

# World Journal of *Gastroenterology*

*World J Gastroenterol* 2021 June 21; 27(23): 3142-3428



### EDITORIAL

- 3142** Pain management in chronic pancreatitis incorporating safe opioid practices: Challenge accepted  
*Shah I, Sheth SG, Kothari DJ*

### EVIDENCE REVIEW

- 3148** Pancreatitis and pancreatic cancer: A case of the chicken or the egg  
*Umans DS, Hoogenboom SA, Sissingh NJ, Lekkerkerker SJ, Verdonk RC, van Hooft JE*

### REVIEW

- 3158** Pancreatic adenocarcinoma: A review of recent paradigms and advances in epidemiology, clinical diagnosis and management  
*Gupta N, Yelamanchi R*
- 3182** Silencing hepatitis B virus covalently closed circular DNA: The potential of an epigenetic therapy approach  
*Singh P, Kairuz D, Arbuthnot P, Bloom K*
- 3208** COVID-19-associated diarrhea  
*Megyeri K, Dernovics Á, Al-Luhaibi ZII, Rosztóczy A*
- 3223** Assessment of liver disease in patients with chronic hepatitis C and unhealthy alcohol use  
*Fuster D, García-Calvo X, Zuluaga P, Bolao F, Muga R*

### MINIREVIEWS

- 3238** Clinical indicators for progression of nonalcoholic steatohepatitis to cirrhosis  
*Seen TK, Sayed M, Bilal M, Reyes JV, Bhandari P, Lourdasamy V, Al-khazraji A, Syed U, Sattar Y, Bansal R*
- 3249** Update on the management and treatment of viral hepatitis  
*Almeida PH, Matielo CEL, Curvelo LA, Rocco RA, Felga G, Della Guardia B, Boteon YL*
- 3262** Large-duct pattern invasive adenocarcinoma of the pancreas—a variant mimicking pancreatic cystic neoplasms: A minireview  
*Sato H, Liss AS, Mizukami Y*
- 3279** Chronic hepatitis B in pregnant women: Current trends and approaches  
*Belopolskaya M, Avrutin V, Kalinina O, Dmitriev A, Gusev D*
- 3290** Viscoelastic tests in liver disease: where do we stand now?  
*Buliarca A, Horhat A, Mocan T, Craciun R, Procopet B, Sparchez Z*

- 3303** Gastrointestinal involvement in paediatric COVID-19 – from pathogenesis to clinical management: A comprehensive review

*Calitri C, Fumi I, Ignaccolo MG, Banino E, Benetti S, Lupica MM, Fantone F, Pace M, Garofalo F*

- 3317** Can control of gut microbiota be a future therapeutic option for inflammatory bowel disease?

*Nishida A, Nishino K, Sakai K, Owaki Y, Noda Y, Imaeda H*

## ORIGINAL ARTICLE

### Basic Study

- 3327** Oncogenic tuftelin 1 as a potential molecular-targeted for inhibiting hepatocellular carcinoma growth

*Wu MN, Zheng WJ, Ye WX, Wang L, Chen Y, Yang J, Yao DF, Yao M*

- 3342** Conditioned secretome of adipose-derived stem cells improves dextran sulfate sodium-induced colitis in mice

*Lee S, Heo J, Ahn EK, Kim JH, Kim YH, Chang HK, Lee SJ, Kim J, Park SJ*

### Case Control Study

- 3357** Pancreatic enzymes and abdominal adipose tissue distribution in new-onset prediabetes/diabetes after acute pancreatitis

*Ko J, Skudder-Hill L, Cho J, Bharmal SH, Petrov MS*

### Retrospective Cohort Study

- 3372** Effect of type 2 diabetic mellitus in the prognosis of acute-on-chronic liver failure patients in China

*Lai RM, Chen TB, Hu YH, Wu G, Zheng Q*

### Observational Study

- 3386** Preliminary prospective study of real-time post-gastrectomy glycemic fluctuations during dumping symptoms using continuous glucose monitoring

*Ri M, Nunobe S, Ida S, Ishizuka N, Atsumi S, Makuuchi R, Kumagai K, Ohashi M, Sano T*

### Prospective Study

- 3396** Real-world treatment patterns and disease control over one year in patients with inflammatory bowel disease in Brazil

*Sasaki LY, Miszputen SJ, Kaiser Junior RL, Catapani WR, Bafutto M, Scotton AS, Zaltman C, Baima JP, Ramos HS, Faria MAG, Gonçalves CD, Guimaraes IM, Flores C, Amarante HMBS, Nones RB, Parente JML, Lima MM, Chebli JM, Ferrari MLA, Campos JF, Sanna MGP, Ramos O, Parra RS, da Rocha JJR, Feres O, Feitosa MR, Caratin RF, Senra JT, Santana GO*

## SYSTEMATIC REVIEWS

- 3413** Local ablation of pancreatic tumors: State of the art and future perspectives

*Granata V, Grassi R, Fusco R, Belli A, Palaia R, Carrafiello G, Miele V, Grassi R, Petrillo A, Izzo F*

**ABOUT COVER**

Editorial Board Member of *World Journal of Gastroenterology*, Paola Ghiorzo, PhD, Professor, Head, Genetics of Rare Cancers Unit, IRCCS Ospedale Policlinico San Martino and Department of Internal Medicine, University of Genoa, L.go R Benzi, Genoa 16129, Italy. [paola.ghiorzo@unige.it](mailto:paola.ghiorzo@unige.it)

**AIMS AND SCOPE**

The primary aim of *World Journal of Gastroenterology* (WJG, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. WJG mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

**INDEXING/ABSTRACTING**

The WJG is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2020 edition of Journal Citation Report® cites the 2019 impact factor (IF) for WJG as 3.665; IF without journal self cites: 3.534; 5-year IF: 4.048; Ranking: 35 among 88 journals in gastroenterology and hepatology; and Quartile category: Q2. The WJG's CiteScore for 2019 is 7.1 and Scopus CiteScore rank 2019: Gastroenterology is 17/137.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: *Yan-Jie Ma*; Production Department Director: *Xiang Li*; Editorial Office Director: *Ze-Mao Gong*.

**NAME OF JOURNAL**

*World Journal of Gastroenterology*

**ISSN**

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

**LAUNCH DATE**

October 1, 1995

**FREQUENCY**

Weekly

**EDITORS-IN-CHIEF**

Andrzej S Tarnawski, Subrata Ghosh

**EDITORIAL BOARD MEMBERS**

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

**PUBLICATION DATE**

June 21, 2021

**COPYRIGHT**

© 2021 Baishideng Publishing Group Inc

**INSTRUCTIONS TO AUTHORS**

<https://www.wjgnet.com/bpg/gerinfo/204>

**GUIDELINES FOR ETHICS DOCUMENTS**

<https://www.wjgnet.com/bpg/gerinfo/287>

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**

<https://www.wjgnet.com/bpg/gerinfo/240>

**PUBLICATION ETHICS**

<https://www.wjgnet.com/bpg/gerinfo/288>

**PUBLICATION MISCONDUCT**

<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/gerinfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>



## Can control of gut microbiota be a future therapeutic option for inflammatory bowel disease?

Atsushi Nishida, Kyohei Nishino, Keitaro Sakai, Yuji Owaki, Yoshika Noda, Hirotsugu Imaeda

**ORCID number:** Atsushi Nishida 0000-0002-1288-3272; Kyohei Nishino 0000-0001-9798-6731; Keitaro Sakai 0000-0001-8131-6717; Yuji Owaki 0000-0001-7932-5016; Yoshika Noda 0000-0003-2358-0565; Hirotsugu Imaeda 0000-0002-5516-8527.

**Author contributions:** Nishida A wrote the paper; Nishino K, Sakai K, Owaki Y, Noda Y, and Imaeda H contributed critical revision of the manuscript.

**Conflict-of-interest statement:** No conflict 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/>

**Manuscript source:** Invited manuscript

**Specialty type:** Gastroenterology

**Atsushi Nishida, Kyohei Nishino, Keitaro Sakai, Yuji Owaki, Yoshika Noda, Hirotsugu Imaeda,** Department of Gastroenterology and Hepatology, Nagahama City Hospital, Nagahama 5268580, Shiga, Japan

**Corresponding author:** Atsushi Nishida, MD, PhD, Chief Doctor, Department of Gastroenterology and Hepatology, Nagahama City Hospital, 313 Oinuicho, Nagahama 5268580, Shiga, Japan. [atsuda@belle.shiga-med.ac.jp](mailto:atsuda@belle.shiga-med.ac.jp)

### Abstract

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract encompassing two main clinical entities, Crohn's disease and ulcerative colitis. Accumulated evidence indicates that an aberrant immune activation caused by the interplay of genetic susceptibility and environmental impact on the gut microbiota may be involved in the pathogenesis of IBD. Rapid advances in next-generation sequencing technology have enabled a number of studies to identify the alteration of the gut microbiota, termed dysbiosis, in IBD. Moreover, the alteration in the metabolites derived from the gut microbiota in IBD has also been described in many studies. Therefore, microbiota-based interventions such as fecal microbiota transplantation (FMT) have attracted attention as a novel therapeutic option in IBD. However, in clinical trials, the efficacy of FMT for IBD remains controversial. Additional basic and clinical studies are required to validate whether FMT can assume a complementary role in the treatment of IBD. The present review provides a synopsis on dysbiosis in IBD and on the association between the gut microbiota and the pathogenesis of IBD. In addition, we summarize the use of probiotics in IBD and the results of current clinical trials of FMT for IBD.

**Key Words:** Inflammatory bowel disease; Dysbiosis; Fecal microbiota transplantation; Short chain fatty acid; Probiotics

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

**Core Tip:** In this review, we discuss the gut microbiota in inflammatory bowel disease and gut microbiota-derived metabolites, especially short chain fatty acids. The anti-inflammatory function of short chain fatty acids on the mucosal immune system in the



and hepatology

**Country/Territory of origin:** Japan**Peer-review report's scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C, C, C, C, C

Grade D (Fair): 0

Grade E (Poor): 0

**Received:** March 17, 2021**Peer-review started:** March 17, 2021**First decision:** April 17, 2021**Revised:** April 23, 2021**Accepted:** May 7, 2021**Article in press:** May 7, 2021**Published online:** June 21, 2021**P-Reviewer:** Kim DJ, Mazzarella G, Sitkin S, Sunkesula V, Truta B, Yang Y**S-Editor:** Zhang L**L-Editor:** Filipodia**P-Editor:** Ma YJ

gastrointestinal tract is also discussed. In addition, we review the efficacy of probiotics on inflammatory bowel disease and the current clinical trials on the effectiveness of fecal microbiota transplantation on inflammatory bowel disease.

**Citation:** Nishida A, Nishino K, Sakai K, Owaki Y, Noda Y, Imaeda H. Can control of gut microbiota be a future therapeutic option for inflammatory bowel disease? *World J Gastroenterol* 2021; 27(23): 3317-3326

**URL:** <https://www.wjgnet.com/1007-9327/full/v27/i23/3317.htm>

**DOI:** <https://dx.doi.org/10.3748/wjg.v27.i23.3317>

## INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC), which are known as inflammatory bowel diseases (IBD), are chronic and relapsing inflammatory disorders of the gastrointestinal tract[1,2]. The precise etiology and pathogenesis remain to be elucidated. Genome-wide association studies have identified over 200 IBD associated-susceptible genes, some of which are known to be involved or implicated in mediating host responses to the gut microbiota[3]. This has evoked the possibility that the gut microbiota is implicated in the pathogenesis of IBD[4-7].

The human digestive tract is inhabited by more than 100 trillion commensal bacteria, which exceeds the total number of human cells of 37 trillion[8,9]. The concentration of human intestinal bacteria has been estimated to be from  $10^{11}$  to  $10^{12}$  cells per gram of luminal contents[10,11]. The intestinal bacteria regulate the balance between each bacterium by interacting with each other, thereby maintaining the homeostasis of the intestinal environment. More than 99% of the bacteria that live in the human intestine belong to the four major phyla: Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria, of which Firmicutes is the most predominant phylum followed by Bacteroidetes[10,12].

Recent studies have shown that the composition of human gut microbiota is closely linked to health and disease[13,14]. Moreover, the gut microbiota contributes to the differentiation and maturation of intestinal epithelial cells and immune cells, the supply of energy to the host through metabolic processes, and protection against infection by pathogens[10]. Humans, on the other hand, provide the gut microbiota with an anaerobic place to reside. In this way, a symbiotic relationship is established between the gut microbiota and human host[15].

Developments in gene sequencing technologies as well as the increased availability of powerful bioinformatic tools have enabled novel insights into the microbial composition of human gut microbiota and the effect of microbial communities on human physiology and disease[16,17]. Recent studies using these technologies have indicated that abnormal microbiota composition, known as "dysbiosis," and a decreased complexity of the gut microbial ecosystem are common features in patients with IBD. Moreover, it has been demonstrated that dysbiosis is involved in the pathophysiology of non-gastrointestinal diseases such as obesity and diabetes[17,18], in addition to gastrointestinal diseases such as IBD and irritable bowel syndrome [6,7, 19].

Recently, it has been widely recognized that the gut microbiota plays a vital role in human immunity, metabolism, and diseases[4,6,20-22], leading to the idea of considering it as an organ. Based on this idea, the gut microbiota is sometimes called a "superorganism" or "forgotten organ"[23]. Considering these various functions of the gut microbiota on human biological functions, controlling its composition and diversity might allow us to treat or cure human diseases.

In this review, we will discuss the relationship between the gut microbiota and IBD, the efficacy of probiotics on IBD, and the current status of fecal microbiota transplantation (FMT) as a therapeutic option for IBD.

## THE GUT MICROBIOTA IN IBD

Various alterations of the gut microbiota have been reported in patients with IBD. The most consistent findings of the gut microbiota in IBD patients are a reduction of

diversity and a reduction of Firmicutes compared to healthy individuals[6,7,16]. Some studies on IBD patients have reported an increase in the phyla Proteobacteria and Bacteroidetes, while others have reported a decrease in these phyla[5,7].

*Faecalibacterium prausnitzii* (*F. prausnitzii*), which belongs to *Clostridium* cluster IV, has been reported to have an anti-inflammatory effect by producing short-chain fatty acids (SCFAs: C2-C6), especially butyrate[24]. It has been reported that there is a reduced abundance of *F. prausnitzii* in patients with CD and that this deficiency is associated with postoperative recurrence of CD[25]. It has been demonstrated that *F. prausnitzii*, *Blautia faecis*, *Roseburia inulinivorans*, *Ruminococcus torques*, and *Clostridium lavalense* are decreased in patients with CD when compared to healthy subjects[25,26] and that the number of *F. prausnitzii* is correlated with the risk of relapse of ileal CD after surgery[27]. Deficient colonization of *F. prausnitzii* was observed in UC patients during remission, and the recovery of the *F. prausnitzii* population after relapse is associated with the maintenance of clinical remission[27]. Moreover, Sokol *et al*[28] showed that human peripheral blood mononuclear cells stimulated with *F. prausnitzii* induce the production of interleukin (IL)-10 and inhibit the production of inflammatory cytokines, such as IL-12 and interferon- $\gamma$ . Furthermore, a significant decrease of *Roseburia spp.* was shown in the gut microbiota of healthy individuals with a high genetic risk for IBD[29].

Another consistent finding from a number of reports is the relative increase in the phylum Proteobacteria, especially *Escherichia coli* (*E. coli*), in CD patients. The CD-associated[30] proinflammatory *E. coli* is known as adhesion-invasive *E. coli*, which is a bacterium isolated from CD patients. Adhesion-invasive *E. coli* has been reported to increase the permeability of the intestinal epithelium and induce intestinal inflammation by adhering directly to it[31].

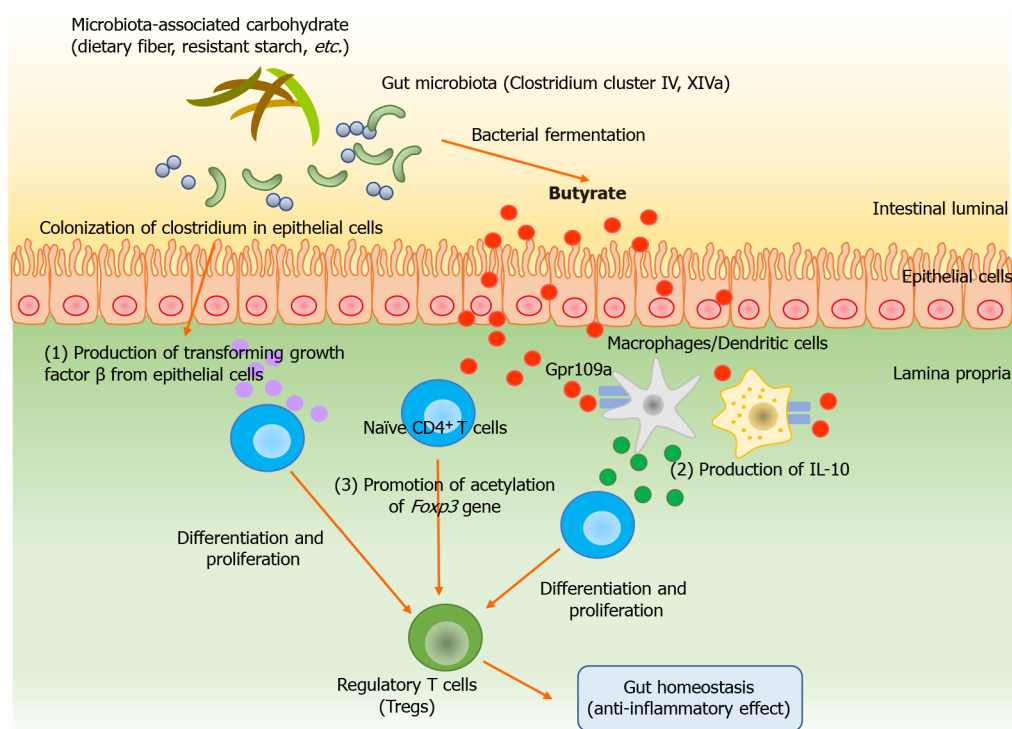
Thus, in IBD enterobacteria, along with a decrease in diversity, a decrease in anti-inflammatory bacteria (Firmicutes phylum) and an increase in proinflammatory bacteria (Proteobacteria phylum) were observed, and these changes have also been observed in IBD. It is possible that these factors contribute to chronic inflammation of the intestinal tract. It is possible that it contributes to chronic inflammation of the intestinal tract.

## ROLE OF SHORT-CHAIN FATTY ACIDS IN THE INTESTINAL TRACT

Although most nutrients are digested and absorbed in the duodenum and small intestine, dietary fiber remains intact until it reaches the colon. Dietary fibers are complex carbohydrates of plant origin broken down by specialized enzymes produced by gut bacteria but indigestible by the host[32]. They have recently been redefined as microbiota-accessible carbohydrates (MACs) and represent the major energy source for colonic bacteria[33]. MACs favor an increase in beneficial bacteria. The composition and function of the gut microbiota are dependent on the availability of MACs[34]. In preclinical studies, low dietary MACs have been shown to aggravate the development of inflammatory diseases, including autoimmune diseases, infections, and allergies [35-38] (Figure 1).

SCFAs, namely, acetate, propionate, and butyrate, are produced in the intestinal tract by the gut microbiota during fermentation of dietary fibers under anaerobic conditions[17]. Among these SCFAs, butyrate is the main energy source for the intestinal epithelial cells. Butyric acid positively modulates mitochondrial function, such as enhancing oxidative phosphorylation and  $\beta$ -oxidation, leading to an increase in oxygen consumption of colonic epithelial cells[32,33,39,40]. As a result, the concentration of oxygen in the intestinal tract decreases, and the number of obligate anaerobic bacteria, including those Firmicutes phylum that produce butyrate, increases[41]. As mentioned above, there is a decrease in butyrate-producing bacteria, such as *F. prausnitzii*, *Clostridium* cluster IV and XIVa, and a decrease in the concentration of butyrate in the gut microbiota in IBD patients[26,42]. Therefore, the decrease of both butyrate-producing bacteria and concentration of butyrate may be involved in the development of IBD and the persistence of chronic intestinal inflammation.

It has been reported that the genus *Clostridium* is important for the induction of regulatory T cells with an immunosuppressive function by producing butyrate from MACs, and in turn, the butyrate suppresses inflammatory cytokines *via* mucin and antimicrobial peptides from intestinal epithelial cells[22,43-45]. Moreover, it has been reported that the genus *Clostridium* promotes the differentiation and proliferation of regulatory T cells by enhancing the production of transforming growth factor  $\beta$  from intestinal epithelial cells[43]. In addition to the direct function of butyrate on T cells,



**Figure 1 Function of butyrate in intestinal mucosa.** Butyrate contributes to the maintenance of gut homeostasis by multiple mechanisms. Butyrate is mainly produced in the intestinal tract by bacteria of the Firmicutes phylum during fermentation of dietary fibers under anaerobic conditions. Butyrate is the main energy source for the intestinal epithelial cells. (1) The genus *Clostridium* promotes the differentiation and proliferation of regulatory T cells by enhancing the production of transforming growth factor  $\beta$  from intestinal epithelial cells; (2) Butyrate enhances the production of the anti-inflammatory cytokine, interleukin-10, produced by macrophages and dendritic cells through GPR109a, which is the G protein-coupled receptor for butyrate; and (3) Butyrate upregulates histone H3 acetylation at regulatory regions of the *Foxp3* gene and promotes the differentiation of naïve CD4<sup>+</sup> T cells into regulatory T cells. IL: Interleukin.

butyrate suppresses the induction of the inflammatory cytokine, IL-6, and enhances the production of the anti-inflammatory cytokine, IL-10, produced by macrophages and dendritic cells through GPR109a, which is the G protein-coupled receptor for butyrate[43,44]. Butyrate is also known to regulate gene expression epigenetically by inhibiting histone deacetylases. Recent studies have demonstrated that butyrate upregulates histone H3 acetylation at regulatory regions of the *Foxp3* gene and promotes the differentiation of naïve CD4<sup>+</sup> T cells into regulatory T cells[45].

Based on these findings, SCFAs play an important role in maintaining intestinal homeostasis through their anti-inflammatory properties. Thus, the decreased concentration of SCFAs in the feces of IBD patients may be involved in the pathophysiology of IBD through multiple points of action.

## THE EFFECT OF PROBIOTICS ON IBD

Probiotics are defined as “live microorganisms that when administered in adequate amounts confer a health benefit on the host”[46]. Over the past decade, there has been a great interest in the use of probiotics as a therapeutic option in IBD. However, highly reliable scientific evidence regarding the efficacy of probiotics in IBD has been lacking.

There is a large double-blind clinical trial to investigate the efficacy of *E. coli* Nissle 1917 on maintaining remission in comparison to mesalamine (1500 mg/d) in UC patients in clinical remission ( $n = 120$ ). The clinical trial showed the similar relapse rate between *E. coli* Nissle 1917 and mesalamine (*E. coli* Nissle 1917 group: 14%, mesalamine group: 16%)[47]. This group conducted a second large trial to examine the efficacy of *E. coli* Nissle 1917 on maintaining UC remission compared to mesalamine (1500 mg/d). This study revealed a comparable clinical relapse rate (*E. coli* Nissle 1917 group: 36%, mesalamine group: 34%)[48].

There is one randomized clinical trial that examined whether the addition of *E. coli* Nissle 1917 to standard therapy increased the rate of remission of patients with active UC. While undergoing the induction therapy, subjects were randomized to *E. coli* Nissle 1917 group and mesalamine group (2400 mg/d). After remission, patients were



maintained on either mesalamine or *E. coli* Nissle 1917. The remission rates were similar in the mesalamine group (75%) and *E. coli* Nissle 1917 group (68%). Moreover, the relapse rates were also similar in mesalamine group (73%) and *E. coli* Nissle 1917 group (67%). Notably, it is the only probiotic mentioned in the European Crohn's and Colitis Organization guidelines as an effective alternative to mesalamine in maintenance of remission in UC patients[49]. Collectively, the efficacy of *E. coli* Nissle 1917 on maintenance of remission was comparable to mesalamine.

To date, the evidence of the use of VSL#3 in UC patients has been accumulated. VAL#3 is a combination of four strains of *Lactobacillus* (*Lactobacillus casei*, *Lactobacillus plantarum*, *Lactobacillus acidophilus*, *Lactobacillus delbrueckii* subsp. *bulgaricus*), three strains of *Bifidobacteria* (*Bifidobacteria longum*, *Bifidobacteria breve*, and *Bifidobacteria infants*) and *Streptococcus salivarius* subsp. *Thermophilus*. Sood *et al*[50] conducted a randomized, double-blind clinical trial to investigate the efficacy of VSL#3 on mild-to-moderately active UC compared to placebo. By week 12, more patients given VSL#3 achieved remission (43%) as compared with those given placebo (15.7%;  $P < 0.001$ ). Furthermore, by week 12, more patients in the VSL#3 group achieved mucosal healing (32%) as compared to the placebo group (15%;  $P < 0.03$ ). Another study with similar design conducted by Tursi *et al*[51] also showed that the remission rate in VSL#3 group was higher than in the placebo group (44% *vs* 32%;  $P = 0.13$ ). Collectively, these results suggest that the use of VSL#3 has a benefit in inducing remission in active UC.

There has been a lack of large clinical trials assessing the efficacy of probiotics in both inducing and maintaining the remission for patients with CD. A Cochrane review published in 2020 assessing the efficacy of probiotics to induce remission in CD patients found two studies that met criteria for inclusion[52]. One study had 11 subjects with mild-to-moderately active CD that randomized assignment to *Lactobacillus rhamnosus* strain GG or placebo. The other study had 35 subjects with active CD, whose CD activity index score of 150 to 450 randomized to receive a symbiotic treatment (freeze-dried *Bifidobacterium longum* and a commercial product) or placebo. The review concluded that there was no evidence to support the use of probiotics for the induction of remission in CD.

A Cochran systematic review published in 2006 assessing the efficacy of probiotics to maintain the remission in CD found seven small controlled studies worthy of inclusion in their review[53]. The review concluded that there was no evidence to suggest that probiotics are beneficial for the maintenance of remission in CD. In summary, large clinical trials in the efficacy of probiotics on active and quiescent CD should be conducted to change these conclusions in the future.

## THE EFFECT OF FMT ON IBD

FMT aims to restore the intestinal microbiota in diseased individuals by transplanting intestinal microbiota from healthy donors[10]. FMT has been reported to be highly effective against recurrent *Clostridium difficile* infection[54]. The success of FMT in treating *Clostridium difficile* infection has attracted attention as a new therapeutic option for IBD. Several clinical studies have been conducted to examine the effect of FMT on IBD, but the results have been inconsistent so it cannot be stated with confidence whether or not the treatment is effective. Furthermore, in these studies, the protocols including donor selection, method of stool administration, and method of stool preparation are not consistent. Collectively, at present FMT has not yet been used clinically as a therapeutic option.

To date, the findings of four randomized controlled trials (RCTs) of FMT for UC patients have been published: two in Gastroenterology in 2015[55,56], one in The Lancet in 2017[57], and the other in the Journal of the American Medical Association in 2019[58] (Table 1). In a report from Canada in 2015, 50 mL of donor stool was administered six times by enema in an FMT group, and 50 mL of water was administered in the same manner in a placebo group. The remission rate in the FMT group was significantly higher than the placebo group [9/38 (24%) *vs* 2/37 (5%);  $P = 0.03$ ][55]. On the other hand, according to a report from the Netherlands in 2015, donor stool was administered to patients at day 0 and 3 wk later using a nasoduodenal tube in an FMT group, and autologous stool was administered to patients in the same manner in a control group. In this study, there was no significant difference in the effect of FMT between the two groups[56]. More recently, two RCTs in patients with mild-to-moderately active UC were reported in 2017 and in 2019. Paramsothy *et al*[57] reported in 2017 that 81 UC patients were randomly assigned FMT or placebo and that the primary outcome was defined as steroid-free clinical remission with endoscopic

**Table 1 Randomized controlled studies of fecal microbiota transplantation in ulcerative colitis**

Ref.	Moayyedi <i>et al</i> [55]	Rossen <i>et al</i> [56]	Paramsothy <i>et al</i> [57]	Costello <i>et al</i> [58]
Date of publication	2015	2015	2017	2019
Reference number	55	56	57	58
Number of patients	38	23	41	38
Number of controls	37	25	40	35
Severity of UC	Mayo 4-12 (mild to severe)	SCCAI 4-11 (mild to moderate)	Mayo 4-10 (mild to moderate)	Mayo 3-10 (mild to moderate)
Donor and Donor stool	6 volunteers fresh or frozen	15 donors fresh	Multi-donors (3-7 donors), frozen	Multi-donors (3-4 donors), frozen
Mode of FMT	Retention enema	Nasoduodenal tube	Colonoscopy and enema	Colonoscopy and enema
Number of FMT	6 1/wk × 6 wk	2 0 and 3 wk	41 First infusion by colonoscopy + 5/wk for 8 wk by enema	3 3/wk (colonoscopy followed by 2 enemas)
Follow-up	6 wk	12 wk	8 wk	8 wk
Pretreatment with antibiotics	No	No	No	No
Primary endpoint	Remission (Mayo ≤ 2 with an endoscopic score of 0)	Remission (SCCAI ≤ 2) combined with ≥ 1-point decrease in Mayo endoscopic score	Steroid-free clinical remission with endoscopic remission or response (Mayo ≤ 2, all subscores ≤ 1, and ≥ 1-point reduction in endoscopy subscore)	Steroid-free remission with endoscopic remission (Mayo ≤ 2 with endoscopic subscore ≤ 1)
Subjects who achieved the primary endpoint	9/38 (24%) treated with FMT <i>vs</i> 2/37 (5%) control ( <i>P</i> = 0.03)	7/23 (30.4%) treated with FMT <i>vs</i> 5/25 (20.0%) control ( <i>P</i> = 0.51)	11/41 (27%) treated with FMT <i>vs</i> 3/40 (8%) control ( <i>P</i> = 0.021)	12/38 (32%) treated with FMT <i>vs</i> 3/35 (9%) control ( <i>P</i> = 0.03)

SCCAI: Simple Clinical Colitis Activity Index; FMT: Fecal microbiota transplantation; UC: Ulcerative colitis.

remission or response at week 8. The rate of primary outcome of the FMT group was significantly higher than the placebo group [11/41 (27%) *vs* 3/40 (8%); *P* = 0.02]. Costello *et al*[58] reported that 73 patients with active UC were enrolled to an FMT group or autologous FMT group (placebo group). The steroid-free remission rate of the FMT group was significantly higher than that of the placebo group [12/38 (32%) *vs* 3/35 (9%); *P* = 0.03].

Since these four RCTs differ in donor selection, method of fecal administration, and the number of fecal administrations, it is difficult to make a direct comparison. It is presumed that increasing the number of FMT will be effective for UC. Based on the clinical data, FMT for UC may remain in clinical trials but not be adopted in practice. More high-quality RCTs are needed to optimize the protocol for FMT.

Sood *et al*[59] reported the effect of FMT in maintenance of remission in UC patients who had achieved clinical remission by FMT. In this pilot study, 61 patients with UC in clinical remission achieved after multisession FMT were randomized to an FMT group (*n* = 31) or placebo group (*n* = 30). There was no significant difference in the rate of steroid-free clinical remission between the FMT group and placebo group [27/31 (87.1%) *vs* 20/30 (66.7%); *P* = 0.111]. Secondary endpoints of endoscopic remission [FMT group: 18/31 (58.1%) *vs* placebo group: 8/30 (26.7%); *P* = 0.026] and histological remission [FMT group: 14/31 (45.2%) *vs* placebo group: 5/30 (16.7%); *P* = 0.033] were achieved in a significantly higher number of patients with FMT. This pilot study suggested that maintenance FMT therapy may be one of the therapeutic options for UC patients in clinical remission.

To date, one pilot randomized controlled study has reported the effects of a single FMT administered *via* colonoscopy in patients with colonic or ileo-colonic CD who achieved clinical remission with systemic corticosteroids[60]. In this pilot study, 8 patients received FMT, and 9 patients received sham transplantation. The primary endpoint was the implantation of the donor microbiota at week 6. None of patients reached the primary endpoint. There was no significant difference in the steroid-free remission rate at week 10 between the FMT group and the sham group Stood [7/8 (87.5%) *vs* 4/9 (44.4%); *P* = 0.13]. The CD Endoscopic Index of Severity decreased significantly 6 wk after FMT [8.5 (4.6; 13.0) *vs* 3.5 (1.0; 8.9); *P* = 0.03] but not after sham

[2.4 (0.0; 8.3) *vs* 2.7 (0.7; 10.0);  $P = 0.8$ ]. Moreover, 6 wk after FMT, C-reactive protein levels remained stable [3.0 (3.0; 3.0) *vs* 3.0 (3.0; 14.2) mg/L;  $P = 0.05$ ], while they had already started to increase in the sham group [3.0 (3.0; 4.2) *vs* 6.9 (4.0; 8.7) mg/L;  $P = 0.008$ ]. This pilot study indicated that the benefit of FMT over sham transplantation was observed for several clinically relevant endpoints, including CD Endoscopic Index of Severity and C-reactive protein level. Several reports have been published on the effects of FMT for CD on a small number of cases, but the results have been inconsistent. A recent systematic review and meta-analysis of 11 studies (four case reports and seven prospective uncontrolled cohort studies) on FMT for CD that included 83 CD patients showed an overall clinical remission rate of 50.5% (42/83) [61]. However, the result of one large study had a great influence on the remission rate. The authors indicated that their overall findings should therefore be treated with caution because of the potential bias from this one study [30].

## CONCLUSION

A convergence of technology, data from clinical studies, and experimental insights have revealed that the gut microbiota and its metabolites markedly contribute to the pathogenesis of IBD. However, it remains unclear whether the dysbiosis of the gut microbiota observed in IBD is a cause or a consequence of chronic intestinal inflammation. To answer this question, more basic approaches to reveal the precise effects of the gut microbiota on intestinal functions, including immune system and barrier system, will be essential. Moreover, intestinal microorganisms other than bacteria, such as viruses, archaea, and fungi should be investigated. The results from these basic studies may help to clarify the situation.

Although there is great promise for novel probiotics, we need to be circumspect when there was a lack of proof in efficacy of probiotics on IBD. There are promising results for *E. coli* Nissle 1917 in maintenance of quiescent UC and VSL#3 in active UC. There is no evidence available to support the use of probiotics in CD. The same results were found in a recently published systematic review [62]. In the future, large clinical trials should be essential to determine the effect of probiotics on IBD.

FMT has attracted attention as a new therapeutic option for IBD. However, despite its significant effect in the treatment of *Clostridium difficile* infection, its therapeutic efficacy in IBD still remains limited. There are many factors that should be taken into consideration to increase the success rate of FMT in IBD, including disease state, selection of stool donors, route of fecal administration, number of infusions, and use of antibiotic pretreatment. Therefore, further basic research as well as clinical studies are required to understand the mechanisms of action of FMT and to improve FMT preparations, modes of administration, and donor selection.

Recently, the techniques of genetic engineering have been introduced into treatments with gut microbiota. Various genetic platforms to deliver therapeutic molecules have been developed and transformed into microorganisms [63]. For disease treatment, the microbial delivery of various therapeutic molecules has been tested [64]. Host proteins, bacterial therapeutic proteins, antigens, and synthetic metabolic pathways have been introduced into the host through heterogeneous production in microbes [64]. As part of another microbiome-based therapy, engineered microbes may open new avenues for the treatment for IBD.

In the future, the combination of gut microbiology, gastroenterology, and epidemiology with advances in the rapid analysis of the gut microbiota, metabolites, molecular signals, and genetic engineering promises the development of novel therapeutic strategies in IBD.

## REFERENCES

- 1 Kaser A, Zeissig S, Blumberg RS. Inflammatory bowel disease. *Annu Rev Immunol* 2010; **28**: 573-621 [PMID: 20192811 DOI: 10.1146/annurev-immunol-030409-101225]
- 2 Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. *Nature* 2011; **474**: 307-317 [PMID: 21677747 DOI: 10.1038/nature10209]
- 3 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 RC, 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](#)]
- 4 **Thaiss CA**, Zmora N, Levy M, Elinav E. The microbiome and innate immunity. *Nature* 2016; **535**: 65-74 [PMID: [27383981](#) DOI: [10.1038/nature18847](#)]
- 5 **Matsuoka K**, Kanai T. The gut microbiota and inflammatory bowel disease. *Semin Immunopathol* 2015; **37**: 47-55 [PMID: [25420450](#) DOI: [10.1007/s00281-014-0454-4](#)]
- 6 **Belkaid Y**, Hand TW. Role of the microbiota in immunity and inflammation. *Cell* 2014; **157**: 121-141 [PMID: [24679531](#) DOI: [10.1016/j.cell.2014.03.011](#)]
- 7 **Kamada N**, Seo SU, Chen GY, Núñez G. Role of the gut microbiota in immunity and inflammatory disease. *Nat Rev Immunol* 2013; **13**: 321-335 [PMID: [23618829](#) DOI: [10.1038/nri3430](#)]
- 8 **Bianconi E**, Piovesan A, Facchin F, Beraudi A, Casadei R, Frabetti F, Vitale L, Pelleri MC, Tassani S, Piva F, Perez-Amodio S, Strippoli P, Canaider S. An estimation of the number of cells in the human body. *Ann Hum Biol* 2013; **40**: 463-471 [PMID: [23829164](#) DOI: [10.3109/03014460.2013.807878](#)]
- 9 **Honda K**, Littman DR. The microbiome in infectious disease and inflammation. *Annu Rev Immunol* 2012; **30**: 759-795 [PMID: [22224764](#) DOI: [10.1146/annurev-immunol-020711-074937](#)]
- 10 **Nishida A**, Inoue R, Inatomi O, Bamba S, Naito Y, Andoh A. Gut microbiota in the pathogenesis of inflammatory bowel disease. *Clin J Gastroenterol* 2018; **11**: 1-10 [PMID: [29285689](#) DOI: [10.1007/s12328-017-0813-5](#)]
- 11 **Human Microbiome Project Consortium**. Structure, function and diversity of the healthy human microbiome. *Nature* 2012; **486**: 207-214 [PMID: [22699609](#) DOI: [10.1038/nature11234](#)]
- 12 **Andoh A**. Physiological Role of Gut Microbiota for Maintaining Human Health. *Digestion* 2016; **93**: 176-181 [PMID: [26859303](#) DOI: [10.1159/000444066](#)]
- 13 **Sommer F**, Anderson JM, Bharti R, Raes J, Rosenstiel P. The resilience of the intestinal microbiota influences health and disease. *Nat Rev Microbiol* 2017; **15**: 630-638 [PMID: [28626231](#) DOI: [10.1038/nrmicro.2017.58](#)]
- 14 **Round JL**, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. *Nat Rev Immunol* 2009; **9**: 313-323 [PMID: [19343057](#) DOI: [10.1038/nri2515](#)]
- 15 **Mazmanian SK**, Round JL, Kasper DL. A microbial symbiosis factor prevents intestinal inflammatory disease. *Nature* 2008; **453**: 620-625 [PMID: [18509436](#) DOI: [10.1038/nature07008](#)]
- 16 **Manichanh C**, Borruel N, Casellas F, Guarner F. The gut microbiota in IBD. *Nat Rev Gastroenterol Hepatol* 2012; **9**: 599-608 [PMID: [22907164](#) DOI: [10.1038/nrgastro.2012.152](#)]
- 17 **Flint HJ**, Scott KP, Louis P, Duncan SH. The role of the gut microbiota in nutrition and health. *Nat Rev Gastroenterol Hepatol* 2012; **9**: 577-589 [PMID: [22945443](#) DOI: [10.1038/nrgastro.2012.156](#)]
- 18 **Flint HJ**. Obesity and the gut microbiota. *J Clin Gastroenterol* 2011; **45** Suppl: S128-S132 [PMID: [21992951](#) DOI: [10.1097/MCG.0b013e31821f44c4](#)]
- 19 **Brown EM**, Kenny DJ, Xavier RJ. Gut Microbiota Regulation of T Cells During Inflammation and Autoimmunity. *Annu Rev Immunol* 2019; **37**: 599-624 [PMID: [31026411](#) DOI: [10.1146/annurev-immunol-042718-041841](#)]
- 20 **Lavelle A**, Sokol H. Gut microbiota-derived metabolites as key actors in inflammatory bowel disease. *Nat Rev Gastroenterol Hepatol* 2020; **17**: 223-237 [PMID: [32076145](#) DOI: [10.1038/s41575-019-0258-z](#)]
- 21 **Belkaid Y**, Harrison OJ. Homeostatic Immunity and the Microbiota. *Immunity* 2017; **46**: 562-576 [PMID: [28423337](#) DOI: [10.1016/j.immuni.2017.04.008](#)]
- 22 **Honda K**, Littman DR. The microbiota in adaptive immune homeostasis and disease. *Nature* 2016; **535**: 75-84 [PMID: [27383982](#) DOI: [10.1038/nature18848](#)]
- 23 **Dalal SR**, Chang EB. The microbial basis of inflammatory bowel diseases. *J Clin Invest* 2014; **124**: 4190-4196 [PMID: [25083986](#) DOI: [10.1172/JCI72330](#)]
- 24 **Mentella MC**, Scaldaferri F, Pizzoferrato M, Gasbarrini A, Miggiano GAD. Nutrition, IBD and Gut Microbiota: A Review. *Nutrients* 2020; **12**: 944 [PMID: [32235316](#) DOI: [10.3390/nu12040944](#)]
- 25 **Fujimoto T**, Imaeda H, Takahashi K, Kasumi E, Bamba S, Fujiyama Y, Andoh A. Decreased abundance of *Faecalibacterium prausnitzii* in the gut microbiota of Crohn's disease. *J Gastroenterol Hepatol* 2013; **28**: 613-619 [PMID: [23216550](#) DOI: [10.1111/jgh.12073](#)]
- 26 **Takahashi K**, Nishida A, Fujimoto T, Fujii M, Shioya M, Imaeda H, Inatomi O, Bamba S, Sugimoto M, Andoh A. Reduced Abundance of Butyrate-Producing Bacteria Species in the Fecal Microbial Community in Crohn's Disease. *Digestion* 2016; **93**: 59-65 [PMID: [26789999](#) DOI: [10.1159/000441768](#)]
- 27 **Varela E**, Manichanh C, Gallart M, Torrejón A, Borruel N, Casellas F, Guarner F, Antolin M. Colonisation by *Faecalibacterium prausnitzii* and maintenance of clinical remission in patients with ulcerative colitis. *Aliment Pharmacol Ther* 2013; **38**: 151-161 [PMID: [23725320](#) DOI: [10.1111/apt.12365](#)]
- 28 **Sokol H**, Pigneur B, Watterlot L, Lakhdari O, Bermúdez-Humarán LG, Gratadoux JJ, Blugeon S, Bridonneau C, Furet JP, Corthier G, Grangette C, Vasquez N, Pochart P, Trugnan G, Thomas G, Blottière HM, Doré J, Marteau P, Seksik P, Langella P. *Faecalibacterium prausnitzii* is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. *Proc Natl Acad Sci USA* 2008; **105**: 16731-16736 [PMID: [18936492](#) DOI: [10.1073/pnas.0804812105](#)]
- 29 **Imhann F**, Vich Vila A, Bonder MJ, Fu J, Gevers D, Visschedijk MC, Spekhorst LM, Alberts R,



- Franke L, van Dullemen HM, Ter Steege RWF, Huttenhower C, Dijkstra G, Xavier RJ, Festen EAM, Wijmenga C, Zhernakova A, Weersma RK. Interplay of host genetics and gut microbiota underlying the onset and clinical presentation of inflammatory bowel disease. *Gut* 2018; **67**: 108-119 [PMID: 27802154 DOI: 10.1136/gutjnl-2016-312135]
- 30 Cui B, Feng Q, Wang H, Wang M, Peng Z, Li P, Huang G, Liu Z, Wu P, Fan Z, Ji G, Wang X, Wu K, Fan D, Zhang F. Fecal microbiota transplantation through mid-gut for refractory Crohn's disease: safety, feasibility, and efficacy trial results. *J Gastroenterol Hepatol* 2015; **30**: 51-58 [PMID: 25168749 DOI: 10.1111/jgh.12727]
- 31 Ahmed I, Roy BC, Khan SA, Septer S, Umar S. Microbiome, Metabolome and Inflammatory Bowel Disease. *Microorganisms* 2016; **4**: 20 [PMID: 27681914 DOI: 10.3390/microorganisms4020020]
- 32 El Kaoutari A, Armougom F, Gordon JI, Raoult D, Henricsson B. The abundance and variety of carbohydrate-active enzymes in the human gut microbiota. *Nat Rev Microbiol* 2013; **11**: 497-504 [PMID: 23748339 DOI: 10.1038/nrmicro3050]
- 33 Daïen CI, Pinget GV, Tan JK, Macia L. Detrimental Impact of Microbiota-Accessible Carbohydrate-Deprived Diet on Gut and Immune Homeostasis: An Overview. *Front Immunol* 2017; **8**: 548 [PMID: 28553291 DOI: 10.3389/fimmu.2017.00548]
- 34 Sonnenburg ED, Sonnenburg JL. Starving our microbial self: the deleterious consequences of a diet deficient in microbiota-accessible carbohydrates. *Cell Metab* 2014; **20**: 779-786 [PMID: 25156449 DOI: 10.1016/j.cmet.2014.07.003]
- 35 Sonnenburg ED, Smits SA, Tikhonov M, Higginbottom SK, Wingreen NS, Sonnenburg JL. Diet-induced extinctions in the gut microbiota compound over generations. *Nature* 2016; **529**: 212-215 [PMID: 26762459 DOI: 10.1038/nature16504]
- 36 Tan J, McKenzie C, Vuillermin PJ, Goverse G, Vinuesa CG, Mebius RE, Macia L, Mackay CR. Dietary Fiber and Bacterial SCFA Enhance Oral Tolerance and Protect against Food Allergy through Diverse Cellular Pathways. *Cell Rep* 2016; **15**: 2809-2824 [PMID: 27332875 DOI: 10.1016/j.celrep.2016.05.047]
- 37 Thorburn AN, McKenzie CI, Shen S, Stanley D, Macia L, Mason LJ, Roberts LK, Wong CH, Shim R, Robert R, Chevalier N, Tan JK, Mariño E, Moore RJ, Wong L, McConville MJ, Tull DL, Wood LG, Murphy VE, Mattes J, Gibson PG, Mackay CR. Evidence that asthma is a developmental origin disease influenced by maternal diet and bacterial metabolites. *Nat Commun* 2015; **6**: 7320 [PMID: 26102221 DOI: 10.1038/ncomms8320]
- 38 Macia L, Tan J, Vieira AT, Leach K, Stanley D, Luong S, Maruya M, Ian McKenzie C, Hijikata A, Wong C, Binge L, Thorburn AN, Chevalier N, Ang C, Marino E, Robert R, Offermanns S, Teixeira MM, Moore RJ, Flavell RA, Fagarasan S, Mackay CR. Metabolite-sensing receptors GPR43 and GPR109A facilitate dietary fibre-induced gut homeostasis through regulation of the inflammasome. *Nat Commun* 2015; **6**: 6734 [PMID: 25828455 DOI: 10.1038/ncomms7734]
- 39 Tingirikari JMR. Microbiota-accessible pectic poly- and oligosaccharides in gut health. *Food Funct* 2018; **9**: 5059-5073 [PMID: 30280147 DOI: 10.1039/c8fo01296b]
- 40 Sartor RB. Gut microbiota: Diet promotes dysbiosis and colitis in susceptible hosts. *Nat Rev Gastroenterol Hepatol* 2012; **9**: 561-562 [PMID: 22890110 DOI: 10.1038/nrgastro.2012.157]
- 41 Kelly CJ, Zheng L, Campbell EL, Saeedi B, Scholz CC, Bayless AJ, Wilson KE, Glover LE, Kominsky DJ, Magnuson A, Weir TL, Ehrentauf SF, Pickel C, Kuhn KA, Lanis JM, Nguyen V, Taylor CT, Colgan SP. Crosstalk between Microbiota-Derived Short-Chain Fatty Acids and Intestinal Epithelial HIF Augments Tissue Barrier Function. *Cell Host Microbe* 2015; **17**: 662-671 [PMID: 25865369 DOI: 10.1016/j.chom.2015.03.005]
- 42 Wang W, Chen L, Zhou R, Wang X, Song L, Huang S, Wang G, Xia B. Increased proportions of Bifidobacterium and the Lactobacillus group and loss of butyrate-producing bacteria in inflammatory bowel disease. *J Clin Microbiol* 2014; **52**: 398-406 [PMID: 24478468 DOI: 10.1128/JCM.01500-13]
- 43 Atarashi K, Tanoue T, Oshima K, Suda W, Nagano Y, Nishikawa H, Fukuda S, Saito T, Narushima S, Hase K, Kim S, Fritz JV, Wilmes P, Ueha S, Matsushita K, Ohno H, Olle B, Sakaguchi S, Taniguchi T, Morita H, Hattori M, Honda K. Treg induction by a rationally selected mixture of Clostridia strains from the human microbiota. *Nature* 2013; **500**: 232-236 [PMID: 23842501 DOI: 10.1038/nature12331]
- 44 Atarashi K, Tanoue T, Shima T, Imaoka A, Kuwahara T, Momose Y, Cheng G, Yamasaki S, Saito T, Ohba Y, Taniguchi T, Takeda K, Hori S, Ivanov II, Umesaki Y, Itoh K, Honda K. Induction of colonic regulatory T cells by indigenous Clostridium species. *Science* 2011; **331**: 337-341 [PMID: 21205640 DOI: 10.1126/science.1198469]
- 45 Furusawa Y, Obata Y, Fukuda S, Endo TA, Nakato G, Takahashi D, Nakanishi Y, Uetake C, Kato K, Kato T, Takahashi M, Fukuda NN, Murakami S, Miyauchi E, Hino S, Atarashi K, Onawa S, Fujimura Y, Lockett T, Clarke JM, Topping DL, Tomita M, Hori S, Ohara O, Morita T, Koseki H, Kikuchi J, Honda K, Hase K, Ohno H. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature* 2013; **504**: 446-450 [PMID: 24226770 DOI: 10.1038/nature12721]
- 46 Schrezenmeir J, de Vrese M. Probiotics, prebiotics, and synbiotics--approaching a definition. *Am J Clin Nutr* 2001; **73**: 361S-364S [PMID: 11157342 DOI: 10.1093/ajcn/73.2.361s]
- 47 Kruis W, Schütz E, Fric P, Fixa B, Judmaier G, Stolte M. Double-blind comparison of an oral Escherichia coli preparation and mesalazine in maintaining remission of ulcerative colitis. *Aliment Pharmacol Ther* 1997; **11**: 853-858 [PMID: 9354192 DOI: 10.1046/j.1365-2036.1997.00225.x]
- 48 Kruis W, Fric P, Pokrotnieks J, Lukás M, Fixa B, Kascák M, Kamm MA, Weismueller J, Beglinger C, Stolte M, Wolff C, Schulze J. Maintaining remission of ulcerative colitis with the probiotic

- Escherichia coli* Nissle 1917 is as effective as with standard mesalazine. *Gut* 2004; **53**: 1617-1623 [PMID: 15479682 DOI: 10.1136/gut.2003.037747]
- 49 **Harbord M**, Eliakim R, Bettenworth D, Karmiris K, Katsanos K, Kopylov U, Kucharzik T, Molnár T, Raine T, Sebastian S, de Sousa HT, Dignass A, Carbonnel F, Crohn's fte, Organisation C. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management. *J Crohns Colitis* 2017; **11**: 769-784 [DOI: 10.1093/ecco-jcc/jjx009]
  - 50 **Sood A**, Midha V, Makharia GK, Ahuja V, Singal D, Goswami P, Tandon RK. The probiotic preparation, VSL#3 induces remission in patients with mild-to-moderately active ulcerative colitis. *Clin Gastroenterol Hepatol* 2009; **7**: 1202-1209, 1209. e1 [PMID: 19631292 DOI: 10.1016/j.cgh.2009.07.016]
  - 51 **Tursi A**, Brandimarte G, Papa A, Giglio A, Elisei W, Giorgetti GM, Forti G, Morini S, Hassan C, Pistoia MA, Modeo ME, Rodino' S, D'Amico T, Sebkova L, Sacca' N, Di Giulio E, Luzzza F, Imeneo M, Larussa T, Di Rosa S, Annese V, Danese S, Gasbarrini A. Treatment of relapsing mild-to-moderate ulcerative colitis with the probiotic VSL#3 as adjunctive to a standard pharmaceutical treatment: a double-blind, randomized, placebo-controlled study. *Am J Gastroenterol* 2010; **105**: 2218-2227 [PMID: 20517305 DOI: 10.1038/ajg.2010.218]
  - 52 **Limketkai BN**, Akobeng AK, Gordon M, Adepoju AA. Probiotics for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2020; **7**: CD006634 [PMID: 32678465 DOI: 10.1002/14651858.CD006634.pub3]
  - 53 **Rolfe VE**, Fortun PJ, Hawkey CJ, Bath-Hextall F. Probiotics for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2006; **4**: CD004826 [PMID: 17054217 DOI: 10.1002/14651858.CD004826.pub2]
  - 54 **van Nood E**, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, Visser CE, Kuijper EJ, Bartelsman JF, Tijssen JG, Speelman P, Dijkgraaf MG, Keller JJ. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med* 2013; **368**: 407-415 [PMID: 23323867 DOI: 10.1056/NEJMoa1205037]
  - 55 **Moayyedi P**, Surette MG, Kim PT, Libertucci J, Wolfe M, Onischi 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]
  - 56 **Rossen NG**, Fuentes S, van der Spek MJ, Tijssen JG, Hartman JH, Duflo A, Löwenberg M, van den Brink GR, Mathus-Vliegen EM, de Vos WM, Zoetendal EG, D'Haens GR, Ponsioen CY. Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis. *Gastroenterology* 2015; **149**: 110-118. e4 [PMID: 25836986 DOI: 10.1053/j.gastro.2015.03.045]
  - 57 **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]
  - 58 **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]
  - 59 **Sood A**, Mahajan R, Singh A, Midha V, Mehta V, Narang V, Singh T, Singh Pannu A. Role of Faecal Microbiota Transplantation for Maintenance of Remission in Patients With Ulcerative Colitis: A Pilot Study. *J Crohns Colitis* 2019; **13**: 1311-1317 [PMID: 30873549 DOI: 10.1093/ecco-jcc/jjz060]
  - 60 **Sokol H**, Landman C, Seksik P, Berard L, Montil M, Nion-Larmurier I, Bourrier A, Le Gall G, Lalande V, De Rougemont A, Kirchgesner J, Dagueneil A, Cachanado M, Rousseau A, Drouet É, Rosenzweig M, Hagege H, Dray X, Klatzman D, Marteau P; Saint-Antoine IBD Network, Beaugerie L, Simon T. Fecal microbiota transplantation to maintain remission in Crohn's disease: a pilot randomized controlled study. *Microbiome* 2020; **8**: 12 [PMID: 32014035 DOI: 10.1186/s40168-020-0792-5]
  - 61 **Paramsothy S**, Paramsothy R, Rubin DT, Kamm MA, Kaakoush NO, Mitchell HM, Castaño-Rodríguez N. Faecal Microbiota Transplantation for Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. *J Crohns Colitis* 2017; **11**: 1180-1199 [PMID: 28486648 DOI: 10.1093/ecco-jcc/jjx063]
  - 62 **Zhang XF**, Guan XX, Tang YJ, Sun JF, Wang XK, Wang WD, Fan JM. Clinical effects and gut microbiota changes of using probiotics, prebiotics or synbiotics in inflammatory bowel disease: a systematic review and meta-analysis. *Eur J Nutr* 2021 [PMID: 33555375 DOI: 10.1007/s00394-021-02503-5]
  - 63 **Riglar DT**, Silver PA. Engineering bacteria for diagnostic and therapeutic applications. *Nat Rev Microbiol* 2018; **16**: 214-225 [PMID: 29398705 DOI: 10.1038/nrmicro.2017.172]
  - 64 **Kang M**, Choe D, Kim K, Cho BK, Cho S. Synthetic Biology Approaches in The Development of Engineered Therapeutic Microbes. *Int J Mol Sci* 2020; **21**: 8744 [PMID: 33228099 DOI: 10.3390/ijms21228744]



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](mailto:bpgoffice@wjgnet.com)

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

<https://www.wjgnet.com>

