World Journal of Immunology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.5411/wji.v3.i3.31

World J Immunol 2013 November 27; 3(3): 31-43
ISSN 2219-2824 (online)

REVIEW

Probiotics in inflammatory bowel disease: Pathophysiological background and clinical applications

Cristiano Pagnini, Gianfranco Delle Fave, Giorgos Bamias

Cristiano Pagnini, Gianfranco Delle Fave, Faculty of Medicine and Psychology, S.Andrea Hospital, Sapienza University, Rome 00189, Italy
Giorgos Bamias, Academic Department of Gastroenterology, Laikon Hospital, Ethnikon and Kapodistriakon University, Athens 11527, Greece
Author contributions: Pagnini C and Bamias G designed the review and wrote the paper; Delle Fave G contributed to the editing of the paper.
Correspondence to: Giorgos Bamias, MD, Consultant in Gastroenterology, Academic Department of Gastroenterology, Laikon Hospital, Ethnikon and Kapodistriakon University, 17 Agiou Thoma Street, Athens 11527, Greece. gbamias@gmail.com
Telephone: +30-210-7456504 Fax: +30-210-7791839
Received: June 30, 2013 Revised: August 6, 2013
Accepted: August 12, 2013
Published online: November 27, 2013

Abstract

Ulcerative colitis and Crohn's disease, collectively termed the inflammatory bowel diseases (IBD), are chronic inflammatory disorders of the gastrointestinal tract. A "dysbiotic" relationship between the commensal gut flora and the intestinal mucosa-associated immune system has been at the core of the pathogenesis of these conditions. Probiotics are "good bacteria" with the ability to benefit the health of the host and their therapeutic application has been studied in IBD. The theoretical basis for such utilization relies upon the ability of probiotic microorganisms to interfere with the dysregulated homeostasis that takes place in IBD and restore the immune-bacterial interaction at the intestinal mucosa. Proposed mechanisms of action include the reconstitution of altered flora composition, enhancement of the integrity of the epithelial barrier, promotion of tolerogenic action by dendritic cells, strengthening of the defensive mechanisms of the innate immunity, and the suppression of pro-inflammatory adaptive immune responses. Despite this abundance of supporting experimental evidence, clinical application of probiotics in IBD has been disappointing. Possible explanations for such discrepancy include the great diversity of microorganisms that fall under the definition of probiotics, the lack of standardization of dosages and administration schemes, the heterogeneity between clinical trials, and the inclusion in the treatment arms of patients with a large variety of clinical phenotypes. Addressing these important issues will be critical for the optimal usage of probiotic-based therapies for patients with IBD.

Key words: Probiotics; Commensal flora; Mucosa-associated immune system; Inflammatory bowel disease; Clinical trials; Pouchitis; Ulcerative colitis; Crohn's disease

Core tip: Inflammatory bowel diseases are chronic debilitating diseases of the gastrointestinal tract. Current therapies are not effective in a great proportion of patients and are associated with serious adverse effects. The use of probiotics has been tried as an alternative and safe treatment. Herein, we review the pathophysiological basis for such an application and summarize the data from the major clinical trials.

Pagnini C, Delle Fave G, Bamias G. Probiotics in inflammatory bowel disease: Pathophysiological background and clinical applications. *World J Immunol* 2013; 3(3): 31-43 Available from: URL: http://www.wjgnet.com/2219-2824/full/v3/i3/31.htm DOI: http://dx.doi.org/10.5411/wji.v3.i3.31

INTRODUCTION

In recent years, great progress has been made regarding our understanding of the structure and function of intestinal microbiota, leading to attractive novel perspectives for different pathologic conditions. An increasing number of investigational studies have shed light to the

pivotal role of the physiologic host-bacterial mutualistic relationship for health maintenance, as well as the pathophysiological relevance of the disturbance of such balance for the occurrence of several human diseases[1]. Research in this field has been directed towards the two main actors of this interplay: the gut microflora and the intestinal mucosal immune system.

The great advancement that has been achieved regarding laboratory techniques for the quantitative and qualitative evaluation of commensal flora has led to the evolution from a culture-based approach to the metagenomic (molecular profile) and metabolomic (metabolic activity) investigation of bacterial species hosted inside the human gut[2]. Modern analytical methodologies provided a large body of information which, on the one hand, has expanded our comprehension of genera- and species-composition of intestinal microbiota; furthermore, the effects of internal (aging, pathology) and external (drugs, diet) factors on the stability and variation of the flora can be accurately determined[1]. On the other hand, paradoxically, data interpretation has become a difficult task, in the face of the growing diversity of flora composition and its temporal and spatial distribution and the need to correctly balance similarity with inter- and intra-individual variability. In an attempt to simplify this complexity, a stable core microbiome has been described for healthy individuals and people affected by some pathologic conditions (enterotype)[3]. Surprisingly, complexity decreases when considering gene expression profile rather than bacterial species definition[4], indicating that functional analysis of microbiota may provide a more solid framework for future studies.

A comprehensive study of the microbiota is inseparable from the parallel investigation of the host counterpart of the intestinal ecosystem, *i.e.*, the innate and adaptive immunity of the intestinal mucosa. Evidence that the host immune system can shape intestinal gut flora relies on data from animal models. Mice with deficiency of T-bet, a T-box transcription factor family member with important roles in adaptive and innate immunological responses, develop spontaneous colitis that is transmissible to immunological intact mice by fecal transplantation[5]. To date, molecular insight into the mechanism of bacterial recognition points to a binomial pathway, which originates from pathogen-associated molecular pattern/pattern recognition receptor (PAMP/PRR) interaction and, through the activation of transduction proteins (*i.e.*, MYD88, IRAK), leads in turn to the activation of specific genes and production of proteins (*i.e.*, mucins, defensins) that are able to modulate intestinal microflora[6]. To further complicate the picture, many external and internal factors may activate molecular modulators with the potential to induce different pathways[7]. Perturbations affecting microflora and/or innate mucosal immunity are likely to alter the physiological balance between the two compartments. The real impact of such alteration on the development of specific diseases represents a challenge for scientists involved in this field of research.

One major application of research in this field is the opportunity to interfere with the host-bacterial cross-talk. One such way of reinforcing the communication to the benefit of the host, is by means of specific bacterial supplements, namely probiotic bacteria. Although the concept of "good bacteria", capable of benefiting individual health is about 100-year-old, it is only in the last decades that the implementation of probiotics for therapeutic purposes has become widely tested. This was driven on the one side by the impulse of microbiota research, and on the other by market suggestions. To date, rigorous scientific evidence for probiotic utilization has been accomplished for few clinical conditions, such as treatment of acute diarrhea in children and post-antibiotic diarrhea prevention[8,9], prevention of *Clostridium difficile* infection[10], and prevention of atopic eczema associated with cow milk allergy[11].

When considering probiotic administration for the treatment of a specific condition several confounding factors need to be taken into account. First, a variety of different bacterial species and compounds fall under the "probiotic" label. As such microbial diversity is inevitably translated into functional variability, individual strain properties may render one product applicable to a specific clinical setting but not in a different one. At the same time, not every probiotic microorganism may be suitable for a particular condition. Second, the majority of evidence is being generated in experimental models, including animal mimics of human diseases. Although the important contribution of such methods to the elucidation pathogenetic mechanisms cannot be overemphasized, data are not directly translatable in clinical scenarios. Finally, therapeutic doses and schemes are far from being characterized, even for the same probiotic species.

Investigation of the role of probiotic bacteria in inflammatory bowel diseases (IBD) is a valid exemplification of the skepticism presented above. IBD represents a heterogeneous group of disorders that are characterized by persistent intestinal inflammation of unknown etiology. The major forms of IBD are ulcerative colitis (UC) and Crohn's disease (CD), which share many clinical, pathological and immunological characteristics, but are also distinguished by unique phenotypic signatures[12]. Despite a large number of studies that has been published in recent years, solid evidence for the efficacy of probiotics in IBD remains scarce. On the other hand, current research has led to clarification of different molecular pathways that are involved in the action of such bacteria, both during the active phase of inflammation (induction of remission) and as prevention of disease flares (maintenance of remission). Such progress should ideally lead to a critical revision of previous clinical experience with probiotic compounds in IBD and will hopefully lead to the design of translational clinical studies.

In the present review, we critically address the influence of commensal flora in IBD, and the current concept of IBD pathogenesis, in order to evaluate the rational of probiotic use and their putative mechanisms of action

in inflammatory conditions. Moreover, we present and discuss current clinical data of probiotic supplementation in IBD, and we try to delineate the indications for future investigation.

PATHOPHYSIOLOGICAL BACKGROUND

The "dysbiotic" microbiota in IBD

Evidence for a "microbiota influence" in IBD originates from observations in both experimental models and patients. Early studies have outlined a "negative" role of commensal bacteria on IBD onset. First, the majority of animal models of IBD do not develop inflammation when raised on "germ free" conditions; furthermore, reintroduction of bacteria in the gut induces the development of colitis[13,14]. Second, antibiotic therapy has been associated with amelioration of the severity of clinical and experimental intestinal inflammation[5,15]. Third, fecal diversion has been proven efficient in ameliorating inflammation in CD patients and reinfusion of fecal content into a previously excluded ileum resulted in reappearance of the disease[16,17]. Nevertheless, more recent studies have questioned the previous data, putting forward the hypothesis that some commensal species may have protective roles against the development of inflammation. In fact, spontaneous ileitis in SAMP1/YitFc mice develops in a germ-free environment, even though with attenuated severity in comparison to their specific-pathogen-free (SPF) counterparts[18]. In addition, DSS-colitis is more severe in germ free than in SPF mice[19].

The development of novel techniques for microbiota evaluation has opened the way for the identification and characterization of a "dysbiotic state" between commensal flora and gut-associated mucosal immune system in IBD patients compared with normal individuals. Although studies so far failed to identify a single etiologic microorganism for the pathogenesis of disease, many studies reported a reduced diversity of intraluminal and mucosa-adherent microbiota in IBD patients[20]. In general, a reduction of *Firmicutes* have been observed in patients with IBD, with consequent relative increase of *Enterobacteriaceae*[21,22]. Controversial data are available regarding differences between UC and CD patients, as well as between inflamed and uninflamed areas from individual patients[20,23-25]. Alteration of the interspecies balance may have detrimental effects on the homeostasis and development of inflammatory disease by two different reasons. First, the reduction of bacterial diversity may favor the overgrowth of "enteropathogens" with pro-inflammatory properties. Along that line, several studies have reported increased concentration of mucosa-adherent-invasive *E. coli* (AIEC) strains with specific virulence factors in IBD patients[26-28]. Such bacteria were isolated in 36% of ileal specimens of CD patients, compared with 6% of normal control[28], and have the ability to stimulate the production of pro-inflammatory cytokines from macrophages both *in vitro* and *in vivo*[29,30]. Conflicting data are also available for the pro-inflammatory role of *Mycobacterium avium sub. paratuberculosis*[31], pathogenic *Yersinia*[32,33] and *Listeria monocytogenes*[34,35]. Alternatively, dysbiosis may be signified by the reduction of "protective" bacterial species. Several members of *Firmicutes* are strong producers of short chain fatty acids metabolites (acetate and butyrate) with anti-inflammatory properties and important trophic function for colonic mucosa[36]. In this regard, of particular relevance are *Clostridial* cluster IV and XIV, which are relatively less abundant in IBD patients compared with normal controls[23]. Moreover, *Bacteroides fragilis* and *Faecalibacterium prausnitzii* are bacteria with anti-inflammatory properties that are reduced in IBD patients[37,38].

Several probiotic bacteria supplements have been shown to affect microbiota composition and, in particular, to increase diversity. *Lactobacillus casei* and *L. plantarum* have been shown to increase Lactobacillus diversity in mouse colon[39]. *L. rhamnosus subsp. GG* (LGG) administered to mothers increases Bifidobacterial diversity in 5-day-old newborns[40]. Several studies indicate that the administration of the multiple probiotic compound VSL#3, a high dose (450 billions/g) supplement of 8 different bacterial species (4 *Lactobacilli*, 3 *Bifidobacteria* and *S. thermophilus*), affects human and mouse gut flora composition, incrementing diversity[41-43]. Still a matter of debate is the question of the real role of the dysbiosis in the IBD pathogenesis. Recent support to the hypothesis that microflora alteration is not just a consequence but may have a causative role in the development of inflammation, is provided by the ability to transfer inflammatory disease in wild type mice by fecal content transplantation from T-bet-deficient mice[5], and by the promising results of microbiota fecal transplantation in humans[44]. Thus, both gut flora composition and mucosal immune response appears to be equally involved and interconnected in homeostasis maintenance and in the onset of inflammation.

Restoring the barrier defect: Stimulating innate immunity and IEC activity

In the last years, the general conception of IBD pathogenesis has been drastically changed. Indeed, focus has been shifted from an over-reactive immune response, mainly driven by activated T cells[45], to a primarily immunodeficient condition whereby the chronic inflammatory reaction is a paradoxical consequence of a defective immune response, in particular of the innate compartment[46]. This leads to an insufficient handling of the bacterial burden at the intestinal mucosa and, eventually, to the onset of pathological chronic inflammation[47]. In this scheme of events, a compromise of the barrier function of intestinal epithelial cells may be the initiating event. Defective barrier function at the mucosal level can be identified at two separate levels: intestinal permeability and anti-bacterial molecule production[48,49]. Several studies have outlined increased intestinal permeability as an early event in IBD[50]. Older studies have reported increased permeability in patients with CD and their first

degree relatives, suggesting a possible primary etiological role of this alteration for disease occurrence[51]. Derangement of tight junctions, with up-regulation of claudin 2 and down-regulation and redistribution of claudins 5 and 8, has been described in patients with mild to moderate CD[52]. In the spontaneous ileitic SAMP/YitFc murine strain, the primary defect leading to the onset of chronic intestinal inflammation appears to be related to an epithelial permeability increment[53].

Additional levels of homeostatic control include the active secretion of mucins and defensins by epithelial cells. Pathologic mucin production and assembly has been described in human IBD[54], and such alterations has been demonstrated to be associated with colitis in experimental models[55,56]. Alterations in α- and β-defensins production, by Paneth cells and enterocytes, has been reported in IBD[57,58]. The possible role of flawed defensin production in the pathogenesis of CD has been further confirmed by the detection of such defects in patients with polymorphisms of the CD-associated genes nucleotide oligomerization domain 2 (NOD2) and autophagy related protein 16-like 1 (ATG16L1)[59,60]. Moreover, importance of epithelial production of NF-kB mediated production of cytokines (IL-1b, IL-8, TNF) for mucosal homeostasis maintenance has been demonstrated[61,62].

Probiotics have been shown to positively stimulate IEC activity and intestinal permeability. LGG effectively improved intestinal permeability in rats with ethanol-induced colitis, by increased gastric production of Muc6 and PGE2[63]. *L. acidophilus* upregulated muc2 and IL-8, IL-1b and TNFα in IEC, thus inhibiting the attachment of *E.coli* O157:H7[64]. VSL#3 increased mucins genes expression and secretion in IEC[65], and improved intestinal permeability in IL-10 deficient mice[66]. VSL#3 and *L. fermentum* improved intestinal permeability by upregulation of human beta defensin 2 by NF-kB and MAPKs related pathways[67]. VSL#3 effectively prevented ileal inflammation in SAMP1/YitFc mice by NF-kB activation in epithelial cells and consequent production of TNFα and restoring of intestinal permeability; notably, the beneficial effect of probiotics was completely abrogated by the concomitant administration of anti-TNF antibodies[68]. In a further study, the direct effect of epithelial TNFα on amelioration of epithelial barrier permeability in this experimental model, via the modulation of tight junctions proteins, occludin and claudin, was confirmed[69].

Dendritic cells

Intestinal dendritic cells (DC) in the lamina propria of the mucosal layer represent a unique population of innate immune cells whose characteristics are shaped by cell-cell and host-bacteria interactions[70]. Among the specific function of those cells are luminal antigen sampling, T-cell stimulation and differentiation, microbial uptake, pathogen defense, and, notably, the modulation of tolerance toward non pathologic stimuli, such as commensal bacteria, by means of IL10/IL12 balance at mucosal side[71]. The possible relevance of DCs alterations in IBD is supported by experimental data in which mice with deregulated DC-related pathways (*i.e.*, A20, β-catenin and phosphotydilinositol-3-kinase) develop either spontaneous colitis or increased susceptibility to experimental colitis[72,73]. Furthermore, in IBD patients, lamina propria DCs and macrophages produce higher amount of pro-inflammatory cytokines compared with normal controls[74].

For their relevance in the mucosal homeostasis maintenance, and for their crucial "bridging" role between innate and adaptive immunity activation, DCs has been indicated as potential targets of probiotic bacteria in IBD. In fact, *L. salivarius Ls33* and *L. rhamnosus Lr32* promoted tolerogenic action of DC *in vitro*, and administration of probiotic-incubated DC ameliorated trinitro-benzene-sulfonic acid induced colitis in mice[75]. A fermentation product of *B. breve* has been shown the potential to modulate DC function in vitro by selective activation of MAPK, GSK3 and PI3K[76]. Five commensal/probiotic bacteria incubated with immature DC induced a distinct cytokines profile and a tolerogenic phenotype through the selection of hyporesponsive T cells[77]. The probiotic mixture VSL#3 increased IL-10 in intestinal and blood DC's from healthy volunteers, and inhibited Th-1 cells and IL-12 production[78].

Immunomodulation of the acquired immune response

IBD has been considered for a long time as a disease primarily caused by dysregulation of acquired immune responses, with over-reactive effector pathways of the Th1 (CD) or Th2 (UC) type. This view was sustained by the observed increase of cytokines of the Th1 pathways (TNF, IFNγ) in CD patients and overexpression of IL-5 and IL-13 in colonic specimens of UC patients[79]. Furthermore, the importance of activated lymphocytes has been confirmed by the development of animal models of IBD with specific up-regulation of Th1 derived cytokines (IL-10 KO, $TNF^{\Delta ARE}$ mice)[80,81], and by the observation that inflammatory disease in experimental models can be induced to SCID mice by the adoptive transfer of specific subpopulations of lymphocytes[82]. The immune imbalance may be due either to defective regulatory pathways (T-regs, IL-10 and TGFβ) and/or the increment of pro-inflammatory Th1 and/or Th2 derived cytokines. In recent years, this schematic paradigm has been consistently disputed: cytokines of both Th1 and Th2 derivation has been observed both in CD and UC patients[46] and efficacy of anti-TNF antibodies in UC confirmed that Th1 cytokines has an important role for inflammation even in UC and not only in CD[83]. At present the classical pathogenic scheme has been replaced by a model in which different mediators (cytokines) interplay in the induction, development and maintenance of inflammatory disease (in CD and UC)[46], thus overcoming the schematic division of the past. Despite the overwhelming recent evidence supporting a primary role of innate immunity in the pathogenic cascade leading to IBD development, the dramatic efficacy of anti-TNF antibodies, the fact that blockage of adaptive immune responses

remains the main target of therapy (*i.e.*, corticosteroids, immunosuppressants), the promising data from leukocytapheresis[84], bone marrow and mesenchymal stem cells transplantation[85], testify that acquired immune response over-activation is a important factor for inflammation onset and maintenance in IBD. In addition, the recent discovery of the relevance of IL23/IL17 pathways, supported by the observation of increased concentration of Th17 lymphocytes (producing IL17 upon stimulation of IL23) in the inflamed mucosa of CD patients[86,87], and the effective amelioration of experimental inflammation by selective blocking of IL23/IL17 pathways[88,89], has given new impulse to the investigation of the role of the adaptive compartment in IBD pathogenesis. Accordingly, monoclonal antibody targeting of the p40 subunit of IL12/IL23 (Ustekinumab) is currently under investigation as potential therapy in CD[90]. Commensal bacteria have an important role in the physiologic maturation of the adaptive compartment of the immune system, since germ-free mice have low number of CD4 T cells producing IL17, IFNγ, TNFα and IL-10[91].

Several probiotic bacteria have a direct inhibitory effect on the pro-inflammatory cytokines production and a concomitant stimulatory function on T-reg cells and modulatory cytokines. The probiotic mixture VSL#3 was shown to induce IL-10 dependent T-reg cells in an animal model of recurrent chemical-induced colitis[92], and to increase tissue levels of IL-10 and reduce pro-inflammatory cytokines, nitric oxide synthesis and mellaproteinase activity in the inflamed pouch[93]. In a microarray analysis, LGG altered the expression of several genes related to immune response and inflammation in human duodenal mucosa[94]. In the IL-10 KO model of colitis, the probiotic bacteria *L. plantarum*, *B. infantis* and *L. salivarius* prevented and/or ameliorated inflammation by down-regulation of pro-inflammatory Th1 derived cytokines[95,96]. Three strains of Lactobacilli reduced Th2 response and activated T-reg frequency in health mice in a strain dependent way[97]. In a pediatric study, rectal enemas with *L. reuteri* ameliorated inflammation by augmenting mucosal expression of IL-10 and reducing of IL1β, TNFα and IL8[98]. *Bifidobacteria* and *S. thermophilus* stimulated the production of TGFβ and the development of T-reg cells in PBMC from humans[99]. Finally, in a mouse model of allergic asthma, *L. gasseri* suppressed the Th-17 pro-inflammatory response[100].

CLINICAL APPLICATION

Despite the large amount of experimental data and the pathophysiological rational for their use in IBD, solid clinical evidence for the applicability of probiotic supplementation in these conditions is still lacking. Existing data are convincing for maintenance of remission in pouchitis, promising for maintenance of remission in UC, but disappointing for CD (Table 1). In fact, a recent workshop of an expert committee expressed a grade A (supported by strong positive studies) recommendation for probiotic use for prevention and maintenance of remission of pouchitis (VSL#3) and for remission maintenance in UC (VSL#3 and *E. coli* Nissle 1917), a grade B (positive-controlled studies but some negative studies) for inducing remission in UC (VSL#3 and *E. coli* Nissle 1917), and a grade C (some positive studies but clearly inadequate amount of work to support the outcome) for induction of remission of pouchitis (VSL #3) and in CD (*E. coli* Nissle 1917, *S. boulardii*, LGG)[101]. Interestingly, in the same expert workshop held three years before, all IBD indications scored a C grade of recommendation, with the sole exception of pouchitis prevention and maintenance of remission (A grade)[102].

One of the major limitations for probiotic utilization is that considerable variability exists between studies in regards to probiotic species used, dosage and duration of therapy, as well as variability of the underlying inflammatory disease and concomitant medication usage. Indeed, IBD comprises a continuum spectrum of disease, which far exceeds the simplistic subdivision in the two main clinical entities of UC and CD. In the two far ends of the spectrum are patients with very mild and limited rectal disease and patients with extended and devastating complications such as perianal and systemic involvement. Thus, it is not surprising that the best results for probiotics have been accomplished in experimental models of IBD, where the inflammatory condition is the consequence of alteration of single specific pathways. Besides the appropriate design of clinical trials which should include clear end-points, satisfactory statistical power, well-selected probiotic formulations given in adequate dose and scheme[103,104], the key for the future clinical investigation of probiotics application in IBD is the comprehension of the complexity of the single conditions and the appropriate selection of patients with similar characteristics in terms of disease activity, extension, phenotype and molecular features.

Pouchitis

Acute and chronic pouchitis are relatively frequent events in patients with Ileal Pouch Anal Anastomosis (IPAA) following colectomy for UC. The application of probiotics for the maintenance of remission after pouchitis represented the earliest and most established clinical indication of probiotics in IBD. The therapeutic administration of probiotics in patients with pouch has been proven effective in the remission maintenance and prevention of pouchitis, and for this indication the probiotic mixture VSL#3 has been included in the European Crohn and Colitis Organization (ECCO) guidelines[105]. In fact, a recent Cochrane systematic review included two studies of VSL#3 *vs* placebo for remission maintenance of pouchitis after remission induced by antibiotics, and probiotic treated patients had significant lower rate of recurrence after 9 mo[106] and 1 year[107]. Accordingly, LGG administration significantly increased the duration time of remission in a three-year follow-up[108]. The same meta-analysis included two studies analyzing the VSL#3 administration

Table 1 Main published randomized control trial on probiotics administration in patients with inflammatory bowel diseases

Author, year	Disease	Indication	Probiotic	*n*	Outcome
Gionchetti *et al*[106] 2000	IPAA	Remission maintenance	VSL#3	20 treated 20 placebo	Superior to placebo
Mimura *et al*[107] 2004	IPAA	Remission maintenance	VSL#3	20 treated 16 placebo	Superior to placebo
Gionchetti *et al*[109] 2003	IPAA	Prevention	VSL#3	20 treated 20 placebo	Superiori to placebo
Gosselink *et al*[108] 2004	IPAA	Prevention	LGG	38 treated 35 no treatment	Superior to no treatment
Pronio *et al*[110] 2008	IPAA	Prevention	VSL#3	16 treated 15 no treatment	Superior to no treatment
Kuisma *et al*[111] 2003	IPAA	Pouchitis	LGG	10 treated 10 placebo	No difference
Rembacken *et al*[117] 1999	UC	Inducing and maintenance remission	*E. coli Nissle* 1917	57 treated 59 mesalamine	Not inferior
Kato *et al*[116] 2009	UC	Inducing remission	Fermented milk (*B. breve*$^+$ *B. bifidum*)	10 treated 10 placebo	No difference
Tursi *et al*[118] 2004	UC	Inducing remission	VSL#3	30 VSL#3$^+$ balsalazide 30 balsalazide 28 mesalamine	VSL#3$^+$ balsalazide better
Furrie *et al*[115] 2005	UC	Inducing remission	Synbiontic (*B. longum*)	9 treated 9 placebo	No difference
Matthes *et al*[124] 2006	UC	Inducing remission	*E. coli Nissle* 1917 (enemas)	20 treated (3 groups different doses) 20 placebo	Superior to placebo
Sood *et al*[126] 2009	UC	Inducing remission	VSL#3	77 treated 70 placebo	Superior to placebo
Miele *et al*[125] 2009	UC (pediatric)	Inducing and maintenance remission	VSL#3	14 treated 15 placebo	Superior to placebo (corticosteroids)
Tursi *et al*[118] 2004	UC	Inducing remission	VSL#3	71 treated 73 placebo	No difference
Kruis *et al*[119] 1997	UC	Remission maintenance	*E. coli Nissle* 1917	58 treated 60 mesalamine	Not inferior
Ishikawa *et al*[127] 2003	UC	Remission maintenance	Bifidobacteria-fermented milk	11 treated 10 placebo	Superior to placebo
Cui *et al*[128] 2004	UC	Remission maintenance	Bifidobacteria	15 treated 15 placebo	Superior to placebo
Kruis *et al*[120] 2004	UC	Remission maintenance	*E. coli Nissle* 1917	162 treated 165 mesalamine	Not inferior
Zocco *et al*[121] 2006	UC	Remission maintenance	LGG	65 LGG 62 LGG$^+$ mesalamine 60 mesalamine	No difference remission rate LGG longer relapse-free time
Wildt *et al*[122] 2011	UC	Remission maintenance	*L. acidophilus LA-5* and *B. animalis subsp. Lactis BB-12*	20 treated 12 placebo	No difference
Malchow *et al*[136] 1997	CD	Remission maintenance	*E. coli Nissle* 1917	10 treated 10 placebo	No difference
Guslandi *et al*[135] 2000	CD	Remission maintenance	*S. boulardii*	16 mesalamine$^+$ probiotic 16 mesalamine	No difference
Prantera *et al*[131] 2002	CD	Remission maintenance (post-surgery)	LGG	18 treated 19 placebo	No difference
Schultz *et al*[134] 2004	CD	Inducing and maintenance remission	LGG	4 treated 5 placebo	No difference
Bousvaros *et al*[133] 2005	CD (pediatric)	Remission maintenance	LGG	39 treated 36 placebo	No difference
Marteau *et al*[139] 2006	CD	Remission maintenance	*L. johnsonii* (LA1)	48 treated 50 placebo	No difference
Van Gossum *et al*[140] 2007	CD	Remission maintenance	*L. johnsonii* (LA1)	34 treated 36 placebo	No difference
Chermesh *et al*[142] 2007	CD	Remission maintenance	Symbiontic 2000	15 treated 15 placebo	No difference

RCT: Randomized control trial; IPAA: Ileal pouch anal anastomosis; UC: Ulcerative colitis; CD: Crohn's disease; LGG: *L. rhamnosus subsp. GG*; *E. coli*: *Escherichia coli*.

in the prevention of pouchitis onset, finding the probiotic mixture superior to placebo[109] and to no treatment[110]. For acute pouchitis data are still sparse and conflicting. LGG was not superior to placebo in a randomized con-

trol trial (RCT)[111], while in an open-label study VSL#3 was effective in patients with mild pouchitis[112].

UC

Probiotic applications in UC are encouraging, although solid evidence for their use is still unproven. Two Cochrane systematic reviews analyzed the utilization of probiotics in induction of remission and in remission maintenance, respectively[113,114]. The first included four studies: two small trials compared a symbiotic preparation with B. longum (n = 9 patients in treatment group *vs* n = 9 controls)[115] and fermented milk supplemented with B. breve and B. bifidum (n = 10 treated *vs* n = 10 controls) to placebo in addition to standard therapy[116]; in one trial supplementation of *E. coli* Nissle 1917 was equal to mesalamine (n = 57 probiotics *vs* n = 59 mesalamine group)[117], and in one study patients treated with balsalazide plus VSL#3 (n= 30) had increased remission compared with patients receiving only balsalazide (n = 30) or mesalamine (n = 28)[118]. The authors concluded that there is no evidence that probiotics are superior to placebo or mesalamine in inducing remission in UC[113]. In the meta-analysis for remission maintenance, four studies were included. Two multicenter studies compared the administration of *E. coli* Nissle 1917 to mesalamine for 3 (n = 58 probiotic and n = 60 mesalamine) and 12 mo (n = 162 probiotic and n = 165 mesalamine), finding no difference in recurrence rate[119,120], and one study compared LGG (n = 65), LGG+ mesalamine (n = 62) and mesalamine alone (n = 60) at 12 mo, finding no difference in remission rate but a longer disease free time in LGG treated group[121]. One small trial compared administration of a probiotic mixture of *L. acidophilus* strain LA-5 and *B. animalis subsp. Lactis* strain BB-12 (n = 20) to placebo (n = 12), finding no difference[122]. The authors of the meta-analysis conclude that there is no evidence that probiotics are superior to mesalamine or placebo for maintenance of remission in UC patients[114]. Another recent meta-analysis analyzed 13 RCT of probiotics utilization in UC, both in induction of remission (n = 7) and in remission maintenance (n = 8, two studies analyzed both the outcomes)[123]. For induction of remission, three supplemental studies were analyzed in addition to the ones already included in Cochrane's review, in which *E. coli* Nissle (only in abstract form[124]) and VSL#3, in a pediatric[125] and adult group of UC patients[126], were tested. Overall, in a total of 399 patients (219 probiotics *vs* 180 standard therapy/placebo) the authors did not report significant difference in inducing remission between probiotic treated and placebo/standard therapy treated patients. In the maintenance of remission, eight clinical trials were included, five of which were previously excluded by the Cochrane meta-analysis due to lack of remission of the patients at the beginning of the trail[117,125,127], short follow-up[128], or because it was not a RCT[129]. A total of 709 patients were globally analyzed (390 probiotics *vs* 319 standard therapy/placebo), and there was a statistically significant difference in favor of probiotic group for remission rate (recurrence rate = 0.69, 95%CI: 0.47-1.01, $P < 0.05$). It is of note that the results of this meta-analysis should be interpreted with caution for the presence of significant heterogeneity across the studies.

CD

A Cochrane meta-analysis analyzed seven RCT (five full papers and two abstracts) for application of probiotic for maintenance of remission in CD patients, with a total of 160 patients[130]. In two studies the remission was surgically-induced[131,132], and in five medically-induced[133-137]. Probiotics tested were LGG[131,133,134,137], VSL#3[132], *E.coli* Nissle 1917[136], and S. Boulardii[135]. Authors conclude that probiotics were not superior to placebo or aminosalycilates. Another recent meta-analysis examined probiotics in the post-operative prophylaxis, including five studies, none of which showed effectiveness of probiotics vs. placebo for the prevention of recurrence[138]. Probiotics tested were *L. johnsonii*[139,140], LGG[131], VSL#3 in a study available only in abstract form[141], and the preparation Symbiontic 2000[142]. Only one small RCT tested the efficacy of probiotic in inducing remission in CD[134], with no difference *vs* placebo. The disappointing results of human studies are confirmed in experimental models: in SAMP/YitFc spontaneous model of CD, administration of VSL#3 was effective only for prevention of disease, and not in established disease, and the preventive effect was obtained only with a 50-times higher dose comparing to the one effective in experimental colitis[68]. Those data underscore that probably the application of probiotics in CD needs to be further improved in terms of dose and timing of administration.

CONCLUSION

The recent expansion of research on gut microbiota opened the way to the application of probiotic therapy for IBD. Probiotic bacteria may be of value in IBD, since consistent experimental work has unraveled potential molecular targets in the pathogenesis of intestinal inflammation. In IBD patients, altered bacterial composition, defects in the barrier function, impairment in innate and adaptive immune response, may lead to a deregulated chronic inflammatory condition. Probiotics are likely to act through different mechanism affecting all the aforementioned defects and restore alterations at several levels, thus promoting gut health and homeostasis. Nonetheless, clinical data are still inconclusive, in particular in CD. It is desirable that the progress in the research in IBD pathogenesis and in host-bacteria interaction will drive to a tailored approach, including appropriate selection of patients with specific features of disease, utilization of bacterial species with proven efficacy, and with the characterization of effective therapeutic schemes.

REFERENCES

1 **Nicholson JK**, Holmes E, Kinross J, Burcelin R, Gibson G, Jia

W, Pettersson S. Host-gut microbiota metabolic interactions. *Science* 2012; **336**: 1262-1267 [PMID: 22674330 DOI: 10.1126/science.1223813]
2 **Fraher MH**, O'Toole PW, Quigley EM. Techniques used to characterize the gut microbiota: a guide for the clinician. *Nat Rev Gastroenterol Hepatol* 2012; **9**: 312-322 [PMID: 22450307 DOI: 10.1038/nrgastro.2012.44]
3 **Arumugam M**, Raes J, Pelletier E, Le Paslier D, Yamada T, Mende DR, Fernandes GR, Tap J, Bruls T, Batto JM, Bertalan M, Borruel N, Casellas F, Fernandez L, Gautier L, Hansen T, Hattori M, Hayashi T, Kleerebezem M, Kurokawa K, Leclerc M, Levenez F, Manichanh C, Nielsen HB, Nielsen T, Pons N, Poulain J, Qin J, Sicheritz-Ponten T, Tims S, Torrents D, Ugarte E, Zoetendal EG, Wang J, Guarner F, Pedersen O, de Vos WM, Brunak S, Doré J, Antolín M, Artiguenave F, Blottiere HM, Almeida M, Brechot C, Cara C, Chervaux C, Cultrone A, Delorme C, Denariaz G, Dervyn R, Foerstner KU, Friss C, van de Guchte M, Guedon E, Haimet F, Huber W, van Hylckama-Vlieg J, Jamet A, Juste C, Kaci G, Knol J, Lakhdari O, Layec S, Le Roux K, Maguin E, Mérieux A, Melo Minardi R, M'rini C, Muller J, Oozeer R, Parkhill J, Renault P, Rescigno M, Sanchez N, Sunagawa S, Torrejon A, Turner K, Vandemeulebrouck G, Varela E, Winogradsky Y, Zeller G, Weissenbach J, Ehrlich SD, Bork P. Enterotypes of the human gut microbiome. *Nature* 2011; **473**: 174-180 [PMID: 21508958 DOI: 10.1038/nature09944]
4 **Turnbaugh PJ**, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, Sogin ML, Jones WJ, Roe BA, Affourtit JP, Egholm M, Henrissat B, Heath AC, Knight R, Gordon JI. A core gut microbiome in obese and lean twins. *Nature* 2009; **457**: 480-484 [PMID: 19043404 DOI: 10.1038/nature07540]
5 **Garrett WS**, Lord GM, Punit S, Lugo-Villarino G, Mazmanian SK, Ito S, Glickman JN, Glimcher LH. Communicable ulcerative colitis induced by T-bet deficiency in the innate immune system. *Cell* 2007; **131**: 33-45 [PMID: 17923086 DOI: 10.1016/j.cell.2007.08.017]
6 **Sansonetti PJ**. War and peace at mucosal surfaces. *Nat Rev Immunol* 2004; **4**: 953-964 [PMID: 15573130 DOI: 10.1038/nri1499]
7 **Kawai T**, Akira S. Toll-like receptors and their crosstalk with other innate receptors in infection and immunity. *Immunity* 2011; **34**: 637-650 [PMID: 21616434 DOI: 10.1016/j.immuni.2011.05.006]
8 **Huang JS**, Bousvaros A, Lee JW, Diaz A, Davidson EJ. Efficacy of probiotic use in acute diarrhea in children: a meta-analysis. *Dig Dis Sci* 2002; **47**: 2625-2634 [PMID: 12452406]
9 **D'Souza AL**, Rajkumar C, Cooke J, Bulpitt CJ. Probiotics in prevention of antibiotic associated diarrhoea: meta-analysis. *BMJ* 2002; **324**: 1361 [PMID: 12052801 DOI: 10.1136/bmj.324.7350.1361]
10 **Johnston BC**, Ma SS, Goldenberg JZ, Thorlund K, Vandvik PO, Loeb M, Guyatt GH. Probiotics for the prevention of Clostridium difficile-associated diarrhea: a systematic review and meta-analysis. *Ann Intern Med* 2012; **157**: 878-888 [PMID: 23362517 DOI: 10.7326/0003-4819-157-12-201212180-00563]
11 **Osborn DA**, Sinn JK. Probiotics in infants for prevention of allergic disease and food hypersensitivity. *Cochrane Database Syst Rev* 2007; **(4):** CD006475 [PMID: 17943912]
12 **Bamias G**, Nyce MR, De La Rue SA, Cominelli F. New concepts in the pathophysiology of inflammatory bowel disease. *Ann Intern Med* 2005; **143**: 895-904 [PMID: 16365470 DOI: 10.7326/0003-4819-143-12-200512200-00007]
13 **Taurog JD**, Richardson JA, Croft JT, Simmons WA, Zhou M, Fernández-Sueiro JL, Balish E, Hammer RE. The germfree state prevents development of gut and joint inflammatory disease in HLA-B27 transgenic rats. *J Exp Med* 1994; **180**: 2359-2364 [PMID: 7964509 DOI: 10.1084/jem.180.6.2359]
14 **Sellon RK**, Tonkonogy S, Schultz M, Dieleman LA, Grenther W, Balish E, Rennick DM, Sartor RB. Resident enteric bacteria are necessary for development of spontaneous colitis and immune system activation in interleukin-10-deficient mice. *Infect Immun* 1998; **66**: 5224-5231 [PMID: 9784526]
15 **Feller M**, Huwiler K, Schoepfer A, Shang A, Furrer H, Egger M. Long-term antibiotic treatment for Crohn's disease: systematic review and meta-analysis of placebo-controlled trials. *Clin Infect Dis* 2010; **50**: 473-480 [PMID: 20067425 DOI: 10.1086/649923]
16 **Rutgeerts P**, Goboes K, Peeters M, Hiele M, Penninckx F, Aerts R, Kerremans R, Vantrappen G. Effect of faecal stream diversion on recurrence of Crohn's disease in the neoterminal ileum. *Lancet* 1991; **338**: 771-774 [PMID: 1681159 DOI: 10.1016/0140-6736(91)90663-A]
17 **D'Haens GR**, Geboes K, Peeters M, Baert F, Penninckx F, Rutgeerts P. Early lesions of recurrent Crohn's disease caused by infusion of intestinal contents in excluded ileum. *Gastroenterology* 1998; **114**: 262-267 [PMID: 9453485 DOI: 10.1016/S0016-5085(98)70476-7]
18 **Bamias G**, Okazawa A, Rivera-Nieves J, Arseneau KO, De La Rue SA, Pizarro TT, Cominelli F. Commensal bacteria exacerbate intestinal inflammation but are not essential for the development of murine ileitis. *J Immunol* 2007; **178**: 1809-1818 [PMID: 17237431]
19 **Kitajima S**, Morimoto M, Sagara E, Shimizu C, Ikeda Y. Dextran sodium sulfate-induced colitis in germ-free IQI/Jic mice. *Exp Anim* 2001; **50**: 387-395 [PMID: 11769541 DOI: 10.1538/expanim.50.387]
20 **Frank DN**, St Amand AL, Feldman RA, Boedeker EC, Harpaz N, Pace NR. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *Proc Natl Acad Sci USA* 2007; **104**: 13780-13785 [PMID: 17699621 DOI: 10.1073/pnas.0706625104]
21 **Ott SJ**, Musfeldt M, Wenderoth DF, Hampe J, Brant O, Fölsch UR, Timmis KN, Schreiber S. Reduction in diversity of the colonic mucosa associated bacterial microflora in patients with active inflammatory bowel disease. *Gut* 2004; **53**: 685-693 [PMID: 15082587 DOI: 10.1136/gut.2003.025403]
22 **Walker AW**, Sanderson JD, Churcher C, Parkes GC, Hudspith BN, Rayment N, Brostoff J, Parkhill J, Dougan G, Petrovska L. High-throughput clone library analysis of the mucosa-associated microbiota reveals dysbiosis and differences between inflamed and non-inflamed regions of the intestine in inflammatory bowel disease. *BMC Microbiol* 2011; **11**: 7 [PMID: 21219646 DOI: 10.1186/1471-2180-11-7]
23 **Andoh A**, Imaeda H, Aomatsu T, Inatomi O, Bamba S, Sasaki M, Saito Y, Tsujikawa T, Fujiyama Y. Comparison of the fecal microbiota profiles between ulcerative colitis and Crohn's disease using terminal restriction fragment length polymorphism analysis. *J Gastroenterol* 2011; **46**: 479-486 [PMID: 21253779 DOI: 10.1007/s00535-010-0368-4]
24 **Manichanh C**, Rigottier-Gois L, Bonnaud E, Gloux K, Pelletier E, Frangeul L, Nalin R, Jarrin C, Chardon P, Marteau P, Roca J, Dore J. Reduced diversity of faecal microbiota in Crohn's disease revealed by a metagenomic approach. *Gut* 2006; **55**: 205-211 [PMID: 16188921 DOI: 10.1136/gut.2005.073817]
25 **Lepage P**, Seksik P, Sutren M, de la Cochetière MF, Jian R, Marteau P, Doré J. Biodiversity of the mucosa-associated microbiota is stable along the distal digestive tract in healthy individuals and patients with IBD. *Inflamm Bowel Dis* 2005; **11**: 473-480 [PMID: 15867587 DOI: 10.1097/01.MIB.0000159662.62651.06]
26 **Martin HM**, Campbell BJ, Hart CA, Mpofu C, Nayar M, Singh R, Englyst H, Williams HF, Rhodes JM. Enhanced Escherichia coli adherence and invasion in Crohn's disease and colon cancer. *Gastroenterology* 2004; **127**: 80-93 [PMID: 15236175 DOI: 10.1053/j.gastro.2004.03.054]
27 **Martinez-Medina M**, Aldeguer X, Lopez-Siles M, González-Huix F, López-Oliu C, Dahbi G, Blanco JE, Blanco J, Garcia-Gil LJ, Darfeuille-Michaud A. Molecular diversity of Escherichia coli in the human gut: new ecological evidence

supporting the role of adherent-invasive E. coli (AIEC) in Crohn's disease. *Inflamm Bowel Dis* 2009; **15**: 872-882 [PMID: 19235912 DOI: 10.1002/ibd.20860]
28 **Darfeuille-Michaud A**, Boudeau J, Bulois P, Neut C, Glasser AL, Barnich N, Bringer MA, Swidsinski A, Beaugerie L, Colombel JF. High prevalence of adherent-invasive Escherichia coli associated with ileal mucosa in Crohn's disease. *Gastroenterology* 2004; **127**: 412-421 [PMID: 15300573 DOI: 10.1053/j.gastro.2004.04.061]
29 **Barnich N**, Carvalho FA, Glasser AL, Darcha C, Jantscheff P, Allez M, Peeters H, Bommelaer G, Desreumaux P, Colombel JF, Darfeuille-Michaud A. CEACAM6 acts as a receptor for adherent-invasive E. coli, supporting ileal mucosa colonization in Crohn disease. *J Clin Invest* 2007; **117**: 1566-1574 [PMID: 17525800 DOI: 10.1172/JCI30504]
30 **Carvalho FA**, Barnich N, Sivignon A, Darcha C, Chan CH, Stanners CP, Darfeuille-Michaud A. Crohn's disease adherent-invasive Escherichia coli colonize and induce strong gut inflammation in transgenic mice expressing human CEACAM. *J Exp Med* 2009; **206**: 2179-2189 [PMID: 19737864 DOI: 10.1084/jem.20090741]
31 **Sartor RB**. Does Mycobacterium avium subspecies paratuberculosis cause Crohn's disease? *Gut* 2005; **54**: 896-898 [PMID: 15951529 DOI: 10.1136/gut.2004.055889]
32 **Lamps LW**, Madhusudhan KT, Havens JM, Greenson JK, Bronner MP, Chiles MC, Dean PJ, Scott MA. Pathogenic Yersinia DNA is detected in bowel and mesenteric lymph nodes from patients with Crohn's disease. *Am J Surg Pathol* 2003; **27**: 220-227 [PMID: 12548169 DOI: 10.1097/00000478-200302000-00011]
33 **Knösel T**, Schewe C, Petersen N, Dietel M, Petersen I. Prevalence of infectious pathogens in Crohn's disease. *Pathol Res Pract* 2009; **205**: 223-230 [PMID: 19186006 DOI: 10.1016/j.prp.2008.04.018]
34 **Liu Y**, van Kruiningen HJ, West AB, Cartun RW, Cortot A, Colombel JF. Immunocytochemical evidence of Listeria, Escherichia coli, and Streptococcus antigens in Crohn's disease. *Gastroenterology* 1995; **108**: 1396-1404 [PMID: 7729631 DOI: 10.1016/0016-5085(95)90687-8]
35 **Walmsley RS**, Anthony A, Sim R, Pounder RE, Wakefield AJ. Absence of Escherichia coli, Listeria monocytogenes, and Klebsiella pneumoniae antigens within inflammatory bowel disease tissues. *J Clin Pathol* 1998; **51**: 657-661 [PMID: 9930068 DOI: 10.1136/jcp.51.9.657]
36 **Hodin R**. Maintaining gut homeostasis: the butyrate-NF-kappaB connection. *Gastroenterology* 2000; **118**: 798-801 [PMID: 10734032 DOI: 10.1016/S0016-5085(00)70150-8]
37 **Mazmanian SK**, Liu CH, Tzianabos AO, Kasper DL. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. *Cell* 2005; **122**: 107-118 [PMID: 16009137 DOI: 10.1016/j.cell.2005.05.007]
38 **Sokol H**, Pigneur B, Watterlot L, Lakhdari O, Bermúdez-Humarán LG, Gratadoux JJ, Blugeon S, Bridonneau C, Furet JP, Corthier G, Grangette C, Vasquez N, Pochart P, Trugnan G, Thomas G, Blottière HM, Doré J, Marteau P, Seksik P, Langella P. Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. *Proc Natl Acad Sci USA* 2008; **105**: 16731-16736 [PMID: 18936492 DOI: 10.1073/pnas.0804812105]
39 **Fuentes S**, Egert M, Jiménez-Valera M, Ramos-Cormenzana A, Ruiz-Bravo A, Smidt H, Monteoliva-Sanchez M. Administration of Lactobacillus casei and Lactobacillus plantarum affects the diversity of murine intestinal lactobacilli, but not the overall bacterial community structure. *Res Microbiol* 2008; **159**: 237-243 [PMID: 18439805 DOI: 10.1016/j.resmic.2008.02.005]
40 **Gueimonde M**, Sakata S, Kalliomäki M, Isolauri E, Benno Y, Salminen S. Effect of maternal consumption of lactobacillus GG on transfer and establishment of fecal bifidobacterial microbiota in neonates. *J Pediatr Gastroenterol Nutr* 2006; **42**: 166-170 [PMID: 16456409 DOI: 10.1097/01.mpg.0000189346.25172.fd]
41 **Kühbacher T**, Ott SJ, Helwig U, Mimura T, Rizzello F, Kleessen B, Gionchetti P, Blaut M, Campieri M, Fölsch UR, Kamm MA, Schreiber S. Bacterial and fungal microbiota in relation to probiotic therapy (VSL#3) in pouchitis. *Gut* 2006; **55**: 833-841 [PMID: 16401690 DOI: 10.1136/gut.2005.078303]
42 **Gaudier E**, Michel C, Segain JP, Cherbut C, Hoebler C. The VSL# 3 probiotic mixture modifies microflora but does not heal chronic dextran-sodium sulfate-induced colitis or reinforce the mucus barrier in mice. *J Nutr* 2005; **135**: 2753-2761 [PMID: 16317116]
43 **Uronis JM**, Arthur JC, Keku T, Fodor A, Carroll IM, Cruz ML, Appleyard CB, Jobin C. Gut microbial diversity is reduced by the probiotic VSL#3 and correlates with decreased TNBS-induced colitis. *Inflamm Bowel Dis* 2011; **17**: 289-297 [PMID: 20564535 DOI: 10.1002/ibd.21366]
44 **Damman CJ**, Miller SI, Surawicz CM, Zisman TL. The microbiome and inflammatory bowel disease: is there a therapeutic role for fecal microbiota transplantation? *Am J Gastroenterol* 2012; **107**: 1452-1459 [PMID: 23034604 DOI: 10.1038/ajg.2012.93]
45 **Podolsky DK**. Inflammatory bowel disease. *N Engl J Med* 2002; **347**: 417-429 [PMID: 12167685 DOI: 10.1056/NEJMra020831]
46 **Bamias G**, Cominelli F. Immunopathogenesis of inflammatory bowel disease: current concepts. *Curr Opin Gastroenterol* 2007; **23**: 365-369 [PMID: 17545770 DOI: 10.1097/MOG.0b013e3281c55eb2]
47 **Turner JR**. Molecular basis of epithelial barrier regulation: from basic mechanisms to clinical application. *Am J Pathol* 2006; **169**: 1901-1909 [PMID: 17148655 DOI: 10.2353/ajpath.2006.060681]
48 **Muniz LR**, Knosp C, Yeretssian G. Intestinal antimicrobial peptides during homeostasis, infection, and disease. *Front Immunol* 2012; **3**: 310 [PMID: 23087688 DOI: 10.3389/fimmu.2012.00310]
49 **Camilleri M**, Madsen K, Spiller R, Greenwood-Van Meerveld B, Verne GN. Intestinal barrier function in health and gastrointestinal disease. *Neurogastroenterol Motil* 2012; **24**: 503-512 [PMID: 22583600 DOI: 10.1111/j.1365-2982.2012.01921.x]
50 **Olson TS**, Reuter BK, Scott KG, Morris MA, Wang XM, Hancock LN, Burcin TL, Cohn SM, Ernst PB, Cominelli F, Meddings JB, Ley K, Pizarro TT. The primary defect in experimental ileitis originates from a nonhematopoietic source. *J Exp Med* 2006; **203**: 541-552 [PMID: 16505137 DOI: 10.1084/jem.20050407]
51 **Hollander D**, Vadheim CM, Brettholz E, Petersen GM, Delahunty T, Rotter JI. Increased intestinal permeability in patients with Crohn's disease and their relatives. A possible etiologic factor. *Ann Intern Med* 1986; **105**: 883-885 [PMID: 3777713 DOI: 10.7326/0003-4819-105-6-883]
52 **Zeissig S**, Bürgel N, Günzel D, Richter J, Mankertz J, Wahnschaffe U, Kroesen AJ, Zeitz M, Fromm M, Schulzke JD. Changes in expression and distribution of claudin 2, 5 and 8 lead to discontinuous tight junctions and barrier dysfunction in active Crohn's disease. *Gut* 2007; **56**: 61-72 [PMID: 16822808 DOI: 10.1136/gut.2006.094375]
53 **Pizarro TT**, Pastorelli L, Bamias G, Garg RR, Reuter BK, Mercado JR, Chieppa M, Arseneau KO, Ley K, Cominelli F. SAMP1/YitFc mouse strain: a spontaneous model of Crohn's disease-like ileitis. *Inflamm Bowel Dis* 2011; **17**: 2566-2584 [PMID: 21557393 DOI: 10.1002/ibd.21638]
54 **Sheng YH**, Hasnain SZ, Florin TH, McGuckin MA. Mucins in inflammatory bowel diseases and colorectal cancer. *J Gastroenterol Hepatol* 2012; **27**: 28-38 [PMID: 21913981 DOI: 10.1111/j.1440-1746.2011.06909.x]
55 **Faure M**, Moënnoz D, Mettraux C, Montigon F, Schiffrin EJ,

Obled C, Breuillé D, Boza J. The chronic colitis developed by HLA-B27 transgenic rats is associated with altered in vivo mucin synthesis. *Dig Dis Sci* 2004; **49**: 339-346 [PMID: 15104381]

56 **Heazlewood CK**, Cook MC, Eri R, Price GR, Tauro SB, Taupin D, Thornton DJ, Png CW, Crockford TL, Cornall RJ, Adams R, Kato M, Nelms KA, Hong NA, Florin TH, Goodnow CC, McGuckin MA. Aberrant mucin assembly in mice causes endoplasmic reticulum stress and spontaneous inflammation resembling ulcerative colitis. *PLoS Med* 2008; **5**: e54 [PMID: 18318598 DOI: 10.1371/journal.pmed.0050054]

57 **Wehkamp J**, Salzman NH, Porter E, Nuding S, Weichenthal M, Petras RE, Shen B, Schaeffeler E, Schwab M, Linzmeier R, Feathers RW, Chu H, Lima H, Fellermann K, Ganz T, Stange EF, Bevins CL. Reduced Paneth cell alpha-defensins in ileal Crohn's disease. *Proc Natl Acad Sci USA* 2005; **102**: 18129-18134 [PMID: 16330776 DOI: 10.1073/pnas.0505256102]

58 **Aldhous MC**, Noble CL, Satsangi J. Dysregulation of human beta-defensin-2 protein in inflammatory bowel disease. *PLoS One* 2009; **4**: e6285 [PMID: 19617917 DOI: 10.1371/journal.pone.0006285]

59 **Wehkamp J**, Harder J, Weichenthal M, Schwab M, Schäffeler E, Schlee M, Herrlinger KR, Stallmach A, Noack F, Fritz P, Schröder JM, Bevins CL, Fellermann K, Stange EF. NOD2 (CARD15) mutations in Crohn's disease are associated with diminished mucosal alpha-defensin expression. *Gut* 2004; **53**: 1658-1664 [PMID: 15479689 DOI: 10.1136/gut.2003.032805]

60 **Cadwell K**, Liu JY, Brown SL, Miyoshi H, Loh J, Lennerz JK, Kishi C, Kc W, Carrero JA, Hunt S, Stone CD, Brunt EM, Xavier RJ, Sleckman BP, Li E, Mizushima N, Stappenbeck TS, Virgin HW. A key role for autophagy and the autophagy gene Atg16l1 in mouse and human intestinal Paneth cells. *Nature* 2008; **456**: 259-263 [PMID: 18849966 DOI: 10.1038/nature07416]

61 **Chen LW**, Egan L, Li ZW, Greten FR, Kagnoff MF, Karin M. The two faces of IKK and NF-kappaB inhibition: prevention of systemic inflammation but increased local injury following intestinal ischemia-reperfusion. *Nat Med* 2003; **9**: 575-581 [PMID: 12692538 DOI: 10.1038/nm849]

62 **Rakoff-Nahoum S**, Paglino J, Eslami-Varzaneh F, Edberg S, Medzhitov R. Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis. *Cell* 2004; **118**: 229-241 [PMID: 15260992 DOI: 10.1016/j.cell.2004.07.002]

63 **Lam EK**, Tai EK, Koo MW, Wong HP, Wu WK, Yu L, So WH, Woo PC, Cho CH. Enhancement of gastric mucosal integrity by Lactobacillus rhamnosus GG. *Life Sci* 2007; **80**: 2128-2136 [PMID: 17499310 DOI: 10.1016/j.lfs.2007.03.018]

64 **Kim Y**, Kim SH, Whang KY, Kim YJ, Oh S. Inhibition of Escherichia coli O157: H7 attachment by interactions between lactic acid bacteria and intestinal epithelial cells. *J Microbiol Biotechnol* 2008; **18**: 1278-1285 [PMID: 18667857]

65 **Caballero-Franco C**, Keller K, De Simone C, Chadee K. The VSL#3 probiotic formula induces mucin gene expression and secretion in colonic epithelial cells. *Am J Physiol Gastrointest Liver Physiol* 2007; **292**: G315-G322 [PMID: 16973917 DOI: 10.1152/ajpgi.00265.2006]

66 **Madsen K**, Cornish A, Soper P, McKaigney C, Jijon H, Yachimec C, Doyle J, Jewell L, De Simone C. Probiotic bacteria enhance murine and human intestinal epithelial barrier function. *Gastroenterology* 2001; **121**: 580-591 [PMID: 11522742 DOI: 10.1053/gast.2001.27224]

67 **Schlee M**, Harder J, Köten B, Stange EF, Wehkamp J, Fellermann K. Probiotic lactobacilli and VSL#3 induce enterocyte beta-defensin 2. *Clin Exp Immunol* 2008; **151**: 528-535 [PMID: 18190603 DOI: 10.1111/j.1365-2249.2007.03587.x]

68 **Pagnini C**, Saeed R, Bamias G, Arseneau KO, Pizarro TT, Cominelli F. Probiotics promote gut health through stimulation of epithelial innate immunity. *Proc Natl Acad Sci USA* 2010; **107**: 454-459 [PMID: 20018654 DOI: 10.1073/pnas.0910307107]

69 **Corridoni D**, Pastorelli L, Mattioli B, Locovei S, Ishikawa D, Arseneau KO, Chieppa M, Cominelli F, Pizarro TT. Probiotic bacteria regulate intestinal epithelial permeability in experimental ileitis by a TNF-dependent mechanism. *PLoS One* 2012; **7**: e42067 [PMID: 22848704 DOI: 10.1371/journal.pone.0042067]

70 **Varol C**, Vallon-Eberhard A, Elinav E, Aychek T, Shapira Y, Luche H, Fehling HJ, Hardt WD, Shakhar G, Jung S. Intestinal lamina propria dendritic cell subsets have different origin and functions. *Immunity* 2009; **31**: 502-512 [PMID: 19733097 DOI: 10.1016/j.immuni.2009.06.025]

71 **Rimoldi M**, Chieppa M, Salucci V, Avogadri F, Sonzogni A, Sampietro GM, Nespoli A, Viale G, Allavena P, Rescigno M. Intestinal immune homeostasis is regulated by the crosstalk between epithelial cells and dendritic cells. *Nat Immunol* 2005; **6**: 507-514 [PMID: 15821737 DOI: 10.1038/ni1192]

72 **Lee EG**, Boone DL, Chai S, Libby SL, Chien M, Lodolce JP, Ma A. Failure to regulate TNF-induced NF-kappaB and cell death responses in A20-deficient mice. *Science* 2000; **289**: 2350-2354 [PMID: 11009421 DOI: 10.1126/science.289.5488.2350]

73 **Manicassamy S**, Reizis B, Ravindran R, Nakaya H, Salazar-Gonzalez RM, Wang YC, Pulendran B. Activation of beta-catenin in dendritic cells regulates immunity versus tolerance in the intestine. *Science* 2010; **329**: 849-853 [PMID: 20705860 DOI: 10.1126/science.1188510]

74 **Kamada N**, Hisamatsu T, Okamoto S, Chinen H, Kobayashi T, Sato T, Sakuraba A, Kitazume MT, Sugita A, Koganei K, Akagawa KS, Hibi T. Unique CD14 intestinal macrophages contribute to the pathogenesis of Crohn disease via IL-23/IFN-gamma axis. *J Clin Invest* 2008; **118**: 2269-2280 [PMID: 18497880]

75 **Foligne B**, Zoumpopoulou G, Dewulf J, Ben Younes A, Chareyre F, Sirard JC, Pot B, Grangette C. A key role of dendritic cells in probiotic functionality. *PLoS One* 2007; **2**: e313 [PMID: 17375199 DOI: 10.1371/journal.pone.0000313]

76 **Hoarau C**, Martin L, Faugaret D, Baron C, Dauba A, Aubert-Jacquin C, Velge-Roussel F, Lebranchu Y. Supernatant from bifidobacterium differentially modulates transduction signaling pathways for biological functions of human dendritic cells. *PLoS One* 2008; **3**: e2753 [PMID: 18648505 DOI: 10.1371/journal.pone.0002753]

77 **Baba N**, Samson S, Bourdet-Sicard R, Rubio M, Sarfati M. Commensal bacteria trigger a full dendritic cell maturation program that promotes the expansion of non-Tr1 suppressor T cells. *J Leukoc Biol* 2008; **84**: 468-476 [PMID: 18511576 DOI: 10.1189/jlb.0108017]

78 **Hart AL**, Lammers K, Brigidi P, Vitali B, Rizzello F, Gionchetti P, Campieri M, Kamm MA, Knight SC, Stagg AJ. Modulation of human dendritic cell phenotype and function by probiotic bacteria. *Gut* 2004; **53**: 1602-1609 [PMID: 15479680 DOI: 10.1136/gut.2003.037325]

79 **Bamias G**, Kaltsa G, Ladas SD. Cytokines in the pathogenesis of ulcerative colitis. *Discov Med* 2011; **11**: 459-467 [PMID: 21616044]

80 **Kühn R**, Löhler J, Rennick D, Rajewsky K, Müller W. Interleukin-10-deficient mice develop chronic enterocolitis. *Cell* 1993; **75**: 263-274 [PMID: 8402911 DOI: 10.1016/0092-8674(93)80068-P]

81 **Kontoyiannis D**, Pasparakis M, Pizarro TT, Cominelli F, Kollias G. Impaired on/off regulation of TNF biosynthesis in mice lacking TNF AU-rich elements: implications for joint and gut-associated immunopathologies. *Immunity* 1999; **10**: 387-398 [PMID: 10204494 DOI: 10.1016/S1074-7613(00)80038-2]

82 **Powrie F**, Leach MW, Mauze S, Caddle LB, Coffman RL. Phenotypically distinct subsets of CD4+ T cells induce or protect from chronic intestinal inflammation in C. B-17 scid mice. *Int Immunol* 1993; **5**: 1461-1471 [PMID: 7903159 DOI: 10.1093/intimm/5.11.1461]

83 **Bamias G**, Sugawara K, Pagnini C, Cominelli F. The Th1 immune pathway as a therapeutic target in Crohn's disease. *Curr Opin Investig Drugs* 2003; **4**: 1279-1286 [PMID: 14758766]

84 **Fukunaga K**, Matsumoto T. Current status and future perspectives of leukocytapheresis for inflammatory bowel disease. *J Gastroenterol Hepatol* 2012; **27**: 997-1003 [PMID: 22414250 DOI: 10.1111/j.1440-1746.2012.07119.x]

85 **Ricart E**. Current status of mesenchymal stem cell therapy and bone marrow transplantation in IBD. *Dig Dis* 2012; **30**: 387-391 [PMID: 22796802 DOI: 10.1159/000338134]

86 **Fujino S**, Andoh A, Bamba S, Ogawa A, Hata K, Araki Y, Bamba T, Fujiyama Y. Increased expression of interleukin 17 in inflammatory bowel disease. *Gut* 2003; **52**: 65-70 [PMID: 12477762 DOI: 10.1136/gut.52.1.65]

87 **Siakavellas SI**, Bamias G. Role of the IL-23/IL-17 axis in Crohn's disease. *Discov Med* 2012; **14**: 253-262 [PMID: 23114581]

88 **Hue S**, Ahern P, Buonocore S, Kullberg MC, Cua DJ, McKenzie BS, Powrie F, Maloy KJ. Interleukin-23 drives innate and T cell-mediated intestinal inflammation. *J Exp Med* 2006; **203**: 2473-2483 [PMID: 17030949 DOI: 10.1084/jem.20061099]

89 **Kullberg MC**, Jankovic D, Feng CG, Hue S, Gorelick PL, McKenzie BS, Cua DJ, Powrie F, Cheever AW, Maloy KJ, Sher A. IL-23 plays a key role in Helicobacter hepaticus-induced T cell-dependent colitis. *J Exp Med* 2006; **203**: 2485-2494 [PMID: 17030948 DOI: 10.1084/jem.20061082]

90 **Sandborn WJ**, Feagan BG, Fedorak RN, Scherl E, Fleisher MR, Katz S, Johanns J, Blank M, Rutgeerts P. A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. *Gastroenterology* 2008; **135**: 1130-1141 [PMID: 18706417 DOI: 10.1053/j.gastro.2008.07.014]

91 **Niess JH**, Leithäuser F, Adler G, Reimann J. Commensal gut flora drives the expansion of proinflammatory CD4 T cells in the colonic lamina propria under normal and inflammatory conditions. *J Immunol* 2008; **180**: 559-568 [PMID: 18097058]

92 **Di Giacinto C**, Marinaro M, Sanchez M, Strober W, Boirivant M. Probiotics ameliorate recurrent Th1-mediated murine colitis by inducing IL-10 and IL-10-dependent TGF-beta-bearing regulatory cells. *J Immunol* 2005; **174**: 3237-3246 [PMID: 15749854]

93 **Ulisse S**, Gionchetti P, D'Alò S, Russo FP, Pesce I, Ricci G, Rizzello F, Helwig U, Cifone MG, Campieri M, De Simone C. Expression of cytokines, inducible nitric oxide synthase, and matrix metalloproteinases in pouchitis: effects of probiotic treatment. *Am J Gastroenterol* 2001; **96**: 2691-2699 [PMID: 11569697 DOI: 10.1111/j.1572-0241.2001.04139.x]

94 **Di Caro S**, Tao H, Grillo A, Elia C, Gasbarrini G, Sepulveda AR, Gasbarrini A. Effects of Lactobacillus GG on genes expression pattern in small bowel mucosa. *Dig Liver Dis* 2005; **37**: 320-329 [PMID: 15843081 DOI: 10.1016/j.dld.2004.12.008]

95 **Schultz M**, Veltkamp C, Dieleman LA, Grenther WB, Wyrick PB, Tonkonogy SL, Sartor RB. Lactobacillus plantarum 299V in the treatment and prevention of spontaneous colitis in interleukin-10-deficient mice. *Inflamm Bowel Dis* 2002; **8**: 71-80 [PMID: 11854603 DOI: 10.1097/00054725-200203000-00001]

96 **McCarthy J**, O'Mahony L, O'Callaghan L, Sheil B, Vaughan EE, Fitzsimons N, Fitzgibbon J, O'Sullivan GC, Kiely B, Collins JK, Shanahan F. Double blind, placebo controlled trial of two probiotic strains in interleukin 10 knockout mice and mechanistic link with cytokine balance. *Gut* 2003; **52**: 975-980 [PMID: 12801954 DOI: 10.1136/gut.52.7.975]

97 **Smelt MJ**, de Haan BJ, Bron PA, van Swam I, Meijerink M, Wells JM, Faas MM, de Vos P. L. plantarum, L. salivarius, and L. lactis attenuate Th2 responses and increase Treg frequencies in healthy mice in a strain dependent manner. *PLoS One* 2012; **7**: e47244 [PMID: 23056616 DOI: 10.1371/journal.pone.0047244]

98 **Oliva S**, Di Nardo G, Ferrari F, Mallardo S, Rossi P, Patrizi G, Cucchiara S, Stronati L. Randomised clinical trial: the effectiveness of Lactobacillus reuteri ATCC 55730 rectal enema in children with active distal ulcerative colitis. *Aliment Pharmacol Ther* 2012; **35**: 327-334 [PMID: 22150569 DOI: 10.1111/j.1365-2036.2011.04939.x]

99 **Donkor ON**, Ravikumar M, Proudfoot O, Day SL, Apostolopoulos V, Paukovics G, Vasiljevic T, Nutt SL, Gill H. Cytokine profile and induction of T helper type 17 and regulatory T cells by human peripheral mononuclear cells after microbial exposure. *Clin Exp Immunol* 2012; **167**: 282-295 [PMID: 22236005 DOI: 10.1111/j.1365-2249.2011.04496.x]

100 **Jan RL**, Yeh KC, Hsieh MH, Lin YL, Kao HF, Li PH, Chang YS, Wang JY. Lactobacillus gasseri suppresses Th17 pro-inflammatory response and attenuates allergen-induced airway inflammation in a mouse model of allergic asthma. *Br J Nutr* 2012; **108**: 130-139 [PMID: 21996276 DOI: 10.1017/S0007114511005265]

101 **Floch MH**, Walker WA, Madsen K, Sanders ME, Macfarlane GT, Flint HJ, Dieleman LA, Ringel Y, Guandalini S, Kelly CP, Brandt LJ. Recommendations for probiotic use-2011 update. *J Clin Gastroenterol* 2011; **45** Suppl: S168-S171 [PMID: 21992958 DOI: 10.1097/MCG.0b013e318230928b]

102 **Floch MH**, Walker WA, Guandalini S, Hibberd P, Gorbach S, Surawicz C, Sanders ME, Garcia-Tsao G, Quigley EM, Isolauri E, Fedorak RN, Dieleman LA. Recommendations for probiotic use--2008. *J Clin Gastroenterol* 2008; **42** Suppl 2: S104-S108 [PMID: 18542033 DOI: 10.1097/MCG.0b013e31816b903f]

103 **Sanders ME**, Guarner F, Guerrant R, Holt PR, Quigley EM, Sartor RB, Sherman PM, Mayer EA. An update on the use and investigation of probiotics in health and disease. *Gut* 2013; **62**: 787-796 [PMID: 23474420 DOI: 10.1136/gutjnl-2012-302504]

104 **Reid G**, Gaudier E, Guarner F, Huffnagle GB, Macklaim JM, Munoz AM, Martini M, Ringel-Kulka T, Sartor B, Unal R, Verbeke K, Walter J. Responders and non-responders to probiotic interventions: how can we improve the odds? *Gut Microbes* 2010; **1**: 200-204 [PMID: 21637034 DOI: 10.4161/gmic.1.3.12013]

105 **Van Assche G**, Dignass A, Bokemeyer B, Danese S, Gionchetti P, Moser G, Beaugerie L, Gomollón F, Häuser W, Herrlinger K, Oldenburg B, Panes J, Portela F, Rogler G, Stein J, Tilg H, Travis S, Lindsay JO. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 3: special situations. *J Crohns Colitis* 2013; **7**: 1-33 [PMID: 23040453 DOI: 10.1016/j.crohns.2012.09.005]

106 **Gionchetti P**, Rizzello F, Venturi A, Brigidi P, Matteuzzi D, Bazzocchi G, Poggioli G, Miglioli M, Campieri M. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000; **119**: 305-309 [PMID: 10930365 DOI: 10.1053/gast.2000.9370]

107 **Mimura T**, Rizzello F, Helwig U, Poggioli G, Schreiber S, Talbot IC, Nicholls RJ, Gionchetti P, Campieri M, Kamm MA. Once daily high dose probiotic therapy (VSL#3) for maintaining remission in recurrent or refractory pouchitis. *Gut* 2004; **53**: 108-114 [PMID: 14684584 DOI: 10.1136/gut.53.1.108]

108 **Gosselink MP**, Schouten WR, van Lieshout LM, Hop WC, Laman JD, Ruseler-van Embden JG. Delay of the first onset of pouchitis by oral intake of the probiotic strain Lactobacillus rhamnosus GG. *Dis Colon Rectum* 2004; **47**: 876-884 [PMID: 15108026 DOI: 10.1007/s10350-004-0525-z]

109 **Gionchetti P**, Rizzello F, Helwig U, Venturi A, Lammers KM, Brigidi P, Vitali B, Poggioli G, Miglioli M, Campieri M. Prophylaxis of pouchitis onset with probiotic therapy: a double-blind, placebo-controlled trial. *Gastroenterology* 2003; **124**: 1202-1209 [PMID: 12730861 DOI: 10.1016/S0016-5085(03)00171-9]

110 **Pronio A**, Montesani C, Butteroni C, Vecchione S, Mumolo G, Vestri A, Vitolo D, Boirivant M. Probiotic administration in patients with ileal pouch-anal anastomosis for ulcerative

colitis is associated with expansion of mucosal regulatory cells. *Inflamm Bowel Dis* 2008; **14**: 662-668 [PMID: 18240282 DOI: 10.1002/ibd.20369]
111 **Kuisma J**, Mentula S, Jarvinen H, Kahri A, Saxelin M, Farkkila M. Effect of Lactobacillus rhamnosus GG on ileal pouch inflammation and microbial flora. *Aliment Pharmacol Ther* 2003; **17**: 509-515 [PMID: 12622759 DOI: 10.1046/j.1365-2036.2003.01465.x]
112 **Gionchetti P**, Rizzello F, Morselli C, Poggioli G, Tambasco R, Calabrese C, Brigidi P, Vitali B, Straforini G, Campieri M. High-dose probiotics for the treatment of active pouchitis. *Dis Colon Rectum* 2007; **50**: 2075-2882; discussion 2082-2884; [PMID: 17934776 DOI: 10.1007/s10350-007-9068-4]
113 **Mallon P**, McKay D, Kirk S, Gardiner K. Probiotics for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2007; (**12**): CD005573 [PMID: 17934776]
114 **Naidoo K**, Gordon M, Fagbemi AO, Thomas AG, Akobeng AK. Probiotics for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2011; **(12)**: CD007443 [PMID: 22161412]
115 **Furrie E**, Macfarlane S, Kennedy A, Cummings JH, Walsh SV, O'neil DA, Macfarlane GT. Synbiotic therapy (Bifidobacterium longum/Synergy 1) initiates resolution of inflammation in patients with active ulcerative colitis: a randomised controlled pilot trial. *Gut* 2005; **54**: 242-249 [PMID: 15647189 DOI: 10.1136/gut.2004.044834]
116 **Kato K**, Mizuno S, Umesaki Y, Ishii Y, Sugitani M, Imaoka A, Otsuka M, Hasunuma O, Kurihara R, Iwasaki A, Arakawa Y. Randomized placebo-controlled trial assessing the effect of bifidobacteria-fermented milk on active ulcerative colitis. *Aliment Pharmacol Ther* 2004; **20**: 1133-1141 [PMID: 15569116 DOI: 10.1111/j.1365-2036.2004.02268.x]
117 **Rembacken BJ**, Snelling AM, Hawkey PM, Chalmers DM, Axon AT. Non-pathogenic Escherichia coli versus mesalazine for the treatment of ulcerative colitis: a randomised trial. *Lancet* 1999; **354**: 635-639 [PMID: 10466665 DOI: 10.1016/S0140-6736(98)06343-0]
118 **Tursi A**, Brandimarte G, Giorgetti GM, Forti G, Modeo ME, Gigliobianco A. Low-dose balsalazide plus a high-potency probiotic preparation is more effective than balsalazide alone or mesalazine in the treatment of acute mild-to-moderate ulcerative colitis. *Med Sci Monit* 2004; **10**: PI126-PI131 [PMID: 15507864]
119 **Kruis W**, Schütz E, Fric P, Fixa B, Judmaier G, Stolte M. Double-blind comparison of an oral Escherichia coli preparation and mesalazine in maintaining remission of ulcerative colitis. *Aliment Pharmacol Ther* 1997; **11**: 853-858 [PMID: 9354192 DOI: 10.1046/j.1365-2036.1997.00225.x]
120 **Kruis W**, Fric P, Pokrotnieks J, Lukás M, Fixa B, Kascák M, Kamm MA, Weismueller J, Beglinger C, Stolte M, Wolff C, Schulze J. Maintaining remission of ulcerative colitis with the probiotic Escherichia coli Nissle 1917 is as effective as with standard mesalazine. *Gut* 2004; **53**: 1617-1623 [PMID: 15479682 DOI: 10.1136/gut.2003.037747]
121 **Zocco MA**, dal Verme LZ, Cremonini F, Piscaglia AC, Nista EC, Candelli M, Novi M, Rigante D, Cazzato IA, Ojetti V, Armuzzi A, Gasbarrini G, Gasbarrini A. Efficacy of Lactobacillus GG in maintaining remission of ulcerative colitis. *Aliment Pharmacol Ther* 2006; **23**: 1567-1574 [PMID: 16696804 DOI: 10.1111/j.1365-2036.2006.02927.x]
122 **Wildt S**, Nordgaard I, Hansen U, Brockmann E, Rumessen JJ. A randomised double-blind placebo-controlled trial with Lactobacillus acidophilus La-5 and Bifidobacterium animalis subsp. lactis BB-12 for maintenance of remission in ulcerative colitis. *J Crohns Colitis* 2011; **5**: 115-121 [PMID: 21453880 DOI: 10.1016/j.crohns.2010.11.004]
123 **Sang LX**, Chang B, Zhang WL, Wu XM, Li XH, Jiang M. Remission induction and maintenance effect of probiotics on ulcerative colitis: a meta-analysis. *World J Gastroenterol* 2010; **16**: 1908-1915 [PMID: 20397271 DOI: 10.3748/wjg.v16.i15.1908]
124 **Matthes H,** Krummenerl T, Giensch M, Wollf C, Schulze J. Treatment of mild to moderate acute attacks of distal ulcerative colitis with rectally-administered E. coli Nissle 1917: dose-dependent efficacy. *Gastroenterology* 2006; **130**: A119
125 **Miele E**, Pascarella F, Giannetti E, Quaglietta L, Baldassano RN, Staiano A. Effect of a probiotic preparation (VSL#3) on induction and maintenance of remission in children with ulcerative colitis. *Am J Gastroenterol* 2009; **104**: 437-443 [PMID: 19174792 DOI: 10.1038/ajg.2008.118]
126 **Sood A**, Midha V, Makharia GK, Ahuja V, Singal D, Goswami P, Tandon RK. The probiotic preparation, VSL#3 induces remission in patients with mild-to-moderately active ulcerative colitis. *Clin Gastroenterol Hepatol* 2009; **7**: 1202-129, 1209. e1 [PMID: 19631292 DOI: 10.1016/j.cgh.2009.07.016]
127 **Ishikawa H**, Akedo I, Umesaki Y, Tanaka R, Imaoka A, Otani T. Randomized controlled trial of the effect of bifidobacteria-fermented milk on ulcerative colitis. *J Am Coll Nutr* 2003; **22**: 56-63 [PMID: 12569115 DOI: 10.1080/07315724.2003.10719276]
128 **Cui HH**, Chen CL, Wang JD, Yang YJ, Cun Y, Wu JB, Liu YH, Dan HL, Jian YT, Chen XQ. Effects of probiotic on intestinal mucosa of patients with ulcerative colitis. *World J Gastroenterol* 2004; **10**: 1521-1525 [PMID: 15133865]
129 **Henker J**, Müller S, Laass MW, Schreiner A, Schulze J. Probiotic Escherichia coli Nissle 1917 (EcN) for successful remission maintenance of ulcerative colitis in children and adolescents: an open-label pilot study. *Z Gastroenterol* 2008; **46**: 874-875 [PMID: 18810672 DOI: 10.1055/s-2008-1027463]
130 **Rolfe VE**, Fortun PJ, Hawkey CJ, Bath-Hextall F. Probiotics for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2006; **(4)**: CD004826 [PMID: 17054217]
131 **Prantera C**, Scribano ML, Falasco G, Andreoli A, Luzi C. Ineffectiveness of probiotics in preventing recurrence after curative resection for Crohn's disease: a randomised controlled trial with Lactobacillus GG. *Gut* 2002; **51**: 405-409 [PMID: 12171964 DOI: 10.1136/gut.51.3.405]
132 **Campieri M,** Rizzello F, Venturi A, Poggioli G, Ugolini F, Helwig U et al. Combination of antibiotic and probiotic treatment is efficacious in prophylaxis of post-operative recurrence of Crohn's disease: a randomized controlled study versus mesalamine. *Gastroenterology* 2000; **118** (4 Suppl 2): A781 [DOI: 10.1016/S0016-5085(00)85267-1]
133 **Bousvaros A**, Guandalini S, Baldassano RN, Botelho C, Evans J, Ferry GD, Goldin B, Hartigan L, Kugathasan S, Levy J, Murray KF, Oliva-Hemker M, Rosh JR, Tolia V, Zholudev A, Vanderhoof JA, Hibberd PL. A randomized, double-blind trial of Lactobacillus GG versus placebo in addition to standard maintenance therapy for children with Crohn's disease. *Inflamm Bowel Dis* 2005; **11**: 833-839 [PMID: 16116318 DOI: 10.1097/01.MIB.0000175905.00212.2c]
134 **Schultz M**, Timmer A, Herfarth HH, Sartor RB, Vanderhoof JA, Rath HC. Lactobacillus GG in inducing and maintaining remission of Crohn's disease. *BMC Gastroenterol* 2004; **4**: 5 [PMID: 15113451 DOI: 10.1186/1471-230X-4-5]
135 **Guslandi M**, Mezzi G, Sorghi M, Testoni PA. Saccharomyces boulardii in maintenance treatment of Crohn's disease. *Dig Dis Sci* 2000; **45**: 1462-1464 [PMID: 10961730]
136 **Malchow HA**. Crohn's disease and Escherichia coli. A new approach in therapy to maintain remission of colonic Crohn's disease? *J Clin Gastroenterol* 1997; **25**: 653-658 [PMID: 9451682 DOI: 10.1097/00004836-199712000-00021]
137 **Zocco MA,** Zileri Dal Verme L, Armuzzi A, Nista EC, Papa A, Candelli M et al. Comparison of Lactobacillus GG and mesalazine in maintaining remission of ulcerative colitis and Crohn's disease. *Gastroenterology* 2003; **124** (4 Suppl 1): A201 [DOI: 10.1016/S0016-5085(03)81006-5]
138 **Doherty GA**, Bennett GC, Cheifetz AS, Moss AC. Meta-analysis: targeting the intestinal microbiota in prophylaxis for post-operative Crohn's disease. *Aliment Pharmacol Ther*

2010; **31**: 802-809 [PMID: 20055785]
139 **Marteau P**, Lémann M, Seksik P, Laharie D, Colombel JF, Bouhnik Y, Cadiot G, Soulé JC, Bourreille A, Metman E, Lerebours E, Carbonnel F, Dupas JL, Veyrac M, Coffin B, Moreau J, Abitbol V, Blum-Sperisen S, Mary JY. Ineffectiveness of Lactobacillus johnsonii LA1 for prophylaxis of postoperative recurrence in Crohn's disease: a randomised, double blind, placebo controlled GETAID trial. *Gut* 2006; **55**: 842-847 [PMID: 16377775 DOI: 10.1136/gut.2005.076604]
140 **Van Gossum A**, Dewit O, Louis E, de Hertogh G, Baert F, Fontaine F, DeVos M, Enslen M, Paintin M, Franchimont D. Multicenter randomized-controlled clinical trial of probiotics (Lactobacillus johnsonii, LA1) on early endoscopic recurrence of Crohn's disease after lleo-caecal resection. *Inflamm Bowel Dis* 2007; **13**: 135-142 [PMID: 17206696 DOI: 10.1002/ibd.20063]
141 **Madsen K,** Backer J, Leddin D, Dieleman L, Bitton A, Feagan B. A randomized controlled trial of VSL3 for the prevention of endoscopic recurrence following surgery for Crohn's disease. *Gastroenterology* 2008; **134** (4 Suppl 1): A361 [DOI: 10.1016/S0016-5085(08)61682-0]
142 **Chermesh I**, Tamir A, Reshef R, Chowers Y, Suissa A, Katz D, Gelber M, Halpern Z, Bengmark S, Eliakim R. Failure of Synbiotic 2000 to prevent postoperative recurrence of Crohn's disease. *Dig Dis Sci* 2007; **52**: 385-389 [PMID: 17211699 DOI: 10.1007/s10620-006-9549-7]

P- Reviewer: Mulero V **S- Editor**: Qi Y **L- Editor**: A
E- Editor: Wu HL

百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Telephone: +852-6555-7188
Fax: +852-3177-9906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com