 4 RCT	459 patients UC 365 CD 94	No	No	RCT 100% mild/moderate Cohort studies 28% mild/moderate 12% moderate/severe	14.5% Refractory 7.8% Active disease 6.9% Hormone dependent	Nasogastric/NJ/ endoscopic duodenal, enema, colonoscopy or rectal tube	Overall CR 28.8% UC CR 21% (95% CI: 8–37) CD CR 30% (95% CI: 10–48) Clinical response 53%	Diarrhea, abdominal pain, borborygmus, fever, urticaria, kidney stones.
Imdad et al./2018 <sup>51</sup> Cochrane Library	4 RCT	277 UC	No	No	RCT 100% mild/moderate	NR	Nasoduodenal/ Colonoscopy/ Enema	8 weeks CR 37% (95% CI: 1.07–3.86, $I^2=50\%$ ) Clinical response 49% (95% CI 0.98–2.95, $I^2=50\%$ )	No serious adverse events between groups

RCT, randomized control trial; UC, ulcerative colitis; CD, Crohn's disease; CR, clinical remission; NR, not registered.

**Table 2** Current ongoing clinical trials for FMT in IBD.

Title	Status	Study results	Conditions	Interventions	Number	Characteristics
Fecal Microbiota Transplantation in Pediatric Patients	Completed	No results available	IBD CD UC	Phase 1: FMT	N = 50 25 CD 25 UC	Failing primary therapy or in a flare.
Standardized Fecal Microbiota Transplantation for Inflammatory Bowel Disease	Unknown status	No results Available	IBD CD UC	Phase 2: FMT Drug: Mesalazine	N = 40 20 CD 20 UC	Efficiency, durability and safety of standardized FMT for IBD treatment.
Efficacy of Fecal Microbiota Transplantation for Inflammatory Bowel Disease	Recruiting	No results available	UC CD Constipation	Phase 3: FMT	N = 80	Efficiency and safety of FMT in a series of 80 patients with moderate to severe UC and CD.
Fecal Microbiota Transplantation for Health Improvement	Enrolling by invitation	No results available	UC IBS CD	Phase: NA FMT	N = 50	Select donors of fecal samples for carrying out the procedure of fecal transplantation of microbiota
FMT in inflammatory bowel disease	Recruiting	No results available	FMT CD UC Microscopic colitis	Cohort FMT	N = 50	Evaluating the use of faecal microbiota transplantation amongst patients with Inflammatory Bowel Disease and Microscopic Colitis
ICON-2 FMT and Bezlotoxumab Compared to FMT and Placebo for Patients With IBD and CDI	Recruiting	No results available	IBD CDI	Phase2: Drug: Bezlotoxumab Drug: Placebo Drug: FMT	N = 120	Clinical and microbiological impacts of FMT in combination with Bezlotoxumab (bezlo) compared to FMT in combination with placebo
Fecal Transplantation for Inflammatory Bowel Disease	Terminated	No results available	IBD	Phase 1: FMT	N = 9	FMT improvement for colitis in IBD patients
Manipulating the microbiome in IBD by antibiotics and FMT	Active, not recruiting	No results available	UC exacerbation, severe activity Crohn's colitis	Phase 4: Drug: antibiotics Drug: corticosteroids	N = 28	Assess the outcome of FMT in those not responding to five days of therapy with antibiotics or corticosteroids
Fecal Microbiota Transplant	Active, not recruiting	No results available	CDI IBD CD UC	Phase: NA FMT	N = 50	Determine the effect of FMT on the gut microbiota through the use of 454 pyrosequencing before and after transplantation in these patients
Bacteriotherapy in pediatric inflammatory bowel disease	Completed	Has results	IBD CD UC	Phase 1: FMT	N = 13	Learn whether this experimental therapy delays the need for starting additional medications to treat pediatric IBD.

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; CDI, *Clostridium difficile* infection; FMT, fecal microbiota transplant \*\*Information extracted from clinicaltrials.gov.



abdominal distention/flatulence (11.6%), nausea/vomiting (6.1%), abdominal pain (5.5%) and others. Most of the complications like fever, sore throat, and gastrointestinal complaints were self-limiting lasting 24h. The reports of death and worse outcomes are scarce in the current information.<sup>51,54</sup>

In terms of preparation of the sample for FMT according to current information, the FMT donor is predominantly a man less than 30-years-old. This could be explained by the higher prevalence of irritable bowel syndrome in women. There is still controversy about the perfect stool donor; in available data, a close relative or friend was chosen. A recent study indicates the importance of matching donors and patients for long-term maintenance of UC; siblings' relationship has a significantly higher maintenance rate compared with a parent-child relationship.<sup>55</sup> Information using mice models suggests a core transferable microbiota is necessary in responders to faecal microbiota transplant in UC to trigger an adequate immune reaction.<sup>56</sup> No significant difference exists between using a frozen-stool FMT compared to fresh stool or the delivery route used (either common upper GI or common lower GI) in UC or CD.<sup>50</sup> Furthermore, from 338 clinical trials regarding FMT, only 10 studies had the characteristics of FMT therapy in IBD patients. In Table 2 are included the current studies from clinicals about FMT and IBD research. However, more data is needed in RCT and prospective studies to evaluate specific donors' microbiome characteristics, the diet that FMT donors are eating due to its relevancy in the outcome of this treatment, and specific therapies used in transplanted patients such as mesalazine or biologic because these data are important considerations for future research.

### Areas under research: synthetic mixtures of microbes

Live biotherapeutic products (LBPs) are a mixture of protective commensal bacteria that modulate inflammation through several levels including interaction with inflammasome and tolerogenic responses. SER-109, a mixture of bacterial spores from 50 bacterial species from healthy donors' fecal matter shows promise to regulate immune responses and several other trials are underway.<sup>57</sup> Furthermore, the precise edition of microbiota composition can ameliorate adverse effects of dysbiosis. Investigational microbe-based immunotherapy called QBECO, formulated from inactivated strains of a gut pathogen showed objective reduction of UC disease pathology by activation of the immune system.<sup>58</sup> Other experimental studies in mice showed that the addition of tungstate-mediated microbiota reduced severity of intestinal inflammation.<sup>59</sup>

### Conclusion

The last decades show a trend toward an increase in IBD and the role of the microbiome in its development and pathogenesis. Several hypotheses about dysbiosis and immuno-regulation correlate with the phenotype of IBD. Many therapies beside the use of steroids, immunomodulators or biologic therapy are still in a constant investigational process. Hereby, several options for the treatment of IBD to

ameliorate dysbiosis were included; some of them have been fully studied but others are under development. The role of novel therapies, such as FMT and precision medicine, is growing and further evaluation of these therapies is needed. There are some characteristics of the FMT donors that should be controlled more in future studies such as a donors' diet in order to assess all possible variables that limit FMT efficacy. According to the knowledge in microbiome pathophysiology in IBD, the study of the microbiome population should be included in all the future RCTs regarding this topic. Limitations in its current study includes the multifactorial pathophysiology of IBD, a lack of evidence in certain modalities of treatment, and some of the data used are based on experimental models and still need validation on clinical grounds.

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### Conflicts of interests

None.

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