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Review

Is there any place for alimentary probiotics, prebiotics or synbiotics, for patients with inflammatory bowel disease?

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The pathogenesis of inflammatory bowel disease (IBD) involves an interaction between genetically determined host susceptibility, dysregulated immune response, and the enteric microbiota. Ecological treatments including probiotics, prebiotics, and synbiotics are actively studied in Crohn's disease (CD), ulcerative colitis (UC) and pouchitis. We review herein the literature on the rational use of probiotics in IBD considering efficacy (as evaluated in randomized controlled trials), mechanisms of action and safety issues. A probiotic effect is strictly restricted to one defined strain and cannot be generalized from one to another. There is evidence of efficacy of some probiotic drugs in pouchitis (VSL#3), and in the prevention of recurrence of UC (*Escherichia coli* Nissle 1917). However, the evidence for efficacy of probiotic drugs in CD is still low as well as that of dietary ecological treatments. Despite an ecological (hopefully nutritional) treatment of IBD is promising, many questions remain unanswered and further clinical and fundamental studies are needed.

Keywords: Crohn / Inflammatory Bowel Disease / Prebiotics / Probiotics / Symbiotics

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1 Introduction

Inflammatory bowel diseases (IBD), which include Crohn's disease (CD) and ulcerative colitis (UC), are chronic relapsing disorders of unknown cause characterized by inflammation of the gastrointestinal tract. Whereas UC is mostly limited to the colon, CD can spread from the mouth to the anus. Both conditions may require extensive surgery, for either life-threatening or neoplasic complications. The pathogenesis of IBD involves an interaction between genetically determined host susceptibility, dysregulated immune response and the enteric microbiota. Host susceptibility is sometimes favoured by polymorphism in intestinal antimicrobial defences (*e.g.* defensin deficiency) or in perception of microbial signals in the enterocytes, immune cells or Paneth cells (*e.g.* NOD2-CARD15 and TLR4 polymorphisms) [1]. The deleterious role of some intestinal microorganisms has been established in murine models and is strongly suspected in humans [2]. However, other microorganisms seem to be protective [3]. This prompted the idea of trying ecological treatments including probiotics, prebiotics and synbiotics in models and patients with IBD. Probiotics are defined as living nonpathogenic microorganisms which, when ingested, exert a positive influence on host health or physiology [4]. They may not only be used as drugs (either as single strain, combination of various strains or genetically modified probiotics) but also in food (mainly fermented dairy products) or food supplements. Probiotics have been used in numerous digestive and some extradigestive inflammatory diseases [5], but still their multiple mechanisms of actions remain to be determined and clinical evidence for efficacy need to be demonstrated.

Prebiotics, described as ‚nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one, or a limited number of bacteria in the colon, thus improving host health' [6]. Synbiotics (combinations of both probiotics and prebiotics) have also been considered in the treatment of IBD [7].

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Abbreviations: CD, Crohn's disease; **ECN**, *Escherichia coli* Nissle 1917; **IBD,** inflammatory bowel disease; **MAMPS,** microbial associated molecular patterns; **PRR,** pattern recognition receptor; **RCT,** randomized controlled trial; **TLR,** toll-like receptor; **UC**, ulcerative colitis

The best evidence for the efficacy of ecological treatments relies on double-blind randomized controlled trials (RCTs). Meta-analysis of trials using different probiotic products should be interpreted very cautiously as their active components may differ [8]. There is now evidence of efficacy of some probiotic drugs in pouchitis, and in the prevention of recurrence of UC. However, the evidence for efficacy of probiotic drugs in CD is still low as well as that of dietary ecological treatments.

We review herein the literature on the rational use of probiotics in IBD considering efficacy (as evaluated in RCT), elements of pharmacokinetics, mechanisms of action and safety issues. A review on the potential use of prebiotics and synbiotics in the treatment of IBD is given in this issue of the journal (Steed *et al.*, DOI: 10.1002/mnfr.200700139).

2 Probiotics for pouchitis

When proctocolectomy is considered in the treatment of IBD (mainly in UC), ileo pouch-anal anastomosis is preferred to ileostomy to preserve faecal continence. Pouchitis, defined as a nonspecific inflammation of intestinal mucosa of the ileal reservoir, may occur in a subset of patients with ileo pouch-anal anastomosis. Pouchitis is associated with an imbalance of the microbiota [9], and nitronidazole and quinolone antibiotics are very effective in treating acute episodes. Two double-blind placebo-controlled trials showed that the probiotic product VSL#3 prevented recurrence of chronic relapsing pouchitis [10, 11] (Table 1). VSL#3 (CSL, Milan, Italy) is commercialized in various countries as sachets containing a mixture of four strains of lactobacilli (*Lactobacillus casei*, *L. plantarum*, *L. acidophilus*, *L. delbrueckii subsp. bulgaricus*), three strains of bifidobacteria (*Bifidobacterium longum*, *B. breve*, *B. infantis*) and one strain of *Streptococcus salivarius subsp. thermophilus*. In their first RCT, Gionchetti *et al*. [10] treated 40 patients with chronic relapsing pouchitis with VSL#3 (3 g daily) or a placebo for 9 months. They observed a relapse of pouchitis in 15% of the subjects in the probiotic group *versus* 100% of those receiving the placebo ($p < 0.001$). In the second RCT, Mimura *et al*. [11] treated 36 subjects with VSL#3 (6 g daily) or a placebo for 12 months, and observed a relapse in 15% of the patients receiving the probiotic *versus* 94% of those treated with the placebo ($p < 0.0001$). In a third RCT, Gionchetti *et al*. [12] showed that VSL#3 prevented the first episode of pouchitis in 40 patients who just had ileo-pouch anal anastomosis for UC. Patients were treated for 12 months, and pouchitis occurred in 10% of those receiving the probiotic (6 g daily) *versus* 40% of those receiving the placebo ($p < 0.01$).

Despite VSL#3 promising efficacy according to these three RCT, its evaluation in clinical practice is not so enthusiastic. Shen *et al*. [13] reported on the clinical use of VSL#3 in 31 UC patients with antibiotic-dependant pouchitis. After remission was achieved with a 2- wk course of ciprofloxacine, VSL#3 was given (6 g/day) for 8 months, with clinical and endoscopic evaluation at the end of the treatment period. Twenty-five out of the 31 treated patients had discontinued VSL#3 therapy (in a mean period of 1.2 months) due to relapsing symptoms ($n = 23$) and adverse events ($n = 2$). In the six remaining patients with clinical remission, the endoscopic activity score (PDAI) was not statistically different from that at baseline (1.8 *vs*. 2.8, $p = 0.27$).

Other probiotics were tried to prevent onset or recurrence of pouchitis, but the evidence of their efficacy is low as the methodology of these trials was suboptimal. In an open trial, including 127 patients, Gosselink suggested that daily administration of *L. rhamnosus GG* (which is commercially available in fermented dairy products and as over-the-counter supplement all over the world) decreased the risk of pouchitis (occurrence of pouchitis at 3 years was 7 *vs*. 29% in historical controls, $p = 0.01$) [14].

3 Ulcerative colitis

UC is a type of IBD that is characterized by a continuous mucosal inflammation from the rectum up the colon. It rarely involves the upper digestive tract and small bowel but may be associated with extraintestinal inflammatory sites. Colonic dysplasia and adenocarcinoma is a complication of longstanding UC. Anti-inflammatory and immunomodulator drugs are the main medical treatments used in this affection. Proctocolectomy is proposed as a curative therapy in patients with severe manifestations of UC and as a prevention of colonic adenocarcinoma.

Escherichia coli Nissle 1917 (ECN), a nonpathogenic Gram-negative strain isolated in 1917 and commercialized in Germany (Mutaflor®, Ardeypharm, Herdecke, Germany), has been proposed for the maintenance therapy of UC. Three double-blind RCT compared the efficacy of ECN to that of mesalazine to prevent relapse of UC [15–17] (Table 1). No trial compared this probiotic to placebo and the evidence for its efficacy relies thus on the demonstration of statistical equivalence with mesalazine (*i.e.* an effective treatment). In the first double-blind RCT, Kruis *et al*. [16] included 120 patients with quiescent UC and treated them for 12 wks with either 5×10^{10} colony forming units (cfu)/day of *ECN* (200 mg/day of Mutaflor) or 1.5 g/day of mesalazine. After 12 wk, 16% of the subjects in the *ECN* group had relapse of UC *versus* 11.3% in the mesalazine group. The statistical power of this trial was low and equivalence could therefore not be unequivocally demonstrated. Rembacken *et al*. [17] published a second RCT comparing again *ECN* (Mutaflor, 400 mg/day) to mesalazine (at the low dose of 1.2 g/day) in 116 patients with UC treated for 1 year [17]. Relapse occurred in 67% in the *ECN* group *ver-*

sus 73% of the patients in the mesalazine group. The percentage of relapse in both groups was surprisingly high. The third RCT used appropriate number of patients and follow-up period and therefore allowed to properly search for equivalence between the two treatments [15]. Three hundred and twenty-seven patients with quiescent UC received either the *ECN* (Mutaflor, 200 mg/day) or mesalazine (1.5 g/day) for 1 year. The relapse rate was 36% in the probiotic group *versus* 34% in the mesalazine group and statistical tests showed equivalence of the two drugs.

The evidence for efficacy of other probiotics in UC is lower (Table 1). Ishikawa *et al*. [18] conducted an RCT to determine whether exacerbations of UC could be prevented by altering the intestinal flora through supplementation with fermented milk containing probiotic strains as a dietary adjunct in combination with the usual medication. These authors gave 100 mL/day of fermented milk for 1 year to 21 subjects with UC. The milk contained *B. bifidum YIT 4007*, *B. breve YIT 4065 and L. acidophilus YIT 0168* in 11 cases, and no probiotics in the remaining 10 cases. There were 27% relapses in the probiotic group *versus* 90% in the control group. It was observed a significant reduction in the relative proportion of *Bacteroides vulgatus* and butyrate concentration in faeces in the probiotic group. Authors hypothesized that these effects could be involved in the beneficial action of the product and called for further investigations in a larger trial before any firm conclusion could be drawn. In a randomized open-label trial, Zocco *et al*. [19] observed no difference in relapse rate at 6 and 12 months among 187 patients with quiescent UC who received *Lactobacillus GG* (18×10^9 viable bacteria/day) or mesalazine 2400 mg/day or *Lactobacillus GG* + mesalazine. However, the treatment with *Lactobacillus GG* alone was more effective than mesalazine (whether or not with probiotics) in prolonging the relapse-free time [19].

A recent randomized double-blind pilot trial suggested that a combination of *B. longum* with fructo-oligosaccharides (a synbiotic combination) could have therapeutic effects in patients with acute UC [20]. A significant decrease in the inflammatory lesions in the colon was observed only in the synbiotic group and several markers of inflammation in the mucosa (TNF-α, IL 1-α and the human-β-defensins 2, 3 and 4) were ameliorated. However, this study should be considered as preliminary as it included only 18 subjects who also used medical treatments.

4 Crohn's disease

CD is characterized by transmural inflammation and skip lesions that can spread all along the gastrointestinal tract. Typical features are granuloma, strictures and fistula. Intestinal (mainly colorectal and small-bowel adenocarcinoma) and extraintestinal cancers may be associated with CD. Medical therapy includes smoking discontinuation, artificial nutrition, anti-inflammatory drugs (aminosalycilates and steroids), immunomodulators, and biotherapy. Unlike in UC, surgery is not a curative treatment in CD. However, it may be considered in patients with severe complications.

The evidence for efficacy of probiotics to prevent recurrence of CD is presently low (Table 1). We performed a double-blind, RCT in 98 patients who had just been operated for CD and who received for 6 months either *L. johnsonii* LA1 (4×10^9 cfu/day) or a placebo. At 6 months, endoscopic recurrence was observed in 49% of patients in the probiotic group, and 64% of patients in the placebo group (no statistically significant difference). There were four clinical recurrences in the LA1 group and three in the placebo group [21]. Van Gossum *et al*. [22] studied the same strain but at the higher dose of 10^{10} cfu/day in 70 patients who had surgery for CD. In this second RCT as well, LA1 was not effective to prevent recurrence. Indeed, the percentage of patients with recurrence of severe endoscopic lesions was 21 and 15% in the LA1 and placebo groups, respectively ($p = 0.33$) and the percentage of patients with clinical relapse was 15 and 13%, respectively ($p = 0.79$).

Initial data from open series suggested efficacy of *L. rhamnosus GG* [23] but a properly statistically powered RCT showed that it was ineffective as an add-on therapy to standard treatment to prevent relapse of CD in 75 children followed-up for 2 years [24]. Prantera *et al*. [25] compared in a double-blind RCT *L. rhamnosus GG* to placebo in 45 adult patients [25], and reported that at 1 year, the percentages of endoscopic or clinical relapse did not differ between the two groups. The statistical power of this RCT was low but there was no trend for efficacy of the probiotic as the endoscopic relapse was higher in the patients who received it (60%) than in those who received the placebo (35%, no statistically significant difference).

The other studies published until now suffer from methodological limitations and are therefore less convincing. Malchow tested *ECN* [26] in a pilot double-blind RCT (28 patients only). At 1 year, there was a nonsignificant trend of lower relapse rate in the probiotic group (30 *vs*. 64% in the placebo group, no statistically significant difference). This study has not been reproduced. Guslandi *et al*. [27] examined the effect of the probiotic drug *Saccharomyces boulardii* in an open label RCT. Thirty-two patients with CD received either 1 g/day of *S. boulardii* plus 2 g/day of mesalazine or 3 g/day of mesalazine. Relapse of CD occurred within 6 months in 6% of the subjects in the probiotic group *versus* 37% in the control group ($p = 0.04$). Confirmation of this positive result in a larger and double-blind RCT is required. Campieri *et al*. [28] carried out a single-blind study to evaluate the efficacy of VSL#3 (two packets/day for 9 months) *versus* mesalazine (4 g/day for 12 months) [28]. Forty patients were randomized after induction of remission by rifaximin and the authors reported a lower rate of severe endoscopic recurrence at 3 and 12 months in patients of the antibiotic – probiotic group (10 and 20% *vs*.

Table 1. RCTs testing probiotics in IBD

Situation	Probiotic	Control	*n*	Duration (months)	Relapse in the probiotic group[a)]	Relapse in the control group[a)]	P	Reference
UC – prevention of relapse	*E. coli* Nissle 1917	5-ASA 1.2 g/day	120	4	16%	11.3%	NS	[16]
UC – prevention of relapse	*E. coli* Nissle 1917	5-ASA 1.2 g/day	120	12	67%	73%	NS	[17]
UC – prevention of relapse	*E. coli* Nissle 1917	5-ASA 1.5 g/day	327	12	36.4%	33.9%	NS[c)]	[15]
UC – prevention of relapse	*S. boulardii* + 5-ASA	5-ASA alone	31	12	30%	35%	NS	[49]
UC	*B. breve*, *B. bifidum*, *L.acidophillus* YIT 0168	Placebo	20	3	Failure 6/10	Failure 6/0	NS	[50]
UC	*B. breve*, *B. bifidum*, *L. acidophillus* YIT 0168		21	12	3/11	9/10	*	[18]
Refractory pouchitis	VSL #3	Placebo	40	9	15%	100%	*	[10]
Refractory pouchitis	VSL #3	Placebo	36	12	15%	94%	*	[11]
Pouchitis – prevention	VSL #3	Placebo	40	12	10%	40%	*	[12]
CD – prevention of POR	*L. rhamnosus GG*	Placebo	45	12	16.6%	10.5%	NS	[25]
CD – prevention of POR	*L. johnsonii* LA1	Placebo	98	6	49%[b)]	64%[b)]	NS	[21]
CD – prevention of POR	*L. johnsonii* LA1	Placebo	70	3	27.9%	33%[b)]	NS	[22]
CD – prevention of POR	VSL #3	5-ASA	28	12	20%[b)]	40%[b)]	*	[28][d)]
CD	*E. coli Nissle* 1917	Placebo	28	12	30%	70%	*	[26]
CD	*S. boulardii* + 5-ASA	5-ASA alone	28	6	6.3%	37.5%	*	[27]
CD	*L. rhamnosus GG*	Placebo	75	24	31%	17%	NS	[24]

UC, ulcerative colitis; CD, Crohn's disease; POR, postoperative recurrence; 5-ASA, 5-aminosalicylic acid (active treatment).
a) Clinical relapse unless stated otherwise.
b) Relapse of endoscopic lesions.
c) Statistical equivalence $p = 0.03$.
d) Published only as an abstract.

40 and 40%, respectively, $p < 0.01$). This study was only presented as an abstract in 2000 [28], and the results have not yet been published in a full paper.

A recently published RCT assessed the potential effect of a symbiotic mixture (four lactic acid bacteria: 10^{10} Pediococcus pentoseceus, 10^{10} L. raffinolactis, 10^{10} L. paracasei susp paracasei 19, and 10^{10} L. plantarum 2362; together with four fermentable fibres: 2.5 g β-glucans, 2.5 g inulin, 2.5 g pectin and 2.5 g resistant starch) in the prevention of postoperative recurrence of CD. This study failed to demonstrate any significant difference in clinical or endoscopic relapse in patients receiving the symbiotic mixture or the placebo but its statistical power was low (30 patients enrolled) [7].

5 Mechanisms of action

Cellular and molecular effects of pro-, pre- and synbiotics are actively studied, especially probiotics. A probiotic effect is strictly restricted to one defined strain and cannot be generalized from one to another [3].

5.1 Effect on the luminal compounds

Some probiotic strains can survive after ingestion within the digestive tract and be found alive in the stools. Probiotics can influence luminal compounds such as pH and composition and biodiversity of the microbiota. Space occupation, competitive exclusion for bacterial substrates and increase in the secreted IgA are the main mechanisms described to explain these modifications [29 – 33]. Restriction in the biodiversity observed in IBD can be restored using probiotics [34]. Certain probiotic strains can induce the secretion of antimicrobial peptides by intestinal cells. Antimicrobial peptides can be secreted either by bacteria (bacteriocins) or specialized epithelial Paneth cells (defensins) and can regulate the bacterial load to the mucosa [35]. Recent studies have shown that CD is associated with a defect in defensins [36], and probiotics, which could enhance these peptides, thus appear as attractive candidates.

5.2 Barrier effect and mucosa integrity

The gut microbiota, mucus and intestinal permeability are major protective factors of the intestinal mucosa. An increase in intestinal permeability is suspected as a major factor in the pathogenesis of IBD [37]. Some probiotics can reinforce integrity of this barrier. VSL#3 is able to normalize intestinal permeability and some lactobacillus can inhibit pathogen adhesion inducing expression of mucins [31, 38, 39].

5.3 Immune effects

Microbial associated molecular patterns (MAMPS) in the intestine are detected by pattern recognition receptors (PRRs), especially the toll-like receptors (TLRs) and the NOD receptors expressed on immune and epithelial cells.

MAMPS include for example LPS, peptidoglycan (PG), demethyleted bacterial DNA (CpG DNA), lipotechoic acid (LTA) and flagelin. They are specifically recognized by PRRs. For example, TLR4 recognizes LPS, TLR5 recognizes flagelin, TLR9 recognizes CpG DNA, and NOD2 recognizes PG. The contact between MAMPS and PRRs can stimulate innate immunity and induce protective response and/or proinflammatory response. Some probiotics sharing MAMPS can stimulate innate immunity and educate adaptive immunity towards Th1, Th2 or Th3 (tolerance) responses. The CpG DNA of VSL#3 exhibits anti-inflammatory involving TLR9 recognition [40]. *E. coli* Nissle 1917 needs TLR2 and TLR4 recognition to exert a probiotic beneficial effect on murine colitis [41]. Prebiotics increase specific groups of bacteria, especially bifidobacteria and/or lactobacilli which could in turn be responsible for biological effects.

6 Safety

Safety concerns mainly regards probiotics, as they theoretically may be responsible for systemic infections, metabolic adverse effects, immune reactions and gene transfer (with a special attention to genetically modified probiotics). There is now a widespread use of probiotics worldwide in functional food and over-the-counter supplements and recommendations to manufacturers for safe development and evaluation of probiotics have been proposed [42].

Currently used products are safe. The strains are not selected among pathogens, and the theoretical risk of infections is thus very low. The risk for immunosuppressed patients is not established. A few cases of infections have been traced back to *S. boulardii* and *L. rhamnosus GG* but this was never observed in a patient with IBD [43 – 47]. Noticeably, the majority of the cases occurred in hospitalized patients who had a central venous catheter [43 – 45]. Translocation of a probiotic from the patient intestine has not been observed until now, even in patients with intestinal ulceration, but one case of endocarditis has been reported in a man with mitral valve regurgitation who had chewed *L. rhamnosus* after dental extraction [46].

7 Conclusions

The rational for trying ecological treatments in IBD is strong. RCTs have demonstrated the efficacy of some probiotic drugs to treat or prevent specific situations of IBD, especially pouchitis and UC. Probiotics differ greatly from one another even at the strain level and therefore results obtained with one strain cannot be extrapolated to another one. Many questions remain unanswered and offer basic and translational research perspectives in that field. Dose-responses studies are too few to establish the dose needed or the optimal number of administrations *per* day. Whether probiotics have to survive in the gastrointestinal tract in order to be efficient is also not established. Hypothesis such as ‚probiotic mixtures should be preferred to single strains', ‚probiotics should only used in prevention' or ‚probiotics should always be used in combination with antibiotics or with prebiotics' are presently unproven. Fermented food (mainly dairy products) and food supplements are a good mode of consumption, but the effective amount of viable bacteria in dietary products containing probiotics needs to be controlled and the efficacy of these kind of probiotics in situation of IBD has not been established.

Further and rational development of probiotics could follow three strategies: specific microbial strains could be selected for particular properties, active microbial components could be tested alone, one should try to counterbalance the dysbiosis [48].

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8 References

[1] Wehkamp, J., Stange, E. F., A new look at Crohn's disease: Breakdown of the mucosal antibacterial defense. *Ann. NY Acad. Sci*. 2006, *1072*, 321 – 331.

[2] Sartor, R. B., Therapeutic manipulation of the enteric microflora in inflammatory bowel diseases: Antibiotics, probiotics, and prebiotics. *Gastroenterology* 2004, *126*, 1620 – 1633.

[3] Marteau, P., Shanahan, F., Basic aspects and pharmacology of probiotics: An overview of pharmacokinetics, mechanisms of action and side-effects. *Best Pract. Res. Clin. Gastroenterol*. 2003, *17*, 725 – 740.

[4] Schrezenmeir, J., de Vrese, M., Probiotics, prebiotics, and synbiotics – approaching a definition. *Am. J. Clin. Nutr.* 2001, *73*, 361S – 364S.

[5] Geier, M. S., Butler, R. N., Howarth, G. S., Inflammatory bowel disease: Current insights into pathogenesis and new therapeutic options; probiotics, prebiotics and synbiotics. *Int. J. Food Microbiol*. 2007, *115*, 1 – 11.

[6] Lim, C. C., Ferguson, L. R., Tannock, G. W., Dietary fibres as "prebiotics": Implications for colorectal cancer. *Mol. Nutr. Food Res*. 2005, *49*, 609 – 619.

[7] Chermesh, I., Tamir, A., Reshef, R., Chowers, Y., *et al*., Failure of Synbiotic 2000 to prevent postoperative recurrence of Crohn's disease. *Dig. Dis. Sci*. 2007, *52*, 385 – 389.

[8] Dendukuri, N., Brophy, J., Inappropriate use of meta-analysis to estimate efficacy of probiotics. *Am. J. Gastroenterol*. 2007, *102*, 201; author reply 202 – 204.

[9] Iwaya, A., Iiai, T., Okamoto, H., Ajioka, Y., *et al*., Change in the bacterial flora of pouchitis. *Hepatogastroenterology* 2006, *53*, 55 – 59.

[10] Gionchetti, P., Rizzello, F., Venturi, A., Brigidi, P., *et al*., Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: A double-blind, placebo-controlled trial. *Gastroenterology* 2000, *119*, 305 – 309.

[11] Mimura, T., Rizzello, F., Helwig, U., Poggioli, G., *et al*., Once daily high dose probiotic therapy (VSL#3) for maintaining remission in recurrent or refractory pouchitis. *Gut* 2004, *53*, 108 – 114.

[12] Gionchetti, P., Rizzello, F., Helwig, U., Venturi, A., *et al*., Prophylaxis of pouchitis onset with probiotic therapy: A double-blind, placebo-controlled trial. *Gastroenterology* 2003, *124*, 1202 – 1209.

[13] Shen, B., Brzezinski, A., Fazio, V. W., Remzi, F. H., *et al*., Maintenance therapy with a probiotic in antibiotic-dependent pouchitis: Experience in clinical practice. *Aliment Pharmacol. Ther*. 2005, *22*, 721 – 728.

[14] Gosselink, M. P., Schouten, W. R., van Lieshout, L. M., Hop, W. C., *et al*., Delay of the first onset of pouchitis by oral intake of the probiotic strain Lactobacillus rhamnosus GG. *Dis. Colon. Rectum*. 2004, *47*, 876 – 884.

[15] Kruis, W., Fric, P., Pokrotnieks, J., Lukas, M., *et al*., Maintaining remission of ulcerative colitis with the probiotic Escherichia coli Nissle 1917 is as effective as with standard mesalazine. *Gut* 2004, *53*, 1617 – 1623.

[16] Kruis, W., Schutz, E., Fric, P., Fixa, B., *et al*., Double-blind comparison of an oral Escherichia coli preparation and mesalazine in maintaining remission of ulcerative colitis. *Aliment Pharmacol. Ther*. 1997, *11*, 853 – 858.

[17] Rembacken, B. J., Snelling, A. M., Hawkey, P. M., Chalmers, D. M., *et al*., Nonpathogenic Escherichia coli versus mesalazine for the treatment of ulcerative colitis: A randomised trial. *Lancet* 1999, *354*, 635 – 639.

[18] Ishikawa, H., Akedo, I., Umesaki, Y., Tanaka, R., *et al*., Randomized controlled trial of the effect of bifidobacteria-fermented milk on ulcerative colitis. *J. Am. Coll. Nutr*. 2003, *22*, 56 – 63.

[19] Zocco, M. A., dal Verme, L. Z., Cremonini, F., Piscaglia, A. C., *et al*., Efficacy of Lactobacillus GG in maintaining remission of ulcerative colitis. *Aliment Pharmacol. Ther*. 2006, *23*, 1567 – 1574.

[20] Furrie, E., Macfarlane, S., Kennedy, A., Cummings, J. H., *et al*., Synbiotic therapy (Bifidobacterium longum/Synergy 1) initiates resolution of inflammation in patients with active ulcerative colitis: A randomised controlled pilot trial. *Gut* 2005, *54*, 242 – 249.

[21] Marteau, P., Lemann, M., Seksik, P., Laharie, D., *et al*., Ineffectiveness of Lactobacillus johnsonii LA1 for prophylaxis of postoperative recurrence in Crohn's disease: A randomised, double blind, placebo controlled GETAID trial. *Gut* 2006, *55*, 842 – 847.

[22] Van Gossum, A., Dewit, O., Louis, E., de Hertogh, G., *et al*., 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.

[23] Schultz, M., Timmer, A., Herfarth, H. H., Sartor, R. B., *et al*., Lactobacillus GG in inducing and maintaining remission of Crohn's disease. *BMC Gastroenterol*. 2004, *4*, 5.

[24] Bousvaros, A., Guandalini, S., Baldassano, R. N., Botelho, C., *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.

[25] Prantera, C., Scribano, M. L., Falasco, G., Andreoli, A., *et al*., 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.

[26] 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.

[27] 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.

[28] Campieri, M., Rizzello, F., Venturi, A., Poggioli, G., *et al*., Combination of antibiotic and probiotic treatment is efficacious in prophylaxis of post-operative recurrence of Crohn's disease: A randomized controlled study vs mesalamine. *Gastroenterology* 2000, *118*, G4179.

[29] Fukushima, Y., Kawata, Y., Hara, H., Terada, A., *et al*., Effect of a probiotic formula on intestinal immunoglobulin. A production in healthy children. *Int. J. Food Microbiol*. 1998, *42*, 39 – 44.

[30] Mack, D. R., Lebel, S., Role of probiotics in the modulation of intestinal infections and inflammation. *Curr. Opin. Gastroenterol*. 2004, *20*, 22 – 26.

[31] Mack, D. R., Michail, S., Wei, S., McDougall, L., *et al*., Probiotics inhibit enteropathogenic E. coli adherence in vitro by inducing intestinal mucin gene expression. *Am. J. Physiol*. 1999, *276*, G941 – G950.

[32] Marteau, P., Seksik, P., Lepage, P., Dore, J., Cellular and physiological effects of probiotics and prebiotics. *Mini Rev. Med. Chem*. 2004, *4*, 889 – 896.

[33] Venturi, A., Gionchetti, P., Rizzello, F., Johansson, R., *et al*., 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.

[34] Kuhbacher, T., Ott, S. J., Helwig, U., Mimura, T., *et al*., Bacterial and fungal microbiota in relation to probiotic therapy (VSL#3) in pouchitis. *Gut* 2006, *55*, 833 – 841.

[35] Flynn, S., van Sinderen, D., Thornton, G. M., Holo, H., *et al*., Characterization of the genetic locus responsible for the production of ABP-118, a novel bacteriocin produced by the probiotic bacterium Lactobacillus salivarius subsp. salivarius UCC118. *Microbiology* 2002, *148*, 973 – 984.

[36] Wehkamp, J., Salzman, N. H., Porter, E., Nuding, S., *et al*., Reduced Paneth cell alpha-defensins in ileal Crohn's disease. *Proc Natl. Acad. Sci. USA* 2005, *102*, 18129 – 18134.

[37] Peeters, M., Geypens, B., Claus, D., Nevens, H., *et al*., Clustering of increased small intestinal permeability in families with Crohn's disease. *Gastroenterology* 1997, *113*, 802 – 807.

[38] Madsen, K., Cornish, A., Soper, P., McKaigney, C., *et al*., Probiotic bacteria enhance murine and human intestinal epithelial barrier function. *Gastroenterology* 2001, *121*, 580 – 591.

[39] Zyrek, A. A., Cichon, C., Helms, S., Enders, C., *et al*., Molecular mechanisms underlying the probiotic effects of Escherichia coli Nissle 1917 involve ZO-2 and PKCzeta redistribution resulting in tight junction and epithelial barrier repair. *Cell Microbiol*. 2007, *9*, 804 – 816.

[40] Rachmilewitz, D., Katakura, K., Karmeli, F., Hayashi, T., *et al*., Toll-like receptor 9 signaling mediates the anti-inflammatory effects of probiotics in murine experimental colitis. *Gastroenterology* 2004, *126*, 520 – 528.

[41] Grabig, A., Paclik, D., Guzy, C., Dankof, A., *et al*., Escherichia coli strain Nissle 1917 ameliorates experimental colitis via toll-like receptor 2- and toll-like receptor 4-dependent pathways. *Infect. Immun*. 2006, *74*, 4075 – 4082.

[42] Joint FAO/WHO Working Group Report on Drafting Guidelines for the Evaluation of Probiotics in Food. 2002.

[43] Hennequin, C., Kauffmann-Lacroix, C., Jobert, A., Viard, J. P., *et al*., Possible role of catheters in Saccharomyces boulardii fungemia. *Eur. J. Clin. Microbiol. Infect. Dis*. 2000, *19*, 16 – 20.

[44] Land, M. H., Rouster-Stevens, K., Woods, C. R., Cannon, M. L. *et al*., Lactobacillus sepsis associated with probiotic therapy. *Pediatrics* 2005, *115*, 178 – 181.

[45] Lherm, T., Monet, C., Nougiere, B., Soulier, M., *et al*., Seven cases of fungemia with Saccharomyces boulardii in critically ill patients. *Intens. Care Med*. 2002, *28*, 797 – 801.

[46] Mackay, A. D., Taylor, M. B., Kibbler, C. C., Hamilton-Miller, J. M., Lactobacillus endocarditis caused by a probiotic organism. *Clin. Microbiol. Infect*. 1999, *5*, 290 – 292.

[47] Rautio, M., Jousimies-Somer, H., Kauma, H., Pietarinen, I., *et al*., Liver abscess due to a Lactobacillus rhamnosus strain indistinguishable from L. rhamnosus strain GG. *Clin Infect Dis*. 1999, *28*, 1159 – 1160.

[48] Sokol, H., Seksik, P., Rigottier-Gois, L., Lay, C., *et al*., Specificities of the fecal microbiota in inflammatory bowel disease. *Inflamm. Bowel Dis*. 2006, *12*, 106 – 111.

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

[50] Kato, K., Mizuno, S., Umesaki, Y., Ishii, Y., *et al*., Randomized placebo-controlled trial assessing the effect of bifidobacteria-fermented milk on active ulcerative colitis. *Aliment Pharmacol. Ther*. 2004, *20*, 1133 – 1141.

