

Gut microbiota and inflammatory bowel disease: The current status and perspectives

Lie Zheng, Xin-Li Wen

ORCID number: Lie Zheng 0000-0002-8243-3736; Xin-Li Wen 0000-0001-5003-862X.

Author contributions: Zheng L wrote and revised the manuscript; Zheng L and Wen XL designed the work and supervised preparation of the manuscript.

Supported by Shaanxi Province Natural Science Basic Research Program-general Project, No. 2019JM-580; Project of Shaanxi Administration of Traditional Chinese Medicine, No. 2019-ZZ-JC0010; and Shaanxi Provincial Hospital of Traditional Chinese Medicine, No. 2018-04.

Conflict-of-interest statement: The authors declare that there are no conflicts of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Lie Zheng, Xin-Li Wen, Department of Gastroenterology, Shaanxi Provincial Hospital of Traditional Chinese Medicine, Xi'an 730000, Shaanxi Province, China

Corresponding author: Xin-Li Wen, Director, Professor, Department of Gastroenterology, Shaanxi Provincial Hospital of Traditional Chinese Medicine, No. 4 Xihuamen, Xi'an 730000, Shaanxi Province, China. xinliwen696@126.com

Abstract

Inflammatory bowel disease (IBD) is a chronic immune-mediated disease that affects the gastrointestinal tract. It is argued that environment, microbiome, and immune-mediated factors interact in a genetically susceptible host to trigger IBD. Recently, there has been increased interest in the development, progression, and treatment of IBD because of our understanding of the microbiome. Researchers have proved that some factors can alter the microbiome and the pathogenesis of IBD. As a result, there has been increasing interest in the application of probiotics, prebiotics, antibiotics, fecal microbiota transplantation, and gene manipulation in treating IBD because of the possible curative effect of microbiome-modulating interventions. In this review, we summarize the findings from human and animal studies and discuss the effect of the gut microbiome in treating patients with IBD.

Key Words: Inflammatory bowel disease; Microbiome; Inflammation; Genetics; Antibiotics; Probiotics

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Inflammatory bowel disease (IBD) is a chronic immune-mediated disease that affects the gastrointestinal tract. Researchers have proved that some factors can alter the microbiome and the pathogenesis of IBD. These include mutations in genes involved in microbiome-immune interactions and microbiota-modulating risk factors such as antibiotic use, cigarette smoking, levels of sanitation, and diet. As a result, there has been increasing interest in the application of probiotics, prebiotics, antibiotics, fecal microbiota transplantation, and gene manipulation in treating IBD because of the possible curative effect of these microbiome-modulating interventions.

Citation: Zheng L, Wen XL. Gut microbiota and inflammatory bowel disease: The current status

[p://creativecommons.org/licenses/by-nc/4.0/](https://creativecommons.org/licenses/by-nc/4.0/)

Manuscript source: Unsolicited manuscript

Specialty type: Medicine, research and experimental

Country/Territory of origin: China

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: October 18, 2020

Peer-review started: October 18, 2020

First decision: November 20, 2020

Revised: November 20, 2020

Accepted: December 6, 2020

Article in press: December 6, 2020

Published online: January 16, 2021

P-Reviewer: Touil-Boukoffa C

S-Editor: Huang P

L-Editor: Filipodia

P-Editor: Li JH



and perspectives. *World J Clin Cases* 2021; 9(2): 321-333

URL: <https://www.wjgnet.com/2307-8960/full/v9/i2/321.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v9.i2.321>

INTRODUCTION

Various microbial organisms are found in the gut, with the number exceeding 100 trillion, including bacteria, fungi, viruses, as well as protozoa^[1,2]. The number of bacteria varies throughout the entire gastrointestinal tract, making a comparison between the colon, stomach, and small intestine difficult as the amount and diversity of bacterial species are higher in the colon^[3,4]. In humans, homeostasis of nutrition, immune development, metabolism, and defense against pathogens is essential, and it is achieved because of the existence of the gut microbiome.

MICROBIOME AND INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) is a chronic immune-mediated disease^[5]. Based on the analysis of numerous animal models, alteration or an aberrant immune response occurs in the microbiome, which may lead to intestinal inflammation^[6]. When pro-inflammatory bacteria or microbiota are transferred from mice with IBD to healthy mice, inflammation is triggered, and colonization of intestinal microbiota in mice from donors with IBD exacerbates colitis by altering immune responses^[7,8]. In human subjects, it was observed that the microbiome plays a fundamental role in the occurrence of IBD^[9]. In addition, during treatment of Crohn's disease (CD), fecal diversion has been proved to be a valuable technique, as disease severity is reduced due to exclusion of the affected bowel segment^[10]. It has been shown that antibiotics are effective in treating certain phenotypes of IBD^[11]. Recently, studies have demonstrated that specific microbes may drive or suppress inflammation, predict response to therapy, and determine the postoperative risk of disease recurrence so as to provide evidence for the curative effect of the microbiome in treating patients with IBD^[12,13] (Table 1).

Genetic mutations, the microbiome, and IBD

Genetic susceptibility plays a key role in the etiology of IBD^[14]. A recent study involving 75000 patients has identified 163 susceptibility loci for IBD, and most of them participated in regulating the interaction between host and gut microbes^[15,16].

The nucleotide-binding oligomerization domain-2 (*Nod2*) gene was initially reported as a susceptibility gene for CD^[17]. *Nod2* is predominantly expressed in Paneth cells of the ileum and can induce immune responses under the stimulation of intestinal flora. The number of mucosa-adherent bacteria increases in IBD patients carrying *Nod2* mutations. Patients with *Nod2* mutations have characteristic changes in gut flora when compared with patients without *Nod2* mutations^[18]: Enterobacter species increase, and *Faeculus* species decrease. In addition, abnormal aggregation of goblet cells and lymphocytes and expression of inflammatory factors can be found in the intestines of *Nod2*^{-/-} mice^[19]. Compromised intestinal barrier function is associated with the imbalance of the intestinal flora, especially the increase of *Bacteroides vulgarius*, and downregulating the abundance of *Bacteroides vulgarius* can reverse the barrier defect in *Nod2*^{-/-} mice^[20].

Mutations in autophagy-related genes are associated with increased risk of CD. IBD patients with both autophagy-related gene 16L1 mutation and *Nod2* mutation have significant changes in intestinal flora, including decreased abundance of *Faebacterium* and increased abundance of *Escherichia coli*^[21]. Selectively knocking out the *ATG16L1* gene in mice can down-regulate the number of regulator T (Treg) cells and T helper (Th)2-mediated cellular immunity^[22]. The abnormal immune effect makes the intestine lose its tolerance to intestinal pathogens and produce immunoglobulins that attack the intestinal commensal bacteria, leading to intestinal flora imbalance. In a recent study, feces from patients with active CD were transplanted into sterile *ATG16L1*-deficient mice, which induced the increase of *Bacteroides ovatus* and the increase of Th17 and Th1 immune cells in intestinal lamina propria, suggesting the effects of gene polymorphisms on IBD rely on the role of intestinal flora^[23].

Glycoprotein CLEC7A, a pattern-recognition receptor expressed by innate immune

Table 1 Microbiota changes associated with inflammatory bowel disease

	Increased	Decreased
Bacteria	<i>Fusobacterium</i> species	<i>Bifidobacterium</i> species
	<i>Pasturellaceae</i>	<i>Bacteroides</i> species
	<i>Proteobacteria</i> (adherent invasive <i>Escherichia coli</i>)	<i>Clostridium</i> XIVa, IV
	<i>Ruminococcus gnavus</i>	<i>Faecalibacterium prausnitzii</i>
	<i>Veillonellaceae</i>	<i>Roseburia</i> species
Fungi	<i>Candida albicans</i>	<i>Suterella</i> species
	<i>Candida tropicalis</i>	<i>Saccharomyces cerevisiae</i>
	<i>Clavispora lusitaniae</i>	
	<i>Cyberlindnera jadinii</i>	
	<i>Kluyveromyces marxianus</i>	
Viruses	<i>Caudovirales</i>	

cells, can mediate the interaction between fungi and intestinal immune system^[24]. The intestinal fungal community changed in *CLEC7A*-deficient mice, along with increased susceptibility to enteritis. Knockout of caspase recruitment domain-containing protein 9 (*CARD9*) gene, a downstream molecule of *CLEC7A*, can also cause changes of the intestinal fungal microecology in mice and increase the susceptibility of mice to dextran sodium sulfate-induced enteritis. Imbalance of fungal gut flora caused by *CARD9* deficiency is closely related to the lack of intestinal Th17 cells. Lanternier *et al*^[25] also found that the colonization of *Malassezia* could increase the severity of CD, and such inflammatory response induced by the fungal colonization was associated with the genetic polymorphisms of *CARD9*.

Although intestinal flora imbalance plays a key role in the etiology of IBD, change of intestinal flora alone does not cause enteritis. Research on genetic polymorphisms reveals the important role of individual differences in the pathogenesis of IBD^[26]. The polymorphism of individual genes can affect the structure of the intestinal flora, and the imbalanced intestinal flora can further activate the immune system and induce intestinal inflammation in the context of genetic susceptibility.

MECHANISMS OF IMMUNE DISORDERS INDUCED BY INTESTINAL FLORA IMBALANCE IN IBD

Intestinal flora imbalance and gene polymorphisms play key roles in the pathogenesis of IBD^[27], although both of them depend on the intestinal immune microenvironment. Physiologically, there is a symbiotic relationship between intestinal microorganisms and the host, and this relationship depends on a variety of immune mechanisms such as the secretion of immunoglobulin (Ig) A from the intestinal mucus and the release of antimicrobial peptides^[28,29]. In addition, intestinal symbiotic bacteria can also inhibit the growth of pathogenic microorganisms, promote immune tolerance, initiate intestinal epithelial repair, and maintain the balance among various immune cell subtypes^[30]. In patients with IBD, however, the unregulated intestinal microecology, together with the body's susceptibility genes, induces abnormal immune responses and causes disorders of the intestinal immune microenvironment^[31].

With regard to humoral immunity, the antibodies secreted by different intestinal microorganisms are closely related to the phenotypes and course of IBD^[32]. Research showed that the combination of anti-*Saccharomyces cerevisiae* mannan antibodies with anti-laminaribiose antibodies and anti-neutrophil cytoplasmic antibodies helped to distinguish IBD patients, non-IBD patients, and healthy individuals^[33]. The levels of these three antibodies significantly differ between CD and ulcerative colitis (UC) patients^[34]. In addition, as the most important antibody in the intestinal mucosa, IgA has an encapsulation effect on microorganisms and thus is a marker for the immune response activated by gut microbes^[35]. These IgA-encapsulated gut microbes can be divided into enteritis IgA⁺ bacteria and intestinal symbiotic IgA-bacteria, among which

the IgA⁺ bacteria include *Prevotellaceae*, *Helicobacter*, and segmented filamentous bacteria. These bacteria can participate in dextran sodium sulfate-induced enteritis in mice. Furthermore, IgA deficiency also increases the risk of CD and UC development^[36,37].

In terms of cellular immunity, gut microbes play an important role in maintaining T cell function. Gut microbes can induce T cells to differentiate into Th17, Treg cells, and other phenotypes by shaping the intestinal microenvironment^[38]. The segmented filamentous bacteria colonizing the small intestine of mice can adhere to the epithelial cells of the small intestine and induce Th17 cells in the intestinal lamina propria to secrete interleukin (IL)-17 and IL-22, thus promoting intestinal inflammation^[39]. On the contrary, some intestinal bacteria promote the proliferation of anti-inflammatory Treg cells. The colonization of clostridium in the intestines of mice can increase the intestinal transforming growth factor- β level, thereby promoting the differentiation of Foxp3⁺ Treg cells^[40]. Research has shown that the intestinal bacteria derived from IBD patients can induce the increase of Th17 and Th2 cells and the decrease of ROR γ t⁺ Treg cells in the mouse intestines. After feces from healthy people were transplanted into mice, a consortium of 11 bacterial strains that induced interferon- γ -producing CD8 T cells in the intestine was isolated, which could relieve intestinal inflammation^[41].

In the intestinal immune microenvironment, antigen-presenting cells can not only deliver gut bacteria-related antigens but also regulate intestinal immune effector cells^[42]. When intestinal commensal bacteria adhere to epithelial cells, CX3CR1⁺ antigen-presenting cells secrete IL-10 under the action of intestinal bacteria antigens to induce Treg cell differentiation, thus maintaining a balanced pro- and anti-inflammatory environment in the gut^[43]. However, when the intestinal flora becomes imbalanced, CX3CR1⁺ antigen-presenting cells can induce Th1 immune cells to mediate intestinal inflammation. In addition, *Ruminococcus gnavus*, which is closely related to CD, can act on toll-like receptor 4 receptors in dendritic cells by secreting polysaccharides, thus inducing the secretion of tumor necrosis factor- α , a proinflammatory cytokine^[44]. Macrophages are also important antigen-presenting cells in the intestinal mucosal barrier. Intestinal bacteria can induce macrophages to secrete IL-1 β through the Nod2-Myd88 signaling pathway to mediate intestinal inflammation. However, intestinal *Helicobacter hepatica* can activate the mitogen activated protein kinase/cyclic adenosine monophosphate response element-binding protein through the toll-like receptor 2 receptor of macrophages to promote the secretion of IL-10 and participate in the anti-inflammatory response in the intestine^[45].

MICROBIAL COMPOSITION AND FUNCTION IN PATIENTS WITH IBD

Decades ago, it was first confirmed that the fecal stream containing bacteria was associated with IBD when surgical diversion was used to induce remission of diseased segments; when continuity was restored, these patients may develop IBD recurrence^[46]. A large number of studies have indicated that alterations in the composition of gut microbiota are associated with IBD. As a result, more and more research has focused on the diagnostic and prognostic potential of microbiota signatures in patients with IBD^[47].

Metagenomics of the gut microbiota in patients with IBD

Although the interaction between intestinal microecology and the body can regulate the intestinal immune microenvironment, the exact mechanisms remain unclear. As the intestinal flora changes, the intestinal metabolites in IBD patients also change. Compared with healthy individuals, IBD patients have remarkably altered intestinal mucosal, fecal, and serum metabolites^[48].

Short-chain fatty acids (SCFA, mainly including butyrate, propionate, and acetate) are the primary products of the breakdown of non-digestible carbohydrates by gut bacteria^[49]. Among them, butyrate, which is produced by *Clostridium*, can inhibit histone deacetylase by activating G protein-coupled receptors and epigenetic effects, thereby enhancing the function of mucosal Treg cells and alleviating enteritis in mice^[50]. The increase in butyrate can also promote the proliferation of Treg cells by inhibiting deacetylase, suppress the Th17-mediated immune response, and promote the secretion of IL-6 in macrophages, thus exerting its protective effect on the gut^[51]. As an agonist of peroxisome proliferator-activated receptor γ , butyrate can also inhibit the synthesis of nitric oxide and the degradation of nitrate in gut, thereby suppressing the proliferation of *Enterobacteriaceae*. However, the abundance of SCFA-producing

bacteria dramatically decreases in the feces of IBD patients, leading to a decrease in intestinal SCFA levels and an increase in intestinal inflammation^[52].

Tryptophan can be converted into biologically active indole metabolites by intestinal bacteria. Studies have shown that there were significant differences in the serum levels of tryptophan metabolites between normal mice and sterile mice, and indole derivatives, which are the metabolites of tryptophan, can also mediate host inflammation^[53]. The intestinal commensal *Peptostreptococcus* can produce indole propionic acid, a special indole derivative, to induce mucin gene expression and activate the nuclear factor E2-related factor 2 pathway, thus exerting its effect in alleviating intestinal inflammation^[54]. *Bacteroides* can metabolize tryptophan into serotonin, the precursor for melatonin, and serotonin can exhibit multiple effects by binding to different serotonin receptors, especially the regulation of intestinal inflammation. However, the metabolism of tryptophan by intestinal bacteria decreases in IBD patients, resulting in the disturbances in intestinal microenvironment and the development of enteritis.

The bile acids produced by the metabolism of intestinal flora can act as agonists of G protein-coupled receptors and farnesoid X receptors. They can regulate host genes, thereby regulating the maturation of immune cells, the release of cytokines, and the defense against microorganisms. Taurine is a secondary bile acid derived from the decomposition of primary bile acid. It can increase microbial diversity by regulating the function of inflammasomes. *Clostridium* can also regulate bile acid metabolism through dehydroxylation and inhibit the intestinal *Clostridium difficile* infection. In addition, conjugated bile acids can also up-regulate the expression of exogenous transporter multidrug resistance protein 1 in CD4⁺ effector T cells to maintain the homeostasis of the body. However, the expression of multidrug resistance protein 1 dramatically declines in IBD patients^[55].

Sphingomyelin is a class of plasma membrane-associated lipids produced by the host and specific bacteria. The cell level and distribution of sphingomyelin significantly differ between inflammatory tissue and non-inflammatory tissue in IBD patients. The colonization of *Bacteroides polymorpha* in sterile mice could maintain the balance of the intestinal environment; however, the colonization of mutant strains without the function of synthesizing sphingomyelin in the intestine caused the increase of IL-6 and monocyte chemotactic protein 1 and thus induced enteritis. Metabonomic studies have also found that the abundance of sphingomyelin derived from *Bacteroides* was low in IBD patients; as the abundance of sphingomyelin in the body decreased, the inflammatory response tended to rise.

Meta-transcriptomics of the gut microbiota in patients with IBD

Some researchers have focused on the functional activity (meta-transcriptomics) instead of the functional potential (metagenomics) of gut microbiota in patients with IBD, and for both there is no accurate correlation^[56]. For example, when comparing patients with UC or those with CD to healthy control subjects, the RNA level in the patient groups was markedly lower than that in the healthy group, while the change in abundance of deoxyribonucleic acid (DNA) increased slightly. This indicated that the patients with IBD may be significantly affected by minor alteration in *R. gnavus* abundance at the DNA level^[57]. Furthermore, when comparing patients with UC and healthy control subjects, it was found that the abundance of *B. fragilis* DNA was much lower than that of RNA. Consequently, based on the results between patients with UC and healthy control subjects, a decreasing trend in both the functional potential and activity of *B. fragilis* was observed. *F. prausnitzii*, *B. vulgatus*, and *Alistipes putredinis* were found to contribute significantly to metabolic pathway transcription in patients with IBD, even when they were not the most abundant organisms present^[58]. In order to confirm these results, *Clostridium hathewayi*, *C. bolteae*, and *R. gnavus* and their genomic abundance were compared, and it was found that the transcriptional activity of *C. bolteae* and *R. gnavus* in patients with IBD was significantly increased, which indicated that they possibly play a more significant role^[59].

Metabolomics of the gut microbiota in patients with IBD

According to the results of a few studies, it is suggested that patients with IBD have a depletion of biologically active and functionally important metabolites^[60]. In addition, SCFA are important anti-inflammatory bacterial metabolites, which are decreased in the bacteria that can produce metabolites in these patients. SCFA plays a role in providing energy for colonic epithelial cells and promoting the expansion of regulatory T cells in the colon^[61]. Furthermore, in these patients, the level of SCFA, including butyrate, as well as the secondary bile acids lithocholate and deoxycholate decreased. Generally, patients with IBD show no deficiencies in sera, but it should be

noted that the vitamins pantothenate (vitamin B5) and nicotinate (vitamin B3) were particularly depleted in the gut. Nicotinate is characterized by its anti-inflammatory and antiapoptotic features. It was noted that other metabolites including sphingolipids and carboximidic acids were overabundant in patients with CD. *B. fragilis*, which is involved in synthesizing sphingolipids and has a similar structure to invariant natural killer T (iNKT) cell agonists, was shown to play a role in reducing iNKT cell activation and expansion triggered by self and microbial stimuli in neonatal mice. As a result, when the neonate grew, the iNKT cell numbers reduced, and experimentally-induced colitis was prevented^[62]. During inflammation, the oxygen concentration may become higher; thus, this environment is poisonous to obligate anaerobes and may lead to a diminished mucus layer.

Role of *F. prausnitzii* in patients with IBD

Among the variety of bacteria mentioned above, more and more attention has been focused on the relationship between *F. prausnitzii* and the pathogenesis of IBD. Some studies have described the low abundance of anti-inflammatory *Firmicutes*, and this may increase the risk of recurrence of ileal disease after surgery^[63]. In addition, it was observed that when *F. prausnitzii* in stool was at a low level, CD relapse in patients in remission could be predicted^[64]. Furthermore, *F. prausnitzii* was protective in dinitrobenzene sulfonic acid-induced colitis in mice. Research has shown that microbial anti-inflammatory molecule (MAM), a special protein produced by *F. prausnitzii*, can resist inflammation and inhibit the nuclear factor kappa B pathway in epithelial cell lines. *L. lactis*, used to deliver a plasmid encoding the MAM protein, is effective in preventing dinitrobenzene sulfonic acid-induced colitis in mice.

VIRUSES IN PATIENTS WITH IBD

Enterovirus is closely related with IBD. It was found that bacteriophages were significantly increased in the colon tissue of CD patients compared with that of healthy individuals. A viromic study demonstrated that the viromic status of CD patients was related to both disease status and treatment. Although individual differences and sample sources have a greater impact on the viromic status than on CD, it has also been found that there were more viruses in the virome of CD patients than in healthy people, and the diversity of viruses in the feces and intestinal tissues of newly diagnosed patients was higher than that in relapsed patients^[65]. It is still unclear whether the decrease in bacterial abundance and the increase in phage abundance are associated with the onset of IBD. Although there are some common viruses in the virome of patients with CD or UC, there are also some unique disease-related phages, such as the phages of *Lactococcus*, *Lactobacillus*, *Clostridium*, *Enterococcus*, and *Streptococcus*^[66].

IBD patients carry more mammalian viruses and human pathogens than healthy individuals, and human endogenous retrovirus (HERV) has also been found in the virome of IBD patients. The expression of HERV protein is related to inflammation. HERV expression is even higher in IBD patients infected with herpes virus^[67]. The significance of such correlation for IBD is unclear; however, infection with other viruses may also trigger HERV expression.

MICROBIOTA-BASED STRATEGIES IN PATIENTS WITH IBD

It is beneficial in patients with IBD to use several methods to regulate the gut microbiota during therapy. For example, when a deficit is identified in anti-inflammatory bacteria, such as *F. prausnitzii*, anti-inflammatory molecules produced by bacteria, such as MAM protein in the case of *F. prausnitzii*, can be augmented or administered^[68]. In this situation, probiotics, prebiotics, and synbiotics can be applied to replenish anti-inflammatory bacteria and their substrates. Another method is to identify the inflammatory bacteria that are overexpressed or toxic, and then antibiotics or phage therapy can be administered to remove the inflammatory bacteria. Fecal microbiota transplantation (FMT) can reset the whole microbiome. Research has shown that the microbiota can be used to deliver medications, for instance, modified organisms that are designed to release anti-inflammatory cytokines or other molecules that can directly reach the site of inflammation^[69]. The microbiome-immune interface has multiple targets that should be studied in further investigations.

Probiotics

Probiotics are a class of live microorganisms. They have shown good efficacy for IBD in animal experiments but have unsatisfactory effectiveness in clinical trials. No definite evidence supports the efficacy of probiotics in the treatment of CD, but these products may be effective in treating UC patients. Probiotics have certain effects in inducing and maintaining remission in UC patients^[70]. Positive research results have been achieved in patients with UC, but due to limitations in study design, availability of effective strains, as well as problems associated with the quality control of available probiotic preparations, the application of these findings in everyday practice may take some time^[71]. It has been confirmed that probiotics can be used to prevent primary and secondary pouchitis. The probiotic preparation that is effective in pouchitis, VSL#3, is a mixture of four strains of *Lactobacillus* species, three strains of *Bifidobacterium* species, and *Streptococcus salivarius*, and it increases the amount of mucosal regulatory T lymphocytes and decreases the mucosal expression of pro-inflammatory cytokine IL-1b messenger ribonucleic acid^[72]. To some extent, probiotics can maintain remission in patients with mild-to-moderate UC, even though they have varied curative effects. It has been found that probiotics are not effective in patients with CD. Due to the composition of specific probiotic preparations used to treat patients with IBD, the results have been varied^[73]. Therefore, it is possible that the unsatisfactory efficacy of probiotics may be because there is no ideal composition, duration of therapy is insufficient, or the intervention is too late when the “pathogenic” microbiota is already present. Studies are required on individualized and personalized therapy in particular IBD phenotypes, including designing probiotics for specific microbial changes.

Antibiotics

Studies have shown that childhood antibiotic exposure increases the risk of IBD, and younger age of exposure and longer antibiotic use are associated with higher incidence of IBD. Antibiotics are not the first-line treatment for IBD, unless co-infection is considered. However, antibiotics have shown certain efficacies in some clinical trials. A meta-analysis shows that the combination of antibiotics can, to a certain extent, improve the clinical symptoms of IBD patients^[74]. Using ciprofloxacin to treat patients appears to result in remission, and although treatment responses were more frequent, the results were not statistically significant. Experiments have been conducted to evaluate the effect of metronidazole in preventing recurrence of CD after small intestinal resection, but no significant effect was obtained compared with biologic therapy^[75]. Following colectomy with ileal pouchanal anastomosis, the microbiome is crucial for driving inflammation in the ileal pouch. Only after the fecal stream is restored through the pouch may pouchitis occur^[76]. A study involving 16 subjects who received ciprofloxacin or metronidazole for 2 wk showed that pouchitis was resolved in all subjects who receive ciprofloxacin therapy and in 76% of subjects who received metronidazole therapy according to the pouchitis disease activity score. In conclusion, antibiotics show efficacy in the treatment of IBD, but there are few reports in the literature to validate this finding.

Diet

Diet is closely related to the compositions of intestinal flora and microbial metabolites. IBD patients were found to have dysregulated intestinal microbiota and decreased floral diversity, including an increase in *Enterococcus* and a decrease in the abundance of *Firmicutes* and *Bacteroides*. Similar changes in the abundance of intestinal flora have also been seen in some healthy people who embark on a low-carb, high-fat diet, indicating that fiber intake reduces the risk of CD, which may be related to the altered intestinal microbiota in genetically susceptible people^[77]. In a recent randomized controlled trial involving pediatric patients with CD, there was no difference in the remission rate between the group receiving partial enteral nutrition and the group receiving exclusive enteral nutrition. These findings indicate that the rebound effect may occur in subjects when they switch to a regular diet; thus, the score for the microbiome composition may return to the baseline level^[78]. A study conducted by Guo *et al*^[79] assessed the effect of different diets, such as diets low in red meat and processed meat, in preventing symptomatic relapse of CD. Thus, more randomized controlled trials determining the effect of diet therapy in the treatment of patients with CD are required in order to determine the benefit of different diet therapies.

FMT

FMT, also known as stool transplantation or bacteriotherapy, has been a research hotspot in recent years^[80]. It transfers gut microbes from a healthy donor into the

gastrointestinal tract for the purpose of restoring the balance of gut microbes. FMT is particularly successful in the treatment of refractory *Clostridium difficile* infection. A meta-analysis showed that the clinical response rates of FMT for UC and CD were 21% and 30%, respectively^[81]. In another study, the clinical response rate of FMT was 20.9% in treating patients with mild to moderate IBD and 32.3% in patients with moderate to severe IBD^[82]. Thus, FMT was more effective in treating patients with moderate to severe IBD, suggesting that FMT may be used as a rescue treatment for refractory IBD. However, the heterogeneity of the currently available studies is high, mainly due to differences in transplantation methods and routes, selection of fresh or frozen feces, and selection of donors. Paramsothy *et al*^[82] have shown that FMT increased the diversity of the intestinal flora and changed the composition of the flora^[83]. *Eubacterium hallii* in fecal and colon samples was more abundant in patients who benefitted from FMT, while these results were not observed in patients who did not benefit. Donor stool containing *Bacteroides* species was associated with remission^[84]. However, *Streptococcus* species in donor stool was related to no response to FMT^[85]. Further studies are necessary to determine better methods for choosing donors to target the microbiome changes in patients with IBD in order to promote the curative effect of FMT.

CONCLUSION

According to the results from animal models, the microbiome can trigger IBD and even make it worse. Clinical data have shown that the microbiome is effective in CD therapy, but the effect is limited. According to recent studies, antibiotics are used to prevent postoperative recurrence of CD and to treat pouchitis and perianal disease.

Some probiotics may be beneficial for preventing pouchitis and in maintaining remission in patients with mild to moderate UC. Diet therapy is also considered to be helpful, especially in children with CD who receive exclusive enteral nutrition. However, further studies on adult patients, especially those with UC, are necessary. To date, only a few studies have provided support for FMT in treating UC, but there is little evidence for FMT in treating patients with CD. In conclusion, the microbiome is an exciting target for the treatment of IBD in future studies.

REFERENCES

- 1 Yu CG, Huang Q. Recent progress on the role of gut microbiota in the pathogenesis of inflammatory bowel disease. *J Dig Dis* 2013; **14**: 513-517 [PMID: 23848393 DOI: 10.1111/1751-2980.12087]
- 2 Sinagra E, Utzeri E, Morreale GC, Fabbri C, Pace F, Anderloni A. Microbiota-gut-brain axis and its affect inflammatory bowel disease: Pathophysiological concepts and insights for clinicians. *World J Clin Cases* 2020; **8**: 1013-1025 [PMID: 32258072 DOI: 10.12998/wjcc.v8.i6.1013]
- 3 Yan PG, Li JN. Advances in the understanding of the intestinal micro-environment and inflammatory bowel disease. *Chin Med J (Engl)* 2020; **133**: 834-841 [PMID: 32106123 DOI: 10.1097/CM9.0000000000000718]
- 4 Holleran G, Lopetuso LR, Ianiro G, Pecere S, Pizzoferrato M, Petito V, Graziani C, McNAMARA D, Gasbarrini A, Scaldaferrri F. Gut microbiota and inflammatory bowel disease: so far so gut! *Minerva Gastroenterol Dietol* 2017; **63**: 373-384 [PMID: 28293937 DOI: 10.23736/S1121-421X.17.02386-8]
- 5 Goethel A, Croitoru K, Philpott DJ. The interplay between microbes and the immune response in inflammatory bowel disease. *J Physiol* 2018; **596**: 3869-3882 [PMID: 29806140 DOI: 10.1113/JP275396]
- 6 Cammarota G, Ianiro G, Cianci R, Bibbò S, Gasbarrini A, Currò D. The involvement of gut microbiota in inflammatory bowel disease pathogenesis: potential for therapy. *Pharmacol Ther* 2015; **149**: 191-212 [PMID: 25561343 DOI: 10.1016/j.pharmthera.2014.12.006]
- 7 Bryan PF, Karla C, Edgar Alejandro MT, Sara Elva EP, Gemma F, Luz C. Sphingolipids as Mediators in the Crosstalk between Microbiota and Intestinal Cells: Implications for Inflammatory Bowel Disease. *Mediators Inflamm* 2016; **2016**: 9890141 [PMID: 27656050 DOI: 10.1155/2016/9890141]
- 8 West CE, Jenmalm MC, Prescott SL. The gut microbiota and its role in the development of allergic disease: a wider perspective. *Clin Exp Allergy* 2015; **45**: 43-53 [PMID: 24773202 DOI: 10.1111/cea.12332]
- 9 Schaubek M, Clavel T, Calasan J, Lagkouvardos I, Haange SB, Jehmlich N, Basic M, Dupont A, Hornef M, von Bergen M, Bleich A, Haller D. Dysbiotic gut microbiota causes transmissible Crohn's disease-like ileitis independent of failure in antimicrobial defence. *Gut* 2016; **65**: 225-237 [PMID: 25887379 DOI: 10.1136/gutjnl-2015-309333]

- 10 **Di Sabatino A**, Lenti MV, Giuffrida P, Vanoli A, Corazza GR. New insights into immune mechanisms underlying autoimmune diseases of the gastrointestinal tract. *Autoimmun Rev* 2015; **14**: 1161-1169 [PMID: 26275585 DOI: 10.1016/j.autrev.2015.08.004]
- 11 **Shamoon M**, Martin NM, O'Brien CL. Recent advances in gut Microbiota mediated therapeutic targets in inflammatory bowel diseases: Emerging modalities for future pharmacological implications. *Pharmacol Res* 2019; **148**: 104344 [PMID: 31400403 DOI: 10.1016/j.phrs.2019.104344]
- 12 **Dagenais M**, Douglas T, Saleh M. Role of programmed necrosis and cell death in intestinal inflammation. *Curr Opin Gastroenterol* 2014; **30**: 566-575 [PMID: 25291357 DOI: 10.1097/MOG.000000000000117]
- 13 **Glick LR**, Sossenheimer PH, Ollech JE, Cohen RD, Hyman NH, Hurst RD, Rubin DT. Low-Dose Metronidazole is Associated With a Decreased Rate of Endoscopic Recurrence of Crohn's Disease After Ileal Resection: A Retrospective Cohort Study. *J Crohns Colitis* 2019; **13**: 1158-1162 [PMID: 30809655 DOI: 10.1093/ecco-jcc/jjz047]
- 14 **Cohen LJ**, Cho JH, Gevers D, Chu H. Genetic Factors and the Intestinal Microbiome Guide Development of Microbe-Based Therapies for Inflammatory Bowel Diseases. *Gastroenterology* 2019; **156**: 2174-2189 [PMID: 30880022 DOI: 10.1053/j.gastro.2019.03.017]
- 15 **Lavoie S**, Conway KL, Lassen KG, Jijon HB, Pan H, Chun E, Michaud M, Lang JK, Gallini Comeau CA, Dreyfuss JM, Glickman JN, Vlamakis H, Ananthakrishnan A, Kostic A, Garrett WS, Xavier RJ. The Crohn's disease polymorphism, *ATG16L1* T300A, alters the gut microbiota and enhances the local Th1/Th17 response. *Elife* 2019; **8**: e39982 [PMID: 30666959 DOI: 10.7554/eLife.39982]
- 16 **Liu JZ**, van Sommeren S, Huang H, Ng SC, Alberts R, Takahashi A, Ripke S, Lee JC, Jostins L, Shah T, Abedian S, Cheon JH, Cho J, Dayani NE, Franke L, Fuyuno Y, Hart A, Juyal R, Juyal G, Kim WH, Morris AP, Poustchi H, Newman WG, Midha V, Orchard TR, Vahedi H, Sood A, Sung JY, Malekzadeh R, Westra HJ, Yamazaki K, Yang SK; International Multiple Sclerosis Genetics Consortium; International IBD Genetics Consortium, Barrett JC, Alizadeh BZ, Parkes M, Bk T, Daly MJ, Kubo M, Anderson CA, Weersma RK. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. *Nat Genet* 2015; **47**: 979-986 [PMID: 26192919 DOI: 10.1038/ng.3359]
- 17 **Ananthakrishnan AN**, Luo C, Yajnik V, Khalili H, Garber JJ, Stevens BW, Cleland T, Xavier RJ. Gut Microbiome Function Predicts Response to Anti-integrin Biologic Therapy in Inflammatory Bowel Diseases. *Cell Host Microbe* 2017; **21**: 603-610. e3 [PMID: 28494241 DOI: 10.1016/j.chom.2017.04.010]
- 18 **Sokol H**, Brot L, Stefanescu C, Auzolle C, Barnich N, Buisson A, Fumery M, Pariente B, Le Bourhis L, Treton X, Nancey S, Allez M, Seksik P; REMIND Study Group Investigators. Prominence of ileal mucosa-associated microbiota to predict postoperative endoscopic recurrence in Crohn's disease. *Gut* 2020; **69**: 462-472 [PMID: 31142586 DOI: 10.1136/gutjnl-2019-318719]
- 19 **Yilmaz B**, Juillerat P, Øyås O, Ramon C, Bravo FD, Franc Y, Fournier N, Michetti P, Mueller C, Geuking M, Pittet VEH, Maillard MH, Rogler G; Swiss IBD Cohort Investigators; Wiest R; Stelling J; Macpherson AJ. Microbial network disturbances in relapsing refractory Crohn's disease. *Nat Med* 2019; **25**: 323-336 [PMID: 30664783 DOI: 10.1038/s41591-018-0308-z]
- 20 **Yilmaz B**, Juillerat P, Øyås O, Ramon C, Bravo FD, Franc Y, Fournier N, Michetti P, Mueller C, Geuking M, Pittet VEH, Maillard MH, Rogler G; Swiss IBD Cohort Investigators; Wiest R, Stelling J, Macpherson AJ. Publisher Correction: Microbial network disturbances in relapsing refractory Crohn's disease. *Nat Med* 2019; **25**: 701 [PMID: 30846883 DOI: 10.1038/s41591-019-0411-9]
- 21 **Chu H**, Khosravi A, Kusumawardhani IP, Kwon AH, Vasconcelos AC, Cunha LD, Mayer AE, Shen Y, Wu WL, Kambal A, Targan SR, Xavier RJ, Ernst PB, Green DR, McGovern DP, Virgin HW, Mazmanian SK. Gene-microbiota interactions contribute to the pathogenesis of inflammatory bowel disease. *Science* 2016; **352**: 1116-1120 [PMID: 27230380 DOI: 10.1126/science.aad9948]
- 22 **Drummond RA**, Franco LM, Lionakis MS. Human CARD9: A Critical Molecule of Fungal Immune Surveillance. *Front Immunol* 2018; **9**: 1836 [PMID: 30127791 DOI: 10.3389/fimmu.2018.01836]
- 23 **Jhingran A**, Kasahara S, Shepardson KM, Junecko BA, Heung LJ, Kumasaka DK, Knoblauch SE, Lin X, Kazmierczak BI, Reinhart TA, Cramer RA, Hohl TM. Compartment-specific and sequential role of MyD88 and CARD9 in chemokine induction and innate defense during respiratory fungal infection. *PLoS Pathog* 2015; **11**: e1004589 [PMID: 25621893 DOI: 10.1371/journal.ppat.1004589]
- 24 **Yamamoto H**, Nakamura Y, Sato K, Takahashi Y, Nomura T, Miyasaka T, Ishii K, Hara H, Yamamoto N, Kanno E, Iwakura Y, Kawakami K. Defect of CARD9 leads to impaired accumulation of gamma interferon-producing memory phenotype T cells in lungs and increased susceptibility to pulmonary infection with *Cryptococcus neoformans*. *Infect Immun* 2014; **82**: 1606-1615 [PMID: 24470469 DOI: 10.1128/IAI.01089-13]
- 25 **Lanternier F**, Mahdavian SA, Barbati E, Chaussade H, Koumar Y, Levy R, Denis B, Brunel AS, Martin S, Loop M, Peeters J, de Selys A, Vanclaire J, Vermeylen C, Nassogne MC, Chatzis O, Liu L, Migaud M, Pedergnana V, Desoubreaux G, Jouvion G, Chretien F, Darazam IA, Schäffer AA, Netea MG, De Bruycker JJ, Bernard L, Reynes J, Amazrine N, Abel L, Van der Linden D, Harrison T, Picard C, Lortholary O, Mansouri D, Casanova JL, Puel A. Inherited CARD9 deficiency in otherwise healthy children and adults with *Candida* species-induced meningoencephalitis, colitis, or both. *J Allergy Clin Immunol* 2015; **135**: 1558-68. e2 [PMID: 25702837 DOI: 10.1016/j.jaci.2014.12.1930]
- 26 **Sokol H**, Conway KL, Zhang M, Choi M, Morin B, Cao Z, Villablanca EJ, Li C, Wijmenga C, Yun SH, Shi HN, Xavier RJ. Card9 mediates intestinal epithelial cell restitution, T-helper 17 responses, and control of bacterial infection in mice. *Gastroenterology* 2013; **145**: 591-601. e3 [PMID:

- 23732773 DOI: [10.1053/j.gastro.2013.05.047](https://doi.org/10.1053/j.gastro.2013.05.047)]
- 27 **Ng SC**, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, Panaccione R, Ghosh S, Wu JCY, Chan FKL, Sung JY, Kaplan GG. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2018; **390**: 2769-2778 [PMID: [29050646](https://pubmed.ncbi.nlm.nih.gov/29050646/) DOI: [10.1016/S0140-6736\(17\)32448-0](https://doi.org/10.1016/S0140-6736(17)32448-0)]
 - 28 **Goethel A**, Turpin W, Rouquier S, Zanello G, Robertson SJ, Streutker CJ, Philpott DJ, Croitoru K. Nod2 influences microbial resilience and susceptibility to colitis following antibiotic exposure. *Mucosal Immunol* 2019; **12**: 720-732 [PMID: [30651577](https://pubmed.ncbi.nlm.nih.gov/30651577/) DOI: [10.1038/s41385-018-0128-y](https://doi.org/10.1038/s41385-018-0128-y)]
 - 29 **Shaw SY**, Blanchard JF, Bernstein CN. Association between the use of antibiotics in the first year of life and pediatric inflammatory bowel disease. *Am J Gastroenterol* 2010; **105**: 2687-2692 [PMID: [20940708](https://pubmed.ncbi.nlm.nih.gov/20940708/) DOI: [10.1038/ajg.2010.398](https://doi.org/10.1038/ajg.2010.398)]
 - 30 **Shaw SY**, Blanchard JF, Bernstein CN. Association between early childhood otitis media and pediatric inflammatory bowel disease: an exploratory population-based analysis. *J Pediatr* 2013; **162**: 510-514 [PMID: [23084703](https://pubmed.ncbi.nlm.nih.gov/23084703/) DOI: [10.1016/j.jpeds.2012.08.037](https://doi.org/10.1016/j.jpeds.2012.08.037)]
 - 31 **Ungaro R**, Bernstein CN, Gearry R, Hviid A, Kolho KL, Kronman MP, Shaw S, Van Kruiningen H, Colombel JF, Atreja A. Antibiotics associated with increased risk of new-onset Crohn's disease but not ulcerative colitis: a meta-analysis. *Am J Gastroenterol* 2014; **109**: 1728-1738 [PMID: [25223575](https://pubmed.ncbi.nlm.nih.gov/25223575/) DOI: [10.1038/ajg.2014.246](https://doi.org/10.1038/ajg.2014.246)]
 - 32 **Park S**, Chun J, Han KD, Soh H, Choi K, Kim JH, Lee J, Lee C, Im JP, Kim JS. Increased end-stage renal disease risk in patients with inflammatory bowel disease: A nationwide population-based study. *World J Gastroenterol* 2018; **24**: 4798-4808 [PMID: [30479466](https://pubmed.ncbi.nlm.nih.gov/30479466/) DOI: [10.3748/wjg.v24.i42.4798](https://doi.org/10.3748/wjg.v24.i42.4798)]
 - 33 **Small CL**, Xing L, McPhee JB, Law HT, Coombes BK. Acute Infectious Gastroenteritis Potentiates a Crohn's Disease Pathobiont to Fuel Ongoing Inflammation in the Post-Infectious Period. *PLoS Pathog* 2016; **12**: e1005907 [PMID: [27711220](https://pubmed.ncbi.nlm.nih.gov/27711220/) DOI: [10.1371/journal.ppat.1005907](https://doi.org/10.1371/journal.ppat.1005907)]
 - 34 **Celiberto LS**, Graef FA, Healey GR, Bosman ES, Jacobson K, Sly LM, Vallance BA. Inflammatory bowel disease and immunonutrition: novel therapeutic approaches through modulation of diet and the gut microbiome. *Immunology* 2018; **155**: 36-52 [PMID: [29693729](https://pubmed.ncbi.nlm.nih.gov/29693729/) DOI: [10.1111/imm.12939](https://doi.org/10.1111/imm.12939)]
 - 35 **Ananthakrishnan AN**, Bernstein CN, Iliopoulos D, Macpherson A, Neurath MF, Ali RAR, Vavricka SR, Fiocchi C. Environmental triggers in IBD: a review of progress and evidence. *Nat Rev Gastroenterol Hepatol* 2018; **15**: 39-49 [PMID: [29018271](https://pubmed.ncbi.nlm.nih.gov/29018271/) DOI: [10.1038/nrgastro.2017.136](https://doi.org/10.1038/nrgastro.2017.136)]
 - 36 **van der Sloot KWJ**, Amini M, Peters V, Dijkstra G, Alizadeh BZ. Inflammatory Bowel Diseases: Review of Known Environmental Protective and Risk Factors Involved. *Inflamm Bowel Dis* 2017; **23**: 1499-1509 [PMID: [28777099](https://pubmed.ncbi.nlm.nih.gov/28777099/) DOI: [10.1097/MIB.0000000000001217](https://doi.org/10.1097/MIB.0000000000001217)]
 - 37 **van der Sloot KWJ**, Weersma RK, Dijkstra G, Alizadeh BZ. Development and validation of a web-based questionnaire to identify environmental risk factors for inflammatory bowel disease: the Groningen IBD Environmental Questionnaire (GIEQ). *J Gastroenterol* 2019; **54**: 238-248 [PMID: [30109418](https://pubmed.ncbi.nlm.nih.gov/30109418/) DOI: [10.1007/s00535-018-1501-z](https://doi.org/10.1007/s00535-018-1501-z)]
 - 38 **Xu S**, Zou H, Zhang H, Zhu S, Zhou R, Li J. Investigation of inflammatory bowel disease risk factors in 4 families in central China. *Exp Ther Med* 2018; **15**: 1367-1375 [PMID: [29399122](https://pubmed.ncbi.nlm.nih.gov/29399122/) DOI: [10.3892/etm.2017.5582](https://doi.org/10.3892/etm.2017.5582)]
 - 39 **Allegretti J**, Eysenbach LM, El-Nachef N, Fischer M, Kelly C, Kassam Z. The Current Landscape and Lessons from Fecal Microbiota Transplantation for Inflammatory Bowel Disease: Past, Present, and Future. *Inflamm Bowel Dis* 2017; **23**: 1710-1717 [PMID: [28858073](https://pubmed.ncbi.nlm.nih.gov/28858073/) DOI: [10.1097/MIB.0000000000001247](https://doi.org/10.1097/MIB.0000000000001247)]
 - 40 **Miyoshi J**, Bobe AM, Miyoshi S, Huang Y, Hubert N, Delmont TO, Eren AM, Leone V, Chang EB. Peripartum Antibiotics Promote Gut Dysbiosis, Loss of Immune Tolerance, and Inflammatory Bowel Disease in Genetically Prone Offspring. *Cell Rep* 2017; **20**: 491-504 [PMID: [28700948](https://pubmed.ncbi.nlm.nih.gov/28700948/) DOI: [10.1016/j.celrep.2017.06.060](https://doi.org/10.1016/j.celrep.2017.06.060)]
 - 41 **Moossavi S**, Miliku K, Sepehri S, Khafipour E, Azad MB. The Prebiotic and Probiotic Properties of Human Milk: Implications for Infant Immune Development and Pediatric Asthma. *Front Pediatr* 2018; **6**: 197 [PMID: [30140664](https://pubmed.ncbi.nlm.nih.gov/30140664/) DOI: [10.3389/fped.2018.00197](https://doi.org/10.3389/fped.2018.00197)]
 - 42 **Parigi SM**, Eldh M, Larssen P, Gabrielsson S, Villablanca EJ. Breast Milk and Solid Food Shaping Intestinal Immunity. *Front Immunol* 2015; **6**: 415 [PMID: [26347740](https://pubmed.ncbi.nlm.nih.gov/26347740/) DOI: [10.3389/fimmu.2015.00415](https://doi.org/10.3389/fimmu.2015.00415)]
 - 43 **Rogier EW**, Frantz AL, Bruno ME, Wedlund L, Cohen DA, Stromberg AJ, Kaetzel CS. Lessons from mother: Long-term impact of antibodies in breast milk on the gut microbiota and intestinal immune system of breastfed offspring. *Gut Microbes* 2014; **5**: 663-668 [PMID: [25483336](https://pubmed.ncbi.nlm.nih.gov/25483336/) DOI: [10.4161/19490976.2014.969984](https://doi.org/10.4161/19490976.2014.969984)]
 - 44 **Coppa GV**, Zampini L, Galeazzi T, Facinelli B, Ferrante L, Capretti R, Orazio G. Human milk oligosaccharides inhibit the adhesion to Caco-2 cells of diarrheal pathogens: Escherichia coli, Vibrio cholerae, and Salmonella ftyris. *Pediatr Res* 2006; **59**: 377-382 [PMID: [16492975](https://pubmed.ncbi.nlm.nih.gov/16492975/) DOI: [10.1203/01.pdr.0000200805.45593.17](https://doi.org/10.1203/01.pdr.0000200805.45593.17)]
 - 45 **Duijts L**, Jaddoe VW, Hofman A, Moll HA. Prolonged and exclusive breastfeeding reduces the risk of infectious diseases in infancy. *Pediatrics* 2010; **126**: e18-e25 [PMID: [20566605](https://pubmed.ncbi.nlm.nih.gov/20566605/) DOI: [10.1542/peds.2008-3256](https://doi.org/10.1542/peds.2008-3256)]
 - 46 **Azad MB**, Konya T, Maughan H, Guttman DS, Field CJ, Chari RS, Sears MR, Becker AB, Scott JA, Kozyrskyj AL; CHILD Study Investigators. Gut microbiota of healthy Canadian infants: profiles by mode of delivery and infant diet at 4 months. *CMAJ* 2013; **185**: 385-394 [PMID: [23401405](https://pubmed.ncbi.nlm.nih.gov/23401405/) DOI: [10.1503/cmaj.121189](https://doi.org/10.1503/cmaj.121189)]

- 47 **Xu L**, Lochhead P, Ko Y, Claggett B, Leong RW, Ananthkrishnan AN. Systematic review with meta-analysis: breastfeeding and the risk of Crohn's disease and ulcerative colitis. *Aliment Pharmacol Ther* 2017; **46**: 780-789 [PMID: 28892171 DOI: 10.1111/apt.14291]
- 48 **Rubio CA**, Langner C, Schmidt PT. Partial to complete abrogation of the subepithelial macrophage barrier against the gut microbiota in patients with ulcerative colitis and Crohn's colitis. *Histopathology* 2018; **72**: 580-587 [PMID: 29023984 DOI: 10.1111/his.13417]
- 49 **Lee T**, Clavel T, Smirnov K, Schmidt A, Lagkouvardos I, Walker A, Lucio M, Michalke B, Schmitt-Kopplin P, Fedorak R, Haller D. Oral versus intravenous iron replacement therapy distinctly alters the gut microbiota and metabolome in patients with IBD. *Gut* 2017; **66**: 863-871 [PMID: 26848182 DOI: 10.1136/gutjnl-2015-309940]
- 50 **Qiao YQ**, Cai CW, Ran ZH. Therapeutic modulation of gut microbiota in inflammatory bowel disease: More questions to be answered. *J Dig Dis* 2016; **17**: 800-810 [PMID: 27743467 DOI: 10.1111/1751-2980.12422]
- 51 **Lavelle A**, Sokol H. Gut microbiota: Beyond metagenomics, metatranscriptomics illuminates microbiome functionality in IBD. *Nat Rev Gastroenterol Hepatol* 2018; **15**: 193-194 [PMID: 29463904 DOI: 10.1038/nrgastro.2018.15]
- 52 **Zhou Y**, Zhi F. Lower Level of *Bacteroides* in the Gut Microbiota Is Associated with Inflammatory Bowel Disease: A Meta-Analysis. *Biomed Res Int* 2016; **2016**: 5828959 [PMID: 27999802 DOI: 10.1155/2016/5828959]
- 53 **Glymenaki M**, Singh G, Brass A, Warhurst G, McBain AJ, Else KJ, Cruickshank SM. Compositional Changes in the Gut Mucus Microbiota Precede the Onset of Colitis-Induced Inflammation. *Inflamm Bowel Dis* 2017; **23**: 912-922 [PMID: 28498157 DOI: 10.1097/MIB.0000000000001118]
- 54 **Kvedaraite E**, Lourda M, Ideström M, Chen P, Olsson-Åkefeldt S, Forkel M, Gavhed D, Lindfors U, Mjösberg J, Henter JI, Svensson M. Tissue-infiltrating neutrophils represent the main source of IL-23 in the colon of patients with IBD. *Gut* 2016; **65**: 1632-1641 [PMID: 26160381 DOI: 10.1136/gutjnl-2014-309014]
- 55 **Zhou Y**, Xu ZZ, He Y, Yang Y, Liu L, Lin Q, Nie Y, Li M, Zhi F, Liu S, Amir A, González A, Tripathi A, Chen M, Wu GD, Knight R, Zhou H, Chen Y. Gut Microbiota Offers Universal Biomarkers across Ethnicity in Inflammatory Bowel Disease Diagnosis and Infliximab Response Prediction. *mSystems* 2018; **3**: e00188-17 [PMID: 29404425 DOI: 10.1128/mSystems.00188-17]
- 56 **Spekhorst LM**, Imhann F, Festen EAM, van Bodegraven AA, de Boer NKH, Bouma G, Fidder HH, d'Haens G, Hoentjen F, Hommes DW, de Jong DJ, Löwenberg M, Maljaars PWJ, van der Meulen-de Jong AE, Oldenburg B, Pierik MJ, Ponsioen CY, Stokkers PC, Verspaget HW, Visschedijk MC, van der Woude CJ, Dijkstra G, Weersma RK; Parelinoer Institute (PSI) and the Dutch Initiative on Crohn and Colitis (ICC). Cohort profile: design and first results of the Dutch IBD Biobank: a prospective, nationwide biobank of patients with inflammatory bowel disease. *BMJ Open* 2017; **7**: e016695 [PMID: 29122790 DOI: 10.1136/bmjopen-2017-016695]
- 57 **Kummen M**, Holm K, Anmarkrud JA, Nygård S, Vesterhus M, Høivik ML, Trøseid M, Marschall HU, Schrumpf E, Moum B, Røsjø H, Aukrust P, Karlsen TH, Hov JR. The gut microbial profile in patients with primary sclerosing cholangitis is distinct from patients with ulcerative colitis without biliary disease and healthy controls. *Gut* 2017; **66**: 611-619 [PMID: 26887816 DOI: 10.1136/gutjnl-2015-310500]
- 58 **Kennedy NA**, Lamb CA, Berry SH, Walker AW, Mansfield J, Parkes M, Simpkins R, Tremelling M, Nutland S; UK IBD Genetics Consortium; Parkhill J; Probert C; Hold GL; Lees CW. The Impact of NOD2 Variants on Fecal Microbiota in Crohn's Disease and Controls Without Gastrointestinal Disease. *Inflamm Bowel Dis* 2018; **24**: 583-592 [PMID: 29462388 DOI: 10.1093/ibd/izx061]
- 59 **Cranston RD**, Regueiro M, Hashash J, Baker JR, Richardson-Harman N, Janocko L, McGowan I. A Pilot Study of the Prevalence of Anal Human Papillomavirus and Dysplasia in a Cohort of Patients With IBD. *Dis Colon Rectum* 2017; **60**: 1307-1313 [PMID: 29112567 DOI: 10.1097/DCR.0000000000000878]
- 60 **Schirmer M**, Franzosa EA, Lloyd-Price J, McIver LJ, Schwager R, Poon TW, Ananthkrishnan AN, Andrews E, Barron G, Lake K, Prasad M, Sauk J, Stevens B, Wilson RG, Braun J, Denson LA, Kugathasan S, McGovern DPB, Vlamakis H, Xavier RJ, Huttenhower C. Dynamics of metatranscription in the inflammatory bowel disease gut microbiome. *Nat Microbiol* 2018; **3**: 337-346 [PMID: 29311644 DOI: 10.1038/s41564-017-0089-z]
- 61 **Henke MT**, Kenny DJ, Cassilly CD, Vlamakis H, Xavier RJ, Clardy J. Ruminococcus gnavus, a member of the human gut microbiome associated with Crohn's disease, produces an inflammatory polysaccharide. *Proc Natl Acad Sci USA* 2019; **116**: 12672-12677 [PMID: 31182571 DOI: 10.1073/pnas.1904099116]
- 62 **Lerouge I**, Vanderleyden J. O-antigen structural variation: mechanisms and possible roles in animal/plant-microbe interactions. *FEMS Microbiol Rev* 2002; **26**: 17-47 [PMID: 12007641 DOI: 10.1111/j.1574-6976.2002.tb00597.x]
- 63 **Liu TH**, Yaghmour MA, Lee MH, Gradziel TM, Leveau JHJ, Bostock RM. An roGFP2-Based Bacterial Bioreporter for Redox Sensing of Plant Surfaces. *Phytopathology* 2020; **110**: 297-308 [PMID: 31483224 DOI: 10.1094/PHYTO-07-19-0237-R]
- 64 **Dang X**, Xu M, Liu D, Zhou D, Yang W. Assessing the efficacy and safety of fecal microbiota transplantation and probiotic VSL#3 for active ulcerative colitis: A systematic review and meta-analysis. *PLoS One* 2020; **15**: e0228846 [PMID: 32182248 DOI: 10.1371/journal.pone.0228846]
- 65 **Kostic AD**, Xavier RJ, Gevers D. The microbiome in inflammatory bowel disease: current status and

- the future ahead. *Gastroenterology* 2014; **146**: 1489-1499 [PMID: [24560869](#) DOI: [10.1053/j.gastro.2014.02.009](#)]
- 66 **Shi Y**, Dong Y, Huang W, Zhu D, Mao H, Su P. Fecal Microbiota Transplantation for Ulcerative Colitis: A Systematic Review and Meta-Analysis. *PLoS One* 2016; **11**: e0157259 [PMID: [27295210](#) DOI: [10.1371/journal.pone.0157259](#)]
- 67 **Parada Venegas D**, De la Fuente MK, Landskron G, González MJ, Quera R, Dijkstra G, Harmsen HJM, Faber KN, Hermoso MA. Corrigendum: Short Chain Fatty Acids (SCFAs)-Mediated Gut Epithelial and Immune Regulation and Its Relevance for Inflammatory Bowel Diseases. *Front Immunol* 2019; **10**: 1486 [PMID: [31316522](#) DOI: [10.3389/fimmu.2019.01486](#)]
- 68 **Regueiro M**, Velayos F, Greer JB, Bougatsos C, Chou R, Sultan S, Singh S. American Gastroenterological Association Institute Technical Review on the Management of Crohn's Disease After Surgical Resection. *Gastroenterology* 2017; **152**: 277-295. e3 [PMID: [27840073](#) DOI: [10.1053/j.gastro.2016.10.039](#)]
- 69 **Santavirta J**, Mattila J, Kokki M, Matikainen M. Mucosal morphology and faecal bacteriology after ileoanal anastomosis. *Int J Colorectal Dis* 1991; **6**: 38-41 [PMID: [2033352](#) DOI: [10.1007/BF00703959](#)]
- 70 **Batista D**, Raffals L. Role of intestinal bacteria in the pathogenesis of pouchitis. *Inflamm Bowel Dis* 2014; **20**: 1481-1486 [PMID: [25046009](#) DOI: [10.1097/MIB.0000000000000055](#)]
- 71 **Limketkai BN**, Wolf A, Parian AM. Nutritional Interventions in the Patient with Inflammatory Bowel Disease. *Gastroenterol Clin North Am* 2018; **47**: 155-177 [PMID: [29413010](#) DOI: [10.1016/j.gtc.2017.09.007](#)]
- 72 **Sharbatdaran M**, Holaku A, Kashifard M, Bijani A, Firozjahi A, Hosseini A, Siadati S. Fecal calprotectin Level in patients with IBD and noninflammatory disease of colon: a study in Babol, Northern, Iran. *Caspian J Intern Med* 2018; **9**: 60-64 [PMID: [29387321](#)]
- 73 **de Lima A**, Zelinkova Z, van der Ent C, Steegers EA, van der Woude CJ. Tailored anti-TNF therapy during pregnancy in patients with IBD: maternal and fetal safety. *Gut* 2016; **65**: 1261-1268 [PMID: [25966992](#) DOI: [10.1136/gutjnl-2015-309321](#)]
- 74 **Gu YB**, Zhang MC, Sun J, Lv KZ, Zhong J. Risk factors and clinical outcome of Clostridium difficile infection in patients with IBD: A single-center retrospective study of 260 cases in China. *J Dig Dis* 2017; **18**: 207-211 [PMID: [28251812](#) DOI: [10.1111/1751-2980.12461](#)]
- 75 **Levine A**, Wine E, Assa A, Sigall Boneh R, Shaoul R, Kori M, Cohen S, Peleg S, Shamaly H, On A, Millman P, Abramas L, Ziv-Baran T, Grant S, Abitbol G, Dunn KA, Bielawski JP, Van Limbergen J. Crohn's Disease Exclusion Diet Plus Partial Enteral Nutrition Induces Sustained Remission in a Randomized Controlled Trial. *Gastroenterology* 2019; **157**: 440-450. e8 [PMID: [31170412](#) DOI: [10.1053/j.gastro.2019.04.021](#)]
- 76 **Bischoff SC**, Escher J, Hébuterne X, Kłęk S, Krznaric Z, Schneider S, Shamir R, Stardelova K, Wierdsma N, Wiskin AE, Forbes A. ESPEN practical guideline: Clinical Nutrition in inflammatory bowel disease. *Clin Nutr* 2020; **39**: 632-653 [PMID: [32029281](#) DOI: [10.1016/j.clnu.2019.11.002](#)]
- 77 **Gassull MA**, Fernández-Bañares F, Cabré E, Papo M, Giaffer MH, Sánchez-Lombrana JL, Richart C, Malchow H, González-Huix F, Esteve M; European Group on Enteral Nutrition in Crohn's Disease. Fat composition may be a clue to explain the primary therapeutic effect of enteral nutrition in Crohn's disease: results of a double blind randomised multicentre European trial. *Gut* 2002; **51**: 164-168 [PMID: [12117873](#) DOI: [10.1136/gut.51.2.164](#)]
- 78 **Bricarello LP**, de Moura Souza A, de Almeida Alves M, Retondario A, Fernandes R, Santos de Moraes Trindade EB, Zanette Ramos Zeni LA, de Assis Guedes de Vasconcelos F. Association between DASH diet (Dietary Approaches to Stop Hypertension) and hypertension in adolescents: A cross-sectional school-based study. *Clin Nutr ESPEN* 2020; **36**: 69-75 [PMID: [32220371](#) DOI: [10.1016/j.clnesp.2020.02.004](#)]
- 79 **Guo XY**, Liu XJ, Hao JY. Gut microbiota in ulcerative colitis: insights on pathogenesis and treatment. *J Dig Dis* 2020; **21**: 147-159 [PMID: [32040250](#) DOI: [10.1111/1751-2980.12849](#)]
- 80 **Costello SP**, Hughes PA, Waters O, Bryant RV, Vincent AD, Blatchford P, Katsikeros R, Makanyanga J, Campaniello MA, Mavrangelos C, Rosewarne CP, Bickley C, Peters C, Schoeman MN, Conlon MA, Roberts-Thomson IC, Andrews JM. Effect of Fecal Microbiota Transplantation on 8-Week Remission in Patients With Ulcerative Colitis: A Randomized Clinical Trial. *JAMA* 2019; **321**: 156-164 [PMID: [30644982](#) DOI: [10.1001/jama.2018.20046](#)]
- 81 **Moayyedi P**, Surette MG, Kim PT, Libertucci J, Wolfe M, Onishi C, Armstrong D, Marshall JK, Kassam Z, Reinisch W, Lee CH. Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial. *Gastroenterology* 2015; **149**: 102-109. e6 [PMID: [25857665](#) DOI: [10.1053/j.gastro.2015.04.001](#)]
- 82 **Paramsothy S**, Kamm MA, Kaakoush NO, Walsh AJ, van den Bogaerde J, Samuel D, Leong RWL, Connor S, Ng W, Paramsothy R, Xuan W, Lin E, Mitchell HM, Borody TJ. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. *Lancet* 2017; **389**: 1218-1228 [PMID: [28214091](#) DOI: [10.1016/S0140-6736\(17\)30182-4](#)]
- 83 **Lai CY**, Sung J, Cheng F, Tang W, Wong SH, Chan PKS, Kamm MA, Sung JYJ, Kaplan G, Chan FKL, Ng SC. Systematic review with meta-analysis: review of donor features, procedures and outcomes in 168 clinical studies of faecal microbiota transplantation. *Aliment Pharmacol Ther* 2019; **49**: 354-363 [PMID: [30628108](#) DOI: [10.1111/apt.15116](#)]
- 84 **Fang H**, Fu L, Wang J. Protocol for Fecal Microbiota Transplantation in Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. *Biomed Res Int* 2018; **2018**: 8941340 [PMID:

30302341 DOI: 10.1155/2018/8941340]

- 85 **Qazi T**, Amaratunga T, Barnes EL, Fischer M, Kassam Z, Allegretti JR. The risk of inflammatory bowel disease flares after fecal microbiota transplantation: Systematic review and meta-analysis. *Gut Microbes* 2017; **8**: 574-588 [PMID: 28723262 DOI: 10.1080/19490976.2017.1353848]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

