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REVIEW

Microbiome-Based Therapeutics and Their Physiological Effects

Inflammatory bowel disease therapeutic strategies by modulation of the microbiota: how and when to introduce pre-, pro-, syn-, or postbiotics?

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Abstract

Inflammatory bowel diseases (IBD), a heterogeneous group of inflammatory conditions that encompass both ulcerative colitis and Crohn's disease, represent a major public health concern. The etiology of IBD is not yet fully understood and no cure is available, with current treatments only showing long-term effectiveness in a minority of patients. A need to increase our knowledge on IBD pathophysiology is growing, to define preventive measures, to improve disease outcome, and to develop new effective and lasting treatments. IBD pathogenesis is sustained by aberrant immune responses, associated with alterations of the intestinal epithelial barrier (IEB), modifications of the enteric nervous system, and changes in microbiota composition. Currently, most of the treatments target the inflammation and the immune system, but holistic approaches targeting lifestyle and diet improvements are emerging. As dysbiosis is involved in IBD pathogenesis, pre-, pro-, syn-, and postbiotics are used/tested to reduce the inflammation or strengthen the IEB. The present review will resume these works, pointing out the stage of life, the duration, and the environmental conditions that should go along with microbiota or microbiota-derived treatments.

IBD; microbiota; n − 6; prebiotic; probiotic

INTRODUCTION

Inflammatory bowel diseases (IBD), a heterogeneous group of conditions that encompass both ulcerative colitis (UC) and Crohn's disease (CD), are complex chronic inflammatory disorders with increasing prevalence worldwide in the past decade (1). IBD are now a major public health problem that affects ~3.6 million people in the United States and Europe (2). IBD onset typically occurs between the second and third decades of life. A majority of affected individuals progress toward a relapsing and chronic disease, characterized by an immune activation and inflammation of the gastrointestinal (GI) tract that severely alters its function. Common IBD symptoms include bleeding, severe diarrhea, abdominal pain, and weight loss. In CD as well as in UC, inflammation of the gut is associated with the breakdown of intestinal epithelial barrier (IEB) integrity, abnormal secretions, and changes in motility patterns. UC features include diffuse mucosal inflammation that extends proximally from the rectum, whereas CD inflammation may be patchy and transmural. This uncontrolled chronic inflammation can result in a complicated disease course with undesirable abdominal abscesses, fistulae, strictures, subsequent bowel obstruction, and an increased risk for GI malignancy. As such, a greater understanding of IBD pathophysiological mechanisms is required.

IBD Etiology

IBD develop in genetically predisposed individuals under the influence of environmental factors. Family aggregation has long been recognized, and first-degree relatives of affected individuals have a relative IBD risk of fivefold or greater. More than 240 genetic risk loci have been associated with IBD (3). Despite susceptibility genes that are for the most part different between CD and UC, 30% of IBD-related loci are common to these two intestinal diseases. These genes are involved in the immune system modulation (immune cell recruitment, innate mucosal defense) as well as in the control of intestinal epithelial barrier (IEB) functions (permeability, repair, and autophagy). Most interestingly, many of

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the known IBD susceptibility genes are associated with recognition and processing of bacteria (4). Environmental factors are also involved, and potentially relevant environmental IBD risks factors encompass major life stressors, diet, and/or lifestyle. They span the spectrum of life from birth and early-life exposures (breastfeeding and antibiotic exposure in infancy) to exposures later on in adulthood (depression, physical activity, low-fiber diet, and low vitamin D) (2).

IBD Pathophysiology

Though the etiology of IBD has not been fully elucidated, it is currently known that IBD pathogenesis is sustained by aberrant immune responses and associated with alterations of the IEB, alterations of the enteric nervous system (ENS), and changes in microbiota composition (5). Patients with IBD are characterized by the infiltration of inflammatory $CD4^+$ T-cells in intestinal tissue encompassing an increase in inflammatory T cells (Th1, Th2, Th9, Th17, and $CD161^+CXCR3^+CCR6^+CD4^+$ Th17.1) response, associated with a reduced regulatory T cells (Treg and Tr1) response (6). In addition, the immune chronic activation in IBD involves a dysfunction of neutrophil granulocytes and phagocytes, T- and B cell selection and activation, and immune inhibitory mechanisms. Another common disease denominator is the defective IEB, that not only presents cell death abnormalities but also deregulation of the permeability, and clinical remission is linked to intestinal mucosal healing (7). In addition, widespread damage of the enteric nervous system (ENS) has been described for a long time in CD and its dysfunction has been recently demonstrated. Structural abnormalities of the ENS have consistently been observed in CD and, less frequently, in UC (8, 9). Coarse nerve fibers and axonal necrosis have been observed in CD ileum or colon (10, 11). In these segments, enteric glial cells have lost their control upon intestinal healing and permeability (12, 13). Finally, dysbiosis has been observed in patients with IBD and in mice models of colitis (14). Dysbiosis could be different between patients with UC and CD, but is observed in both pediatric and adult populations, in active or quiescent phases of the pathology and in treatment-naive patients with CD (15). The most consistent observation in IBD is a reduced bacterial diversity, with a decrease of *Firmicutes* phylum and *Bifidobacteriaceae* family, an increase of the *Enterobacteriacea* and *Akkermensia* genera (*Akkermensia muciniphila*). Periods of disease activity are also marked by increased transient microbial changes (16). The species *Faecalibacterium prausnitzii* is not only decreased in patients with CD compared with healthy subjects, but its absence is also correlated with the risk of relapse of ileal CD after surgery, and its recovery is associated with the maintenance of clinical remission (17–20). Increasing studies describe how *F. prausnitzii* can dampen the inflammation through reduction of proinflammatory cytokines production, regulation of Treg or intestinal epithelial cells (IEC) (21, 22). Altogether, these studies highlight the concept that host-microbiota interactions play a central role in IBD pathogenesis and are potential therapeutic targets (23, 24).

Treatments

At present, the mainstays of IBD treatment are immunosuppressive and immune-modulating agents. Therapeutic agents comprising anti-TNF demonstrated significant changes in our ability to induce and maintain remission but reached limitations. A significant percentage of patients with IBD do not respond primarily to the treatment or lose responsiveness over time (25). The inability to provide a surgical treatment due to physical extension and/or mislocalization of lesions represents as well a major challenge in the management of IBD (26, 27). Various new agents targeting cytokines, adhesion molecules, or tyrosine kinases are currently in clinical trials. Modulating the gut microbiota emerges as an attractive novel therapeutic approach for IBD, and therapies targeting/based on the gut microbiome are under extensive investigation with varying success.

Microbiota-Based Interventions

A microbiota is defined as an "assemblage of microorganisms (all the bacteria, archaea, protists, fungi, and viruses) present in a defined environment" found in all multicellular organisms (28). The gut microbiome, that encompasses ~600,000 microbial genes, contributes to trophic functions, metabolism, barrier function, and immune stimulation. Host-microbiota interactions play a key role in human health, with alterations of the microbiota associated with numerous neurological and chronic diseases (29, 30). The imbalance of the microbiota in its composition and metabolism is encompassed in a global concept of dysbiosis (31). This definition remains challenging as the definition of a healthy microbiota is complex and in constant need of refinement (32).

Resulting from this, different strategies are evaluated to compensate or restore the default observed in microbiota-host communication and treat dysbiosis and/or inflammation. Among many influencing factors, the diet is now well recognized for being able to rapidly and reproducibly modify or modulate the gut microbiota (33). In a more targeted way, the use of prebiotics aims at enriching the microbiome, and fecal transplantation or ingestion of microorganisms is under study in preventive as well as therapeutic strategies. Thanks to increasing knowledge on their function in host regulation, the use of products derived from or associated with the microbiota is being tested. The present review will examine the use of pre-, pro-, syn-, or postbiotics, fecal microbiota transplantation. and diet modification in the IBD patient care.

PREBIOTICS

Prebiotics Definition

A prebiotic is "a substrate selectively used by micro-organisms of the host conferring benefits for his health" (34). Prebiotics are found naturally in vegetables, fruits, and cereals but also in human milk as human milk oligosaccharides (35, 36). They mainly include oligosaccharides, nondigestible carbohydrates, and potentially polyphenols or polyunsaturated fatty acids (37). Because of their modulatory effects on the microbiota, fructans like the fructo-oligosaccharides (FOS) and inulin, but also galactans like galacto-oligosaccharides (GOS) represent the most studied prebiotics (35, 37).

Effects

Prebiotics can act on multiple organs/system apart from the gut (35). The functions of the prebiotics are supported by different mechanisms of action that may be direct,

through interaction with cell surface receptors, or indirect through the products of their fermentation by specific commensal bacteria (35). Prebiotics contribute not only to the defense against pathogens but also to the enhancement of tolerance (e.g., Treg and dendritic cells promotion) (35). Prebiotics promote the growth of healthy bifidogenic strains populations like *Bifidobacterium* species (38). They also promote barrier integrity, so influencing as well functions such as wound repair and intestinal permeability (35, 37). Among the products of bacterial fermentation, short-chain fatty acids (SCFAs) are bioactive metabolites that can regulate epithelial and immune cells (35). They have a broader impact on gut functions through the regulation of the enteric nervous system and gut motility, and are thereby interesting in the context of IBD treatment (39).

In Vitro Studies

Different mixtures of prebiotics [GOS, GOS + FOS, GOS + FOS + acidic oligosaccharides (AOS)] were tested on primary equine peripheral blood mononuclear cells (PBMC) before and during inflammation (Table 1) (40). These prebiotics potentially enhanced inflammation and decreased tolerance by changing cytokines production. A second study used orange pectin and side chain-derived polysaccharides on the murine macrophage cell line RAW 264.7 before the induction of inflammation (41). Both prebiotics promoted anti-inflammatory effects by suppressing the IL-6 secretion induced by inflammation (41). The acidic fraction of human milk oligosaccharides reduced lymphocytes and neutrophils adhesion to human umbilical vein endothelial cells (HUVEC) and IFN-γ production (45, 46). Prebiotics like inulin increased on the contrary proinflammatory cytokines (47). Regarding T cells maturation, short chain GOS + long chain FOS treatment on dendritic cells led to Treg differentiation (48). In addition to the regulation of maturation and functions of the immune cells, prebiotics can regulate intestinal epithelial cells, mainly through decrease of cytokine production (42, 43).

Positive changes of microbiota activity through SCFA production and changes of composition were promoted in vitro by prebiotics. Indeed, apple pectin increased in vitro the abundance of butyrate-producing bacteria, including *F. prausnitzii,* and butyrate concentrations in feces from patients with UC and CD (49). Prebiotics modulated the expression of genes toward a decrease of potential barrier damage and of inflammation. Namely, an upregulation of MUC1 and Occludin expressions were induced by fermented chicory pulp supernatant in a GI tract model, while TNF and cyclooxygenase-2 (COX-2) were downregulated (44).

Preclinical Studies

FOS administration to Wistar rats promoted caecal SCFA production, which lowered the luminal pH (Table 1). Acidification of the luminal content may inhibit the development of pathogens and enhance the growth of lactic acid bacteria (52). GOS attenuated Citrobacter *rodentium* colitis severity (38). The decrease of clinical symptoms and colitis severity by prebiotics intake was linked notably to a decrease of immune cells gut infiltration and of proinflammatory cytokines secretion (41).

Prebiotics as early-life treatment was mainly investigated in postweaned rats and mice (Table 1). Disease severity and clinical symptoms were improved by prebiotics intake early in life for these animal models. FOS increased fecal *Bifidobacterium* spp. and decreased fecal *Enterobacteriaceae* in HLA-B27 TG rats, whereas inulin increased caecal butyrate concentration in 4-wk-old C57BL/6 mice. The production of proinflammatory cytokines was decreased by 3-sialyllactose human-identical milk oligosaccharide (HMO) intake in *IL-10*$^{-/-}$ mice (62). Germinated barley stuff reduced the dextran sulfate sodium (DSS)-induced disruption of collagen and reticulin fibers in the intestinal mucosa, so improving the IEB (66). In adult animal models, an overall improvement of colonic damages, histological scores, and disease index were observed following prebiotic treatment.

To this day, colitis prevention studies have been mainly performed in adult murine models, and while they show for the most part, protective effects (53, 76–78), two studies described how inulin supplementation potentiated the severity of colitis (63, 79). Recently, in line with our work, one study analyzed the effect of maternal intake of inulin on colitis development in rats, and described how it exacerbated intestinal damage and inflammation induced by DSS (80). The increased disease activity index, myeloperoxidase activity and IL-1β mRNA expression observed in this model were associated with an increase in the abundances of *Bacteroidetes*, Bacteroides, and *Parasutterella* (80).

Clinical Studies

Clinical studies were achieved in adults and exclusively used prebiotics to treat IBD (Table 1). Potential prebiotics such as oat and wheat bran were also tested as dietary fibers. They have interesting properties like the enhancement of immune and intestinal functions (81). The microbiota composition and metabolism were impacted, with an increase of fecal *Bifidobacteria* after the intake of the mix "Prebio 1" of FOS and inulin (71). Oat bran increased fecal butyrate concentrations (57). Immunological parameters were affected by prebiotics consumption, as evidenced by a change in dendritic cells cytokines production and populations (72). Prebiotics decreased inflammation markers and symptoms in patients, leading to the decrease of steroid medication, as seen with germinated barley foodstuff (GBF) for patients with UC in remission (60, 73). Even though the clinical disease activity index and recurrence rate might decrease with prebiotics intake (60), more withdrawals of patients were observed for supplemented groups (72, 82). Withdrawals took place mostly in studies where patients with CD had moderately active disease. This result underlined worsening symptoms and side effects that can accompany the supplementation in prebiotics.

Conclusion on Prebiotics

Promising results were achieved in vitro and in vivo, and showed beneficial effects of prebiotics on IBD prevention and treatment at early age and adulthood. However, more mitigated results were achieved in clinical trials that only focused on treatment of IBD. A better tolerance of prebiotics was observed in patients with UC in remission or with mild

Table 1. *Prebiotic impact on colitis, prevention, and treatment of IBD*

Reference	Prebiotic Type	Model or Study Design	Age of Supplementation	Mechanisms/Global Impact on Colitis or IBD
		In vitro		
40	GOS, GOS/FOS, GOS/FOS/AOS	Primary equine PBMC ± LPS		Increase or decrease in IL-10 and TNF-α mRNA expression depending on the prebiotic used
38	GOS	Hep-2 cell line ± *Citrobacter rodentium*		Antiadhesive effect observed in vitro only
41	Pectin	RAW264.7 cell line ± LPS or Pam3CSK4		Suppressed IL-6 production
42	Oligosaccharides, α3-sialyllactose, or fructooligosaccharides	Caco-2 cells		Decrease TNF-α production and NF-κB activation through PGlyRP3 and PPARg
43	Galactosyloligosaccharides, human HMO	H4, T84, NCM-460 cell lines, immature human small intestinal tissue ± TNF-α, *S. enterica* or *L. monocytogenes*.		Decrease IL8 or MIP3A expression induced by stressors
44	4–25 HMO mix, filtered fermentation supernatant of inulin, chicory root, chicory or citrus pulp, rye bran, soya hulls.	PSIc1, IPEC-J2 cell lines, pig GI tract model ± LPS.		Reduced inflammation: change of cell proliferation and cytokines production, increased SCFA/Bifidobacterium
		Prevention		
38	GOS	*C. rodentium* infection ± GOS in drinking water	7-wo C57BL/6 female	In vivo reduction in disease severity independent of the antiadhesive effect observed in vitro only
41	Pectin	DSS or TNBS ± pectin supplemented in diet	7–8 wo C57BL/6 male	Amelioration of TNBS-induced Colitis by orange pectin, no effect on T cell differentiation or infiltration but decreased TNFa or IL17A concentrations
45–48	aHMO, nHMO, fucoidan, 3′NeuAc-Lac, 3′NeuAc-3Fuc-Lac, FOS, inulin, GOS, goat milk oligosaccharides, scGOS/lcFOS	HUVEC cell line, human/Wistar rat immune cells, TLR4$^{-/-}$ or mice splenocytes ± hrTNF-α, PMA/ionomycin, LPS		Influenced lymphocyte function, maturation and adhesion, and inflammatory cytokines secretion. Reduced adhesion and increased CD25 expression.
49	Grape-derived prebiotic, apple pectin	Healthy subjects, patients with UC and CD		Promoted SCFA production and SCFA-producing bacteria.
50	Glucan EPS P and L polymers	Colonic mucosa of patients with CD		Reduced proinflammatory cytokines production.
51	Potential prebiotic: feruloylated oligosaccharides of rice bran	Murine BMDC or T cells from: C3H/HeN, C3H/HeJ, C57BL/6, TLR2 KO or NF-κB/luciferase transgenic mice	C57BL/6	Induced maturation of dendritic cells, enhanced T cell immune response
52, 53	Inulin, FOS	Acute DSS and TNBS colitis induction	Male Sprague-Dawley and Wistar rats	Decreased colonic damages, body weight loss, and PGE2 release. Change of gut microbiota composition and SCFA
38, 41, 54, 55	GOS. Potential prebiotic: quinoa, orange, citrus pectin, native potato starch, pea starch, Chinese Yam starch.	Acute DSS and TNBS or *C. rodentium* colitis induction	6–8 wo C57BL/6 mice	Decreased clinical and histopathological parameters, changed gut microbiota composition, and SCFA. GOS increased *C. rodentium* number in distal colon and spleen.
56	Inulin or FOS	Spontaneous colitis. Before colitis induction	4–16 wo HLA-B27 TG rats	Reduced histological score and IL-1β, change of gut microbiota composition.
57	Potential prebiotics: oat bran	Controlled pilot trial: quiescent UC patients + oat bran	Adult patients (>18 yr)	No effect on SCFA concentrations. Could not demonstrate a benefit of oat bran.
58	Potential prebiotics: amylose-associated resistant starch (RS)	Remission UC patients + high and low RS/wheat bran (WB)		Decreased abdominal pain and gastroesophageal reflux for patients with UC, increased butyrate concentration. No impact of RS diet on UC, changed SCFA concentrations

Continued

Table 1.— *Continued*

Reference	Prebiotic Type	Model or Study Design	Age of Supplementation	Mechanisms/Global Impact on Colitis or IBD
59	Potential prebiotic: curcumin (2 g/day)	Multicenter DB RPCT: quiescent UC patients UBT		Decreased the recurrence status, CAI and endoscopic index. 2/43 relapsed during 6 mo of therapy, whereas 8 of 39 patients in the placebo group relapsed ($P = 0.040$)
60, 61	GBF	Multicenter NC OLT, NR OLT, OLT, pilot OLT: patients with UC in remission		Lowered the cumulative recurrence rate. Maintained remission and anti-inflammatory.
		Treatments		
62, 63	2FL, inulin (ICD) or pectin	IL10$^{-/-}$ mice or C57BL/6J ± acute colitis	After weaning: 21 days to 6 wo	Decreased diarrhea, histological score and intestinal permeability. Impact on cytokines and SCFA production, gut microbiota composition. ICD worsened colitis: higher body weight loss, gut, and spleen remodeling.
64	Chondroitin sulfate, α-glucan butyrogenic resistant starch + β-glucans + mannaoligosaccharides	IBD dogs of different breeds.	Mean age = 4.85 yr old	No effect on IBD index score, decreased histological score
65	Purified soluble fibers (including inulin, arabinoxylan)	Mice colonized with a synthetic microbiota + *C. rodentium* colitis	8-9 wo Germ-free Swiss Webster mice	Did not prevent mucus barrier erosion, increased Bacteroides abundance
66, 67, 68	Raftilose Synergy 1, germinated barley foodstuff, Chinese Yam polysaccharides/inulin	Spontaneous colitis, acute colitis, "chronic" TNBS colitis	7–11 wo SPF housed HLA-B27 and Sprague-Dawley rats	Decreased DAI, histological scores, mucosal mast cells infiltration and damage. Changed proinflammatory cytokines and SCFA production, gut microbiota composition. Anti-inflammatory and improved gut microbiota
69	Potential prebiotics: wheat bran (WB)	Single-blind RCT: patients with active CD + wheat bran	Adult patients (>18 yr)	Increased IBDQ scores and decreased pHBI scores for patients with CD. No impact of WB diet on UC, changed SCFA concentrations. Improved quality of life and gastrointestinal function
70	GBF	Mild/moderately active UC and UBT		Improved the clinical activity index
71, 72, 73, 74	Prebio 1/Synergy 1, oligofructose-enriched inulin (OF-IN)	Pilot NC OLT, DB RPCT: patients with moderately active CD UBT + Prebio 1/Synergy 1. Pilot RPCT: mild/moderately active UC patients UBT and lower fiber diet + Synergy 1 DB RPCT: patients with inactive/mild/moderately active CD UBT + OF-IN.		Prebio 1/Synergy 1 increased flatulence, borborygmi and abdominal pain. Synergy 1 and OF-IN induced more withdrawals. Decreased DAI, changed cytokines and SCFA production, gut microbiota composition. Anti-inflammatory and improved gut microbiota
75	Lactulose	Prospective pilot RCT: patients with active UC and CD		No effect on UC or CD diseases, improved IBDQ for patients with UC. No effect on CD but improved quality of life

aHMO, acidic fraction of human-identical milk oligosaccharide (HMO); AOS, acidic oligosaccharides; BMDC, bone marrow-derived dendritic cells; CAI, clinical activity index; CBMC, cord blood mononuclear cells; CD, Crohn's disease; DAI, disease activity index; DB, double-blind; DSS, dextran sulfate sodium; EPS, extracellular polymeric substances; 2-FL, 2-fucosylated lactose; FOS, fructo-oligosaccharides; GBF, germinated barley foodstuff; GI, gastrointestinal; GOS, galacto-oligosaccharides; IBD, inflammatory bowel disease; IBDQ; inflammatory bowel disease questionnaire; HUVEC, human umbilical vein endothelial cells; ICD, inulin-containing diet; LPS, lipopolysaccharides; NC, noncontrolled; nHMO, neutral fraction of HMO; NR, nonrandomized; Olt, open-label trial; PBMC, peripheral blood mononuclear cells; PGlyRP3, peptidoglycan recognition protein 3; pHBI, Harvey–Bradshaw index; PMA, phorbol 12-myristate 13-acetate; PPARg, peroxisome proliferator-activated receptor gamma; RCT, randomized controlled trial; RPCT, randomized placebo controlled trial; SCFA, short-chain fatty acids; TLR, Toll-Like receptor; TNBS, 2,4,6-trinitrobenzenesulfonic acid; TSLP, thymic stomal lymphopietin; UBT, under baseline treatment; UC, ulcerative colitis; wo, weeks old.

active disease, accompanied by an improvement of clinical symptoms.

Additional homogenized studies, especially clinical trials, are needed to better understand the preventive effects of prebiotics and to determine the window of opportunity for the treatment of IBD with prebiotics. The age and stage of disease of the individual represent important parameters to take into account. Currently, it is too early to suggest this strategy. We have to understand more precisely the mechanisms of prebiotic interactions with the host at immune, microbial, metabolic, and transcriptomic levels and the part of these systems to explain the IBD treatment or prevention.

Preclinical and in vitro studies will be crucial to treat these questions. New large interventional clinical studies with a homogenous design (same age, same prebiotic, same dose, and same duration of supplementation) using prebiotics on patients with IBD with different degree of disease severity have to be done. Only prebiotics from agricultural materials or enzymatically synthesized (lacking the structural complexity of dietary fibers) have been tested in this context. In the future it will be relevant to use synthetic glycans spanning the chemical and structural diversity of dietary glycans that can be efficiently and consistently produced. Synthetic glycans enable a wide range of targeted changes to the microbiome and potentially open new avenues for the prevention and treatment of disease (83). HMO are other new interesting prebiotics to test in the context of IBD by their natural properties to support the immune system maturation, the cognitive function, the digestive health, and the development of gut microbiome (84).

Key Ideas: Prebiotics

In vitro and in vivo reduction of inflammation with prebiotics: *1*) modulation of immune and intestinal epithelial cells functions/maturation and host genes expression; *2*) modification of microbiota activity/composition; and *3*) mitigated results for preclinical studies or clinical trials. Patients with UC in remission showed a decrease of clinical symptoms after prebiotics intervention but more withdrawals were observed in case of an active disease. Limitations: lack of harmonization of protocols and of studies on prevention and at early age.

PROBIOTICS

Probiotics and IBD Treatment

Probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" (85). Probiotics have different mechanism of action, including competitive interactions with deleterious bacteria via a production of antimicrobial metabolites such as bacteriocins and defensins. They have immunomodulatory properties mediated by anti-inflammatory molecules and may increase the mucus layer (86). Probiotics further show beneficial effects on the pathogenesis of IBD. The gut microbiota of patients with IBD is characterized by a lack of bacteria with anti-inflammatory activities such as *F. prausnitzii* (Firmicutes), together with an enrichment of bacteria with inflammatory functions (87). Consumption of probiotics with anti-inflammatory activities thus appeared as a promising strategy in the management of IBD. Pioneer in vitro studies identified immunomodulatory bacteria and their beneficial impact on colitis in vivo (88). Meta-analysis of clinical trials then indicated the beneficial effect of a selected probiotic preparation, in the context of IBD (89). This opens avenues for thorough characterization of the immunomodulatory role of such microorganisms, and of combinations thereof, from in vitro to clinical studies.

In Vitro Studies

VSL#3 is a probiotic mixture of four strains of *Lactobacillus*, three strains of *Bifidobacteria*, and 1 *Streptococcus thermophilus* strain (90). Pretreatment with VSL#3 on disrupted intestinal cell lines improved epithelial barrier integrity by increasing tight junction proteins (91) (Table 2). *Saccharomyces boulardii* pretreatment of inflamed colonic cells suppressed inflammation-mediated NF-κB activation (100). As for *Escherichia coli* Nissle 1917 (EcN1917), only one study showed that its treatment reverted the increased permeability and restored the disrupted epithelial barrier in Caco-2 cells challenged by proinflammatory cytokines. Other bacteria such as *Propionibacterium freudenreichii* showed anti-inflammatory effects, including on human PBMC by increasing the IL-10-to-IL-12 (IL-10/IL-12) ratio (121). Such effects in vivo reportedly coincide with a healing effect in preclinical models of IBD (88).

Preclinical Studies

Preclinical models of IBD, mainly murine models of spontaneous or induced colitis, revealed the protective effects of selected strains of probiotics (122). VSL#3 pretreatment reduced colonic inflammation and improved IEB function in wild-type (WT) and Muc2$^{-/-}$ DSS-treated mice (92) (Table 2). These effects are correlated with a restoration of antimicrobial peptide gene expression and an increase of commensal bacterial abundance, mediated by SCFAs (92). Pretreatment of mice with EcN1917 promoted recovery of inflammation by modulating tight junction proteins, decreasing proinflammatory cytokines secretion and increasing mucins expression (96, 97). Regarding *P. freudenreichii* CIRM-BIA (CB) 129, two studies highlighted its preventive effects on colitis models in mice by reduction of COX-2 expression and of proinflammatory cytokines levels (105, 106).

As treatment, VSL#3 probiotic mixture restored the loss of tight junction protein observed in DSS-treated mice (109). Another study however demonstrated no anti-inflammatory effects of VSL#3 in mice with colitis (110). *F. prausnitzii* as curative approach reduced colitis severity in mice and rats, associated with an increase of colonic tight junction (TJ) proteins, reduction of intestinal permeability, and levels of proinflammatory cytokines (107, 118, 119, 123). Besides, *F. prausnitzii* regulated Th17/Treg ratio and induced Treg cells (119).

Such promising in vivo results opened the way to clinical studies, provided that the safety of the implemented strain (s) was established.

Clinical Studies

Few studies investigated the ability of probiotics to maintain remission in children with CD (Table 2). No protective effect of *Lactobacillus rhamnosus* GG (LGG) was found in children with CD on standard therapy (108). Regarding adult patients with CD, *S. boulardii* showed encouraging effects in maintaining the remission in CD by reducing the Crohn's disease activity index (CDAI) and improving IEB integrity (101–103). LGG was tested on adult patients with active CD but failed to induce remission (120).

Children with acute UC and receiving the VSL#3 probiotic mixture exhibited reduced inflammatory markers levels, a modification of gut microbiota, but also adverse effects (124). Two clinical studies showed that VSL#3 supplementation was effective to induce remission in adult patients with mild to moderate UC (90, 125). In addition, mucosal healing rate was higher with VSL#3 (90, 93). For *S. boulardii*, a clinical trial showed that its supplementation to UC adult patients

Table 2. *Prevention and treatment of colitis or IBD with probiotics*

Reference	Probiotic Type	Model or Study Design	Age of Supplementation	Mechanisms	Effect on IBD
			Prevention		
91–95	VSL#3	IEC in vitro +/− inflammation		No effect on mucin secretion	
				Restored TJ proteins via an activation pf p38 and ERK pathways	Improved IEB integrity
				Attenuated ROS production by macrophages	Anti-inflammatory
		Colitis in mice (WT and Muc2$^{-/-}$)	10–12 wo	Increased abundance of gut commensal bacteria	Improved gut microbiota
				Increased expression of β2 defensin via the regulation of NF-κB and AP-1/restoration of antimicrobial peptide gene expression and VEGF	
		Patients with inactive UC	Adult patients (>18 yr)		Remission was higher in the VSL#3 group vs. placebo
96–99	*Escherichia coli* Nissle 1917 (EcN 1917)	IEC in vitro +/− inflammation		Restored the localization and altered distribution of claudin-1	Improved IEB integrity
		Induced colitis and mucositis in mice	7–9 wo	Ameliorated the decreased expression of TJ proteins	
				Inhibited the decrease of claudin-1 expression	
				Reduced the increase expression of ICAM-1	
				Restored the indices of richness and diversity to normal values	Improved gut microbiota
				Attenuated the increase of Firmicutes phylum and increased Cyanobacteria	
				Restored the of Firmicutes/Bacteroidetes ratio	
				Ameliorated expression of Muc-2 and -3	Effect on colonic mucosa
		Patients with inactive UC	Adult patients (>18 yr)		Efficacy and safety equivalent to the gold standard mesalazine in patients with UC
100–104	*Saccharomyces boulardii*	IEC in vitro +/− inflammation		Upregulated PPAR-γ, thus suppressed NF-κB activation leading to a decrease IL-8 expression	Anti-inflammatory
		Colon from patients with IBD		Enhanced E-cadherin delivery to the cell surface	Improved IEB integrity
		Patients with inactive CD	Adult patients (>18 yr)	Improved gut permeability	
				Decreased lactulose/mannitol ratio	Clinical relapses were less frequent in patients receiving *S. boulardii* with current treatment
105, 106	*Propionibacterium freudenreichii*	Human PBMC		Increased IL-10/IL-12 ratio	Anti-inflammatory
		Induced colitis in mice	8 wo	Modulated local and systemic inflammatory markers (proinflammatory cytokines, MPO, Cox-2)	
				Decreased secretory IgA concentration in small bowel	
				Increased zo-1 mRNA levels	Improved IEB integrity
				No effect on gut microbiota	
19, 107	*Faecalibacterium prausnitzii*	Induced colitis in mice	6–8 wo	Decreased proinflammatory cytokines and increased IL-10	Anti-inflammatory
				Corrected dysbiosis	Improved gut microbiota
108	*Lactobacillus rhamnosus GG* (LGG)	Children with inactive CD	5–21 yr		No extension of time before relapse in children with CD when given as an adjunct to standard therapy
			Treatment		
109–112	VSL#3		6–8 wo		

Continued

Table 2.— *Continued*

Reference	Probiotic Type	Model or Study Design	Age of Supplementation	Mechanisms	Effect on IBD
		Induced colitis in mice and rats		Decreased proinflammatory markers and increased IL-10 levels in colonic tissues and serum	Anti-inflammatory (controversial data)
				No effect on gut inflammation and severity of colitis	Improved gut permeability by preventing the decreased expression and distribution of TJ protein
				Improved IEB integrity	Prevented the increase in apoptotic cell level
				No effect on mucin secretion	
		Modulated the gut microbiota composition (increased Bifidobacterium spp. And Lactobacillus spp) and activity (increased capacity to ferment lactose, sucrose etc.)	Improved gut microbiota		
		Gastric ulcer in rats. Treatment after ulcer induction.	No data	Enhanced gastric ulcer healing	Improved IEB integrity
		Children with active UC	3–17 yr	Modification of the gut microbiota	Remission was achieved in 56% of children, response in 6% and bi change/or worsening in 39%
				Reduction of inflammatory markers	Adverse effects: 67% (bloating and flatulence)
Patients with active UC	Adult patients (>18 yr)	Mucosal healing rate was significantly higher in patients in the VSL#3 groups vs. placebo	Remission was achieved in >50% of patients		
113–115	EcN 1917	IEC in vitro +/− inflammation			Improved IEB integrity
		Induced colitis in mice (WT and TLR-2 and $-4^{-/-}$).	No data	Decreased proinflammatory cytokines via TLR-2 and -4 dependent pathways	Anti-inflammatory
		Patients with active UC	Adult patients (>18 yr)		Equivalent effect to the gold standard mesalazine in patients with UC
100, 116, 117	*Saccharomyces boulardii*	Induced colitis in mice.	8–12 wo	Decreased proinflammatory mediators via an upregulation of PPARγ Decreased proinflammatory mediators via an upregulation of PPARγ Limited the infiltration of lymphocyte T helper in inflamed colon	Anti-inflammatory
		Patients with active UC	Adult patients (>18 yr)		17/24 patients achieved clinical remission
107, 118, 119	*F. prausnitzii*	Induced colitis in mice and rats.	6–8 wo	Reduced proinflammatory cytokines and T-cell levels Induced Treg by inhibiting the IL-6/STAT-3/IL-17 pathway Secreted butyrate that regulated Th17/treg balance by inhibiting HDAC-1	Anti-inflammatory
				Improved gut permeability	Improved IEB integrity

Continued

Table 2.— *Continued*

Reference	Probiotic Type	Model or Study Design	Age of Supplementation	Mechanisms	Effect on IBD
				Improved increased TJ proteins (claudin-4, occludin, ZO-1 and E-cadherin) in colonic samples No significant differences were observed in the passage of *E. Coli* K12	
120	LGG	Patients with active CD	Adult patients (>18 yr)		Could not demonstrated a benefit of LGG in inducing remission

CD, Crohn's disease; COX-2, cyclooxygenase-2; ERK, extracellular signal-regulated kinases; hDAC, histone deacetylase; ICAM-1, intercellular adhesion molecule; IBD, Inflammatory bowel diseases; IEB, intestinal epithelial barrier; IEC, intestinal epithelial cells; MPO, myeloperoxidase; PBMC, peripheral blood mononuclear cells; ROS, reactive oxygen species; TJ, tight junction; VEGF, vascular endothelial growth factor; TLR4, Toll-like receptor 4; UC, ulcerative colitis; wo, weeks old; WT, wild-type.

with clinical flare-up was effective to reach remission (116). EcN1917 efficacy in the treatment of UC is mitigated, with a study showing no difference between the EcN1917 group and the mesalazine control group and another presenting EcN1917 as an alternative to mesalazine for maintenance of remission in UC (113, 126). Meta-analysis of clinical studies dealing with IBD and probiotics concluded on a "strong evidence" for VSL#3 in the context of IBD, yet a "moderate" evidence for *S. boulardii* and a "weak to not effective" for *L. rhamnosus* GG and for *E. coli* Nissle 1917.

Conclusions on Probiotics

To conclude, in vitro studies suggested an action of probiotics on the IEB, gut microbiota, and anti-inflammatory effects. Animal studies supported the protective effects of probiotics against colitis development via a reduction of inflammation. However, knowledge about the role of probiotics on pediatric IBD at preclinical and clinical levels as well as data on CD is still missing. Beneficial effects of probiotics were more reported in UC than in CD. Larger clinical trials implementing probiotics are needed to confirm that they can favor remission in IBD.

Key Ideas: Probiotics

Actions of probiotics in vitro and in vivo: *1*) improved IEB via the regulation of tight junction proteins and mucin secretion; *2*) modification of gut microbiota composition and activity; and *3*) reduction of inflammation. VSL#3 appears to be the most effective probiotic for maintenance of remission in IBD and also in its induction at preclinical scale. Limitations: lack of preclinical studies and clinical trials both on probiotics as preventive and therapeutic strategies, especially at early age, on CD.

POSTBIOTICS

Definition of Postbiotics

Postbiotics refer to microbial components as well as microbial metabolites secreted by live bacteria or released after bacterial lysis (127). All these components may have local and systemic effects. Their advantages over probiotics include reduced risk of infection and side effects triggered by certain bacteria. Indeed, the administration of viable probiotics to individuals with weaker immune systems could enhance inflammatory responses and turn "generally recognized as safe" harmless probiotic bacteria into detrimental microorganisms. The inactivation of bacteria can be achieved by physical methods such as heat or chemical treatment, resulting in bacteria unable to grow but with maintained health benefits (127). Postbiotics can be divided in gut microbial components and metabolites.

Gut Microbial Components

Cell surface protein.

Surface-layer proteins (Slp) constitute a semipermeable cell envelope component in certain bacteria. Pretreatment with Slp from *Lactobacillus acidophilus NCFM* improved IEB in vitro by increasing transepithelial electrical resistance (TEER) and reducing permeability, which was partly due to a restoration of TJ proteins expressions (Table 3). Slp pretreatment also attenuated inflammation via the reduction of proinflammatory cytokines level (128). In a noninflammatory context, SlpA from *L. acidophilus* CICC 6074 increased proinflammatory mediators by activating MAPK/NF-κB pathway in a macrophage cell line. Regarding treatment, this protein suppressed Toll-like receptor 4 (TLR4) signaling activation triggered by LPS stimulation thus inhibited MAPK/NF-κB signaling (Table 3) (129). Furthermore, Slp from *P. freudenreichii* CIRM-BIA129 revealed anti-inflammatory properties, with SlpB inducing high IL-10 secretion in swine peripheral blood mononuclear cells (PBMC) and mesenteric lymph node immune cells (MLNC) under inflammation (149). Interestingly, pretreatment with SlpA from *L. acidophilus* NCFM in a DSS-induced colitis mouse model reduced inflammatory cytokines, as well as TLR4 and COX2 proteins, in colon tissues, demonstrating protective effects (129).

To conclude, Slp proteins can have anti-inflammatory effects on inflamed IEC, or and proinflammatory effects on immune cells in the absence of inflammatory stimuli (128–130, 149, 150, 175).

Peptidoglycan.

Peptidoglycans (PGN) are major cell wall components in both Gram-positive and Gram-negative bacteria (133). PGN

Table 3. *Prevention and treatment of colitis or IBD with postbiotics*

Reference	Postbiotic Type	Model or Study Design	Age of Supplementation	Effect on IBD	Mechanisms
			Prevention		
121, 128–132	Slp	IEC or immune cells in vitro +/− inflammation		Improved IEB integrity	Decreased TEER and permeability Restored TJ proteins
				Anti-inflammatory	Decreased proinflammatory cytokines and increased IL-10 via an inhibition of MAPK/NF-κB
				Proinflammatory	Increased proinflammatory mediators via an inhibition of PKC leading to an activation of MAPK/NF-κB pathway
		Induced colitis in mice. Before colitis induction.	No data	Anti-inflammatory	Reduction of inflammatory markers Inhibited the colitis-induced expression of TLR-4, iNOS and COX-2 in colon tissue
133	PGN	Induced colitis in mice. Before colitis induction.	6–7 wo	Protected against colitis, decreased inflammation parameters	Reduced IL-1β, IL-6 and TNF-α levels, reduced colonic gene expression but increased colonic IL-10 protein expression through NOD2 signaling
134–137	LTA	Goblet cells in vitro +/− inflammation		Effect on mucus secretion	Increased MUC-2 expression via TLR-2/NF-κB
				Anti-inflammatory	Decreased proinflammatory cytokines through TLR-2 leading to an inhibition of MAPK/NF-κB pathway
		IEC or immune cells in vitro +/− inflammation		Proinflammatory	Lactobacillus deficient in LTA: decreased proinflammatory cytokines and increased anti-inflammatory cytokines via TLR-2
		Induced colitis in mice. Before colitis induction.	No data	Proinflammatory	Lactobacillus deficient in LTA: reduced colitis score and increased colonic IL-10 level
138–146	SCFA	IEC or immune cells in vitro +/− inflammation		Anti-inflammatory	Decreased proinflammatory expression and increased IL-10 via different pathways: via MCT-1 and NF-κB pathway, by inhibiting HDAC through GPR109A and via ERK 1/2 pathway
		Induced colitis in mice. Before colitis induction.	6–9 wo	Anti-inflammatory	Decreased proinflammatory cytokines via an inhibition of NF-κB pathway Low concentration of acetate acted as a low chemotactic index for neutrophils Butyrate induced colonic IL-18 via GPR109A and regulated Treg and IL-10 producing CD4+ T cell frequency in the colon, thus increasing IL-10 secretion by macrophages Acetate activated NLRP3 inflammasome by binding to GPR43 on colonic epithelial cells lead to a K+ efflux and a hyperpolarization
				Proinflammatory	Increased ROS production and phagocytic activity

Continued

Table 3.— *Continued*

Reference	Postbiotic Type	Model or Study Design	Age of Supplementation	Effect on IBD	Mechanisms
		Patients with inactive UC	Adult (>18 yr)	No change in the daily symptoms score and DAI	No change in the CRP, MPO and CAI Increased IL-10/IL-12 ratio
147, 148	MCFA/LCFA	IEC in vitro +/− inflammation		Anti-inflammatory Improved IEB integrity	Inhibited IL-8 secretion Suppressed the increased permeability and the decreased TEER Restored occludin, ZO-1/-2, claudin-1 and -3 expression and MLCK Decreased TNFR2 and increased GPR40
		Postbiotics before colitis induction in mice	6–10 wo	Improved IEB integrity Anti-inflammatory	Suppressed the increased permeability Decreased metabolites derived from $n-6$ PUFA known for their proinflammatory properties Increased PGE2 and 8-HETE
			Treatment		
129, 149–151	Slp	Piglets PMBC and MLNC, RAW 264.7 cells, HT-29 cells, Caco-2 cells, U937 cells		Anti-inflammatory Anti-inflammatory SlpB is involved in adhesion to HT29 cells. Anti-inflammatory properties on Caco-2 cells proinflammatory properties on U935 cells	Induced IL-10 secretion, inhibited TNF-α and IFN-γ release Decreased TNF-α, IFNa, IFNb, IL-10, IL-1β, COX-2 and iNOS levels, suppressed TLR4 signaling, attenuated NLRP3 inflammasome and NOD2 signaling Increased inflammation via TLR2, inhibition of NF-kB/p65 translocation into the nucleus
133, 152–154	PGN	RAW264.7 cells, colonic lamina propria monunuclear cells (LPMC) from colitis-induced mice, murine dendritic cells, Caco-2 cells with over- or underexpression of hPepT1		Anti-inflammatory Anti-inflammatory Anti-inflammatory Proinflammatory	Inhibited NO synthesis, iNOS and COX2 expression, decreased LPS-induced expression of TNF-α and IL-6 Inhibited IL-6 synthesis through inhibition of NF-kB Partial maturation of DC: increased IL-10/IL-12 ratio via NOD2 signaling Increased IL-8 expression through NF-kB pathway, activation of NOD1/2 signaling and increased IL-1β
142, 143, 155–157	SCFA	In vitro: human and mouse PBMC, macrophages, myofibroblast +/− IEC, HT-29, NMC460 cells		Anti-inflammatory properties M2 macrophage polarization and migration Induced mucoprotective prostaglandin profile NLRP3 inflammasome activation	Decreased NO, IL-6, TNF-α, and IL-12 release through GPR43 Decreased NO, IL-6, TNF-α, and IL-12 release due to an inhibition of HDAC Increased STAT-6 phosphorylation and decreased H3K9 deacetylase Increased CCL2 expression Increased PGE1/PGE2, promoted MUC2 expression in co-culture with IEC GPR43 signaling activation
157–160		SCFA after colitis induction in mice	No data	Limited colitis induction	Decreased colonic IL-6, IL-1β, and TNF-α increased colonic expression of Arg1 increased activation of the H3K9/STAT6 signaling pathway

Continued

Table 3.— *Continued*

Reference	Postbiotic Type	Model or Study Design	Age of Supplementation	Effect on IBD	Mechanisms
					Promoted IL-10 production, activated Th1 cell STAT3 and mTOR
					Critical role for GPR43-mediated recruitment of PMN to contain intestinal bacterial translocation
161–166		Mild activate adult CD	Adult (>18 yr)	No difference	No difference in clinical, histological and endoscopic score
		Active UC		No difference	No difference in the endoscopic appearance of the mucosa
				Tend to improve pathological score	Improved DAI: 33% in the SCFA group and 20% in the placebo group
				Decreased DAI	Anti-inflammatory properties mediated by an inhibition of NF-kB in macrophages, reduced the number of neutrophils in epithelium
167–174	SBA	Rat IEC, Caco-2, and HT-29 cells, differentiated macrophages, Jurkat T cells		DCA: proinflammatory UDCA: no effect	DCA increased IL-8 secretion, 2 mM DCA cytotoxic UDCA: no effect on IL-8 secretion or capacity of enterocytes to limit bacterial translocation
				DCA proinflammatory	DCA increased IL-8 secretion via NF-κB activation
				Anti-inflammatory	Activated NF-κB pathway via TGR5-cAMP signaling and inhibited pro-inflammatory cytokines production
					Inhibited Th1 differentiation, inhibited ERK phosphorylation and decreased Th1 cytokines
		Induced colitis in rats. After colitis induction.	No data	Mitigated colitis severity	
		Induced colitis in mice. After colitis induction.	6–8 wo	Decreased colitis and colonic inflammation	Reduced leukocytes infiltration and promoted TGR5 pathway
			Postweaned mice	DCA exacerbated DSS-colitis	NLRP3 inflammasome activation, increased pro-inflammatory cytokines production by macrophages
					Promoted ileal and colonic inflammation, gut dysbiosis

CAI, clinical activity index; CCL2, chemokine ligand 2; DAI, disease activity index; DCA, deoxycholic acid; DSS, dextran sulfate sodium; HDAC, histone deacetylase; HETE, hydroxyeicosatetraenoic acid; IBD, inflammatory bowel diseases; IEB, intestinal epithelial barrier; IEC, intestinal epithelial cell; iNOS, inducible nitric oxide synthase; GPR, G protein-coupled receptor; LCA, litocholic acid; LTA, litocholic acid; LCFA, long-chain fatty acid; MCFA, medium-chain fatty acids; MCT1, monocarboxylate transporter 1; MLNC, mesenteric lymph node immune cells; mTOR, mammalian target of rapamycin; NLRP3, NOD-like receptor family, pyrin domain containing 3; PBMC, peripheral blood mononuclear cells; PGE2, prostaglandin E2; PGN, proteoglycan; PMN, polymorphonuclear leukocytes; PUFA, polyunsaturated fatty acids; ROS, reactive oxygen species; SBA, secondary bile acid; SCFA, short-chain fatty acid; Slp, surface layer protein; TGR5, Takeda-G protein receptor 5; TEER, electrical transepithelial resistance; TJ, tight junction; TLR, Toll-like receptor; UDCA = ursodeoxycholic acid; wo, weeks old.

have two main receptors, TLR2 and NOD1/2, which are expressed by antigen-presenting cells such as dendritic cells (DC), macrophages, and IEC (176, 177).

PGN from certain *Lactobacillus* strains decreased the expression of LPS-induced TNF and IL-6 through inhibition of the NF-κB signaling pathway in vitro and in colitis model (152, 178). Moreover, PGN from *L. acidophilus* inhibited inducible nitric oxide synthase (iNOS) and COX-2 expression (179, 180). Most of the studies dealing with PGNs nevertheless focused on their effects under physiological conditions to investigate their signaling pathway. Under basal condition, PGN increased the expression of proinflammatory cytokines in IEC and DC (153, 177). These studies suggested proinflammatory effects of PGNs. Nonetheless, murine DC underwent partial maturation when treated with *L. salivarius* 33 (Ls33) PGN, resulting in an increased IL-10/IL-12 ratio (133).

In vivo, PGN from *L. salivarius* Ls33 protected against 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis induction by decreasing inflammatory parameters, but this protection was absent in IL-10-deficient mice or NOD2-deficient mice (Table 3) (133). No clinical data was found on Slp administration.

To conclude, in vitro studies indicated anti-inflammatory properties of PGN when cells were stimulated by an inflammatory stimulus, whereas PGN induced in basal condition a proinflammatory response.

Lipoteichoic and teichoic acids.

Lipoteichoic acids (LTA) and teichoic acids (TA) are molecules anchored in the cell wall of Gram-positive bacteria. LTA belong to microbe-associated molecular patterns, which are recognized by pattern recognition receptors. One in vitro study used human monocytic THP1 cells stimulated with PGN from *Shigella flexniri* as an IBD model (Table 3) (181). Pretreatment with LTA from *L. plantarum* reduced proinflammatory cytokines in these inflamed cells (181). On the other hand, LTA from *L. acidophilus* NCFM decreased the IL-10/IL-12 ratio in cultured dendritic cells (134). In IEC, the immunomodulatory effects were also controversial. LTA from *L. paracasei* D3-5 decreased proinflammatory cytokines in murine intestinal goblet cells and increased MUC2 protein level expression (135). However, another study showed that LTA purified from *L. rhamnosus* GG increased *IL-8* mRNA expression in Caco-2 cells (136). Two studies demonstrated in a murine model of colitis that LTA-deficient *Lactobacillus* mutants were protective, with a rise of colonic IL-10 level and a reduced colitis score (Table 3) (134, 137).

The effects of LTA may differ within the same bacterial species. Therefore, screening for immunomodulatory properties in specific bacterial strains is essential. Preclinical studies suggested that LTA have proinflammatory properties on murine colitis models (134, 137).

Gut Microbial Metabolites

SCFAs.

In humans, SCFAs are found in different tissues but mostly within the colon lumen. They include acetate, propionate, butyrate, and valerate and are produced by anaerobic bacteria through the fermentation of dietary fibers. Butyrate is mainly produced by gut bacteria that belong to the phylum *Firmicutes*, such as *F. prautsnitzii,* whereas propionate and acetate production are mainly produced by *Bifidobacterium* bacterial species (182). SCFAs, the main energy source for colonocytes, participate in diverse intestinal functions, such as digestive motility, immunomodulation, and modification of gene transcription (35, 39, 183). SCFAs improve the gut barrier function and impact the intestinal microbiota (155, 184). Patients with IBD have reduced levels of SCFAs in the mucosa and feces (185). Most studies support anti-inflammatory benefits of SCFAs (63). All these data suggest an involvement of SCFAs in IBD pathogenesis.

Indeed, pretreatment with SCFAs reduced the inflammatory response on both IEC and immune cells (138–140). SCFAs inhibited IL-8 secretion induced by inflammatory stimulus in human fetal cell line, fetal intestinal organoids, and fetal mouse intestine (141). Regarding therapeutic effects, treatment of challenged-immune cells with butyrate or acetate reduced proinflammatory mediators release by interacting with the GPR43 receptor (Table 3) (142, 156). Butyrate facilitated M2 macrophage polarization after stimulation with both butyrate and IL-4, a Th2 cytokine (157). Besides, butyrate promoted migration of macrophages by increasing chemokine ligand 2 (CCL2) expression. Furthermore, treatment with SCFAs on cocultures of IEC and myofibroblasts induced a mucoprotective prostaglandin profile, reflected by an increased PGE1/PGE2 ratio in myofibroblast supernatants (155). Finally, acetate induced a NLRP3 inflammasome activation in colonic epithelial cells through GPR43 and Ca^{2+} signaling (143).

Acetate protected in vivo against colitis, improved IL-10 production, and reduced proinflammatory cytokines (Table 3) (142–144). Regarding treatment, SCFAs attenuated gut inflammation in DSS-treated mice (Table 3) (157, 158). Indeed, SCFAs stimulated colonic IL-10 secretion in mice with colitis (158). Butyrate decreased the histological score in DSS-treated mice by inducing M2 macrophage (158).

Only few studies have examined the therapeutic effect of SCFAs in active Crohn's disease and they are not conclusive about the efficiency of SCFAs to treat CD (Table 3). More literature exists on the preventive and therapeutic effects of SCFAs in UC. No differences in improvement of clinical, histological, and endoscopic scores were shown between butyrate and 5-aminosalicylate (5-ASA) supplementation (161). Butyrate combined with current treatments induced an increase of the IL-10/IL-12 ratio but did not change C-reactive protein, myeloperoxidase, or clinical activity index (186). Regarding curative effects of SCFAs on active UC, most studies failed to show a difference between SCFAs and current treatments (162–164). A study showed that butyrate enema improved disease activity index (DAI) in patients with UC, reduced both the number of neutrophils in crypt and surface epithelia (165).

To conclude, in vitro studies suggested an anti-inflammatory role of SCFAs on IEB via NF-κB pathway and the GPR43 receptor. Furthermore, in vivo studies suggested that SCFAs mitigated intestinal inflammation in induced-colitis model. Clinical studies are however not successful in terms of SCFA efficiency.

Medium-chain fatty acid/long-chain fatty acid.

Medium-chain fatty acids (MCFAs) and long-chain fatty acids (LCFAs) mostly derive from diet, but bacteria can also generate these lipids via the biohydrogenation pathway (187, 188). Recent evidence for their relevance in IBD is emerging with a recent study highlighting the possible use of bacteria-derived long-chain fatty acid that exhibited anti-inflammatory properties in colitis. Indeed, *E. coli* EcN1917 produced a high level of 3-hydroxyoctadecaenoic acid (C18-3OH) compared with other strains. Administration of C18-3OH in a mice model of colitis improved colitis and restored gut dysbiosis (147). Besides, 10-hydroxy-*cis*-12-octadecenoic acid (HYA), a derivate of linoleic acid ($n-6$), protected against inflammation by restoring tight junction proteins expression and modulating the expression of the TNF receptor TNFR2 in cultured IEC (148).

Secondary bile acids.

Bile acids (BAs) are produced in the liver from the cholesterol metabolism and are further metabolized by gut bacteria. Cholesterol is converted to primary BAs, such as chenodeoxycholic acid (CDCA) and cholic acid (CA) that are released after a meal in the intestine, where they are metabolized by gut bacteria. Gut anaerobic bacteria deconjugate the liver-derived BAs to their respective free BAs and then convert primary BAs into secondary BAs (SBAs) in the colon. CA is transformed into deoxycholic acid (DCA), and CDCA is

transformed into litocholic acid (LCA) and ursodeoxycholic acid (UDCA). SBAs have different functions, including regulation of energy homeostasis, anti-inflammatory effects, and antimicrobial functions (189). Patients with IBD have reduced level of SBA in stools but not of total fecal BA concentrations, suggesting that this decrease is due to an impaired gut microbiota BA metabolism (190).

DCA increased in vitro IL-8 secretion by IEC, but high concentrations of DCA were toxic on Caco-2 cells (Table 3) (167–169). Furthermore, DCA and LCA inhibited TNF production in differentiated macrophages stimulated by commensal bacterial antigen or LPS. Pretreatment of $CD4^+$ Th cells with LCA inhibited Th1 differentiation (170).

Mice with DSS-induced colitis pretreated with LCA or UDCA displayed an improvement in the severity of colitis (147, 148). Colonic alkaline phosphatase (AP) activity, a marker of leukocyte infiltration, was significantly reduced by UDCA in rats with colitis. DCA exacerbated DSS-colitis and triggered NLRP3 inflammasome, therefore, increased proinflammatory cytokines production of macrophages (171). Regarding the curative mode, DCA and LCA improved colitis by decreasing colonic inflammation and disease parameters (Table 3) (191). UDCA also had beneficial effects on acute and chronic colitis induced by 2,4,6-trinitrobenzenesulfonic acid (TNBS) (172). SBAs reduced leukocytes infiltration and exerted an anti-inflammatory effect, in part dependent on the TGR5 bile acid receptor, in three murine colitis models (191). However, other studies did not show beneficial effects of SBAs.

To conclude, SBAs appeared to have beneficial effects in an inflammatory context. However, caution should be taken in the use of SBAs as DCA was toxic in some studies (167).

Key Ideas: Gut Microbial Components

Most of gut microbial components reduce inflammation. Limits: lack of in vivo studies and absence of clinical trials to conclude on their value in the prevention/treatment of IBD.

Key Ideas: Gut Microbial Metabolites

SCFAs are the most studied postbiotics in IBD; however, clinical studies are insufficient. The cited metabolites apart from SCFAs also showed promising results.

SYNBIOTICS

Definition

Synbiotics are products combining prebiotics and probiotics (192). Their benefit for the host relies on the synergic or additive action of both components to ensure an effective implementation of an improved microbiota by enhancing the survival of specific bacterial strains and/or their metabolism. Such strategy may help to preserve the intestinal functions and prevent diarrhea or constipation for the individual (193). Strengthening of the immune system and of the intestinal barrier is also investigated together with inhibition of pathogens (192). So synbiotics reportedly have a greater efficacy than pro-/prebiotics alone (193). Synbiotic administration may reduce cost and treatment duration, thus enhancing compliance (194). For all those reasons, synbiotics represent an attractive field of study for IBD care.

In Vitro Studies

Synbiotic supplementation was used only as treatment (Table 4). Altogether, in vitro studies underlined a positive effect of synbiotics via different mechanisms. An increased diversity of the microbiota and production of SCFA were observed after incubation of a synbiotic composed of *Bacillus* strains and a mix of FOS, xilooligosaccharides (XOS), and GOS in a synthetic human GI tract called M-SHIME (196). Human immune cells like PBMC were also impacted by the synbiotics, through the influence of the prebiotics part of synbiotic, for instance short-chain GOS and long-chain FOS (scGOS/lcFOS), which induce the production of IL-10 by dendritic cells (48). Metabolites derived from synbiotics like SCFAs also play a role, as seen with the SCFAs derived from the synbiotic inulin + *Lactobacillus rhamnosus* GG ATCC 53013 that reduced the production of inflammatory cytokines by LPS-stimulated human PBMCs (216).

Preclinical Studies

In general, the literature on synbiotics at preclinical level is scarce and seems to focus on the preventive aspect of synbiotics (Table 4). Promising results were achieved in the described preventive studies, with a reduction of the disease severity and colonic damages. The mechanisms found were the same as in in vitro studies: increased microbiota diversity, production of SCFAs, and secretion of IL-10 (199). Interestingly, a restoration of the gut barrier was seen after a supplementation by *Bifidobacterium infantis* + XOS in male C57BL/6 mice under acute DSS-induced colitis via the increase of tight junction proteins ZO-1 and claudin-1 expression (202). It appears that a supplementation of synbiotics mitigates the development of colitis in murine models.

Two other preclinical studies were found on the treatment of colitis with synbiotics. A synbiotic constituted of *L. paracasei* B21060 + FOS + arabinogalactan was given after DSS induction for 1 wk in male BALB/c AnNHsd mice. Another study used an acute DSS induction on C57BL/6 mice with a synbiotic composed of *Lactobacillus gasseri* 505 + *Cudrania tricuspidata* extract. Both studies showed anti-inflammatory effects, with a decrease of colonic damages and TNF production and a restoration of the gut barrier.

Clinical Studies

Surprisingly, more data were available on clinical trials but only for treatment with synbiotics. Indeed, no study was found with a use of synbiotics as preventive mean for IBD (Table 4). The heterogeneity of the studies is striking. Different types of synbiotics were used such as "Synbiotic 2000," which included inulin, β-glucans, resistant starch, and pectin. The recruited patients with IBD were mostly patients with UC (only 2 studies with patients with CD) with a broad range of disease severity, from remission to severe disease activity. The number of tested individuals is small (<50/condition) and underlines a need for clinical trials with a more consequent number of participants to ensure a relevant analysis of the effects of synbiotics.

One study focused on children with UC of ~12 yr old in remission for whom a synbiotic composed of *B. longum* R0175 + inulin was given for 10 mo (203). The result of this

Table 4. *Studies of synbiotic uses as prevention and/or treatment for colitis or IBD*

Reference	Synbiotic	Model or Study Design	Age of Supplementation	Effect on IBD	Mechanisms
			Prevention		
195	Oligoalternan + *B. breve* R0070 + *L. lactis* R1058	HT-29 cell line + LPS/IFN-γ		Improved IEB integrity	Inhibited cell proliferation
48	scGOS/lcFOS + *L. rhamnosus* or *B. breve*	Immature primary human immune cells + PMA/ionomycin		Anti-inflammatory	Induced IL-10 secretion
196	MegaSporebiotic + MegaPrebiotic	In vitro human gastrointestinal tract M-SHIME, each with fecal inoculum of a different human adult		Improved gut microbiota	Increased microbiota diversity and SCFA production
197	Synbiotic Multilac Baby	Pathogens culture: either *E. coli* EPEC, *Sh. sonnei*, *S. typhimurium*, *K. pneumonia*, and *C. difficile*			Higher growth inhibition of all pathogens with the synbiotic compared with probiotics alone
198	Synbiotic Instant Mixture = *Lactobacilli* + *Bifidobacteria* + inulin	HLA-B27–β2-microglobulin rats + spontaneous colitis. Synbiotic before colitis induction	2 mo old	Improved gut microbiota	Reduced histological score, increased microbiota diversity
199	*L. paracasei B21060* + FOS + arabinogalactan	BALB/c AnNHsd mice + acute DSS colitis. Synbiotic before colitis induction	10 wo	Improved IEB integrity	Reduced colonic damages. Restoration of gut barrier, increased IL-10
200	*L. rhamnosus GG* + tagatose	BALB/c mice + acute DSS colitis. Synbiotic before colitis induction	6 wo	Improved gut microbiota	Reduced clinical symptoms, recovery of gut microbiota dysbiosis
201	Green banana resistant starch + *Bacillus coagulans MTCC5856*, whole plant sugar cane fiber Kfibre + *Bacillus coagulans MTCC5856*	C57BL/6 mice + acute DSS colitis. Synbiotic before colitis induction	7 wo		Reduced disease and histological scores, increased SCFA production
202	*Bifidobacterium infantis* + xylooligosaccharide	C57BL/6 mice + acute DSS colitis. Synbiotic before colitis induction	6–7 wo	Anti-inflammatory and improved IEB integrity	Reduced DAI, inflammatory cytokines. Strengthened gut barrier
203	*B. longum R0175* + inulin	Single-blind RPCT: UC patients in remission	Mean age: 12.6 yr old.	Improved quality of life	Improved quality-of-life score
204	*B. longum* + psyllium	RCT: mild/in remission UC patients	Mean age (synbiotic, prebiotic, probiotic): 35, 37 and 36 yr old.		Improvement of IBDQ
205	Synbiotic 2000	DB RPCT: CD patients undergoing resection	Mean age at surgery (synbiotic, placebo): 36.1 and 34.7 yr old.	No effect	No effect on postoperative recurrence of CD
206	*B. breve Yakult* + GOS	Open-label RCT: patients with active/in remission UC	Mean age (synbiotic, control): 43.6 and 47.4 yr old.	Improved gut microbiota	Reduced endoscopic score, change of gut microbiota
			Treatment		
199	*L. paracasei B21060* + FOS + arabinogalactan	Male BALB/c AnNHsd mice + acute DSS colitis. Synbiotic after colitis induction	10 wo	Anti-inflammatory and improved IEB integrity	Reduced colonic damages. Restoration of gut barrier, increase of IL-10
207	*L. gasseri 505* + Cudrania tricuspidata extract	C57BL/6 mice + acute DSS colitis. Synbiotic after colitis induction	5 wo	Anti-inflammatory	Reduced serum TNF-α, nitric oxide
208, 209	*B. longum* + Synergy 1	DB RPCT: patients with active UC and CD.	Mean age (synbiotic, placebo): 45–46.3 and 38–49 yr old.	Anti-inflammatory and improved gut microbiota	Reduced disease activity, inflammatory cytokines. Increased regeneration of tissue and change of gut microbiota

Continued

Table 4.— *Continued*

Reference	Synbiotic	Model or Study Design	Age of Supplementation	Effect on IBD	Mechanisms
210	*L. paracasei B20160* + arabinogalactan + XOS	RPCT: patients with mild/moderate UC UBT.	Mean age (synbiotic, placebo): 46 and 48 yr old.	Anti-inflammatory	Decreased serum IL-6, IL-8
211	Inulin + *L. plantarum, L. gasseri, L. casei, B. infantis, L. salivarius, L. acidophilus, S. thermophilus, L. sporogenes*	Randomized open-label trial: patients with mild/moderately active UC UBT		Increased remission.	
212	*Enterococcus faecium, L. plantarum, S. thermophilus, B. lactis, Lactobacillus acidophilus, B. longum* + FOS	RPCT: patients with mild/moderately active UC.	Mean age (synbiotic, placebo): 44.94 and 40 yr old.	Reduced DAI	
213	*S. faecalis T-110 JPC, C. butyricum TO-A, B. mesentricus TO-A JPC, L. sporogenes* + prebiotic	Open-label RCT: patients with moderately/severe active UC UBT.	Adult patients (>18 yr)	Increased remission.	Reduced relapse and disease severity. Increased remission duration, reduction of steroid dosage
214	Depending on parameter, 4–5 studies included	Meta-analysis of several diseases including IBD.	Depends on study	Anti-inflammatory	Reduced CRP and TNF-α
215	Lactocare	DB RPCT: patients with mild/moderately active UC UBT.	Adult patients (>18 yr)	Reduced SCCAI.	

CD, Crohn's disease; DAI, disease activity index; DB, double-blind; FOS, fructo-oligosaccharides; GOS, galacto-oligosaccharides; IBD, inflammatory bowel diseases; IBDQ, inflammatory bowel disease questionnaire; IEB, intestinal epithelial barrier; LAB, lactic acid bacteria; LPS, lipopolysaccharides; PMA, phorbol 12-myristate 13- acetate; RCT, randomized controlled trial; RPCT, randomized placebo controlled trial; SCCAI, simple clinical colitis activity index; SCFA, short-chain fatty acids; UBT, under baseline treatment; UC, ulcerative colitis; XOS, xilooligosaccharides; wo, weeks old.

study is encouraging as no severe symptoms were observed and an improvement of the quality of life was assessed.

Treated patients were aged of 18–60 yr old, and treatment time ranged from 4 wk to 1 yr. Apart from two studies where no effect of synbiotics were seen on CD recurrence or microbiota, and despite the heterogeneity of disease severity and disease type, the majority of the clinical trials presented a beneficial effect of synbiotic through a clinical improvement (205, 217). The tested synbiotics appeared also effective to reduce the production of inflammatory cytokines like IL-6 or IL-8 (210). For instance, two studies used *B. longum* and "Synergy 1," a preferential inulin/oligofructose growth substrate for this strain, on patients with either active CD or UC for 1 to 6 mo (208, 209). Both trials showed a reduction of disease severity after supplementation. This can be linked to a modulation of the microbiota and an enhancement of the tissue regeneration. Moreover, synbiotics contributed also to maintain remission and to reduce treatment dosage, as seen in a clinical trial with patients with active UC supplemented with a synbiotic containing patented *Streptococcus faecalis* T-110 JPC, *Clostridium butyricum* TO-A, *Bacillus mesentricus* TO-A JPC, *Lactobacillus sporogenes*, and a prebiotic (213).

Conclusions on Synbiotics

Few studies are available at in vitro and preclinical levels but all of them pointed out the beneficial effects of synbiotics on inflammation: reduction of colonic damages and inflammatory cytokines production, restoration of the microbiota diversity, and strengthening of the gut barrier. Synbiotics appeared to be more effective as pre- or probiotics alone. These observations were also seen at clinical level, with a reduction of disease activity and an extension of remission. However, robust homogenized clinical trials are lacking to fully characterize the effects of synbiotics and their design should be supported by preliminary data generated from preclinical studies. The distinctions of disease type and disease severity are also an important factor.

Key Ideas: Synbiotics

Beneficial effects observed at all levels for synbiotics: *1*) restored diversity of the microbiota; *2*) decreased anti-inflammatory cytokines production; *3*) strengthened the gut barrier; and *4*) improved disease severity, which led to an extended remission for patients with UC. Limitations: lack of robust in vitro/preclinical and clinical studies, especially for prevention; more data should be collected to describe precisely the effects of synbiotics for UC and CD, at different disease stages and different age of the individual.

FECAL MICROBIOTA TRANSPLANTATION

Definition

Because IBD is associated with alteration in the gut microbiota (reduced diversity, increased pathogens, and low commensals), fecal microbiota transplantation (FMT) is increasingly considered for the therapeutic treatment of IBD. FMT consists of the transfer of fecal material from a healthy donor to a recipient patient to restore the pathology-induced alterations of the intestinal microbiota. FMT can be administered through the lower gastrointestinal tract (enema, colonoscopy, and sigmoidoscopy) or upper gastrointestinal tract (endoscopy, nasoduodenal tube, and capsule ingestion). Although this method has been proven to be effective in cases

of recurrence of *Clostridium difficile* infection (218), it is still under study for IBD.

Preclinical Studies

Few preclinical studies have investigated the role of FMT in the treatment of colitis (219–222). In a DSS-induced murine model of colitis, FMT of untreated mouse microbiota decreased weight loss and reduced colonic inflammation as measured by increased colonic length and fewer histological alterations (220–222). FMT also improved homeostasis of the gut microbiota with an increase in *Lactobacillus* and *Bifidobacterium* bacteria and restoration of tryptophan and SCFA levels similar to that of untreated mice (221, 222). Mechanisms by which FMT promotes the recovery of DSS-induced colitis may be mediated by the regulation of the immune system with higher IL-10 production as well as aryl hydrocarbon receptor (Ahr) activation (220). In another study, colonization of gnotobiotic mice with IBD donor-derived microbiotas induces an IBD-like phenotype characterized by abnormal immune cell profile (abundant Th17 cells and lower tolerogenic RORgt+ Treg cell) and higher susceptibility to colitis (219). Transplantation of healthy human donor microbiota in IBD mice favored a tolerogenic immune response with increased proportion of RORgt+ Treg cells that may protect from colitis. Thus, therapeutic effects of the FMT on IBD likely involve the remodeling of the gut microbiota and regulation of intestinal immunity.

Clinical Studies

Four studies have now been published on the treatment of IBD using FMT (223–226). They concern patients with UC in the active phase of the disease were intended to induce remission. Overall, 277 patients with UC receiving FMT (n = 140) or placebo treatment (n = 137) were followed over 8 to 12 wk posttreatment. Clinical remission was achieved in 28% of patients who received FMT compared with 9% in the placebo group. However, one of the randomized controlled trial (RCT) studies did not find any significant difference between FMT and placebo groups in improving remission (223). These discrepancies may rely on FMT frequency and mode of administration as well as donor microbiota. Microbial analysis of patients who achieved remission shows higher microbial diversity following FMT compared with those who did not and compared with placebo. Specific bacterial family (*Clostridium* clusters IV and XIVa or *Roseburia* species) were correlated with disease improvement while others (*Fusobacterium* or *Escherichia* species) were associated with the lack of remission. Specifically, better outcomes were observed for patients with UC who had a shift in microbiota composition toward the donor composition (223, 227). Microbial functional changes were also observed in patients who achieved remission following FMT with an increase in SCFA and secondary bile acid levels (227). One pilot RCT on pediatric UC population also suggests that FMT improves symptoms and inflammatory indexes through microbial changes and the regulation of mucosal inflammation (228).

In CD, fewer studies have been conducted and the results are scarce. One reason could be the heterogeneous nature of CD for which FMT advantage may not be observed in all phenotype. Only one randomized controlled study showed that the incidence of flare was lower following FMT compared with the placebo group despite no significant differences in clinical remission rate at 10- and 24-wk posttransplantation. However, patients who received FMT had a decrease in Crohn's disease endoscopic index of severity and, contrary to sham group, had no increase of C-reactive protein level after 6 wk (229). Similar to UC studies, maintenance of remission was associated with a greater colonization of the donor microbiota in patients.

Conclusions on FMT

To conclude, despite a small number of enrolled patients and short-term evaluation of clinical remission, the efficacy of FMT in improving clinical response and in the induction of remission in patients with UC are promising but larger studies are needed in patients with CD. Also, the few studies are encouraging regarding the safety of FMT treatment since the patients who had received FMT only had rare adverse events with mostly mild transient gastrointestinal symptoms (diarrhea, gas, or bloating). Overall, this suggests that FMT could be an effective therapeutic approach in IBD. However, several questions remain to be addressed. One is the definition of the material to be transplanted: how can we define a healthy microbiota? Should we prefer one donor or several? Is there a "super-donor"? Is there any donor-recipient matching required to improve FMT effects? Another question is about the FMT procedure: what is the best mode of delivery? Which frequency is needed? As Moayyedi et al. (224) observed that early diagnosed (<1 yr) patients with UC had a better FMT outcomes, should we determine any specific window of action during IBD course to favor FMT efficacy? Also, the question of the microbiota resilience arises: will the transplanted bacteria become sustainably established in the host? Is there a need for repeated FMT? The durability of therapeutic effects of FMT is still unclear but recent studies reported mid-term outcomes in patients with UC with remission greater than 6 mo up to over 1 yr when associated with a maintenance of FMT or dietary modification (228, 230). Finally, the main question concerns the active compounds of the FMT: what are the mediators (bacterial products, metabolites, bacteria) of the beneficial effects of FMT and mechanisms? These questions will need to be addressed in large clinical studies for patients with both UC and CD to demonstrate that FMT could be an effective (personalized) treatment for IBD.

Key Ideas: Fecal Microbiota Transplantation

Beneficial effects observed in preclinical and clinical studies: *1*) restored the diversity of the microbiota; *2*) restored an anti-inflammatory and tolerogenic immune profile; *3*) promoted clinical remission; and *4*) improved disease severity that led to an extended remission for patients with UC. Limitations: lack of randomized clinical studies, especially for CD; lack of reproducibility among studies (FMT procedure, donor type, etc.); more data should be collected to describe precisely the effects of FMT in UC and CD, at different disease stages and different patient phenotypes.

DIET

Several studies underline the protective effect of a healthy diet as well as the high consumption of fruits and vegetables

against the risk of CD development (231, 232). On the contrary, diets enriched in fat and/or sugars constitute risk factors for IBD development (232, 233). The composition of the diet may influence several biological systems: the immune system, the microbiota, and the host response. Epigenetic effects can be induced by diet, as seen in an in vivo study where a methyl-donor maternal diet increases colitis susceptibility in offspring (234). Diet represents an interesting research field for IBD care, especially due to its ease of implementation. The impact of numerous types of diet or diet components have been tested on IBD or colitis model, from high salt to dietary fiber, high-fat, or spicy food, and we cannot be exhaustive in this review to summarize them. Nevertheless, we wanted to mention two particular supplemented diet: vitamin D and $n-3$ or $n-6$ polyunsaturated fatty acids (PUFA) enriched diet, because they represent diets tested long time ago and are among the most investigated nutrients with a potential association to IBD. In addition, they have a renewed interest especially because they regulate and/or are regulated by key elements of digestive homeostasis: lipids and microbiota (147, 235, 236).

Vitamin D

Vitamin D is a lipophilic compound that induces calcium absorption from the gut after binding to the vitamin D receptor (VDR). Deficiency in vitamin D is associated with increased IBD disease activity and clinical relapse (237).

Two in vitro studies on intestinal epithelial and immune cells studied the protective effects of vitamin D, while two others examined therapeutic effects. According to a study on Caco-2 cells challenged with adherent-invasive *E. coli* (AIEC) strain LF82, Vitamin D pretreatment protected against AIEC-induced IEB disruption by maintenance of the tight-junction distribution (Table 5) (273). In addition, pretreatment of immune and intestinal epithelial cells with vitamin D stimulated NOD2 expression, HBD2, and antimicrobial cathelicidin expression (274). In regard to treatment, Vitamin D3 downregulated claudin-1 and -2 and upregulated claudin-4 and -7 in colonic biopsies from patients with UC (Table 5). Besides, vitamin D3 inhibited IL-13 and IL-6 expression (267). Finally, another study found that vitamin D reduced permeability and increased TEER of disrupted IEB (268).

One in vivo study evidenced the protective effect of vitamin D toward colitis in early life. Vitamin D prevented the increase of intestinal permeability in DSS-treated mice as well as the disruption of IEB by AIEC *E. coli* (Table 5) (273). High dose of vitamin D was however deleterious, inducing a more severe colitis and an increase of proinflammatory cytokines expression. Furthermore, microbial composition of mice fed with high dose of vitamin D was similar to that of DSS-treated mice, indicating a negative impact of strong doses of vitamin D on the gut microbiota (275).

All clinical studies were performed in adults, and very few studies investigated the ability of vitamin D to maintain remission in patients with UC (Table 5). Vitamin D maintained gut permeability of patients with CD in remission, decreased C-reactive protein level, but did not change the CDAI score (276). Interestingly, a high dose induced a better rate of relapse than a low dose. Furthermore, vitamin D3 improved anxiety and depression scores (277). A pilot study exhibited the beneficial effects of vitamin D3 supplementation on patients with active CD with improved CDAI and quality-of-life scores (269).

Patients with UC in remission with low serum level of vitamin D (<35 ng/mL) have higher risk of clinical relapse (278). However, there is a lack of studies investigating the effects of vitamin D supplementation to sustain patients with UC in remission. Vitamin D supplementation reduced intestinal inflammation in patients with active UC (270). Besides, patients with active UC presented an increase of *Enterobacteriaceae* but no change in gut microbiota diversity (270). A decrease in UCDAI was observed correlated with an increase in serum vitamin D, a reduction in C-reactive protein, and calprotectin. Patients with active UC who received vitamin D presented decreased DAI, serum C-reactive protein, and TNF level (271). However, another study demonstrated no difference of DAI or inflammatory markers on patients with UC supplemented with vitamin D (272).

$n-3$ or $n-6$ PUFA Supplementation

Because of their attractive anti-inflammatory effects, diets enriched in $n-3$ PUFA and/or diet with an increased $n-3$-to-$n-6$ ($n-3/n-6$) ratio have been tested in different inflammatory digestive pathologies including IBD. In addition, association studies correlated high $n-3$ PUFA concentrations with a reduction of CD and protection from UC (279–281). $n-3$ PUFA modulate the microbiota, by increasing butyrate-producing bacterial genera but also by decreasing *Faecalibacterium,* for instance (282). $n-3$ PUFA are considered anti-inflammatory fatty acids and they may, for example, counter $n-6$ PUFA inflammatory effects by competition (283). Resolvins, protectins, and other proresolving molecules derived from $n-3$ PUFA modulate the immune response toward a resolution of inflammation, and strengthen the barrier by increasing epithelial proliferation (284, 285). Nevertheless, studies showing the protective effects of $n-6$ (12, 13, 286) or those highlighting defects in the metabolites of $n-6$ in patients with IBD (7), reshuffle the cards.

In Vitro Studies

Preincubating cells with $n-3$ PUFA resulted in anti-inflammatory effects, with a decrease of IL-17RA, IL-12B expression in monocytes, and an induction of tolerance by an increase of IL-10 production by dendritic cells (Table 5) (238, 241). A reinforcement of the gut barrier was achieved by increasing the transepithelial resistance, reducing the increase of permeability induced by inflammation, and by preventing barrier disruption (243). The duration of exposure to $n-3$ PUFA is heterogeneous, as well as the mean of inflammation. 15-Hydroxyeicosatetraenoic acid (15-HETE) or 11βPGF2α have $n-6$ PUFA metabolites presented also IEB strengthening properties as they decrease IEB permeability and increase IEB healing (12, 13). Thus, promising results were achieved in vitro for prevention.

Effects are more mitigated for in vitro of $n-3$ PUFA as a treatment (Table 5). Fish oil decreased the production of proinflammatory mediators like PGE_2 and the expression of COX_2, but induced at the same time apoptosis (261, 263). Interestingly, fish oil modified the composition of peripheral blood mononuclear cells and plasma phosphatidylcholine.

Table 5. *Prevention and treatments studies with diet in IBD*

Reference	Food Substrate	Model or Study Design	Age of Supplementation	Effect on IBD	Mechanisms
			Prevention		
238	Krill oil (EPA + DHA)	THP1 cells + LPS, Citrobacter *rodentium*, PMA.	Before inflammation	Anti-inflammatory	Decreased inflammatory cytokines production, induced macrophages M2 differentiation and enhanced bacterial killing.
		White Yorkshire x Landrace pigs, C3H/HeNCr mice + *Trichuris suis* or *C. rodentium* infection	9–10 wo pigs5 wo mice	Anti-inflammatory and improved gut microbiota	Reduced the increase of crypts length, body weight loss, inflammatory cytokines expression. Improved spleen index, changed gut microbiota composition.
239, 240	EPA + DHA	DB RPCT: patients with CD in remission with 5-ASA	Mean age = 10.13 yr old	Reduced relapse.	
		DB RPCT: EPIC-1 (patients with CD in remission), EPIC-2 (patients with active CD UBT)	EPIC-1 mean age (placebo, $n - 3$): 38.2 and 40. 5 yr old. EPIC-2 mean age (placebo, $n - 3$): 40 and 38.5 yr old.	Failed to prevent relapse	No difference in CDAI or SF-36 scores
241, 242	EPA, PA or DHA	BALB/c mice bone marrow-derived DCs, primary HIMEC cells + LPS, IL-1β	Before inflammation	Anti-inflammatory	Increased IL-10 production, reduced VCAM-1 and VEGFR2 expression.
243–246	ALA, EPA, DHA, LA, GLA, AA, fat blend	RAW 264.7, 293 T, T84 cells lines + LPS, IFN-γ/TNF-α, IL4, heat stress		Improved IEB integrity	Reduced NF-κB activation, COX-2 expression. Reinforced the barrier by changing tight junction proteins distribution and morphology.
247–249	LA:ALA, LA:LC $n - 3$ PUFA, $n - 3/n - 6/n - 9$ diets at different ratios	Sprague-Dawley rats + acute DSS or TNBS colitis. Before colitis induction	Postweaning	Anti-inflammatory	Reduced DAI, colon histological score, pro-inflammatory cytokines expression, anemia and inflammatory cytokines. Changed colon phospholipid fatty acids profile.
242, 250, 251	ALA-rich oil, fish oil	Sprague-Dawley rats + acute TNBS colitis. Before colitis induction	7–8 wk inferred	Anti-inflammatory and improved IEB integrity	Decreased adhesion molecules, inflammatory cytokines expression. Anti-angiogenic effect.
252, 253	Extra virgin olive oil (EVOO), polyphenol extract (PE), EVOO + PE, fish oil	Wild-type or Rag2−/− C57BL/6 mice Acute T transfer or DSS colitis (induction + rest). Before colitis induction.	6–12 wo		Reduced DAI, colon histological score, inflammatory cytokines expression and cell proliferation. Fish oil: no effect on IBD score, modified lipid concentrations.
254	Fish oil (n-3 PUFA) + corn oil (n-6 PUFA)	C57BL/6 mice + acute *C. rodentium* colitis. Before infection	4 wo	Improved gut microbiota.	Protected against colitis but increased mortality with impairment of infection-induced responses. Increased Lactobacillus and Bifidobacteria abundances.
255	Fish oil or n-3 PUFA	Meta-analysis: CD and UC patients in remission	Depends on study	No effect	No benefit for UC. N-3 PUFA reduced risk of relapse for CD patients but heterogeneity. Risk of upper GI tract symptoms.

Continued

Table 5.— *Continued*

Reference	Food Substrate	Model or Study Design	Age of Supplementation	Effect on IBD	Mechanisms
256	Atlantic salmon	Pilot study: UC patients UBT	Mean age = 50 yr old		Reduced SCCAI and increased AIFAI in plasma and rectal biopsies.
257–259	EPA-FFA	Controlled study: patients with CD and UC in remission UBT Pilot study, RCT: patients with UC in remission UBT.	Mean age-controlled study (CD, UC, healthy) = 39, 34, 28 yr old Mean age pilot study (control, EPA-FFA) = 22–48, 45 yr old Mean age RCT (placebo, EPA-FFA) = 42.7, 47.1 yr old	Anti-inflammatory and improved gut microbiota	Improved histological inflammation, maintained clinical remission, changed gut microbiota composition.
260	Grounded flaxseed (GF), flaxseed oil (FO)	Open-labeled RCT: patients with UC UBT	Mean age (control, GF, FO) = 32.52, 29.92, 32.30 yr old	Anti-inflammatory	Reduced inflammatory cytokines, Mayo score. Increased IBDQ-9 score.
			Treatment		
261, 262	Fish oil (EPA + DHA), extra virgin olive oil, OA-BSA, LA-BSA, AA, EPA	Caco-2, HT-29, NIH 3T3, RAW 264.7 cells + PMA		Improved IEB integrity	Induced apoptosis, cell differentiation. Decreased cell proliferation.
263, 264	Fish oil + vitamins A, C, E/selenium or enteral elemental diet EO28	CD patients PBMC, plasma phosphatidylcholine, Colonic biopsies of active UC and CD patients + LPS, ConA		Anti-inflammatory	Modified PBMC and plasma phosphatidylcholine compositions. Decreased cytokines and increased IL-1ra production.
265	Extra virgin olive oil	Chronic DSS colitis	6 wk old Sprague-Dawley rats		Decreased DAI and inflammatory cytokines expression, improved histological score.
266	Seal oil (EPA, DPA, DHA)	Pilot study: patients with CD and UC RCT: patients with IBD.	Pilot study age range (CD, UC, control): 27–42, 41–57, 50–67 yr old. RCT age range (CD, UC): 21–44 and 16–55 yr old.		Reduced of SF-36 assessed bodily pain.
267–272	Vitamin D	Inflamed or not biopsies of colon from active UC patients, Caco-2 cells	Adult (>18 yr)	Anti-inflammatory and improved IEB integrity	Anti-inflammatory, improved IEB (Downregulated claudin-1 and -2, upregulated claudin-4 and -7, inhibited IL-13 and IL-6 expression)
		Mild to moderate active CD			Improved IEB (reduced permeability and increased TEER restored expression and localization of ZO-1, claudin 1 and occludin 1)
		Active adult patients with CD		Improved DAI	Improved CDAI (improved of circulating vitamin D level, no change in cytokines level)
		Patients with active UC and inactive UC		Anti-inflammatory	Improved DAI (decreased fecal calprotectin levels and increased albumin increased Enterobacteriaceae but no change in gut microbiota diversity)
		Patients with active UC Patients with mild to moderate active UC			Improved DAI and anti-inflammatory properties (decreased of C-reactive protein and calprotectin, activation of NFκB pathway)

Continued

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Table 5.— *Continued*

Reference	Food Substrate	Model or Study Design	Age of Supplementation	Effect on IBD	Mechanisms
		Patients with active UC		No effect	No difference in DAI or inflammatory markers

AA, arachidonic acid; AIFAI, anti-inflammatory fatty acid index; ALA, linolenic acid; 5-ASA, 5-aminosalicylate; BSA, bovine serum albumin; CD, Crohn's disease; CDAI, Crohn's disease activity index; CLA, conjugated linoleic acid; DAI, disease activity index; DB, double-blind; DBP, diastolic blood pressure; DC, dendritic cells; DGLA, di-homo-gamma-linolenic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; DSS, dextran sulfate sodium; EPA, eicosapentaenoic acid; EPA-FFA, EPA free fatty acid; EPIC, European Prevalence of Infection in Intensive Care; GLA, γ-linolenic acid; IBD, inflammatory bowel diseases; IBDQ-9 = inflammatory bowel disease questionnaire-short form; IEB, intestinal epithelial barrier; IEL, intestinal epithelial lymphocyte; LA, linoleic acid; LC $n-3$ PUFA (polyunsaturated fatty acids), C20:5 $n-3$ and C22:6 $n-3$; LPL, lamina propria lymphocyte; MLN, mesenteric lymph node; LBP, LPS binding protein; OA, oleic acid; PA, palmitic acid; PBMC, peripheral blood mononuclear cells; PBS, phosphate-buffered saline; PMA, phorbol 12-myristate 13- acetate; PG, prostaglandin; RBC, red blood cell; RPCT, randomized placebo controlled trial; RR, relative risk; SBP, systolic blood pressure; SI, small intestine; TEER, transepithelial electrical resistance; TNBS, 2,4,6-trinitrobenzenesulfonic acid; UBT, under baseline treatment; UC, ulcerative colitis; wo, weeks old.

Preclinical Studies

More in vivo data are available on the preventive effects of $n-3$ PUFA, including at early age (Table 5). Postweaning but also as adult, animals supplemented with $n-3$ PUFA showed a reduction of disease severity and improved clinical symptoms. Like in vitro studies, the supplementation modulated proinflammatory cytokines, with a reduction of IL-6 and iNOS (247). Gene expression was also impacted, with a decrease of the colonic NF-κB DNA binding activity (250).

Only one study investigated $n-3$ PUFA treatment at early age (Table 5). In postweaned mice, the $n-3$ diet ameliorated colitis but increased mortality by an impaired response to infection like LPS dephosphorylation ability (254). In adults, extra virgin olive oil reduced disease activity and abrogated DSS-induced gene expression of proinflammatory components like COX-2 and iNOS (265). To conclude on preclinical studies, $n-3$ PUFA intervention as prevention seemed effective, with an improvement of disease severity by similar mechanisms observed in vitro, i.e., a modulation of immune cytokines and gene expression. It should however be noted that the main model of inflammation induction was acute, so the chronic aspect of IBD is lacking and should be taken into consideration for future studies.

Clinical Studies

$n-3$ PUFA diet was mainly studied as treatment (Table 5). Clinical trials on the effects of $n-3$ PUFA at early age are scarce; only one study is enlisted and described the effects of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in 10-yr-old patients with CD in remission. As complement to 5-ASA, $n-3$ PUFA reduced the relapse risk. In adults, 10 studies including 1 meta-analysis and 2 robust studies (~190 CD patients/condition) were listed and comprised a consequent part of small studies (239, 255). EPA, EPA-free fatty acid, and DHA were the main $n-3$ PUFA analyzed. Patients in remission but also with moderately active disease presented decreased disease severity after $n-3$ PUFA consumption. The main effects were on the $n-3/n-6$ ratio, a decrease of proinflammatory cytokines production like IFN-γ and IL-17 by CD4+ and CD8+ T cells of peripheral blood (256, 287). However, in the EPIC-1 and -2 clinical trials that comprised the highest number of participants, $n-3$ PUFA diet failed to prevent relapse and to improve disease severity in patients with CD, active or in remission.

Conclusion on Diet Intake

In vitro and preclinical studies showed clearly beneficial effects of $n-3$ PUFA on inflammation, at different ages and both as preventive and therapeutic mean. However, at clinical level, the heterogeneity of $n-3$ PUFA intake duration and a lack of early age treatment studies do not allow full comparison. Especially, two clinical trials of great number of patients do not corroborate the positive results seen in smaller pilot studies. Also, preventive studies are needed at clinical level to complete the investigation of the potential of $n-3$ PUFA and predictive IBD markers (environmental factors, dysbiosis, etc.) should be taken into account for the recruitment of patients. Overall, diets rich in $n-3$ PUFA are disappointing due to their low efficiency. In view of their benefic effects on the digestive functions, diets rich in $n-6$ PUFA may be considered (7, 12, 13, 286). For example, the arachidonic acid metabolite 11β-PGF2α induces intestinal epithelial healing (13). Another arachidonic acid metabolite, the 15-HETE decreases IEB permeability, and the prostaglandin I2 supplementation alleviates colitis (7, 12). Altogether, implementing a supplementation with not only $n-3$ PUFA, but perhaps $n-6$ PUFA and/or their derived metabolites, represents a relevant direction of study for IBD treatment.

Concerning Vitamin D, the available clinical trials do not have standardization of doses and routes of administration. Despite its inflammatory processes, vitamin D presented opposite effect at different doses, underlining the need for standardized studies to establish how the supplementation should be performed and the doses to be administered.

Key Ideas: Diet

Lack of studies in general, both in prevention and treatment, with homogenized design and not only association studies. $n-3$ PUFA supplementation was beneficial in vitro and at preclinical level but failed to present any robust evidence in clinical trials. In contrast to diets that are globally enriched in $n-6$, recent studies focused on $n-6$ PUFA-metabolites and their interest as supplementation for patients with CD showed promising results.

GENERAL CONCLUSIONS

From pre- to postbiotic, all levels of interventions have been or are being tested to reinforce and restore the microbiota, or mimic its effects. Although preclinical studies show very encouraging results, the transition to the clinic is less easy and will require many additional studies. Can all types of patients with IBD be treated and when? What is the better strategy? Prebiotics have a broad impact and up to now not entirely known. Their low specificity may lead to the fear of amplification of numerous physiological but also pathological processes, and thus the appearance of undesirable effects as recently described with inulin. Our knowledge has largely increased concerning probiotics or cocktails of probiotics, their interactions and their uses for the benefit of the host. They are relatively important means to restore digestive functions or reinforce the homeostasis of the digestive tract. Similarly, FMT is attractive, but many questions remain to be addressed to make progress on the subject. Better understanding of the effect of FMT, identification of super-donors, and of the protective members of their microbiota should lead to the development of next-generation probiotics (288, 289). In this respect, the present development of capsules containing freeze-dried raw microbiota of donors constitutes a first step (290). In general, the use of bacteria to treat is a concept that still needs to be promoted to many clinicians, in particular by demonstrating its safety and effectiveness. In this sense, postbiotics would be safer, but they are, to date, less effective. Nevertheless, we can suppose that a cocktail of postbiotics and means of administration that would allow to control and maintain their concentration would allow to improve this.

The development of bioinformatic modeling, the results of shotgun metagenomics, and metabolomics as well as the use of organoids or organ-on-chip human models should help us precise and define how microbiota-based strategies can improve host homeostasis. Even so, it seems reasonable to think that interventions improving the microbiota or using the microbiota should at least complete and improve the therapies used to treat patients with IBD.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

A.L. and M.M prepared figures; A.L, M.M., and J.M. drafted manuscript; J.M., M.B., G.J., and M.R.-D edited and revised manuscript; A.L., M.M., J.M., M.B., G.J., and M.R.-D approved final version of manuscript.

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