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REVIEW

Modulation of microbiota as treatment for intestinal inflammatory disorders: An uptodate

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Abstract

Alterations of intestinal microflora may significantly contribute to the pathogenesis of different inflammatory and autoimmune disorders. There is emerging interest on the role of selective modulation of microflora in inducing benefits in inflammatory intestinal disorders, by as probiotics, prebiotics, synbiotics, antibiotics, and fecal microbiota transplantation (FMT). To summarize recent evidences on microflora modulation in main intestinal inflammatory disorders, PubMed was searched using terms microbiota, intestinal flora, probiotics, prebiotics, fecal transplantation. More than three hundred articles published up to 2015 were selected and reviewed. Randomized placebo-controlled trials and meta-analysis were firstly included, mainly for probiotics. A meta-analysis was not performed because of the heterogeneity of these studies. Most of relevant data derived from studies on probiotics, reporting some efficacy in ulcerative colitis and in pouchitis, while disappointing results are available for Crohn's disease. Probiotic supplementation may significantly reduce rates of rotavirus diarrhea. Efficacy of probiotics in NSAID enteropathy and irritable bowel syndrome is still controversial. Finally, FMT has been recently recognized as an efficacious treatment for recurrent *Clostridium difficile* infection. Modulation of intestinal flora represents a very interesting therapeutic target, although it still deserves some doubts and limitations. Future studies should be encouraged to provide new understanding about its therapeutical role.

Key words: Microbiota; Inflammation; Gut; Probiotic; Prebiotic

Core tip: Alterations of intestinal microflora may signi-

ficantly contribute to the pathogenesis of different inflammatory and autoimmune disorders. It is conceivable that selective modulation of intestinal microflora may induce benefits. In this article we tried to summarize recent evidences on microflora modulation in main intestinal inflammatory disorders, providing practical perspectives on its therapeutical role in these conditions.

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INTRODUCTION

Gut microbiota

Definition: The human intestinal microflora, known as "microbiota", includes 100 trillion (10^{14}) bacteria, quadrillion viruses, fungi, parasites, and archaea for a total weight of about 1 kg[1]. The stomach and small intestine are colonized only by a few species of bacteria, mainly because of the acid environment, the presence of bile and pancreatic secretions, and the peristaltic activity limiting bacteria stable colonization[2]. On the contrary, the colon harbours about 10^{12} microorganisms[3]. Also several yeasts ("gut mycome") are included in the gut microbiota, but their role is still not well established[1,4,5].

Composition: Colonization of human gut starts few days after birth. Pattern of intestinal microbiota may be firstly influenced by type of delivery and type of diet[2] and, later, by immune stimulaton and environmental factors, becoming more stable after the first two years[6], even though it can be modified under some circumstances, such as diarrhea, antibiotic treatment, or dietary interventions. Gut microflora may be characterized by conventional culturing techniques which fail to detect more than 30% of total bacteria in the gut, therefore molecular approaches, such as metagenomic analysis and 16S ribosomal RNA gene sequencing, are now commonly used[7].

Bacteria in stomach, duodenum, and jejunum are mostly represented by oropharyngeal origin aerobic gram-positive ones, whereas in the ileum coliforms are the predominant species. Post ileocecal valve, there is a growing of bacterial anaerobic species, mainly Bacteroides, Bifidobacteria, Clostridi and Lactobacilli[8].

Functions: The main metabolic function is represented by the fermentation of large polysaccharides and some oligosaccharides, unabsorbed sugars, and host-derived carbohydrates from mucus glycoproteins[9]. The major products of carbohydrate metabolism are gasses (hydrogen and carbon dioxide), ethanol and short chain fatty acids (SCFAs)[2,9]. These latter, represented by butyric, propionic, and acetic acid, are important energy sources for colonocytes, and may inflence glucose metabolism[10]. Colonic bacteria are also involved in vitamin synthesis, absorption of calcium, magnesium, and iron[11,12].

Differentiation and proliferation of epithelial cells is greatly influenced by interaction with resident microflora. This effect is mainly mediated by the SCFAs which promote the development of intestinal microvilli[13].

Intestinal microbiota plays also a pivotal role in development of the gut immune system, especially during early life, establishing an efficacious "cross-talk" with the host[14,15]. Germ-free animals are characterized by a different and less complex gut immune system than normal animals, showing defects in gut-associated lymphoid tissue and antibody production[15]. On the contrary, immediately after exposure to luminal microbes, development of a complete and helpful immune system is stimulated by increase in the number of intraepithelial lymphocytes and production of both mucosal immunoglobulin in germinal centers than in serum[2,15]. It is known that cells of innate immunity are able to discriminate between pathogenic and harmless microbial components by "pattern recognition receptors". Among them, toll-like receptors, mainly present on macrophages, neutrophils, dendritic cells (DCs), intestinal epithelial cells, enable these cells to recognize typical molecules present on microorganism, like lipopolysaccharides, peptidoglycans, flagellins, described as pathogen-associated molecular patterns, or better, microbe-associated molecular patterns[16-19]. It is probably that different populations of DCs are responsible for induction of tolerance for commensal while stimulating immune response for pathogens, by differentiation of naïve T cells into either regulatory T cells or effectors cells indispensable for clearing infections[15,19-22]. Components of normal microflora thus induce in the gut a state of "physiological" inflammatory response, maintained by balanced and controlled responses[19].

Non-pathogenic bacteria can also avoid access of pathogen bacteria into intestinal lumen by attachment to the epithelial cells[2]. Microbiota can regulate the production of the mucins from intestinal goblet cells, thus limiting access to pathogens. Moreover, commensal bacteria compete for nutrient availability in ecological niches[15].

RATIONAL AND APPROACHES OF MODULATION OF INTESTINAL MICROBIOTA

It is now generally accepted that the intestinal flora plays a key role in maintaining the host's health status, while its alteration or a dysregulation of the intestinal

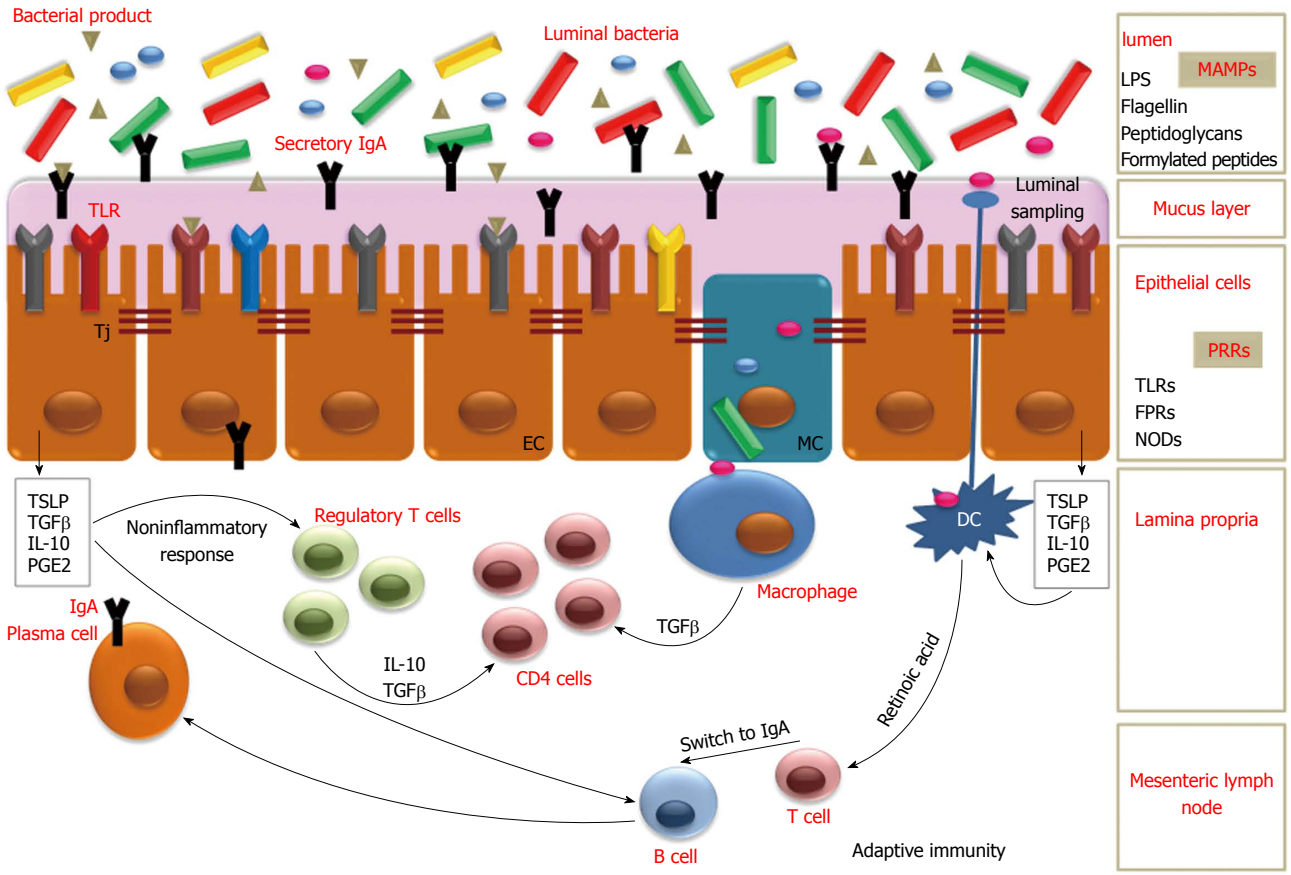

Figure 1 Interactions between luminal bacteria and intestine. The interaction between luminal bacteria and EC causes the production of cytokines, such as TGF-β, TSLP, IL-10 that may induce inflammatory cytokines synthesis from DC and mononuclear cells. These substances, together with retinoic acid produced by DC, can also promote the IgA switch in B cells. In Peyer's patches DC and macrophages uptake bacterial antigens. The TSLP produced by TLR signaling, enhance APRIL and BAFF production from DC. Anti-inflammatory response is mainly mediated by TGF-β production by epithelial cells and IL-10 from mononuclear cells. Moreover, the interaction with commensal bacteria can result in T-cell expansion and regulation of Th-cells. Probiotics may modulate intestinal function, and in particular mucosal immunity, by secreted factors and by direct interactions with immune cells and the intestinal epithelium. EC: Enterocytes; MC: M cells; Tj: Tight junctions; TGF: Transforming growth factor; TNF: Tumor necrosis factor; TSLP: Thymic stromal lymphopoietin; DC: Dendritic cells; TLR: Toll-like receptors; APRIL: A proliferation-inducing factor; BAFF: B-cell activating factor; IL-10: Interleukin-10; MAMPs: Microbial Associated Molecular Patterns; LPS: Lipopolysaccharide; PRRs: Pattern Recognition Receptors; FPRs: Formylated peptide receptors; NODs: Nucleotide-binding oligomerization domain-like receptors.

immune response to normal bacterial environment may significantly contribute to the pathogenesis of different inflammatory and autoimmune disorders[23,24]. As for example, broad-spectrum antibiotics may suppress components of normal microbiota, leading other pathogenic organisms to grow up and cause disease. Otherwise, normal cross-talk host-microbiota may be altered and the constituents of the normal intestinal flora may be recognized not as friends, thus triggering an inappropriate inflammatory response. Moreover, when gut mucosa is injured, the "leaky gut" lets bacteria to pass from the gastrointestinal tract through the epithelial layer to the submucosa and even to the circulation, potentially disseminating throughout the body and causing sepsis, shock and multisystem organ failure[2,23].

For all these reasons, in the last years, interest on the eventual role of selective modulation of microflora in inducing benefits in inflammatory intestinal disorders has been growing.

At this regards, different approaches have been investigated, mainly represented by probiotics, but also prebiotics, synbiotics, antibiotics, and, lastly, fecal transplantation.

Probiotics

Probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the consumer"[25]. Probiotics include both bacteria and yeast. Most of probiotics include *Lactobacillus* species, *Bifidobacterium* species, *Escherichia coli* (*E. coli*), *Streptococcus* species, *Lactococcus lactis* and some *Enterococcus* species[26]. The most commonly used yeast is *Saccharomyces boulardii.* Probiotics must survive gastric acid and bile, so they can exert their effect in the small and large intestine[27,28]. Probiotics colonize the gut temporarily and act modifying colonic environment according to the fecal persistence of the ingested strains[28]. Different mechanisms are involved in the protective role of probiotics and are represented both by direct interaction with the host and by indirect modulation of

Table 1 Mechanisms of probiotics

Increase in barrier function
Maintenance of epithelial tight junctions integrity
Increase mucin production (Globet cells)
Increase in trefoil factors and defensins production (Paneth Cells)
Modulation of immune response
Increase secretory IgA
Production of anti-inflammatory cytokines and inhibition of pro-inflammatory cytokines
Promotion tolerogenic dendritic cells and regulatory T cells
Enhance of natural killer activity
Antagonism of pathogens
Direct killing of bacteria
Reduction of pathogen adherence
Inhibition of pathogenic bacteria growth by antimicrobial and antitoxin compound production (*i.e.*, SCFA, bacteriocins and microcins)
Production of substances
Production of enzymatic activities and/or beneficial metabolites to the host
Promotion pain relief in visceral hyperalgesia

SCFA: Short chain fatty acids.

the intestinal microbiota[29] (Figure 1 and Table 1).

These mechanisms include: (1) Enhancement of the natural gastrointestinal barrier function providing a physical barrier, also know as "colonization resistance"; in particular at level of: (a) tight junctions: probiotics can induce structural changes in epithelial tight junctions, mainly by upregulating the expression of zona-occludens 1, a tight junction protein, or by preventing redistribution of the other proteins, so stabilizing the intercellular integrity[27,30,31]; (b) mucus barrier: probiotics can increase mucin expression and secretion by goblet cells, thereby creating a mucus barrier for bacterial passage toward intestinal surface[32] and by trefoil factors and defensins produced by intestinal Paneth cells; (2) Modulation of the local and systemic immune responses; in particular by production of: (a) secretory IgA: probiotics can stimulate production of IgA in the lamina propria and secretion of IgA into the luminal mucous layer, thus limiting bacterial colonization by binding with their antigens[28]; (b) anti-inflammatory cytokines: probiotics may have many other immunomodulatory effects in the gut, helping to keep intestinal homeostasis. They can modulate the immune response, including promoting tolerogenic DCs and regulatory T cell phenotypes, improving activities of macrophages and NK cells, regulating the nuclear factor-κB (NF-κB) pathway, inducing the apoptosis of T cells, and reduce the secretion of proinflammatory factors[32-34]; (3) Antagonism of pathogens: some probiotics can directly antagonize pathogenic bacteria or their growth *via* expression of antimicrobial factors such as SCFA and "bacteriocins" or "microcins"[35]. SCFA can disrupt the outer membranes of gram-negative pathogens such as *Enterohemorrhagic E. coli*, *P. aeruginosa*, and *S. typhimurium*, causing inhibition of pathogen growth[34]. Bacteriocins can either permeabilize the inner membrane of gram-negative bacteria, leading to disruption, or interfere with cell wall synthesis and cause the formation of pores[34]. Finally, probiotics may decrease luminal pH, thus creating an inhospitable environment for pathogens[26-29]; and (4) production of helpful substances: some probiotics may produce enzymatic activities and/or beneficial metabolites for the host, may activate receptors in the enteric nervous system as to alter pain responses and promote pain relief in the setting of visceral hyperalgesia[28,29].

There is great variation in the number and combination (single or multiple strains) of probiotic organisms provided in various supplements. The effects of various probiotics may reflect species-specific properties; however, whether a probiotic mixture may yield more beneficial effects because of a synergistic action among the individual organisms, in respect to a single strain, is still matter of debate[27].

Prebiotics

Prebiotic are currently defined as "selectively fermented ingredients that result in specific changes in the composition and/or activity of the GI microbiota, thus conferring benefits upon host health"[36].

Some examples of prebiotics are dietary fiber (as for example arabinoxylan, a non-starch polysaccharide found in many cereal grains[37]) and some types of oligosaccharides, although only inulin-type fructans and galacto-oligosaccharides fulfill all the criteria for prebiotic classification[23,38]. Some polysaccharides can also be found in seaweeds and microalgae[36]. These food ingredients may modify the gut microbiota, mainly at the level of individual strain, selectively stimulating growth of health-promoting species already residing in the colon[23,39-41].

Because of their chemical structure and consequent lack of the host's capability to digest them, prebiotics are directly fermented in the colon by endogenous bacteria to SCFA[42], with consequent decrease of pH. By this process, they can exert antinflammatory effects, stimulating for example increase of T-regulatory cells (Treg) and reduction of IFN-γ[43,44]. Animal models also showed that some heteropolysaccharide (for example isolated from the fruit body of *L. edodes*) can restore the age-attenuated immune responses by increasing cytokine levels in peripheral blood[45]. Prebiotics can also inhibit the adherence of pathogens to gut epithelium, preventing them from translocating across the epithelial GI cells[36,37].

Finally, animals studies reported that prebiotics trigger an increase in the mucosa layer, with elongation of the microvilli, and an increase in the number of epithelial cells[36].

Synbiotics

About 20 years ago, the term "synbiotic" was firstly introduced to describe "a mixture of probiotics and prebiotics that beneficially affects the host by improving

the survival and implantation of live microbial dietary supplements in the gastrointestinal tract, by selectively stimulating the growth and/or by activating the metabolism of one or a limited number of health-promoting bacteria, and thus improving host welfare"[28,46]. Commonly combinations include *Bifidobacteria* and fructooligosaccharides (FOS), *Lactobacillus rhamnosus* GG (LGG) and inulin, and *Bifidobacteria* and *Lactobacilli* with FOS or inulin[28,46,47].

Antibiotics

Manipulation of the enteric microbial flora by means of antibiotics represents a possible therapeutic option[48]. The most used systemic antibiotics in intestinal disorders are represented by metronidazole and ciprofloxacin, efficacious respectively against anaerobic bacteria and some parasites, and Gram-positive e Gram-negative bacteria such as *E. coli* and *Enterobacteriacee*[49]. Nevertheless, use of antibiotics may have some disadvantages, since the occurrence of side effects, antibiotic resistance and *Clostridium difficile* (*C. difficile*) superinfection. Metronidazole is known to be associated with various untoward effects (peripheral neuropathy, metallic taste, gastrointestinal disturbances *etc*.) with a reported incidence of 50% or more[48,50]. Ciprofloxacin is better tolerated, but more expensive, and can induce nausea, diarrhea, skin rashes, with an increasing evidence of tendinitis and tendon rupture[48,51]. In the last years, growing interest has been reserved to rifaximin, a minimally absorbed (< 0.4%) antibiotic, associated with a more favourable safety/tolerability profile than systemic antibiotics[52]. Rifaximin has also demonstrated a broad spectrum antibiotic efficacy, in particular against both Gram-positive and Gram-negative aerobic and anaerobic intestinal bacteria, with minimal potential for development of bacterial resistance[52].

Fecal transplantation

Fecal microbiota transplantation (FMT) consists of the infusion of a fecal suspension from a healthy individual into gut of another one[53].

FMT can be performed by various way, that are nasogastric or nasoduodenal tube, colonoscope, enema, or capsule[54]. The suggested mechanisms of action include the competition for nutrients, the direct inhibition of growth of the pathogen, the modulation the immune system of the host by interaction with normal flora[52-55].

It has been speculated that FMT may be more effective than probiotics in the restoration of altered gut microbiota, since fecal infusion overcomes the intrinsic quantitative gap of probiotics by a durable alteration of the recipient's gut microbiota while probiotics are able to colonize the gut lumen only for a temporary period[56]. Molecular techniques demonstrated that intestinal flora of the host and the donor closely resembled about 2 wk after FMT and persisted for more than a month, with a predominance of *Bacteroides* spp.[57].

MODULATION OF MICROFLORA IN INTESTINAL INFLAMMATORY DISORDERS

Inflammatory bowel disease

The involvement of an aberrant immune response to intestinal flora in the pathogenesis of the inflammatory bowel disease (IBD), mainly in susceptible individuals, has been widely suggested[58]. Moreover, IBD is not seen in germ-free animals[26] and different studies reported a decline in bacterial diversity microbial in IBD subjects[58-60]. Nevertheless, disease-specific bacterial or fungal communities have not been identified, although *Mycobacterium paratuberculosis* and invasive *E. coli,* have been etiologically linked to Crohn's disease (CD)[60]. Pathogens may trigger intestinal inflammation in genetically predisposed individuals by disruption of the mucosal barrier and consequent increase of translocation of luminal antigens, mimicry of self-antigens, and activation of the mucosal immune system by modulation of transcription factors such as NF-κB[61].

An extensive literature supports the impact of various probiotics in experimental models of IBD[26,61-64]. Up to now, most of studies in humans were focused on induction of remission and prevention of relapse[65-90]. The strongest evidences derive from clinical trials conducted with VSL#3, a probiotic mixture containing 900 billion viable lyophilized bacteria represented by four strains of Lactobacilli (*L. casei, L. Plantarum*, *L. acidophilus, L. bulgaricus*), three of Bifidobacteria (*B. longuum, B. breve* and *B. infantis*), and one of *Streptococcus salivaris* subspecie *thermophilus*[69-71].

As regarding ulcerative colitis (UC), previous meta-analysis reported insufficient evidence about the efficacy of probiotics both for induction[86] or maintenance of remission[87], while the more recent data support their role[88-90] (Table 2). In particular VSL#3 was effective in maintaining remission in mild to moderately active disease, conversely than for moderate-severe disease[88-90]. Probiotics also showed similarity of efficacy when compared with mesalazine in preventing the relapse of disease[88-90].

Nevertheless, there are many limitations in the different meta-analysis linked to the heterogeneity of the cited studies, including variations in the selection of subjects, dosage, type and concentrations of the probiotics, duration of therapy, concomitant medications.

As for example, Kruis *et al*[75] found equivalent percentages of efficacy and safety in maintaining remission in 162 UC patients giving probiotic Escherichia coli Nissle 1917 (200 mg once daily) in respect to 165 patients giving mesalazine (500 mg three times daily) for 12 mo[75]. Twenty-nine newly diagnosed UC

Table 2 Role of probiotics in inflammatory bowel diseases

Ref.	No. (intervention/control)	Probiotic	Control	Results
Remission induction in UC				
Kato *et al*[68]	20 (10/10)	*B. breve*, *B. bifidum*, *L. acidophilus* + 5ASA/SASP	Placebo	slight ↑
Tursi *et al*[69]	90 (30/60)	VSL#3 + balsalazide	Balsalazide alone 5ASA	↑
Miele *et al*[70]	29 (14/15)	VSL#3	Placebo	↑
Sood *et al*[71]	147 (77/70)	VSL#3	Placebo	↑
Matthes *et al*[72]	57 (46/11)	*E. coli* Nissle 1917	Placebo	↑
Tursi *et al*[73]	144 (71/73)	VSL#3	Placebo	↑
Maintenance of remission				
Kruis *et al*[74]	103 (50/53)	*E. coli* Nissle 1917	5ASA	Similar efficacy
Kruis *et al*[75]	327 (162/165)	*E. coli* Nissle 1917	5ASA	Similar efficacy
Zocco *et al*[76]	187 (127/60)	*Lactobacillus* GG *Lactobacillus* GG + 5ASA	5ASA	Similar efficacy (LGG more effective than 5ASA alone in prolonging relapse free time)
Miele *et al*[70]	29 (14/15)	VSL#3	Placebo	↑
Wildt *et al*[77]	32 (20/12)	*L. acidophilus* La5, *B. animalis* subs *P. lactis* BB-12	Placebo	Similar effect
Maintenance of remission in Pouchitis				
Gionchetti *et al*[78]	40 (crossover)	VSL#3	Placebo	↑
Gionchetti *et al*[79]	40 (20/20)	VSL#3	Placebo	↑
Mimura *et al*[80]	36 (20/16)	VSL#3	Placebo	↑
Maintenance of remission in CD				
Prantera *et al*[81]	45 (23/22)	*Lactobacillus* GG	Placebo	Similar effect
Bousvaros *et al*[82]	75 (39/36)	*Lactobacillus* GG	placebo	Similar effect
Raju *et al*[83]	90 (43/47)	*L. johnsonii*	placebo	Similar effect
Van Gossum *et al*[84]	70 (34/36)	*L. johnsonii*	placebo	Similar effect
Induction of remission in CD				
Steed *et al*[85]	24 (13/11)	*B. longum*, Synergy 1 + conventional therapy	Placebo + conventional therapy	Similar effect

All article are randomized controlled trials. 5ASA: Mesalazine; UC: Ulcerative colitis; CD: Crohn's disease.

children were randomized by Miele *et al*[70] to receive either VSL#3 (weight-based dose, range: 450-1800 billion bacteria/day) or placebo together with steroid (induction period) or mesalamine (remission period). Results showed achievement of remission in 13 patients (92.8%) treated with VSL#3 *vs* 4 patients (36.4%) treated with placebo[70]. Relapse within 1 year of follow-up occurred in 3 of 14 (21.4%) patients on probiotic *vs* 11 of 15 (73.3%) patients on placebo[70]. Sood *et al*[71] enrolled adult patients with mild-to-moderate UC who were randomly given 3.6×10^{12} CFU VSL#3 (n = 77) or placebo (n = 70), twice daily for 12 wk, showing that both at week 6 than week 12, improvement in clinical score was significantly higher in the probiotic group (25; 32.5%) than in the placebo group (32.5% *vs* 10% and 42.9% *vs* 15.7%, respectively)[71]. In conclusion, these data are interesting and encouraging, but well-designed randomized controlled trials are still limited about this topic and further works are still warranted to support these promising results

Patients undergoing ileo pouch-anal anastomosis for UCs may develop pouchitis up to 50% of cases[91]. Only a few studies have been published about the use of probiotics in the treatment of active pouchitis. Instead many studies are available on the assessment of the potential of probiotics in the prevention of relapses. For this indication the most studied is the multispecies preparation VSL#3[26,75-79] (Table 2).

Gionchetti *et al*[79] studied 40 patients with ileal pouch-anal anastomosis receiving VSL#3 (n.20) or placebo (n.20), reporting occurrence of pouchitis in 10% of patients giving probiotic *vs* 14% patients receiving placebo. In the study by Mimura *et al*[80] on 36 patients with pouchitis, randomly assigned to receive VSL#3 6 g (20 patients) or placebo, maintenance of remission after one year was achieved in 17 patients (85%) on VSL#3 and in one patient (6%) on placebo[80]. Protective role of probiotics *vs* placebo in the management of pouchitis was also confirmed in a meta-analysis by Elahi *et al*[92] and Nikfar *et al*[93]. Based on these results, also confirmed by European guidelines[94], use of VSL#3 is suggested for the prevention and the maintenance of remission of pouchitis[94].

In contrast to the encouraging findings in UC, data on probiotics in CD patients are still disappointing[22,58,81-85,89,90] (Table 2). Butterworth *et al*[95] in the Cochrane Collaboration review concluded for not sufficient evidences supporting role of probiotics in inducing remission in CD[95]. These findings were confirmed in meta-analysis by Rahimi *et al*[96], as well as, later,

by Fujiya *et al*[89] and Shen *et al*[90]. The most of the analyzed studies showed no significant effects on either the induction or maintenance of remission in CD. In their meta-analysis, Shen *et al*[90] proposed that the different efficacy of probiotics between UC and CD patients may be explained by the dissimilar inflammatory pattern in the two conditions. For example an impaired production of the regulatory cytokine interleukin (IL)-10 (not influcenced by probiotics) has been showed in CD4+ T cells of CD patients, as well as presence of circulating antibodies against bacterial antigens and deficiency in human defenses[90].

In conclusion, to date, probiotics have some efficacy in UC and in pouchitis, while disappointing results are available for CD.

Evidences regarding the use of prebiotics for IBD therapy are less stronger than for probiotics[58]. The efficacy of prebiotics in IBD, showed in *in vitro* and animal models[97,98], was investigated only in few human studies involving a small number of patients[99,100]. In 2002, Bamba *et al*[100] reported that germinated barley foodstuff (at doses of 20-30 g of Germinated Barley Foodstuff daily) may induce remission in 11 patients with mild to moderate active UC in respect to 7 patients receiving standard therapy[100]. However, sample study was too small to draw any final conclusion. In a more recent study[101], 103 CD patients were treated with 15 g/d FOS or placebo for 4 wk. Results showed no clinical improvement in patients on prebiotics, although differences in inflammatory pattern of lamina propria DCs, with reduced of levels of IL-6-in and increased IL-10 were described[101].

As regarding patients with pouchitis, Preidis *et al*[101] demonstrated that inulin ingestion may induce increased level of butyrate, lower concentration of *Bacteroides fragilis* and reduced pH and bile acids.

As for prebiotics, also for role of synbiotics in IBD, there are only few available and inconclusive studies[67,101,102]. It has been speculated that enteral nutrition may influence composition and activity of the gut microbial flora, but it deserves further exploration[103,104]. Leach *et al*[103] found in six CD children that enteral nutrition may significantly change intestinal bacterial composition, when compared with controls. Tjellström *et al*[104] found that 79% of the 13 children with small bowel/colonic CD responded clinically positively to enteral nutrition treatment, by a modulation of gut microflora activity with decreased levels of pro-inflammatory acetic acid as well as increased concentrations of anti-inflammatory butyric acids and also of valeric acids.

In patients with IBD, antimicrobial therapy, mainly by ciprofloxacin and metronidazole, is usually reserved for those with septic complications[105]. As regarding human studies, data on antibacterial agents, such as oral vancomycin and intravenous metronidazole in UC subjects, are limited and results are still controversial[64].

Also for pouchitis, available data are not conclusive[64,93,106]. As for example, a single study by Shen *et al*[107] showed that therapy with either metronidazole (1000 mg/d) or ciprofloxacin (20 mg/kg per day) for 2 wk induced a significant improvement in clinical and endoscopic scores of pouchitis, while a meta-analysis by Nikfar *et al*[93] showed that antibiotic were not significantly more effective than placebo in managment of pouchitis.

The role of antibiotics in uncomplicated CD has not been clearly demonstrated[49]. Different randomized trials have shown that metronidazole is efficacious in inducing remission in patients with active CD with colic and ileo-colic localization[49,108,109], while results on ciprofloxacin, alone or in association with metronidazole, in patients with active CD, remain uncertain[49,110-115]. A recent meta-analysis by Khan *et al*[116] suggested role of antibiotcs as primary therapy of CD, although the 2010 "Consensus on the diagnosis and management of Crohn's disease", did not recommend their use except for the treatment of septic complications, symptoms linked to bacterial overgrowth, or perianal disease[117].

Only few data are available for FMT in IBD[57]. Patients with refractory UC may benefit from FMT, although multiple infusions seem to be required. Nevertheless, only few cases have been reported yet and large clinical trials are lacking[57]. Moayyedi *et al*[118] in the first randomized trial demonstrate efficacy of FMT in UC. FMT induces remission in a significantly greater percentage of patients with active UC than placebo, with no difference in adverse events. Fecal donor and time of UC appear to affect outcomes. Wei *et al*[119] in an uncontrolled pilot clinical trial in fourteen IBD patients (11 UC and 3 CD) demonstrate that FT improves quality of life in patients with IBD. In conclusion, available data are too scanty and further and well-designed study are necessary.

Infectious diarrhea

Different probiotics were tested in regard to their efficacy for preventing nosocomial diarrhea and, in particular, rotavirus-associated diarrhea[101]. Most of data derived from pediatric studies. A systematic review of 23 RCTs, involving a total of 1917 participants[120], reported beneficial effects of probiotics in reducing the duration of acute gastroenteritis compared with placebo. Three RCTs (including 1043 children) tested LGG supplementation showing a significant lower incidence of nosocomial rotavirus diarrhea, with a concomitant shortening of the duration of the illness[121-123]. Moreover, a recent meta-analysis including 15 RCTs (2963 participants) showed that LGG significantly reduced the duration of diarrhoea when compared with placebo or no treatment, mainly when used at a daily dose $\geqslant 10^{10}$ CFU than at a daily dose $< 10^{10}$ CFU[124]. Also a meta-analysis by Salari *et al*[125] showed that probiotics decrease the duration of diarrhea and fever significantly in children, while these results were not confirmed in adults' diarrhea, amoebiasis, *C. difficile*-associated diarrhea, diarrhea in HIV positive patients, radiation-induced diarrhea, and chemotherapy-induced diarrhea[125]. On the other hand, few other trials[126,127] did not show any benefit. Taken together, these findings

may suggest that that not all probiotics are equally effective for preventing nosocomial diarrhea.

Therefore, up to now, probiotic use may be advised in acute gastroenteritis, mainly rotavirus-associated diarrhea, while it is not recommended for critically ill hospitalized patients in prevention of nosocomial infections.

Clinical studies of both prebiotic and synbiotic preparations in the treatment of specific acute gastroenteritis are limited. One prospective RCT enrolling 496 children in day care centres tested a synbiotic blend of *Bifidobacterium lactis* oligofructose, and acacia gum, showing a 20% reduction in the number of days with diarrhea[128].

Further studies are necessary to confirm these preliminary results.

Antibiotic treatment strategies are limited, can worsen clinical course of disease, exacerbating toxin-mediated effects. For treatment of travelers' diarrhea (TD), the Infectious Diseases Society of America (IDSA) guidelines recommended three antibiotics, that are the fluoroquinolones, rifaximin, and azythromicyn[129]. Nevertheless, there is a growing concern about using of systemic antibiotics since the occurrence of side effects; therefore, increasing evidences support the use of rifaximin, which is currently recommended for the empiric treatment of afebrile, non-dysenteric forms of TD[101,129].

Antibiotic-associated diarrhea

Antibiotic-associated diarrhea (AAD) and *C. difficile*-associated diarrhea (CDAD) are common complication linked to antibiotic use, mainly cephalosporins, clindamycin, broad-spectrum penicillins and fluoroquinolones[130].

A large systematic review and meta-analysis on role of probiotics in preventing AAD, including 63 randomized clinical trials and involving almost 12000 participants, showed a significant reduction in AAD in the probiotic groups compared with the control group[131]. However, heterogeneity in effectiveness among the patients, differences in the antibiotics and probiotic strains should be considered.

In more recent meta-analysis, Szajewska *et al*[132] evaluated the efficacy of LGG in preventing AAD in children and adults. They showed significant results only in children and in the subgroup of adult patients receiving antibiotics for *Helicobacter pylori* eradication. Also in this work, some questions remained answered, as the best treatment regimens, duration of LGG therapy and the optimal dose of LGG for preventing AAD[132].

Moreover, since AAD does not occur in the majority of patients and when it occurs, it is usually self-limiting, identifying populations most likely to benefit from adjunct probiotics should be desirable.

At this regards, only a small number of RCTs were performed on elderly participants. In a double-blind RCT of 135 hospital elderly patients, administration of *L. casei*, *L. bulgaricus*, and *S. thermophilus*, in combination with antibiotics and for one week after cessation, significantly reduced the risk of developing antibiotic-associated diarrhea[133].

Otherwise, Ehrhardt *et al*[134] in a multicenter, randomized, placebo-controlled trial, showed no beneficial effect of *S. boulardii* in preventing AAD or CDAD in a population of hospitalized patients giving systemic antibiotics. As the same, the large PLACIDE trial did not find a lower incidence of AAD or CDAD in elderly inpatients receiving supplementation with Lactobacilli and Bifidobacteria[135].

Finally, a recent meta-analysis by Xie *et al*[136], showed that probiotics may not reduce the risk of AAD and *C. difficile*-associated diarrhea in older patients, while Szajewska *et al*[137] showed that *S. boulardii* significantly reduces the risk of diarrhoea in patients treated with antibiotics in general, also in those of extreme ages. However, since *S. boulardii* can cause fungaemia, particular concern is required for more susceptible populations[137].

In conclusion, although available data on probiotics are encouraging, a more prudent and selected use of antibiotics represents the best strategy of preventing AAD.

Antibiotic use can lead to dysbiosis (microbial imbalance), and this allows *C. difficile* to flourish[138]. Up to now, studies documenting a reduction in *C. difficile*-associated diarrhea (CDAD) by probiotics are far fewer and remain the subject of controversy[65]. A series of systematic reviews showed promising but no definite results[125,139]. In particular, Johnston *et al*[139], in a meta-analysis including twenty trials and 3818 participants, concluded that moderate-quality evidence suggests probiotic prophylaxis as strategy in reducing CDAD without an increase in clinically important adverse events.

Waiting for more consistent data, actual clinical practice guidelines do not recommend the use of probiotics for the primary prevention of *C. difficile* infection (CDI)[27,65,101].

As regarding prebiotics and synbiotics in preventing CDAD, only few and RCT are available and data are not consistent to support this strategy[140,141].

In the last years, FMT has been recognized as an efficacious treatment for recurrent *C. difficile* infection (rCDI) by remodulation of intestinal microflora *via* donor feces. Patients with rCDI showed reduced levels fecal of *Bacteroidetes* and *Firmicutes* as compared to patients with just one episode of CDI or antibiotic-associated diarrhoea[57]. There has been an average 87%-90% cure rate (defined by resolution of diarrhea) for the over 500 cases that have been reported in the literature[142,143].

A systematic review on 36 studies evaluating a total of 536 patients receiving with FMT for CDI, showed that 467 (87%) experienced resolution of diarrhea following the first FMT procedure. The higher

Table 3 Role of probiotics in irritable bowel syndrome

Ref.	Diagnostic criteria	No. participant	Probiotic	Time (wk)	Results (*vs* placebo)
O'Sullivan *et al*[147]	Rome	25	*Lactobacillus* GG	20	No difference
Nobaek *et al*[148]	Rome	60	*L. plantarum*	4	↓ pain and flatulence
Kim *et al*[149]	Rome Ⅱ	25	VSL#3	8	↓ bloating
O'Mahony *et al*[150]	Rome Ⅱ	80	*L. salivarius* UCC4331, *B. infantis* 35624	8	↓ symptoms and pro-inflammatory cytokines (only for *B. infantis*)
Kajarder *et al*[151]	Rome/Rome Ⅱ	103	Mixture of *L. rhamnosus* GG, *L. rhamnosus* LC705, *B. breve* Bb99, *P. freudenreichii*	24	↓ symptoms
Kim *et al*[152]	Rome Ⅱ	48	VSL#3	8	↓ flatulence
Niv *et al*[153]	Rome Ⅱ	54	*L. reuteri* ATCC55730	24	No difference
Whorwell *et al*[154]	Rome Ⅱ	362	*B. infantis* 35624	4	↓ symptoms (only at dose of 1×10^8 CFU)
Guyonnet *et al*[155]	Rome Ⅱ (C-IBS)	274	*B. animalis* DN173010	4	↑ QoL and bloating score
Kajander *et al*[156]	Rome Ⅱ	86	*L. rhamnosus* GG, *L. rhamnosus* Lc705, *P. freudenreichii* sp *P. Shermanii* JS, *B. animalis* sp *P. lactis* Bb-12	20	↓ bloating and abdominal pain
Zeng *et al*[157]	Rome Ⅱ (D-IBS)	29	*S. thermophilus*, *L. bulgaricus*, *B. longum*	4	↓intestinal permeability and symptoms
Drouault-Holowazcz *et al*[158]	Rome Ⅱ	100	*B. longum* LA101, *L. acidophilus* LA102, *Lactocuccus lactis* LA103, *S. thermophilus* LA104	4	↑ QoL ↓ flatulence, pain and bloating
Sinn *et al*[159]	Roma Ⅲ	40	*L. acidophilus* SDC 2012, 2013	4	↓ symptoms
Simrén *et al*[160]	Rome Ⅱ	74	*L. paracasei* F19, *L. acidophilus* La5, *B. lactis* Bb-12	8	No difference
Søndergaard *et al*[161]	Rome Ⅱ	52	*L. paracasei* F19, *L. acidophilus* La5, *B. lactis* Bb-12	8	No difference
Guglielmetti *et al*[162]	Rome Ⅲ	122	*B. bifidum* MIMBb75	4	↓ symptoms ↑ QoL
Ducrotté *et al*[163]	Rome Ⅲ (D-IBS)	214	*L. plantarum* 299v	4	↓ pain and bloating
Kruis *et al*[164]	Rome Ⅱ (D-IBS)	120	*E. coli* Nissle 1917	12	No difference
Ki Cha *et al*[165]	Roma Ⅲ (D-IBS)	50	*L. acidophilus*, *L. plantarum*, *L. rhamnosus*, *B. breve*, *B. lactis*, *B. longum*, *S.thermophilus*	8	↑ QoL
Dapoigny *et al*[166]	Rome Ⅲ	50	*L. caseirhamnosus*	4	↓ symptoms
Roberts *et al*[167]	Rome Ⅲ	179	*B. lactis* CNCMI-2494	12	No difference
Shavatehi *et al*[168]	Rome Ⅱ	160	*Lactobacillus*, *Bifidobacterium strains* and *Streptococcus thermophiles*	2	No difference
Yoon *et al*[169]	Rome Ⅲ	80	*L. acidophilus*, *L. rhamnosus*, *B. breve*, *B. actis*, *B. longum*, *S.thermophilus*	4	↓ symptoms
Pineton de Chambrun *et al*[170]	Rome Ⅲ	179	*S. cerevisiae*	8	↓ pain and discomfort

All the studies are randomized controlled trials *vs* placebo. QoL: Quality of life.

response rate (93%) was achieved by fecal infusion *via* colonoscopy[56]. The literature to date supports FMT for use in CDI as a safe, well-tolerated, effective treatment with few adverse events[144].

Irritable bowel syndrome

Evidences suggest alterations in gut microbiota in patients with irritable bowel syndrome (IBS)[132] with a dysbiosis of the luminal and mucosal colonic microbiota that is frequently characterised by a reduction in species of Bifidobacteria[145].

This is also supported by the hypothesis that IBS may be induced by bacterial gastroenteritis (postinfectious IBS)[23]. Therefore, targeting the intestinal microbiota for the treatment of this condition has been hypothesized as a valid approach.

Recent pre-clinical data on mouse reported beneficial effects of probiotics on visceral nociceptive reflexes[23,146]. As regarding human studies, different probiotic species have been shown to improve individual symptoms in IBS, such as bloating, flatulence, and constipation, but only a few products affect pain and global symptoms[147-170]. Results of more relevant studies were summarized in Table 3.

Results of meta-analyses were still controversial, mainly since the clinical and statistical heterogeneity. Demographic features of the study populations, length of follow up and dosage and type of probiotics used were very different among the reviewed studies. Moreover, clinical score was evaluated by different scales.

In a meta-analysis by Nikfar *et al*[171] including 8 randomized placebo controlled clinical trials, probiotics were reported to significantly increase clinical improvement compared to placebo[171]. One large systematic review including 19 studies on IBS patients concluded that probiotics significantly improved clinical outcomes[172]. This finding was confirmed by Moayyedi *et al*[173], who reviewed 19 RCT performed in 1650 patients with IBS, and Didari *et al*[174], who analyzed 1793 IBS patients.

On the other hand, two trials and a meta-analysis

by Brenner *et al*[175] in adults did not show clinical benefit above placebo[160,176]. Nevertheless, it is possible that a subgroup of IBS subjects, such as those who developed the disease following gastroenteritis or an antibiotic course, show better beneficial effects by probiotics, as reported in a recent study involving 120 IBS patients[164], thus supporting the hypothesis of a greater efficacy of probiotics in patients with a dysbiosis as main plausible cause of their IBS[177].

In conclusion, probiotics seem to have a beneficial therapeutic role in IBS patients if administered accurately, although these data need to be confirmed by further well-designed trials. Recent United Kingdom guidelines formulated by the British Dietetic Association have made strain specific recommendations; in particular *Bifidobacteria lactis* DN 173010 showed limited weak evidence in improving overall symptoms, abdominal pain and urgency in constipation-predominant IBS, while VSL#3 showed limited weak evidence in reducing flatulence[178].

Few studies evaluated role of prebiotics for IBS. Few available data suggest that higher doses of prebiotics may have a negative impact on symptoms, maybe because increase of luminal gas production following fermentation and consequent worsening of intestinal symptoms[179]. Otherwise, some recent studies suggest that prebiotics may have some benefits in IBS[180,181]. Nevertheless, there are insufficient prospective and adequately powered studies to permit definitive conclusions to be drawn[23].

Also for synbiotics there are promising but too scanty results in IBS management[182].

Based on the hypothesis that alteration of intestinal microbiota could represent a cause of IBS, rifaximin, a nonabsorbable antibiotic, has been studied in IBS subjects and now represents the only antibiotic with a proven long-term benefit in these subjects[101,183]. Two double-blind, placebo-controlled trials (TARGET 1 and TARGET 2), involving more than 1200 patients with IBS (without constipation), showed that treatment with rifaximin for 2 wk provides significant relief of IBS symptoms[183]. It is conceivable that rifaximin exerts its effect by reducing bacterial products that negatively influence the host, or by reducing local immune responses of the host, or both of them[183].

FMT used in the treatment of IBS has been reported in some clinical studies and mainly in case series. Conclusions on the effectiveness cannot be made because the available data are limited and subject to bias[142].

Other conditions

Intestinal bacteria could play a role in initiation of colorectal cancer (CRC) through production of carcinogens, cocarcinogens, or procarcinogens[2,184]. Up to now, only a human study showed reduction of recurrence of adenoma atypia after 4 years of *Lactobacillus casei* administration[185]. Also for prebiotic and synbiotics, studies in CRC patients are not only insufficient but, in several aspects, inconclusive[186]. Therefore, available data are too scanty to draw any final conclusion.

Radiotherapy and chemotherapy kill replicating cells in small and large intestine. Probiotics can reduce side effects of these therapies, with some successful results in mice and animals[187-191] and also some trials on patients undergoing radiation and chemo therapy showed a reduction of radiation induced diarrhea and bowel toxicity at the end of the treatment[188-191]. Also in allergic disorders alterations of gut microbiota have been reported, with an imbalance between "beneficial" and potentially harmful bacteria, dysbiosis is not only a consequence but also a cause of allergy[192]. It has been reported that children with food allergies are found to exhibit, *i.e.*, decreased *Lactobacilli*, *Bifidobacteria* and *Enterococcus* species and increased coliforms, *Staphylococcus aureus* and *Clostridium* species, suggesting that microbial inhabitants of the human body, may play either a pathogenic or protective role in allergies[192].

Probiotics have been studied as possible dietary interventions for allergic disorders, although the majority of studies have evaluated eczema as the main outcome rather than food or other allergies[192-194]. However, recently, the World Allergy Organization stated that "probiotics do not have an established role in the prevention or treatment of pediatric allergy. No single probiotic supplement or class of supplements has been demonstrated to efficiently influence the course of any allergic manifestation or long-term disease or to be sufficient to do so"[195].

For prebiotics and synbiotics, very few and not definitive results are available.

Intestinal bacteria are essential for the development of NSAID-induced small bowel lesions, since "germ-free" animals were found to be resistant to indomethacin injuries[196]. Moreover, NSAID ingestion may modify composition of intestinal flora, inducing the overgrowth of Gram-negative and anaerobic bacterial species, responsible for lower mucosal defense and an increase susceptibility to damage[197,198].

Therefore, modulation of intestinal flora could provide protection against NSAID-induced enteropathy, as already reported *in vitro* studies[199,200]. So far, only few studies have been performed in humans and results are not all concordant[201-204]. Gotteland *et al*[202] found in 16 healthy volunteers that the ingestion of live LGG may preserve the integrity of the gastric mucosal barrier against indomethacin, but has no effect at intestinal level. More recently, in a double-blind, cross-over trial on twenty healthy volunteers receiving indomethacin, the concomitant ingestion of a probiotic mixture (VSL#3) reduced small bowel inflammation, evaluated by fecal calprotectin concentrations[203]. Later, in a randomized, controlled trial on 35 chronic users of low-dose enteric-coated aspirin (100 mg daily) plus omeprazole (20 mg daily), the Authors reported a

significant decrease in the number of mucosal breaks evaluated by videocapsule endoscopy in the *L. casei* group than in the control group[204]. Nevertheless, as stated in a recent review on this topic, current evidences supporting the role of probiotics in NSAID enteropathy are promising, but still weak e further and larger studies are necessary[14]. No significant data are available as regarding prebiotics, synbiotics and other therapeutic approaches targeting intestinal microflora in NSAID enteropathy.

CONCLUSION

Gut microbiota has a pivotal role in inducing a state of "physiological", balanced and controlled, inflammatory response. Alterations of intestinal bacterial flora, or a dysregulation of the intestinal immune response to normal bacterial environment, may significantly contribute to the pathogenesis of different inflammatory and autoimmune disorders. For all these reasons interest is rising on the eventual role of selective modulation of microflora in inducing benefits in inflammatory intestinal disorders, mainly by probiotics, prebiotics, synbiotics, antibiotics, and, lastly, by fecal transplantation.

Most of larger and well-conducted studies, including review and meta-analysis, evaluated the role of probiotics in different gastrointestinal disease. However, several limitations are important to consider in interpreting the results, since the great heterogeneity in probiotic strains, dosage, age groups, treatment lengths, and outcomes.

Probiotics have been demonstrated of some efficacy in induction and maintaining of remission in UC and in particular in pouchitis, while disappointing results are available for CD. Moreover a definite role of antibiotics has been established for treatment of pouchitis. It is possible that probiotic supplementation may significantly reduce rates of rotavirus diarrhea. Efficacy of probiotic in IBS is still controversial, while a significant benefit has been reported for rifaximin in IBS patients without constipation. For food allergic disorders, modulation of intestinal microflora is not convincing and use of probiotics and prebiotics is not recommended. The role of probiotics in NSAID enteropathy is promising but still weak. Finally, FMT has been recently recognized as an efficacious treatment for recurrent *C. difficile* infection but these finding need to be confirmed by larger studies.

In conclusion, while representing a very interesting therapeutic target, modulation of intestinal flora still deserves some doubts and limitations. Firstly, the actual gut microbiota composition in healthy individuals is still unclear, since high cost for more specific methods of characterization and the lack of a standardization. Then, despite increasing evidences for probiotics, intestinal bioavailability of bacterial strains, the optimal dose, and treatment time are still matter of debate.

It is conceivable that future studies will provide a better gut microbiota characterization, leading to a more selective modulation by the above described means, that could improve its composition and, consequently, the host's health status.

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