® Postepy Hig Med Dosw (online), 2018; 72: 159-174
e-ISSN 1732-2693

www.phmd.pl
Review

Received: 26.04.2017
Accepted: 04.09.2017
Published: 19.03.2018

Effectiveness and safety of probiotic preparations in clinical treatment of inflammatory bowel disease*

Efektywność i bezpieczeństwo preparatów probiotycznych stosowanych w terapii nieswoistych zapaleń jelit

Ewa Wasilewska, Barbara Wroblewska

Department of Immunology and Food Microbiology in the Institute of Animal Reproduction and Food Research of the Polish Academy of Sciences, Olsztyn, Poland

Summary

Inflammatory bowel disease (IBD) is characterized by an aggressive immune response to luminal antigens including those of commensal microbiota, which are essential for intestinal homeostasis and appear to play a role in tolerance and immunity. Its disturbances can result in intestinal dysbiosis and the development of disease. The precise role of luminal bacteria in the pathogenesis of IBD has yet to be elucidated; however, considerable evidence implicates changes to bacterial communities associated with the gut mucosa in the disease state. It is also well known that beneficial microbes can confer a functional health benefit to the host. We analysed the effectiveness of probiotics to relieve symptoms in patients suffering from IBD. Using the Medline database and manually searching articles, we reviewed clinical trials performed with probiotics and lactic acid bacteria as supportive or alternative IBD treatments. The article summarizes IBD microenvironment and the efficiency of probiotic preparations in attenuating the symptoms of Crohn's disease, ulcerative colitis, and pouchitis. The safety of probiotic intake is also analyzed based on existing outcomes of clinical trials and case reports. Strong evidence exists that probiotics are effective as supportive therapy for IBD; however, only a few preparations have well documented efficiency and safety. Clinical studies demonstrated that probiotics were more effective in preventing recurrence of the disease symptoms than in the management of its active stage. Some products may increase the risk of complications in specific patient groups; therefore, the use of probiotics should be considered with caution in the case of severe active IBD, especially with disrupted mucosa.

Keywords: **inflammatory bowel disease • nutrition • commensal microbiota • probiotics • safety**

GICID 01.3001.0011.6471
DOI: 10.5604/01.3001.0011.6471
Word count: 11074
Tables: 3
Figures: –
References: 120

Author's address: Ewa Wasilewska, Institute of Animal Reproduction and Food Research of the Polish Academy of Sciences, Tuwima 10 str., 10-748 Olsztyn, Poland; e-mail: e.wasilewska@pan.olsztyn.pl

*This research was supported by the National Science Centre project DEC-2011/01/B/NZ9/07136.

Introduction

Inflammatory bowel disease (IBD) comprises a group of gastrointestinal disorders that cause prolonged inflammation of the colon and small intestine. They are chronic, often intermittent, and primarily affect the young population. Many etiological theories for IBD have been proposed including infectious, allergic, extrinsic (i.e. environmental), psychological, and autoimmune derivations. However, no theory has held up under the scrutiny of multiple scientific studies, and thus a combination of factors is more likely to be the cause. According to current knowledge, the main cause of this disease is an immune reaction that the body has against its own intestinal tissue. It is also likely that intestinal bacteria are involved in the initiation and development of IBD. The dominant theory explaining the occurrence of IBD assumes that the adaptive immune system is hyper-responsive to the commensal gut microbiota in genetically predisposed individuals [119].

The normal microbiota of a healthy adult human is an extensive and diversified microbial community composed of bacteria belonging to numerous phylogenetic clusters [23,114]. Despite this, these bacteria coexist in the healthy gut in a sustainable way, providing mutual benefits to both the microbes and their host. A well-balanced microbiota in a healthy gut contributes to the host's health and participates in metabolic, nutritional, physiological, and immunological processes. It prevents infections of the digestive tract by competing for nutrients and producing substances that are antagonistic to pathogenic bacteria (e.g. lactic acid and bacteriocins). Gut inhabitants stimulate the production of natural antibodies that react with pathogens entering the body and compete for binding sites on epithelial cells. The ability to colonize mucous membranes and to adapt to the colonized niche is a distinguishing feature of microbial inhabitants of the healthy gut. For this commensal relationship, minimal inflammation and autogenous restoration after microbial community disturbances (e.g. through antibiotic therapy) are of crucial importance.

Microorganisms present in the gut are either resident members of the intestinal microbiota or transit bodies introduced from the environment. Altogether, they form a source of countless antigens that continually stimulate the intestinal immune system (gut associated lymphoid tissue - GALT). An active interaction between commensal microorganisms and the host immune system exists to control the growth of microorganisms in the gut and to preserve intestinal homeostasis, resulting in differential host responses to commensal and pathogenic bacteria [60,71]. The mechanisms that are in place to achieve such control are not yet understood. However, it is agreed that resident gut microbiota can contribute to the induction and maintenance of immune tolerance, to the induction of control mechanisms against pathogens, and to autoaggressive and allergic reactions. It is the task of GALT to distinguish invasive pathogens from harmless saprophytic microbes that are indispensable for proper tissue functioning. In healthy conditions, the gut microbiota and GALT are in mutual equilibrium, in a state of intestinal homeostasis, without the induction or inhibition of immune responses to saprophytic microbes. Concurrently, invasive pathogens are identified and eliminated through the stimulation of an immune response. This process is regulated by many factors, the most important of which combines the proper structure and function of the intestinal epithelium with the regulatory mechanisms of the immune system. There is no doubt that the commensal microbiota has a decisive influence on the proper functioning of the intestine [23]. Unfortunately, poor dietary habits, stress, antibiotic therapies, unfavourable environmental factors, and genetic predispositions lead to disorders in the composition and function of the gut microbiota, resulting in the development of diseases. Imbalanced gut microbiota is increasingly listed among crucial factors involved in the etiopathogenesis of inflammatory diseases of the gut.

Intestinal microenvironment in IBD - role of commensal microbiota

There is no unequivocal evidence, but rather a range of factors that supports the idea that the gut flora participates in the pathogenesis of inflammatory diseases in the gastrointestinal tract. Most often inflammatory changes occur in the final segment of the small intestine and in the colon, regions with the highest concentration of commensal microbes. Antibiotics, particularly those that are broad-spectrum, mitigate symptoms of chronic inflammation [52]. In experimental IBD, intestinal inflammation does not occur in animals maintained in sterile conditions (germ-free animals) [92]. Furthermore, diversion of the faecal stream proximal to the inflamed area in patients who had undergone curative ileocolonic resection with ileocolonic anastomosis and temporary protective proximal loop ileostomy was shown to decrease disease activity [17]. In animal studies, adoptive transfer of microbiota from mice with colitis to healthy recipients was sufficient to induce disease [29]. Mutations in genes encoding proteins that are either responsible for identification of bacterial antigens, such as NOD2/CARD15, or that regulate host responses to that antigens increase susceptibility to IBD development [74]. Advanced genome-wide associated studies have revealed many IBD-related loci associated with the interaction between gut microbiota and mucosal inflammation [49,89].

There are interlinked relationships between the host and microbes in the gut. Microbes reside in the human body in the early life and co-exist and co-evolve with the host throughout the life, finally having protective, metabolic, trophic and immunological functions. The collective being they (microbes and host) mutually form is composed of more than 90% microbial cells and 10 million microbial genes [73]. The gastrointestinal tract

is colonized by huge, complex and dynamic populations of microorganism; thus, it is also the major site where communication between microbes, and between microbiota and host takes place. Any microbial imbalance or maladaptation in the gut at early life, and possibly later in life, may result in serve immunodeficiency and risk of disease [9,49,89,114]. Although the aetiology of IBD is unknown, there is an assumption that inflammation might be triggered by the translocation of luminal components into the host. The intestinal tract has the large interface between the body and external environment. In the healthy gut, a complex intestinal barrier, newly defined as a functional entity separating the gut lumen from the inner host, and consisting of mechanical elements (mucus, epithelial layer), humoral elements (defensins, IgA), immunological elements (lymphocytes, innate immune cells), and muscular and neurological elements, prevents the entry of pathogenic microorganisms and toxic luminal substances into the body at the same time regulating the absorption of nutrients, electrolytes and water from the lumen into the circulation [9]. Simultaneously, a continuous cross talk between the endogenous microbiota (symbionts) and the host mucosal innate immune system favours mutual growth, survival and inflammatory control of the intestinal ecosystem. Disruption of this symbiotic relationship between the host and microbiota can lead to immune pathologies. Perturbations and defects of the established defence mechanisms may weaken the protection against microbial adhesion and invasion. A defective mucus layer, alterations of patter-recognition receptors (PPRs), disturbed antimicrobial peptides production, increased epithelial barrier permeability or changes in the autophagy process allow more bacteria to come in direct contact with the epithelium and immune system mechanisms [2]. One of the most critical risk factors for IBD development is that the mucus layer overlaying the epithelium becomes more permeable to bacteria and bacterial products [48]. Significant evidence exist that IBD patients display intestinal epithelial barrier dysfunction and increased paracellular permeability [2,96]. Intestinal permeability is determined by interactions among barrier components, and is defined as a functional feature of the intestinal barrier at given sites, measurable by analyzing flux rates across the intestinal wall as a whole or across wall components of defined molecules that are largely inert during the process and that can be adequately measured in these settings [9]. Among others, the detection of gut derived bacterial markers like circulating endotoxins is considered as definite evidence of increased intestinal permeability [26]. High incidence of systemic endotoxemia was reported in patients with UC and CD during clinical relapse [28]. The "leaky gut hypothesis" implies that the intestinal dysfunction includes chronic low-grade inflammation in various target organs owing to microbial products crossing the intestine or other pro-inflammatory luminal factors that may activate inflammatory cascades [9,26]. The presence of increased intestinal permeability, immune dysregulation and altered gut microbiota may result in uncontrolled inflammation and IBD development [26]. Abnormal intestinal permeability was detected in first-degree healthy relatives of patients with IBD, which indicates that probably other disorders are necessary for the disease development [96]. Recent studies showed that epithelial tight junctions (TJs), a branching network of sealing strands, are the key element of the intestinal barrier affecting intestinal permeability [105]. A decreased expression and redistribution of TJs and junctional adhesion molecules (JAM) combined with increased circulating endotoxins levels have been documented in IBD patients [2;43,118]. Furthermore, colonic biopsy samples from IBD patients revealed a correlation between disease activity and epithelial myosin light chain kinase (MLCK) expression and activity [16]. MLCK is as a key regulator of tight junction permeability. The intestinal bacteria and probiotics change the expression and distribution of TJ proteins and influence intestinal barrier function [105]. It results from many animal and *in vitro* studies that commensal bacteria and probiotics promote intestinal barrier integrity [104,117].

The composition of intestinal microbiota in patients with inflammatory bowel diseases has been intensively studied over the last decade, and a large amount of research has revealed differences between microbial populations of IBD patients and those of healthy individuals [64]. Differences in microbiota composition were observed between ulcerative colitis (UC) and Crohn's disease (CD) patients, and also between active and non-active stages of the disease, as well as between inflamed and non-inflamed regions of the intestine [1,110]. Despite advanced studies, there are still no microbial constituents that are specific to UC or CD, because inter-individual variations are much larger than inter-diseases changes. However, most studies have shown increased total bacterial numbers and reduced diversity in the gut microbiota of IBD patients, and the most consistent fluctuations were a reduction in Firmicutes and an increase in Proteobacteria [62,64,100]. Among the Firmicutes, a decrease in the *Clostridium leptum* groups, especially *Faecalibacterium prausnitzii*, has been repeatedly reported, particularly in CD patients [62,97]. This results in dysbiosis and disorders of the intestine, as *F. prausnitzii* has anti-inflammatory properties based on the large amounts of butyrate that it produces in the gut. Quite often increases in populations of pathogenic bacteria that have increased adhesiveness and virulence such as some *Bacteroides* and *Enterobacteriaceae* species, concurrently with decreases in populations of beneficial microbes, such as bifidobacteria and lactobacilli, are detected [91,114]. However, results indicating changes in the abundance of *Bacteroides, Bifidobacterium, Lactobacillus*, or *Enterobacteriaceae* species are not consistent among studies. Willing et al. [114] reported an increase in *Enterobacteriaceae,* including *Escherichia coli,* and *Ruminococcus gnavus* numbers in ileal mucosal samples of patients with Crohn's disease, whereas the population sizes of symbiotic *Faecalibacterium* and *Roseburia* populations were decreased. *Ruminococcus gnavus*

has significant mucolytic activities, but *Faecalibacterium* and *Roseburia* exert a protective effect on the epithelium as they are prominent producers through the production of short-chain fatty acids (SCFAs, especially butyrate), which have important roles in improving barrier function and protecting intestinal integrity. SCFAs have anti-inflammatory properties, and are important energy sources for epithelial cells. A study of the largest paediatric CD cohort of newly diagnosed, treatment-native CD patients revealed a general increase in the abundance of epithelium-associated bacteria including *Enterobacteriaceae*, *Pasteurellaceae*, *Veillonellaceae*, and *Fusobacteriaceae*, and decreased abundance of Erysipelotrichales, Bacteroidales, and Clostridiales [30].

Mucosal surfaces are in continuous contact with microbes, and consequently mucosa-associated lymphoid tissue functions to distinguish between beneficial and pathogenic microbes to control the latter. However, commensal microbiota provides continuous antigenic stimulation that has the potential to activate pathogenic T cells and, subsequently, cause chronic intestinal injury [49]. The microbial community in the stools of patients with established IBD generally consists of less strict anaerobes that are necessary for the maintenance of intestinal homeostasis. Round et al. [87] demonstrated that the strictly anaerobic prominent gut commensal *Bacteroides fragilis* activates the TLR2 pathway on T lymphocytes to establish host-microbial symbiosis. The oxygen level in the intestinal lumen increases with intestinal inflammation, and thus the gut microbiota probably initiates a shift toward more aerotolerant microorganisms in response to ensuing oxidative stress [30,68]. Crohn's disease lesions are easily colonized by adherent and invasive *E. coli* via adhesion to CEACAM6 expressed in inflamed tissue, which in turn induces the production of hypoxia inducible factor (HIF)-1α and activation of VEGF/VEGFR (vascular endothelial growth factor receptor) signalling [68]. These exemplary studies indicate that it might be not a single species or a group of bacteria that is responsible for the disease onset but rather imbalanced gut microbiota causing inappropriate activation of intestinal mucosal immunity in susceptible hosts.

Effectiveness of probiotics for IBD prophylaxis and treatment

If disturbances to the normal intestinal microbiota play a role in the pathogenesis of IBD, it could also be concluded that beneficial microbes should be effective for IBD prophylaxis and treatment. The promising results in animal studies in addition to some clinical observations have led to important research on probiotic preparations and their utilization in IBD treatment in humans. We reviewed the existing evidence for the efficiency of probiotics and lactic acid bacteria in attenuating the symptoms of ulcerative colitis, Crohn's disease and pouchitis. Ulcerative colitis and Crohn's disease are the most common types of IBD. Their clinical symptoms are chronic and intermittent, and in CD, lesions are most often situated in the lower part of the small intestine, although they can occur anywhere along the intestinal tract. In contrast, UC affects the colon alone. The inflammatory events in CD involve the entire thickness of the bowel wall, whereas in UC they are confined to the mucosa. This is potentially why probiotic therapies show the most promise in UC patients and in pouchitis. Pouchitis is the inflammation of the ileal pouch, an artificial rectum surgically created from ileal gut tissue in patients who have undergone a proctocolectomy. It is formed for the management of UC in patients that do not respond to medical therapy. Acute or chronic inflammation of the ileal pouch, caused by, among other things, the spread of bacteria, is a common complication in UC patients.

Colitis ulcerosa and pouchitis

Results of clinical trials reported in the Medline database testing the efficacy of probiotic preparations in reducing active disease or extending remission in patients with UC are shown in detail in table 1. Among18 preparations tested in 28 clinical studies, only one, Probio-Tec AB-25, had no effect on UC patients [113]. The other treatments ameliorated disease symptoms to some extent, depending on the experimental settings. Nevertheless, only three preparations, *Escherichia coli* strain Nissle 1917 (EcN; known as Mutaflor, Ardeypharm, GmbH), VSL#3 probiotic formulation (VSL Pharmaceuticals, Inc), and Bio-Three (TOA Pharmaceutical Co., Ltd.) were tested in at least two independent clinical trials. Profermin (Nordisk Rebalance) was tested twice, however in the same investigating group. Administration of the non-pathogenic *E. coli* Nissle 1917 appeared to be effective in preventing relapse of UC. Kruis et al. [55,56] demonstrated the efficiency of EcN (administered at an oral dose of 5 x 10^{10} bacterial cells per day) in maintaining UC remission, which was comparable to results obtained using the standard mesalazine (1,500 mg a day). These results were based on two randomized, double-blind clinical trials involving 327 and 120 UC patients in remission, as determined by clinical activity index (CAI ≤ 4), endoscopic index (EI ≤ 4), and histological examination. Similar results were achieved by Rembacken et al. [85]. However, the latter study reported that the addition of *E. coli* to standard medical therapy did not increase the chance of remission for active UC. Later, Petersen et al. [79] reported no benefit for the use of *E. coli* Nissle as an add-on treatment to conventional therapies for active UC. However, Matthes et al. [65] observed a dose-dependent effect of a rectal EcN application in patients with active, mild-to-moderate distal UC. The researchers suggested EcN enemas as a well-tolerated alternative or supplementary treatment to aminosalicylates or glucocorticoids in patients with active, mild-to-moderate distal UC. In 2017, based on the foregoing studies, World Gastroenterology Organisation (WGO) officially recommended *Escherichia coli* Nissle 1917 for maintenance of clinical remission of ulcerative colitis (in dose 5x10^{10} via-

Table 1. Results of clinical trials testing probiotics in ulcerative colitis (UC) patients

Probiotic factor/Dose	Study design/ Time[1]	Patients number	Clinical effectiveness of probiotic factor	References
A cocktail of *L. rhamnosus, L. plantarum, L. casei, L. acidophilus* and *B. infantis* strains/ 6.6×10^9 CFU/day	O/ 36 days	N = 50	Administered as adjuvant to standard treatment; resulted in reduction of disease activity.	[80]
BIFICO (mixture of enterococci, bifidobacteria and lactobacilli)/ 1.26 g/day	R, PC/ 8 weeks	N = 30	Combined with standard treatment with sulfasalazine and glucocorticoid; was effective in maintaining remission and preventing the relapse of UC.	[15]
Bifidobacteria-fermented milk/ 100 mL/day	R, PC/ 1 year	N = 21	Introduced as dietary adjunct in the treatment of UC. It was successful in maintaining remission and had possible preventive effects on the relapse of UC.	[46]
B. breve Yakult and GOS/ 3×10^9 CFU and 5.5 g/day	R/ 1 year	N = 41	The clinical status of the UC patients assessed by colonoscopy was significantly improved.	[47]
B. infantis 35624/ 1×10^{10} CFU/day	R, DB, PC/ 8 weeks	N = 44	Combined with standard mesalazine treatment (5-ASA) resulted in reduction of systemic pro-inflammatory biomarkers.	[36]
B. longum with Synergy 1/ 2×10^{11} cells and 6 g/ twice daily	R, DB, PC/ 1 month	N = 18	Improvement of full clinical appearance of chronic inflammation.	[27]
B. longum and Psyllium - alone or combined/ 2×10^9 CFU and/ or 8.0 g/day	R/ 4 weeks	n=120	Only symbiotic, consisting of *B. longum* and psyllium; significantly improved total IBD questionnaire scores in patients with UC after a 4-week treatment regimen.	[24]
BFM/ 100 mL (10 billion bacteria)/daily[2]	R, PC/ 12 weeks	N = 20	Combined with standard treatment; significantly reduced the clinical and endoscopic activity indexes in UC patients.	[50]
Bio-Three/ 9 tablets/day[3]	O/ 4 weeks	N = 20	Improved the clinical symptoms and endoscopic findings in patients with UC.	[101]
Bio-Three/ 9 tablets/day	R, PC/ 12 months	N = 60	Effective in maintaining clinical remission in patients with quiescent UC. Treatment in addition to ongoing medications.	[116]
E. coli Nissle 1917/ 200 mg/day (day 1–4, 100 mg)[4]	R, DB, PC/ 12 weeks	N = 120	Had an equivalent effect to mesalazine (500 mg/day) in maintaining remission and preventing relapse of the disease.	[56]
E. coli Nissle 1917/ 100 mg/ twice daily	R, DB/ 12 months	N = 116	Had an equivalent effect to mesalazine (800 mg/triple daily) in maintaining remission after acute attack of UC. At entry into the study, patients were given a 1-week course of oral gentamicin 80 mg/three times daily; next, during the first 12 weeks remission was induced with standard therapy.	[85]
E. coli Nissle 1917/ 200 mg/day (day 1-4, 100 mg/day)	R, DB/ 12 months	N = 327	Efficacy and safety in maintaining remission equivalent to mesalazine (500 mg/triple daily)	[55]
E. coli Nissle 1917/ 10, 20 or 40 ml (10^8 CFU/mL)/ daily enemas	R, DB/ 8 weeks	N = 90	The Jonckheere-Terpstra rank correlation for dose-dependent efficacy indicated a significant correlation of per-protocol responder rates ($p = 0.0446$, 2-sided). Time to remission was shortest with EcN 40 ml, followed by EcN 20 ml.	[65]
E. coli Nissle 1917/ 100 mg/ twice daily (day 1–4 once daily)	R, DB, PC/ 8 weeks	N = 100	No benefit in the use of EcN. An add-on treatment, after one week administration of ciprofloxacin or placebo.	[79]
L. casei DG/ 8×10^8 CFU administered orally or rectally/ twice daily	R/ 8 weeks	N = 26	Combined with standard mesalazine treatment 2.4 g/day. Mesalazine alone or together with oral *L. casei* DG failed to affect colonic flora and TLR expression in a significant manner, but when coupled with rectally administered *L. casei* DG, it modified colonic microbiota by increasing *Lactobacillus* spp. and reducing *Enterobacteriaceae*. It also significantly reduced TLR-4 and interleukin IL-1β mRNA levels and significantly increased mucosal IL-10.	[18]
L. delbrueckii and *L. fermentum*/ 10 billion CFU/day	R/ 8 weeks	N = 30	Combined with sulfasalazine therapy (2400 mg/day); significantly ameliorated the inflammation by decreasing the colonic concentration of IL-6, expression of TNF-alpha, NF-κB p65, and leukocyte recruitment, as demonstrated by a decrease in colonic MPO activity, and the level of faecal calprotectin.	[42]

Probiotic factor/Dose	Study design/ Time[1]	Patients number	Clinical effectiveness of probiotic factor	References
L. reuteri ATCC 55730/ 10^{10} CFU/ daily/rectal infusion	P, R, PC/ 8 weeks	N = 40	Combined with oral mesalazine treatment; was effective in improving mucosal inflammation and changing cytokines involved in the IBD in children with active distal UC.	[76]
L. rhamnosus GG/ 18×10^{9} bacteria/day	R/ 12 months	N = 187	Treatment with *Lactobacillus* GG was more effective than treatment with mesalazine 2400 mg/day in prolonging the relapse-free time ($P < 0.05$).	[120
Probio-Tec AB-25/ 1.5×10^{11} CFU/day[5]	R, DB, PC/ 52 weeks	N = 32	No significant clinical benefit in comparison with placebo for maintaining remission in patients with left-sided UC. Treatment combined with therapy with 5-ASA.	[113]
Profermin/ ca. 450 mL/day[6]	O/ 24 weeks	N = 39	Effective in reducing symptoms and inducing remission of active UC.	[53]
Profermin/ ca. 490 mL/day	O/ 8 weeks	N = 74	Twice more effective in reducing symptoms of UC than Fresubin.	[54]
S. boulardi/ 250 mg three times a day	O/ 4 weeks	N = 25	Administered during maintenance treatment with mesalazine; was effective in remission induction, confirmed endoscopically.	[39]
VSL#3/ 5×10^{11} cells/g, 2× 3 g/day[7]	O/ 12 months	N = 20	Effective in remission maintenance in UC patients intolerant or allergic to 5-aminosalicylic acid (5-ASA).	[108]
VSL#3/ 300 billion CFU/g, 3g/ day	R/ 8 weeks	N = 90	Combined with balsalazide (2.25 g/day); was more effective than balsalazide alone or mesalazine in inducing remission of UC.	[102]
VSL#3/ 2x1800 billion CFU/day	O/ 6 weeks	N = 34	Treatment of patients with mild-to-moderate UC, not responding to conventional therapy, with VSL#3 resulted in a combined induction of remission/response rate of 77% with no adverse events.	[8]
VSL#3/ 3.6×10^{12} CFU/twice daily	R, DB, PC/ 12 weeks	N = 147	Effective in achieving clinical responses and remission in patients with mild-to-moderately active UC.	[98]
VSL#3/ 450–1800 billion CFU/ day	P, PC, DB/ 1 year	N = 29	The efficacy and safety in active UC and in maintenance of remission. Therapy was in conjunction with concomitant steroid induction and mesalamine maintenance treatment.	[67]
VSL#3/ 3600 billion CFU/day	R, DB, PC/ 8 weeks	N = 144	Reduction of UC disease activity scores in patients affected by relapsing mild-to-moderate UC who were under concomitant treatment with 5-ASA and/ or immunosuppressants. The VSL#3 improved rectal bleeding and probably re-induced remission in relapsing UC patients after 8 weeks of treatment, although these parameters did not reach statistical significance.	[103]

[1] Clinical experiment and duration: R – randomized, PC – placebo-controlled, DB – double-blinded, P – prospective, O – open. [2]Commercially produced fermented milk containing *Bifidobacterium breve*, *Bifidobacterium bifidum*, and *Lactobacillus acidophilus* (Yakult Co., Japan). [3]Tablets containing a mixture of *Enterococcus faecalis* T-110 (2 mg), *Clostridium butyricum* TO-A (10 mg), and *Bacillus mesentericus* TO-A (10 mg). [4]Mutaflor 100 mg contains 25×10^{9} CFU (Mutaflor, Ardeypharm, GmbH). [5]Containing *Lactobacillus acidophilus* La-5 and *Bifidobacterium animalis* subsp. *lactis* BB-12. [6]Oat-based drink consisting of water, fermented oats, barley malt, lecithin, and *Lactobacillus plantarum* 299v (>10^{8} CFU/mL). [7]A mixture of *Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus bulgaricus, Bifidobacterium breve, B. longum, B. infantis* and *Streptococcus thermophilus.*

ble bacteria twice daily) [37]. We did not find any information regarding the efficiency of EcN in the prevention or treatment of pouchitis.

VSL#3 is a multispecies probiotic formulation containing a mixture of eight bacterial strains including *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Lactobacillus casei*, *Lactobacillus plantarum*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *Bifidobacterium infantis*, and *Bifidobacterium longum*. Similar to *E. coli* strain Nissle 1917, it has been widely tested in IBD management in independent clinical trials, and has had success for both inducing and maintaining remission in patients suffering from UC (table 1) and pouchitis (Table 2). At first, Venturi et al. [108] applied the VSL#3 probiotic formulation to 20 UC patients in remission who were intolerant or allergic to 5-aminosalicylates. It was observed that 15 out of 20 patients remained in remission, four relapsed, and one did not undergo a follow-up after 12 months of treatment. The researchers suggested that VSL#3 might be useful in maintaining remission in UC patients intolerant to standard therapy. Subsequently, Tursi et al. [102] suggested that the VSL#3 probiotic cocktail combined with balsalazide therapy might be a good choice for the treatment of active, mild-to-moderate ulcerative colitis, instead of balsalazide or mesalazine alone. Also, the research of Bibiloni et al. [8] showed that VSL#3 might be helpful in controlling active colitis in patients with mild-to-moderate UC that are not responding to conventional therapy. Among the 34 patients who completed the 6-week VSL#3 treatment described by Bibiloni's group, 18 achieved remission (53%) and eight

Table 2. The results of clinical trials testing probiotics in UC patients with pouchitis

Probiotic Factor/Dose	Study Design/ Time[1]	Patients number	Clinical effectiveness of probiotic factor	References
Fermented milk with lactobacilli (La-5) and bifidobacteria (Bb-12)/ 500 mL/day	O 4 weeks	N = 51	Reduced disease symptoms and inflammatory changes based on histopathology.	[59]
Ecologic 825 / 7.5×10^9 CFU/ twice daily[2]	O T=8 weeks	N = 16	Restoration of mucosal barrier, a feasible factor in prevention of recurrence during maintenance treatment in UC patients, was stated. Probiotic was introduced after antibiotic treatment.	[78]
L. rhamnosus GG/ 0.5-1×10^{10} CFU/twice daily	P, R, DB, PC 3 months	N = 20	Changed the pouch intestinal bacterial flora, but was ineffective as primary therapy for a clinical or endoscopic response.	[58]
L. rhamnosus GG/ 1×10^{10} bacteria/day	RS 12 years	N = 117	Provided significant clinical benefit and delayed the first onset of pouchitis in UC patients who underwent an ileal pouch-anal anastomosis.	[35]
Trilac/ 2 capsules/three times and 1 capsule/ twice daily, during first month and next months, respectively[3]	R, PC/ 9 months	N = 43	Applied in patients after restorative proctocolectomy; reduced DAI and pouchitis occurrence, and decreased pyruvate kinase and calprotectin.	[4]
VSL#3/ 30×10^{11} bacteria/day[4]	R DB, PC 9 months	N = 40	Effective in maintaining remission and preventing flare-ups of chronic pouchitis.	[33]
VSL#3/ 900 billion CFU/day	R, DB, PC 1 year	N = 40	Effective in the prevention of acute pouchitis onset and improved the quality of life in patients.	[31]
VSL#3/ 1800 billion CFU/day	R, PC 1 year	N = 36	The probiotic was effective in maintaining antibiotic-induced remission for at least a year in patients with recurrent or refractory pouchitis.	[69]
VSL #3/ 6 g/day	O 8 months	N = 31	Only a minority of patients with antibiotic-dependent pouchitis remained on probiotic therapy and in symptomatic remission after 8 months. Probiotic was introduced after positive ciprofloxacin therapy (500 mg/day/2 weeks).	[93]
VSL#3/ 3600 billion CFU/day	O 4 weeks	N = 23	Effective in the treatment of mild pouchitis, and induced remission.	[32]
VSL#3/ 1800 billion CFU/day	R 12months	N = 31	Administration of the VSL#3 in patients with IPAA reduced the disease activity index and expanded the number of mucosal regulatory T cells.	[82]

[1] Clinical experiment and duration: R – randomized, PC – placebo-controlled, DB – double-blinded, P – prospective, RS – retrospective, O – open. [2] A mixture of *Lactobacillus acidophilus* W22, *Lactobacillus casei* W56, *Lactobacillus paracasei* W20, *Lactobacillus plantarum* W62, *Lactobacillus salivarius* W24, *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W51, *Bifidobacterium lactis* W52, and *Lactococcus lactis* W19, FOS, inulin, enzymes and a mineral mix (Winclove Probiotics BV, Amsterdam, the Netherlands). [3] Each capsule contained 0.6×10^9 *Lactobacillus acidophilus,* 0.4×10^9 *Lactobacillus delbrueckii* subsp. *bulgaricus,* and 0.6×10^9 *Bifidobacterium bifidum* (Allergon AB, Angelholm, Sweden). [4] A mixture of *L. acidophilus, L. plantarum, L. paracasei, Lactobacillus bulgaricus, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis* and *Streptococcus thermophilus.*

responded with a decrease in UCDAI (24%). Among the remaining patients, three did not respond, the condition of three patients became worse and two did not have the final endoscopic assessment. No biochemical or clinical adverse events related to VSL#3 were stated. These findings were confirmed in a multicentre, randomised, double-blinded, placebo-controlled trial (147 patients with mild-to-moderate active UC) by Sood et al. [98]. It appeared that VSL#3-administered patients had significantly greater decreases in UC disease activity index (UCDAI) scores and individual symptoms compared to those of the placebo group. Miele et al. [67] determined remission to be 92.8% in children with newly diagnosed active UC when VSL#3 preparation was combined with the standard therapy; herein, standard therapy combined with placebo was only successful in 36.4% of patients. Only 21.4% of patients treated with VSL#3 relapsed during a 12-month follow-up compared to 73.3% in the placebo group. Subsequent research by Tursi et al. [103] confirmed that VSL#3 supplementation is safe and could reduce UCDAI scores in patients affected by relapsing mild-to-moderate UC under treatment with 5-ASA and/or immunosuppressants. Naidoo et al. [72] analysed the results of randomized controlled trials (RCTs) that compared probiotics against placebo or any other intervention for the maintenance of remission in ulcerative colitis. There was no statistically significant difference between probiotics and mesalazine; however, the authors stated that there is insufficient evidence to make general conclusion about the efficacy and benefit

of probiotics for maintenance of UC remission, due to the small number of patients and events (four trials) in the polled analysis and the high risk and unclear risk of bias in the included studies.

The VSL#3 multispecies probiotic cocktail appeared to be effective in the prevention of pouchitis; it has greatly improved the quality of life of patients suffering from UC (Table 2). Gionchetti et al. [33] evaluated the efficiency of the VSL#3 preparation in maintaining the remission of chronic pouchitis by administering a dose of 3×10^{12} of viable lyophilized bacteria per day. Herein, the VSL#3 formulation was effective in preventing flare-ups of chronic pouchitis. The same team showed that VSL#3 was able to prevent the onset of acute pouchitis after ileal pouch-anal anastomosis [31]. Mimura et al. [69] found that a single daily dose of 1800 billion bacteria of the VSL#3 cocktail was effective in maintaining antibiotic-induced remission for at least one year in patients with recurrent or refractory pouchitis. Nevertheless, Shen et al. [93] described an open-label uncontrolled trial, in which only a minority of patients with antibiotic-dependent pouchitis remained on the probiotic therapy and maintained symptomatic remission during 8 months of VSL#3 treatment. The majority of patients were not able to continue the long-term probiotic therapy. Studies by the Gionchetti group [32] revealed that high doses of the VSL#3 probiotic were effective in the treatment of mild pouchitis, defined as a score between 7 and 12 on the pouchitis disease activity index (PDAI). Pronio et al. [82] conducted an open-label study and revealed that VSL#3 administration in patients with ileal-pouch-anal-anastomosis (IPAA) modulates the PDAI and expands the number of mucosal regulatory T cells. Therapy of pouchitis with VSL#3 increases the richness and diversity of the mucosa associated microbiota in the gut, especially anaerobic flora, which has the potential to activate T cells [57]. Singh et al. [95] assessed the quality of findings on the use of probiotics in pouchitis prevention and treatment using the Cochrane risk of bias tool and GRADE criteria [41,44]. Herein, both for maintenance of remission in chronic pouchitis and for the prevention of pouchitis, low quality evidence suggest that VSL#3 may be more effective than placebo.

The VSL#3 probiotic cocktail earned recognition of WGO. The GWO experts stated that there is good evidence for the usefulness of VSL#3 probiotic cocktail in preventing an initial attack of pouchitis and in preventing a further relapse of pouchitis after the induction of remission with antibiotics [37]. According to WGO, the VSL#3 also appear safe and effective as conventional therapy in achieving higher response and remission rates in mild to moderately active ulcerative colitis. WGO recommends VSL#3 cocktail in dose of 900 billion CFU daily for treatment of active pouchitis and in a dose of 1800 billion CFU daily for inducing the remission of UC or for maintaining clinical remission of pouchitis.

The probiotic Bio-Three containing *Bacillus mesentericus* TO-A, *Enterococcus faecalis* T-110, and *Clostridium butyricum* TO-A symbiotic strains was twice successfully applied in UC therapy. Tsuda et al. [101] evaluated the efficiency of Bio-Three therapy for mild-to-moderate distal UC that was refractory to conventional therapies. Among 20 tested patients, remission was observed in nine patients, response occurred in two patients, no response was observed in eight patients, and one patient experienced worsening symptoms. Recently, Yoshimatsu et al. [116] confirmed the effectiveness of Bio-Three therapy for suppressing relapse in patients with inactive UC.

The *Lactobacillus rhamnosus* GG strain (Culturelle, i-Health, Inc.) has been well studied, including its ability to treat IBD. Just as previously discussed probiotics, the GG strain seems to be useful for UC and pouchitis treatment. Originally, Kuisma et al. [58] showed that although administration of the GG strain changed the pouch intestinal bacterial flora, it was ineffective as a primary therapy for the induction of a clinical or endoscopic response in patients with pouchitis. Also, Singh et al. [95] stated that there was no difference in clinical improvement between *Lactobacillus* GG and placebo in this study. However, the subsequent results from retrospective studies by Gosselink et al. [35] demonstrated that the GG strain delayed pouchitis. Similarly, in a randomized, placebo-controlled trial, performed on a large scale (187 patients with quiescent UC) by Zocco et al. [120], the *Lactobacillus* GG strain appeared to be effective for maintaining remission in patients with UC. The authors concluded that the strain represents a good therapeutic option for preventing relapse in this group of patients.

There is evidence, albeit less documented, describing the anti-inflammatory activities in UC patients of other microorganisms and probiotic preparations, mainly those containing beneficial *Lactobacillus* and *Bifidobacterium* strains (Table 1). When cocultured with inflamed tissues of active ulcerative colitis patients, *B. longum* could inhibit NF-kB activation in lamina propria mononuclear cells and down-regulate the secretion of inflammatory cytokines [3]. According to pilot trials, strains of *B. breve, B. infantis, B. longum, L. acidophilus, L. casei, Lactobacillus delbrueckii, Lactobacillus fermentum, L. plantarum, Lactobacillus reuteri* or *L. rhamnosus* alone, in mixture, or in combination with prebiotics improved to some extent the clinical status and pro-inflammatory biomarkers of UC patients [4,18,24,27,36,42,47,76,78,80]. The therapeutic effect of bifidobacteria-fermented milk, administered as a dietary adjunct, for the treatment of UC was also demonstrated [46,50]. The Bifico, a mixture of non-pathogenic *E. faecalis* and beneficial *B. longum,* and *L. acidophilus* strains, combined with standard treatment, was effective for maintaining remission and preventing relapse in UC patients [15]. Krag et al. [53,54] determined that Profermin, oat-based drink fermented with *L. plantarum* 299 v (Nordisk Rebalance, Denmark) is safe and well-tolerated and is able to reduce clinical colitis activity index scores at a statistically and clinically signifi-

cant level in patients with mild-to-moderate UC with a flare-up. However, despite the promising results, further confirming studies are necessary to authorize its effectiveness in the clinical management of IBD. Laakeet et al. [59] observed a clinical improvement of symptoms and a reduction in inflammation in patients with UC, who had underwent ileal-pouch-anal-anastomosis (IPAA), during four weeks of intervention with fermented milk containing live bifidobacteria and lactobacilli. Also, *Saccharomyces boulardii* has the potential for UC management, but perhaps it has been insufficiently examined. In a small non-controlled pilot study by Guslandi et al. [39], this strain appeared to be effective in inducing UC remission; however, further studies are required to confirm its effectiveness and safety.

Crohn's disease

There are no medications or surgical procedures that can effectively cure CD. Acute treatment involves the use of drugs such as antibiotics and aminosalicylates or corticosteroids to eliminate infections and reduce inflammation. Applying antibiotics poses the risk of overgrowth of refractory pathogens, whereas prolonged use of corticosteroids has significant side effects. As the aetiology of Crohn's disease is unknown, its therapy remains empiric or is used for the relief of specific symptoms. Finally, a trade-off is offered to the patients, i.e., an operation. However, despite advances in the surgical treatment of CD, the overall reported postoperative recurrence rates remain high [115]. A large number of patients require subsequent, more complex operations, often associated with an increased risk of morbidity.

Table 3 summarizes the results of 14 clinical trials, testing eight probiotic formulations in the management of CD. Contrary to UC, most experimental probiotic treatments appeared to be ineffective for Crohn's disease treatment. Malchow [61] performed a small pilot placebo-controlled study that demonstrated the positive effect of *E. coli* Nissle in maintaining remission in patients with CD. According to this study, inclusion of EcN in the treatment decreased the risk of disease recurrence and the need to administer glucocorticoids. Unfortunately, the study was not continued, and more data is necessary to confirm the benefits of *E. coli* strain Nissle 1917 as a therapeutic agent to maintain remission of colonic CD. Similarly, despite the promising results observed for UC and pouchitis management, there is a lack of sufficient evidence on the effectiveness of the VSL#3 probiotic formulation in CD treatment. Recently, Fedorak et al. [22] described a randomized, double-blind, placebo control study performed on 119 CD patients treated with ileocolonic resection and re-anastomosis. Although there were no statistical differences in endoscopic recurrence rates between the VSL#3 and placebo groups, patients receiving VSL#3 had reduced mucosal inflammatory cytokine levels compared to those of the placebo group ($P<0.05$). Among the other trials demonstrating improved clinical symptoms of CD, only *Lactobacillus* GG or *Saccharomyces boulardii* were tested more than once by unrelated scientific teams. Gupta et al. [38] first reported that the GG strain mitigated symptoms and positively affected intestinal mucosal integrity in children suffering from CD. However, subsequent retrospective, placebo-controlled studies showed that the GG strain does not influence the severity of CD, and also does not contribute to the induction or maintenance of remission in CD patients [11,81,90]. Similarly, the studies on effectiveness of *S. boulardii* in CD management appeared to be not consistent. According to Guslandi et al. [40] *S. boulardii,* when combined with baseline therapy, turned out to be effective in maintaining remission and preventing clinical relapses of CD. Subsequently, Vilela et al. [109] observed that *S. boulardii* added to baseline therapy improved intestinal permeability. However, similar to the case of the GG strain, the most recent report performed on a large scale demonstrated no beneficial effects for *S. boulardii* in CD treatment. A prospective study of 165 patients who achieved remission after treatment with steroids or salicylates, performed by Bourreille et al. [10], revealed that *S. boulardii* does not prevent relapse of CD. As regards the other preparation tested, Steed et al. [99] demonstrated that high doses of *B. longum* combined with Synergy 1 decreased the disease activity index and histological scores in patients with active CD. Similarly, Fujimori et al. [25] described the effectiveness of high-dose probiotic (*Lactobacillus* and *Bifidobacterium*, 7.5×10^{10} CFU daily) and prebiotic (psyllium, 9.9 g daily) co-therapy for the treatment active CD. There is still insufficient evidence for the efficiency of probiotics for the induction or maintenance of remission in Crohn's disease. Larger trials are required to determine whether they are of any benefit in CD [12,86].

Despite the existing evidence suggesting that antibiotics delay postoperative recurrence, none of the foregoing clinical trials have provided supporting evidence encouraging the use of probiotics in the prevention of postoperative recurrence in Crohn's disease patients [14,63,81,107]. Probiotics were not superior to placebo for any outcome measured [19].

Possible risk of probiotic administration in IBD

Although uncommon, cases of bacterial endocarditis, bacteraemia, urinary tract infections, pneumonia, septic arthritis or meningitis have been described, in which strains commonly regarded as safe (with GRAS status, generally recognized as safe) were isolated from the infected tissue or blood [13,45]. Some of them have been considered to be closely related to probiotics intake [83,88]. None of the pre-cited trials proved biochemical or clinical adverse events of probiotic intake in the IBD patients participating in the projects. However, some patients had to discontinue probiotic cure. Shen et al. [93] described a trial with patients with antibiotic-dependent pouchitis showing clinical symptoms and endoscopic inflammation that responded quickly to ciprofloxacin or metronidazole with recurrence of

Table 3. Results of clinical trials testing probiotics in Crohn's disease (CD) patients

Probiotic factor/Dose	Study design/ Time[1]	Patients number	Clinical effectiveness of probiotic factor	References
B. longum with Synergy 1/ 2×10^{11} cells and 6 g/ twice daily, respectively	R, DB, PC/ 6 months	N = 35	Effect in improving clinical symptoms. Disease activity index and histological scores in patients with active CD were significantly decreased.	[99]
E. coli Nissle 1917/ 100 mg/day[2]	PC/ 12 weeks	N = 28	Effective in maintenance of remission in patients administered probiotic with prednisolone.	[61]
L. johnsonii LA1/ 4×10^9 CFU/day	R, DB, PC/ 6 months	N = 98	Lack of sufficient effect to prevent endoscopic recurrence of CD in patients after intestinal resection.	[63]
L. johnsonii LA1/ 10^{10} CFU/day	R, PC/ 12 weeks	N = 70	Lack of influence on early endoscopic recurrence after ileo-caecal resection.	[107]
L. rhamnosus GG/ 1×10^{10} CFU/twice daily	O/ 6 months		Significant improvement in clinical activity, disease activity index and intestinal permeability.	[38]
L. rhamnosus GG/ 12 billion CFU/day	R, PC/ 1 year	N = 45	Lack of influence on endoscopic recurrence and on severity of recurrent lesions in CD patients after surgery.	[81]
L. rhamnosus GG/ 2×10^9 CFU/day	R, PC/ 6 months	N = 11	Lack of visible benefit on inducing or maintaining remission. Combined with antibiotic and steroid treatment during the first 2 weeks and 3 months, respectively.	[90]
L. rhamnosus GG with inulin/ 10^{10} CFU and 295 mg, respectively/ twice daily	R, PC/ 2 years	N = 75	Lack of influence on time to relapse. Combined with standard therapy with aminosalicylates, 6-ercaptopurine, azathioprine, and low-dose alternate day corticosteroids.	[11]
Mix of YACULT BL, ISAGOL and psyllium/ 60×10^9 CFU, 15×10^9 CFU and 9.9 g/day, respectively[3]	O/ 13 ± 4.5 months	N = 10	The applied probiotics (*B. breve, L. casei, B. longum*) and prebiotic (psyllium) co-therapy combined with standard treatment was effective for the treatment of active CD. Significantly reduced disease severity was observed.	[25]
S. boulardii/ 1 g/ day	R/ 6 months	N = 32	Added to baseline therapy with mesalamine (1 g/twice daily) was more effective than mesalamine alone in maintaining remission and preventing clinical relapses.	[40]
S. boulardii/ 1 g/ day	R, PC/ 3 months	N = 34	When added to baseline therapy improved intestinal permeability, even though complete normalization was not achieved. Baseline medications: mesalamine, azathioprine, prednisone, metronidazole and/or thalidomide.	[109]
S. boulardi / 1 g/ day	P, PC/ 52 weeks	N = 165	Lack of visible beneficial effect for patients with CD in remission after steroid or salicylate therapies.	[10]
Synbiotic 2000/ 4×10^{10} bacteria and 10 g of fibre/day[4]	P, R, DB, PC/ 24 months	N = 30	Synbiotic had no effect on postoperative recurrence of patients with CD.	[14]
VSL#3/ 900 billion CFU/day[5]	R, DB, PC/ 1 year	N = 119	Lack of influence, but lower mucosal levels of inflammatory cytokines and lower rate of recurrence was observed at day 90.	[22]

[1] Clinical experiment and duration: R – randomized, PC – placebo-controlled, DB – double-blinded, P – prospective, O – open. [2] Mutaflor 100 mg contains 25×10^9 CFU (Mutaflor, Ardeypharm, GmbH, Germany). [3] YACULT BL contained *B. breve* and *L. casei* (Yakult Co., Japan), ISAGOL contained *B. longum* (Fibro Pharmaceutical Co., Japan), psyllium (*Plantago ovata*). [4] A cocktail of *Pediococcus pentosaceus, Lactobacillus raffinolactis, Lactobacillus paracasei* subsp *paracasei* 19, and *Lactobacillus plantarum* 2362, and a mixture of β-glucans, inulin, pectin, and resistant starch. [5] A mixture of *Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus bulgaricus, Bifidobacterium breve, B. longum, B. infantis* and *Streptococcus thermophilus.*

symptoms soon (within 2 weeks) after stopping the antibiotics. Patients received 2 weeks of ciprofloxacin 500 mg b.d. followed by VSL#3 6 g/day for 8 months. At the 8-month follow-up, 25 of 31 patients participating in the study had to discontinue therapy due to either the recurrence of symptoms during treatment (patients were in remission when VSL#3 was started) or the development of adverse effects, such as: intolerable constipation, bloating, bleeding, or worsening abdominal pain or diarrhoea persisting for more than 2 weeks. Concerning other published IBD outcomes, we found three case reports describing infections related to probiotics or relative bacteria. Firstly, Farina et al. [21] described a case of *L. casei* subsp. *rhamnosus* repeatedly isolated in the blood culture of a 43-year-old woman with active ulcerative colitis, but treated only with prednisone and cyc-

losporine, without probiotic supplementation. Later on, Vahabnezhad et al. [106] described a case of *Lactobacillus* bacteraemia in a 17-year-old boy with ulcerative colitis managed with systemic corticosteroids and infliximab, who presented with fever, flushing, and chills 1 week after starting *Lactobacillus rhamnosus* GG probiotic. 16S rRNA sequence analysis identified the organism from a patient's blood culture and probiotic capsule as *L. rhamnosus* with a 99.78% match for both the strain. Similarly, Meini et al. [66] reported on a case of bacteraemia caused by *L. rhamnosus* GG in an adult patient (64 years) affected by severe active ulcerative colitis under treatment with corticosteroids and mesalazine. Earlier, due to a persistently relapsing fever associated with negative blood cultures, the patient was empirically treated with different antibiotic regiments which in turn yielded *Staphylococcus epidermidis* and *Candida albicans* in the patient's blood. *Lactobacillus* bacteraemia occurred while the patient was receiving a probiotic formulation ($6x10^9$cfu daily, to restore the gut microbiota), and was being constantly treated with intravenous vancomycin (because of candidemia), to which the *Lactobacillus* strain appeared to be resistant. Salminen et al. [88] have analysed risk factors and outcomes for 85 described cases of patients with different clinical disorders and *Lactobacillus* bacteraemia; including *L. rhamnosus, L. rhamnosus* GG, and other *Lactobacillus* species. Species of *L. casei* and *L. rhamnosus* were the most common cause of infection, and the infective strains appeared to be most sensitive to erythromycin and clindamycin and most resistant to vancomycin.

Other detrimental effects of probiotic intake – most important incidents

A great many other trials were performed throughout the last two decades in which probiotics were given to thousands of patients with different diseases of varying severity and health consequences. Most frequently, the trials showed a lack of influence or a reduction in disease activity index scores, mortality, sepsis, or infections, and only very few found significant increases in negative clinical sequelae [7,84,112]. Patients after liver transplants who were receiving postoperative enteral nutrition with Synbiotic 2000 (Medipharm, Sweden) consisting of *Pediococcus pentosaceus, Leuconostoc mesenteroides, L. paracasei, L. plantarum* and four bioactive fibres (betaglucan, inulin, pectin and resistant starch) showed biliary tract stenosis, fistulas and lienalis steal syndrome, which did not occur in the group receiving bioactive fibres alone, and intensified abdominal haemorrhage and acute renal failure which were, however, observed in both groups [84]. All the same, the symbiotic effectively prevented post-operative bacterial infections in the high risk surgical subjects. In another trial, there was significantly higher surgical intervention, organ failure and mortality in the group of patients with severe acute pancreatitis who were receiving enteral nutrition with Ecologic 641 (Winclove Bio Industries, Netherlands) consisting of *L. acidophilus, L. casei, L. salivarius, L. lactis, B. bifidum* and *B. lactis,* as compared to the control group receiving placebo [7]. However, there were no significant differences in the incidence of infectious complications between the groups, and no infections were confirmed to be caused by the administered probiotic strains. Some patients receiving probiotic (6%) developed bowel ischemia that did not occur in the control group, among them two serious adverse events leading to death were reported; both patients died.

According to published case reports, adverse events in patients receiving support with probiotics occurred mainly after the administration of probiotic bacteria *Lactobacillus rhamnosus* GG or the yeast *S. boulardii*, resulting in bacteraemia or fungemia, respectively [112]. Thus far, lactobacilli have been frequently associated with infective endocarditis, meningitis, pneumonia, and local suppurative conditions in the absence of probiotic supplementation, although a few reports directly linked cases of *Lactobacillus* sepsis to probiotic intake, especially *Lactobacillus rhamnosus* GG [13,88]. *Lactobacillus* species are generally resistant to metronidazole, aminoglycosides and ciprofloxacin. They belong to dominative microbiota in human gut. Gut microbiota imbalance and concurrent antibiotics may incalculably enhance their multiplicity in the imbalanced gut, and thus increase the risk of translocation of bacterial cells through the inflamed epithelium. Among the *Lactobacillus* strains most extensively used in a variety of commercial products, *L. acidophilus* is susceptible to penicillin and vancomycin, whereas *L. rhamnosus and L. casei* are resistant to metronidazole and vancomycin [34]. This should be taken into account while arranging antibiotic therapy in high-risk patients.

S. cerevisiae is a common colonizer of mucosal surfaces and part of the normal flora of the human gut. Many clinical trials and experimental studies demonstrated that administration of *S. boulardii* may be effective way to prevent and treat gastrointestinal disorders [51]. Nevertheless, its overgrowth can cause a wide variety of clinical syndromes, such as pneumonia, empyema, liver abscess, peritonitis, vaginitis, esophagitis, urinary tract infection, cellulitis, unexplained fever, or septic shock [70,77]. The presence of *S. cerevisiae* in naturally sterile fluids has been frequently described in patients with ruptured local barriers or with very high fungal loads [70]. Antibodies against *Saccharomyces cerevisiae* (ASCAs) are detectable in the serum of patients with Crohn's disease, and have been proposed as one of the serological markers for CD diagnosis [6]. On the other hand, *S. boulardii* (subtype of *S. cerevisiae*) possess the potential to UC and even CD management, especially when combined with baseline therapy (Table 1, 3) [39,40]. Vilela et al. [109] observed that *S. boulardii*, added to baseline therapy, improved intestinal permeability in patients with Crohn's disease in remission. Nevertheless, the use of *Saccharomyces* in IBD patients is not without risk and caution should be taken in patients with risk factors for adverse events. Thus far, probiotic products con-

taining *Saccharomyces* strains have been directly linked to an increased risk of complications in special risk group patients, such as immunocompromized subjects and transplant patients [77]. According to Munoz et al. [70], *S. cerevisiae* should be also considered as a well-established cause of nosocomially acquired yeast infection, particularly in patients receiving prophylaxis or treatment with the probiotic Ultralevura (Bristol-Myers Squibb), containing *S. boulardii,* which should be considered a risk factor for nosocomial bloodstream infection in patients with predisposing underlying conditions.

Bifidobacterium preparations may pose a risk factor for infections in adults and infants. Ohishi et al. [75] published a case report describing *Bifidobacterium* septicaemia caused by postoperative *B. breve* BBG-01 (Yakult Honsya Co Ltd, Tokyo, Japan) therapy in neonate with omphalocele. There are also reports describing cases of *Bifidobacterium longum* subspecies *infantis* bacteraemia in very preterm infant groups receiving probiotic Infloran (containing *L. acidophilus* and *B. infantis*) [5,20]. By comparative genomics, it was confirmed that the strains isolated from infected infants originated from the probiotics. *Bifidobacterium longum* and *Bifidobacterium dentium* caused bacteraemia in adults. However, in adults, the role of probiotic administration is unknown, as there is lack information on use of probiotics in the adult cases [111].

Thus far, the complications associated with probiotic therapy appeared mainly in immunocompromized and critically ill subjects. The majority of these patients had received antibiotics, or had intravenous access via a central venous catheter or a peripheral venous catheter, posing additional risk factors for probiotic infection. Thus, there is no clearly identified group hazardous to probiotic intake. The affected patients differed in age, had diagnoses of various major organ disorders, and were receiving enteral and/or parenteral nutrition. Since microbes used as probiotics are non-pathogenic inhabitants of the gut, it is also difficult to identify inherent strain properties that may be related to health risks, as well as to unequivocally distinguish probiotic strain from all these strains naturally occurring in the intestine. It should be also remembered that cases of infections due to probiotic intake are very rare regarding their widespread usage. Simkins et al. [94] performed a retrospective study at the large academic medical centre and determined the incidence of probiotic-related bloodstream infection due to *Lactobacillus acidophilus/Lactobacillus bulgaricus.* Only two out of 1,176 (0.2%) patients, including the in-patients that could be considered at high risk for probiotic-related bloodstream infection, developed a potential probiotic-related bloodstream infection during the 8-year period (2000-2008). The first case was a 66-year-old female with history of diabetes mellitus and end-stage renal disease, who was receiving a probiotic *L. acidophilus/L. bulgaricus* for *C. difficile* infection and who presented with fever and a right lower extremity cellulitis. The second case was a 73-year-old female with a history of diabetes mellitus, cholangiocarcinoma (status post chemotherapy), and hepaticojejunostomy. She presented with a 2-day history of fever, nausea, vomiting, and abdominal pain.

Conclusions

In conclusion, probiotics have the potential for IBD management, especially for UC and pouchitis. However, only some that have been well characterized are recognized for their beneficial activity, and they display no side effects during IBD treatment; for these, effectiveness has been proven in a small number of large-scale, randomized clinical studies from multicentre trials. *E. coli* Nissle 1917 appeared to be safe and effective in preventing relapse of UC, whereas the VSL#3 bacterial cocktail, especially when combined with standard therapy, was successful for both the induction of remission and maintenance of UC and pouchitis. Bio-Three could be used for maintaining clinical remission in UC patients, whereas *L. rhamnosus* GG was shown to delay the first onset of pouchitis. For other probiotics, only pilot clinical studies have been performed, and are thus not definitive. These trials were insufficiently controlled, and although they were promising, they need to be confirmed on a larger scale in randomized double-blind placebo controlled clinical trials.

To sum up, probiotic therapies seem to be more effective for preventing disease recurrence than for treatment of active stage. It is well known that probiotics exert strain-specific beneficial effects on the host. Most probiotic-containing products are generally regarded as safe in healthy populations. However, the application of probiotic therapy in persons with compromised immune functions or a serious underlying disease should be restricted to the strains and indications with proven efficacy. It should also be remembered that, in acute IBD, where an extensive damage of intestinal mucus membrane is present, there might be an increased risk of translocation causing bacteraemia; therefore, the use of probiotics should be considered with the greatest caution, especially that *Lactobacillus* and *Saccharomyces* spp. possess a potential to translocate from the intestinal lumen to the blood during the disruption of the physiologic architecture of the intestinal mucosa.

References

[1] Andoh A., Imaeda H., Aomatsu T., Inatomi O., Bamba S., Sasaki M., Saito Y., Tsujikawa T., Fujiyama Y.: Comparison of the faecal microbiota profiles between ulcerative colitis and Crohn's disease using terminal restriction fragment length polymorphism analysis. J. Gastroenterol., 2011; 46: 479-486

[2] Antoni L., Nuding S., Wehkamp J., Stange E.F.: Intestinal barrier in inflammatory bowel disease. World J. Gastroenterol., 2014; 20: 1165-1179

[3] Bai A.P., Ouyang Q., Xiao X.R., Li S.F.: Probiotics modulate inflammatory cytokine secretion from inflamed mucosa in active ulcerative colitis. Int. J. Clin. Pract., 2006; 60: 284-288

[4] Banasiewicz T., Stojcev Z., Walkowiak J., Marciniak R., Grochowalski M., Burdyński R., Krokowicz P., Krokowicz L., Paszkowski J., Gronek P., Pyda P., Drews M.: Long-term use of probiotics *Lactobacillus* and *Bifidobacterium* has a prophylactic effect on the occurrence and severity of pouchitis. A randomized prospective study. Biomed. Res. Int., 2014; 2014: 208064

[5] Bertelli C., Pillonel T., Torregrossa A., Prod'hom G., Fischer C.J., Greub G., Giannoni E.: *Bifidobacterium longum* bacteremia in preterm infants receiving probiotics. Clin. Infect. Dis., 2015; 60: 924-927

[6] Bertin D., Grimaud J.C., Lesavre N., Benelmouloud C., Desjeux A., Garcia S., Desplat-Jégo S.: Targeting tissular immune response improves diagnostic performance of anti-*Saccharomyces cerevisiae* antibodies (ASCA) in Crohn's disease. PLoS One, 2013; 8: e80433

[7] Besselink M.G., van Santvoort H.C., Buskens E., Boermeester M.A., van Goor H., Timmerman H.M., Nieuwenhuijs V.B., Bollen T.L., van Ramshorst B., Witteman B.J., Rosman C., Ploeg R.J., Brink M.A., Schaapherder A.F., Dejong C.H., et al.: Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. Lancet, 2008; 371: 651-659

[8] Bibiloni R., Fedorak R.N., Tannock G.W., Madsen K.L., Gionchetti P., Campieri M., De Simone C., Sartor R.B.: VSL#3 probiotic-mixture induces remission in patients with active ulcerative colitis. Am. J. Gastroenterol., 2005; 100: 1539-1546

[9] Bischoff S.C., Barbara G., Buurman W., Ockhuizen T., Schulzke J.D., Serino M., Tilg H., Watson A., Wells J.M.: Intestinal permeability – a new target for disease prevention and therapy. BMC Gastroenterol., 2014; 14: 189

[10] Bourreille A., Cadiot G., Le Dreau G., Laharie D., Beaugerie L., Dupas J.L., Marteau P., Rampal P., Moyse D., Saleh A., Le Guern M.E., Galmiche J.P., FLORABEST Study Group: *Saccharomyces boulardii* does not prevent relapse of Crohn's disease. Clin. Gastroenterol. Hepatol., 2013; 11: 982-987

[11] Bousvaros A., Guandalini S., Baldassano R.N., Botelho C., Evans J., Ferry G.D., Goldin B., Hartigan L., Kugathasan S., Levy J., Murray K.F., Oliva-Hemker M., Rosh J.R., Tolia V., Zholudev A., et al: 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

[12] Butterworth A.D., Thomas A.G., Akobeng A.K.: Probiotics for induction of remission in Crohn's disease. Cochrane Database Syst. Rev., 2008; 3: CD006634

[13] Cannon J.P., Lee T.A., Bolanos J.T., Danziger L.H.: Pathogenic relevance of *Lactobacillus:* a retrospective review of over 200 cases. Eur. J. Clin. Microbiol. Infect. Dis., 2005; 24: 31-40

[14] 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

[15] Cui H.H., Chen C.L., Wang J.D., Yang Y.J., Cun Y., Wu J.B., Liu Y.H., Dan H.L., Jian Y.T., Chen X.Q.: Effects of probiotic on intestinal mucosa of patients with ulcerative colitis. World J. Gastroenterol., 2004; 10: 1521-1525

[16] Cunningham K.E., Turner J.R.: Myosin light chain kinase: pulling the strings of epithelial tight junction function. Ann. NY Acad. Sci., 2012; 1258: 34-42

[17] D'Haens G.R., Geboes K., Peeters M., Baert F., Pennickx F., Rutgeerts P.: Early lesions of recurrent Crohn's disease caused by infusion of intestinal contents in excluded ileum. Gastroenterology, 1998; 114: 262-267

[18] D'Inca R., Barollo M., Scarpa M., Grillo A.R., Brun P., Vettorato M.G., Castagliuolo I., Sturniolo G.C.: Rectal administration of *Lactobacillus casei* DG modifies flora composition and Toll-like receptor expression in colonic mucosa of patients with mild ulcerative colitis. Dig. Dis. Sci., 2011; 56: 1178-1187

[19] Doherty G., Bennett G., Patil S., Cheifetz A., Moss A.C.: Interventions for prevention of post-operative recurrence of Crohn's disease. Cochrane Database Syst. Rev., 2009; 4: CD006873

[20] Esaiassen E., Cavanagh P., Hjerde E., Simonsen G.S., Stoen R., Klingenberg C.: *Bifidobacterium longum* subspecies *infantis* bacteremia in 3 extremely preterm infants receiving probiotics. Emerg. Infect. Dis., 2016; 22: 1664-1666

[21] Farina C., Arosio M., Mangia M., Moioli F.: *Lactobacillus casei* subsp. *rhamnosus* sepsis in a patient with ulcerative colitis. J. Clin. Gastroenterol., 2001; 33: 251-252

[22] Fedorak R.N., Feagan B.G., Hotte N., Leddin D., Dieleman L.A., Petrunia D.M., Enns R., Bitton A., Chiba N., Paré P., Rostom A., Marshall J., Depew W., Bernstein C.N., Panaccione R., et al: The probiotic VSL#3 has anti-inflammatory effects and could reduce endoscopic recurrence after surgery for Crohn's disease. Clin. Gastroenterol. Hepatol., 2015; 13: 928-935.e2

[23] Flint H.J., Scott K.P., Louis P., Duncan S.H.: The role of the gut microbiota in nutrition and health. Nat. Rev. Gastroenterol. Hepatol., 2012; 9: 577-589

[24] Fujimori S., Gudis K., Mitsui K., Seo T., Yonezawa M., Tanaka S., Tatsuguchi A., Sakamoto C.: A randomized controlled trial on the efficacy of synbiotic versus probiotic or prebiotic treatment to improve the quality of life in patients with ulcerative colitis. Nutrition, 2009; 25: 520-525

[25] Fujimori S., Tatsuguchi A., Gudis K., Kishida T., Mitsui K., Ehara A., Kobayashi T., Sekita Y., Seo T., Sakamoto C.: High dose probiotic and prebiotic cotherapy for remission induction of active Crohn's disease. J. Gastroenterol. Hepatol., 2007; 22: 1199-1204

[26] Fukui H.: Increased intestinal permeability and decreased barrier function. Does it really influence the risk of inflammation? Inflamm. Intest. Dis., 2016; 1: 135-145

[27] Furrie E., Macfarlane S., Kennedy A., Cummings J.H., Walsh S.V., O'Neil D.A., Macfarlane G.T.: Synbiotic therapy (*Bifidobacterium longum*/Synergy 1) initiates resolution of inflammation in patients with active ulcerative colitis: a randomized controlled pilot trial. Gut, 2005; 54: 242-249

[28] Gardiner K.R., Halliday M.I., Barclay G.R., Milne L., Brown D., Stephens S., Maxwell R.J., Rowlands B.J.: Significance of systemic endotoxaemia in inflammatory bowel disease. Gut, 1995; 36: 897-901

[29] Garrett W.S., Lord G.M., Punit S., Lugo-Villarino G., Mazmanian S.K., Ito S., Glickman J.N., Glimcher L.H.: Communicable ulcerative colitis induced by T-bet deficiency in the innate immune system. Cell, 2007; 131: 33-45

[30] Gevers D., Kugathasan S., Denson L.A., Vázquez-Baeza Y., Van Treuren W., Ren B., Schwager E., Knights D., Song S.J., Yassour M., Morgan X.C., Kostic A.D., Luio C., González A., McDonald D., et al: The treatment-naive microbiome in new-onset Crohn's disease. Cell Host Microbe, 2014; 15: 382-392

[31] Gionchetti P., Rizzello F., Helwig U., Venturi A., Lammers K.M.,

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

[32] 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: 2075-2082

[33] 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

[34] Goldstein E.J., Tyrrell K.L., Citron D.M.: *Lactobacillus* species. Taxonomic complexity and controversial susceptibilities. Clin. Infect. Dis., 2015; 60 (Suppl. 2): S98-S107

[35] Gosselink M.P., Schouten W.R., van Lieshout L.M., Hop W.C., Laman J.D., Ruseler-van Embden J.G.: Delay of the first onset of pouchitis by oral intake of the probiotic strain *Lactobacillus rhamnosus* GG. Dis. Colon Rectum, 2004; 47: 876-884

[36] Groeger D., O'Mahony L., Murphy E.F., Bourke J.F., Dinan T.G., Kiely B., Shanahan F., Quigley E.M.: *Bifidobacterium infantis* 35624 modulates host inflammatory processes beyond the gut. Gut Microbes, 2013; 4: 325-339

[37] Guarner F., Sanders M.E., Eliakim R., Fedorak R., Gangl A., Garisch J., Kaufmann P., Karakan T., Khan A.G., Kim N., De Paula J.A., Ramakrishna B., Shanahan F., Szajewska H., Thomson A., Le Mair A.: Probiotics and Prebiotics. World Gastroenterology Organization Global Guidelines, 2017: 1-35

[38] Gupta P., Andrew H., Kirschner B.S., Guandalini S.: Is *lactobacillus* GG helpful in children with Crohn's disease? Results of a preliminary, open-label study. J. Pediatr. Gastroenterol. Nutr., 2000; 31: 453-457

[39] Guslandi M., Giollo P., Testoni P.A.: A pilot trial of *Saccharomyces boulardii* in ulcerative colitis. Eur. J. Gastroenterol. Hepatol., 2003; 15: 697-698

[40] Guslandi M., Mezzi G., Sorghi M., Testoni P.A.: *Saccharomyces boulardii* in maintenance treatment of Crohn's disease. Dig. Dis. Sci., 2000; 45: 1462-1464

[41] Guyatt G.H., Oxman A.D., Vist G.E., Kunz R., Falck-Ytter Y., Alonso-Coello P., Schünemann H.J., GRADE Working Group: GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Br. Med. J., 2008; 336: 924-926

[42] Hegazy S.K., El-Bedewy M.M.: Effect of probiotics on pro-inflammatory cytokines and NF-κB activation in ulcerative colitis. World J. Gastroenterol., 2010; 16: 4145-4151

[43] Heller F., Florian P., Bojarski C., Richter J., Christ M., Hillenbrand B., Mankertz J., Gitter A.H., Bürgel N., Fromm M., Zeitz M., Fuss I., Strober W., Schulzke J.D.: Interleukin-13 is the key effector Th2 cytokine in ulcerative colitis that affects epithelial tight junctions, apoptosis, and cell restitution. Gastroenterology, 2005; 129: 550-564

[44] Higgins J.P., Altman D.G., Gotzsche P.C Jüni P., Moher D., Oxman A.D., Savovic J., Schulz K.F., Weeks L., Sterne J.A.; Cochrane Bias Methods Group; Cochrane Statistical Methods Group: The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Br. Med. J., 2011; 343: d5928

[45] Husni R.N., Gordon S.M., Washington J.A., Longworth D.L.: *Lactobacillus* bacteremia and endocarditis. Review of 45 cases. Clin. Infect. Dis., 1997; 25: 1048-1055

[46] 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

[47] Ishikawa H., Matsumoto S., Ohashi Y., Imaoka A., Setoyama H., Umesaki Y., Tanaka R., Otani T.: Beneficial effects of probiotic *Bifidobacterium* and galacto-oligosaccharide in patients with ulcerative colitis. A randomized controlled study. Digestion, 2011; 84: 128-133

[48] Johansson M.E., Gustafsson J.K., Holmén-Larsson J., Jabbar K.S., Xia L., Xu H., Ghishan F.K., Carvalho F.A., Gewirtz A.T., Sjövall H., Hansson G.C.: Bacteria penetrate the normally impenetrable inner colon mucus layer in both murine colitis models and patients with ulcerative colitis. Gut, 2014; 63: 281-291

[49] Jostins L., Ripke S., Weersma R.K., Duerr R.H., McGovern D.P., Hui K.Y., Lee J.C., Schumm L.P., Sharma Y., Anderson C.A., Essers J., Mitrovic M., Ning K., Cleynen I., Theatre E., et al: Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature, 2012; 491: 119-124

[50] 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

[51] Kelesidis T., Pothoulakis C.: Efficacy and safety of the probiotic *Saccharomyces boulardii* for the prevention and therapy of gastrointestinal disorders. Therap. Adv. Gastroenterol., 2012; 5: 111-125

[52] Khan K.J., Ullman T.A., Ford A.C., Abreu M.T., Abadir A., Marshall J.K., Talley N.J., Moayyedi P.: Antibiotic therapy in inflammatory bowel disease. A systematic review and meta-analysis. Am. J. Gastroenterol., 2011; 106: 661-673

[53] Krag A., Israelsen H., von Ryberg B., Andersen K.K., Bendtsen F.: Safety and efficacy of Profermin® to induce remission in ulcerative colitis. World J. Gastroenterol., 2012; 18: 1773-1780

[54] Krag A., Munkholm P., Israelsen H., von Ryberg B., Andersen K.K., Bendtsen F.: Profermin is efficacious in patients with active ulcerative colitis - a randomized controlled trial. Inflamm. Bowel Dis., 2013; 19: 2584-2592

[55] Kruis W., Fric P., Pokrotnieks J., Lukás M., Fixa B., Kascák M., Kamm M.A., 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

[56] 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

[57] Kühbacher T., Ott S.J., Helwig U., Mimura T., Rizzello F., Kleessen B., Gionchetti P., Blaut M., Campieri M., Fölsch U.R., Kamm M.A., Schreiber S.: Bacterial and fungal microbiota in relation to probiotic therapy (VSL##3) in pouchitis. Gut, 2006; 55: 833-841

[58] 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

[59] Laake K.O., Bjorneklett A., Aamodt G., Aabakken L., Jacobsen M., Bakka A., Vatn M.H.: Outcome of four weeks' intervention with probiotics on symptoms and endoscopic appearance after surgical reconstruction with a J-configurated ileal-pouch-anal-anastomosis in ulcerative colitis. Scand. J. Gastroenterol., 2005; 40: 43-51

[60] Macpherson A.J., Harris N.L.: Interactions between commensal intestinal bacteria and the immune system. Nat. Rev. Immunol., 2004; 4: 478-485

[61] Malchow H.A.: 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

[62] 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

[63] Marteau P., Lémann M., Seksik P., Laharie D., Colombel J.F., Bouhnik Y., Cadiot G., Soulé J.C., Bourreille A., Metman E., Lerebours E.,

Carbonnel F., Dupas J.L., Veyrac M., Coffin B., et al: Ineffectiveness of *Lactobacillus johnsonii* LA1 for prophylaxis of postoperative recurrence in Crohn's disease: a randomized, double blind, placebo controlled GETAID trial. Gut, 2006; 55: 842-847

[64] Matsuoka K., Kanai T.: The gut microbiota and inflammatory bowel disease. Semin. Immunopathol., 2015; 37: 47-55

[65] Matthes H., Krummenerl T., Giensch M., Wolff C., Schulze J.: Clinical trial: probiotic treatment of acute distal ulcerative colitis with rectally administered *Escherichia coli* Nissle 1917 (EcN). BMC Complement. Altern. Med., 2010; 10: 13

[66] Meini S., Laureano R., Fani L., Tascini C., Galano A., Antonelli A., Rossolini G.M.: Breakthrough *Lactobacillus rhamnosus* GG bacteremia associated with probiotic use in an adult patient with severe active ulcerative colitis: case report and review of the literature. Infection, 2015; 43: 777-781

[67] Miele E., Pascarella F., Giannetti E., Quaglietta L., Baldassano R.N., 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

[68] Mimouna S., Goncalves D., Barnich N., Darfeuille-Michaud A., Hofman P., Vouret-Craviari V.: Crohn disease-associated *Escherichia coli* promote gastrointestinal inflammatory disorders by activation of HIF-dependent responses. Gut Microbes, 2011; 2: 335-346

[69] Mimura T., Rizzello F., Helwig U., Poggioli G., Schreiber S., Talbot I.C., Nicholls R.J., Gionchetti P., Campieri M., Kamm M.A.: Once daily high dose probiotic therapy (VSL#3) for maintaining remission in recurrent or refractory pouchitis. Gut, 2004; 53: 108-114

[70] Munoz P., Bouza E., Cuenca-Estrella M., Eiros J.M., Pérez M.J., Sánchez-Somolinos M., Rincón C., Hortal J., Peláez T.: *Saccharomyces cerevisiae* fungemia. An emerging infectious disease. Clin. Infect. Dis., 2005; 40: 1625-1634

[71] Nagy A., Jędrychowski L., Gelencsér É., Wróblewska B., Szymkiewicz A.: Induction of specific mucosal immune responses by viable or heat denatured probiotic bacteria of *Lactobacillus* strains. Acta Aliment., 2005; 34: 33-39

[72] Naidoo K., Gordon M., Fagbemi A.O., Thomas A.G., Akobeng A.K.: Probiotics for maintenance of remission in ulcerative colitis. Cochrane Database Syst. Rev., 2011; 12: CD007443

[73] Nicholson J.K., Holmes E., Wilson I.D.: Gut microorganisms, mammalian metabolism and personalized health care. Nat. Rev. Microbiol., 2005; 3: 431-438

[74] Ogura Y., Bonen D.K., Inohara N., Nicolae D.L., Chen F.F., Ramos R., Britton H., Moran T., Karaliuskas R., Duerr R.H., Achkar J.P., Brant S.R., Bayless T.M., Kirschner B.S., Hanauer S.B., et al: A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. Nature, 2001; 411: 603-606

[75] Ohishi A., Takahashi S., Ito Y., Ohishi Y., Tsukamoto K., Nanba Y., Ito N., Kakiuchi S., Saitoh A., Morotomi M., Nakamura T.: *Bifidobacterium* septicemia associated with postoperative probiotic therapy in a neonate with omphalocele. J. Pediatr., 2010; 156: 679-681

[76] Oliva S., Di Nardo G., Ferrari F., Mallardo S., Rossi P., Patrizi G., Cucchiara S., Stronati L.: Randomized 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

[77] Pérez-Torrado R., Querol A.: Opportunistic strains of *Saccharomyces cerevisiae*. A potential risk sold in food products. Front. Microbiol., 2016; 6: 1522

[78] Persborn M., Gerritsen J., Wallon C., Carlsson A., Akkermans L.M., Söderholm J.D.: The effects of probiotics on barrier function and mucosal pouch microbiota during maintenance treatment for severe pouchitis in patients with ulcerative colitis. Aliment. Pharmacol. Ther., 2013; 38: 772-783

[79] Petersen A.M., Mirsepasi H., Halkjaer S.I., Mortensen E.M., Nordgaard-Lassen I., Krogfelt K.A.: Ciprofloxacin and probiotic *Escherichia coli* Nissle add-on treatment in active ulcerative colitis: a double-blind randomized placebo controlled clinical trial. J. Crohns Colitis, 2014; 8: 1498-1505

[80] Porbén S.S.: Influence of a combination of *lactobacilli* and *bifidobacteria* upon disease activity, stool pattern and nutritional status of ulcerative colitis patients. Nutr. Hosp., 2010; 25: 971-983

[81] Prantera C., Scribano M.L., 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

[82] 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

[83] Rautio M., Jousimies-Somer H., Kauma H., Pietarinen I., Saxelin M., Tynkkynen S., Koskela M.: Liver abscess due to a *Lactobacillus rhamnosus* strain indistinguishable from *L. rhamnosus* strain GG. Clin. Infect. Dis., 1999; 28: 1159-1160

[84] Rayes N., Seehofer D., Theruvath T., Schiller R.A., Langrehr J.M., Jonas S., Bengmark S., Neuhaus P.: Supply of pre- and probiotics reduces bacterial infection rates after liver transplantation - a randomized, double-blind trial. Am. J. Transplant., 2005; 5: 125-130

[85] Rembacken B.J., Snelling A.M., Hawkey P.M., Chalmers D.M., Axon A.T.: Non-pathogenic *Escherichia coli* versus mesalazine for the treatment of ulcerative colitis: a randomized trial. Lancet, 1999; 354: 635-639

[86] Rolfe V.E., Fortun P.J., Hawkey C.J., Bath-Hextall F.J.: Probiotics for maintenance of remission in Crohn's disease. Cochrane Database Syst. Rev., 2006; 4: CD004826

[87] Round J.L., Lee S.M., Li J., Tran G., Jabri B., Chatila T.A., Mazmanian S.K.: The Toll-like receptor 2 pathway establishes colonization by a commensal of the human microbiota. Science, 2011; 332: 974-977

[88] Salminen M.K., Rautelin H., Tynkkynen S., Poussa T., Saxelin M., Valtonen V., Järvinen A.: *Lactobacillus* bacteremia, species identification, and antimicrobial susceptibility of 85 blood isolates. Clin. Infect. Dis., 2006; 42: e35-e44

[89] Sartor R.B.: Genetics and environmental interactions shape the intestinal microbiome to promote inflammatory bowel disease versus mucosal homeostasis. Gastroenterology, 2010; 139: 1816-1819

[90] Schultz M., Timmer A., Herfarth H.H., Sartor R.B., Vanderhoof J.A., Rath H.C.: *Lactobacillus* GG in inducing and maintaining remission of Crohn's disease. BMC Gastroenterol., 2004; 4: 5

[91] Seksik P., Rigottier-Gois L., Gramet G., Sutren M., Pochart P., Marteau P., Jian R., Doré J.: Alterations of the dominant faecal bacterial groups in patients with Crohn's disease of the colon. Gut, 2003; 52: 237-242

[92] Sellon R.K., Tonkonogy S., Schultz M., Dieleman L.A., Grenther W., Balish E., Rennick D.M., Sartor R.B.: 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

[93] Shen B., Brzezinski A., Fazio V.W., Remzi F.H., Achkar J.P., Bennett A.E., Sherman K., Lashner B.A.: Maintenance therapy with a probiotic in antibiotic-dependent pouchitis: experience in clinical practice. Aliment. Pharmacol. Ther., 2005; 22: 721-728

[94] Simkins J., Kaltsas A., Currie B.P.: Investigation of inpatient probiotic use at an academic medical center. Int. J. Infect. Dis., 2013; 17: e321-e324

[95] Singh S., Stroud A.M., Holubar S.D., Sandborn W.J., Pardi D.S.: Treatment and prevention of pouchitis after ileal pouch-anal anas-

tomosis for chronic ulcerative colitis. Cochrane Database Syst. Rev., 2015; 11: CD001176

[96] Söderholm J.D., Olaison G., Lindberg E., Hannestad U., Vindels A., Tysk C., Järnerot G., Sjödahl R.: Different intestinal permeability patterns in relatives and spouses of patients with Crohn's disease: an inherited defect in mucosal defense? Gut, 1999; 44: 96-100

[97] Sokol H., Pigneur B., Watterlot L., Lakhdari O., Bermúdez-Humarán L.G., Gratadoux J.J., Blugeon S., Bridonneau C., Furet J.P., Corthier G., Grangette C., Vasquez N., Pochart P., Trugnan G., Thomas G., et al: *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

[98] Sood A., Midha V., Makharia G.K., Ahuja V., Singal D., Goswami P., Tandon R.K.: The probiotic preparation, VSL#3 induces remission in patients with mild-to-moderately active ulcerative colitis. Clin. Gastroenterol. Hepatol., 2009; 7: 1202-1209.e1

[99] Steed H., Macfarlane G.T., Blackett K.L., Bahrami B., Reynolds N., Walsh S.V., Cummings J.H., Macfarlane S.: Clinical trial: the microbiological and immunological effects of synbiotic consumption - a randomized double-blind placebo-controlled study in active Crohn's disease. Aliment. Pharmacol. Ther., 2010; 32: 872-883

[100] Tong M., Li X., Parfrey L.W., Roth B., Ippoliti A., Wei B., Borneman J., McGovern D.P., Frank D.N., Li E., Horvath S., Knight R., Braun J.: A modular organization of the human intestinal mucosal microbiota and its association with inflammatory bowel disease. PLoS One, 2013; 8: e80702

[101] Tsuda Y., Yoshimatsu Y., Aoki H., Nakamura K., Irie M., Fukuda K., Hosoe N., Takada N., Shirai K., Suzuki Y.: Clinical effectiveness of probiotics therapy (BIO-THREE) in patients with ulcerative colitis refractory to conventional therapy. Scand. J. Gastroenterol., 2007; 42: 1306-1311

[102] Tursi A., Brandimarte G., Giorgetti G.M., Forti G., Modeo M.E., 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

[103] Tursi A., Brandimarte G., Papa A., Giglio A., Elisei W., Giorgetti G.M., Forti G., Morini S., Hassan C., Pistoia M.A., Modeo M.E., Rodino S., D'Amico T., Sebkova L., Sacca N., et al.: Treatment of relapsing mild-to-moderate ulcerative colitis with the probiotic VSL#3 as adjunctive to a standard pharmaceutical treatment. A double-blind, randomized, placebo-controlled study. Am. J. Gastroenterol., 2010; 105: 2218-2227

[104] Ukena S.N., Singh A., Dringenberg U., Engelhardt R., Seidler U., Hansen W., Bleich A., Bruder D., Franzke A., Rogler G., Suerbaum S., Buer J., Gunzer F., Westendorf A.M.: Probiotic *Escherichia coli* Nissle 1917 inhibits leaky gut by enhancing mucosal integrity. PLoS One, 2007; 2: e1308

[105] Ulluwishewa D., Anderson R.C., McNabb W.C., Moughan P.J., Wells J.M., Roy N.C.: Regulation of tight junction permeability by intestinal bacteria and dietary components. J. Nutr., 2011; 141: 769-776

[106] Vahabnezhad E., Mochon A.B., Wozniak L.J., Ziring D.A.: *Lactobacillus* bacteremia associated with probiotic use in a pediatric patient with ulcerative colitis. J. Clin. Gastroenterol., 2013; 47: 437-439

[107] 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 ileo-caecal resection. Inflamm. Bowel Dis., 2007; 13: 135-142

[108] Venturi A., Gionchetti P., Rizzello F., Johansson R., Zucconi E., Brigidi P., Matteuzzi D., Campieri M.: Impact on the composition of the faecal flora by a new probiotic preparation: preliminary data on maintenance treatment of patients with ulcerative colitis. Aliment. Pharmacol. Ther., 1999; 13: 1103-1108

[109] Vilela E.G., Ferrari M.D., Torres H.O., Pinto A.G., Aguirre A.C., Martins F.P., Goulart E.M., Da Cunha A.S.: Influence of *Saccharomyces boulardii* on the intestinal permeability of patients with Crohn's disease in remission. Scand. J. Gastroenterol., 2008; 43: 842-848

[110] Walker A.W., Sanderson J.D., Churcher C., Parkes G.C., Hudspith B.N., 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

[111] Weber E., Reynaud Q., Suy F., Gagneux-Brunon A., Carricajo A., Guillot A., Botelho-Nevers E.: *Bifidobacterium* species bacteremia. Risk factors in adults and infants. Clin. Infect. Dis., 2015; 61: 482-484

[112] Whelan K., Myers C.E.: Safety of probiotics in patients receiving nutritional support: a systematic review of case reports, randomized controlled trials, and nonrandomized trials. Am. J. Clin. Nutr., 2010; 91: 687-703

[113] Wildt S., Nordgaard I., Hansen U., Brockmann E., Rumessen J.J.: A randomized 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

[114] Willing B.P., Dicksved J., Halfvarson J., Andersson A.F., Lucio M., Zheng Z., Järnerot G., Tysk C., Jansson J.K., Engstrand L.: A pyrosequencing study in twins shows that gastrointestinal microbial profiles vary with inflammatory bowel disease phenotypes. Gastroenterology, 2010; 139: 1844-1854.e1

[115] Yamamoto T.: Factors affecting recurrence after surgery for Crohn's disease. World J. Gastroenterol., 2005; 11: 3971-3979

[116] Yoshimatsu Y., Yamada A., Furukawa R., Sono K., Osamura A., Nakamura K., Aoki H., Tsuda Y., Hosoe N., Takada N., Suzuki Y.: Effectiveness of probiotic therapy for the prevention of relapse in patients with inactive ulcerative colitis. World J. Gastroenterol., 2015, 21: 5985-5994

[117] Zakostelska Z., Kverka M., Klimesova K., Rossmann P., Mrazek J., Kopecny J., Hornova M., Srutkova D., Hudcovic T., Ridl J., Tlaskalova-Hogenova H.: Lysate of probiotic *Lactobacillus casei* DN-114 001 ameliorates colitis by strengthening the gut barrier function and changing the gut microenvironment. PLoS One, 2011; 6: e27961

[118] Zeissig S., Bürgel N., Günzel D., Richter J., Mankertz J., Wahnschaffe U., Kroesen A.J., Zeitz M., Fromm M., Schulzke J.D.: 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

[119] Zhang Y.Z., Li Y.Y.: Inflammatory bowel disease. Pathogenesis. World J. Gastroenterol., 2014; 20: 91-99

[120] Zocco M.A., dal Verme L.Z., Cremonini F., Piscaglia A.C., Nista E.C., Candelli M., Novi M., Rigante D., Cazzato I.A., 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

The authors have no potential conflicts of interest to declare.