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Use of probiotics in gastrointestinal disorders: what to recommend?

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***Abstract*:** Perturbation of bacterial microflora of the gastrointestinal (GI) tract may play an important role in the pathophysiology of some GI disorders. Probiotics have been used as a treatment modality for over a century. They may restore normal bacterial microflora and effect the functioning of the GI tract by a variety of mechanisms. Probiotics are not currently regulated and only few randomized controlled trials exist investigating their efficacy in different GI disorders. They are available in a variety of formulations and delivery systems making interpretation and comparison of studies even more difficult. The efficacy of probiotics, either as a single strain or a combination of probiotics, has been tested in antibiotic-associated diarrhea, *Clostridium difficile* colitis, infectious diarrhea, ulcerative colitis, Crohn's disease, pouchitis, and irritable bowel syndrome, among other disorders. Results of the studies are reviewed in this article and recommendations for probiotic use in these disorders are made. Although probiotics appear to be generally safe in an outpatient setting, the situation may be different in immunocompromised, hospitalized patients who may be at a greater risk of developing probiotic sepsis. No studies exist addressing the issue of safety specifically. Many questions regarding use of probiotics in GI disorders remain to be answered in future studies, such as most optimal doses, duration of treatment, physiological and immunological effects, efficacy of specific probiotics in specific disease states, and safety in debilitated patients.

***Keywords*:** antibiotic-associated diarrhea, *Clostridium difficile* colitis, Crohn's disease, irritable bowel syndrome, pouchitis, probiotics, review, ulcerative colitis

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Introduction

Probiotics are being used with increasing frequency as a treatment for several medical conditions, such as allergic diseases (atopic dermatitis, possibly allergic rhinitis), bacterial vaginosis, urinary tract infections, and prevention of dental caries or respiratory infections. Probiotics are used as a treatment for a variety of gastrointestinal (GI) disorders. In this review, the historical perspectives, proposed mechanisms of action, formulations and delivery systems, safety, and specific GI disorders for which probiotics have been used are discussed.

Historical perspectives

Probiotics have been used therapeutically for many centuries in different parts of the world for their contribution to longevity and digestive health. The World Health Organization has defined probiotics as 'live organisms which when administered in adequate amounts confer a health benefit on the host'. Categories of probiotics in use today include: bacteria such as lactic-acid bacteria (LAB) and *Escherichia coli* strains (such as *E. coli* Nissle 1917), as well as yeast species including most prominently *Saccharomyces boulardii* among others (Table 1). Prebiotics such as lactulose, inulin, psyllium, and other oligosaccharides (found in onions, garlic, asparagus, leeks, artichoke, bananas, tomatoes, wheat, oats, soy beans, and other plants) are non-digestible food ingredients that stimulate the growth or activity of bacteria in the GI tract which are beneficial to the health of the body [Grajek *et al.* 2005]. Synbiotics are a combination of a prebiotic and a probiotic, such as inulin and *Lactobacillus rhamnosus* GG or *Bifidobacter longum*. Antibiotics, in contrast, are compounds that kill or inhibit the growth of bacteria.

Probably the first person of Western medicine to publish on the topic of probiotics in the early

Table 1. Common probiotic formulations.

Single-organism probiotics	Composite probiotics
Escherichia coli 1917 Nissle *Lactobacillus salivarius* UCC4331 *Lactobacillus reuteri* *Lactobacillus casei* *Lactobacillus plantarus* 299v *Lactobacillus rhamnosus* GG *Bifidobacterium infantis* 35624 *Bifidobacterium animalis* DN-173010 *Bifidobacterium longum* *Saccharomyces boulardii*	VSL #3: *Streptococcus thermophilus, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus bulgaricus* Lacteol Fort: *L.acidophilus*, lactose monohydrate, anhydrous lactose

20th century was the Russian Nobel Prize winner Ilya Metchnikoff, when he described longevity in people in Eastern Europe who lived largely on milk fermented by LAB. He theorized that proteolytic microbes in the colon produced toxic substances responsible for the aging process and proposed that consumption of fermented milk would coat the colon with LABs, decreasing intestinal pH, suppressing proteolytic bacteria and thus leading to slowing of the aging process [Gordon, 2008]. Metchnikoff and his followers ingested milk fermented with this 'Bulgarian Bacillus' and reported health benefits [Vaughan, 1965].

In 1917, during World War I, Alfred Nissle isolated a strain of *E. coli* from the feces of a soldier who did not develop enterocolitis during a severe outbreak of shigellosis. Nissle used the *E. coli* strain with considerable success in acute cases of infectious intestinal diseases such as salmonellosis and shigellosis [Nissle, 1959]. *E. coli* Nissle 1917 is still in use today and is one of the few examples of a non-LAB probiotic.

Researchers and clinicians have studied and used probiotics in a variety of medical conditions. In the last decade, over 5000 articles were published in the medical literature. Furthermore, the use of probiotics has surged dramatically as a result of direct-to-consumer marketing as probiotics are not regulated.

Mechanisms of action

The GI tract plays an important role as an interface between the host and the environment. It is colonized by about 10 trillion microbes of many different species, amounting to 1–2 kg in weight [O'Hara and Shanahan, 2006]. Only a minority (300–500) of these species can be cultured *in vitro* and studied [O'Hara and Shanahan, 2006]. Intestinal epithelial cells have the capacity to distinguish pathogenic from nonpathogenic bacteria on the basis of their invasiveness and the presence of flagella, although the exact mechanisms that allow them to do this have not been elucidated fully [Borchers *et al.* 2009].

The precise mechanism(s) of action of probiotics has not thus far been clarified. Potential mechanisms to consider include: (1) modulation of GI immunity by altering inflammatory cytokine profiles and downregulating proinflammatory cascades or inducing regulatory mechanisms in a strain-specific manner; (2) displacement of gas-producing, bile salt-deconjugating bacterial species and thus possibly inhibiting pathogenic bacterial adherence; (3) alteration of bacterial flora by acidification of the colon by nutrient fermentation; (4) enhancement of epithelial barrier function; (5) induction of μ-opioid and cannabinoid receptors in intestinal epithelial cells; (6) reduction of visceral hypersensitivity, spinal afferent traffic, and stress response [Borchers *et al.* 2009; Lin *et al.* 2008; Vanderpool *et al.* 2008; Lawton *et al.* 2007; Quigley and Flourie, 2007; Rousseaux *et al.* 2007; Yan *et al.* 2007; Focareta *et al.* 2006; Makras *et al.* 2006; Roselli *et al.* 2006; Candela *et al.* 2005; Collado *et al.* 2005, 2007; Cotter *et al.* 2005; Matsumoto *et al.* 2005; Paton *et al.* 2005; Sherman *et al.* 2005; Smits *et al.* 2005; Sturm *et al.* 2005; Hart *et al.* 2004; Mukai *et al.* 2004; Pathmakanthan *et al.* 2004; Servin, 2004; McCarthy *et al.* 2003; Pena and Versalovic, 2003; Borruel *et al.* 2002].

Probiotic formulations and delivery systems

Probiotics are available in a wide variety of formulations ranging from tablets and powders to yogurts, milk, and juices. Physicians tend to

Table 2. Criteria for use as a probiotic, adapted from Borchers *et al.* [2009].

1. The organism must be fully identified: genus, species and strain
2. It must be safe for consumption:
   - Not pathogenic or carrying antibiotic resistance genes
   - Not degrading to intestinal mucosa or conjugating for bile acids
3. It must survival intestinal transit: Acid and bile tolerant
4. It must adhere to mucosal surface and colonize the intestine (at least briefly)
5. It must possess documented health effects:
   - Produce antimicrobial substances and antagonize pathogenic bacteria
   - At least one phase 2 study documenting benefit
6. It must be stable during processing and storage

recommend tablets and powders; other formulations are heavily promoted by direct-to-consumer marketing.

To qualify as a probiotic, certain criteria need to be met: a bacterial strain must be fully identified, be safe for ingestion, adhere to the luminal mucosa, colonize the gut, and possess documented health benefits (Table 2). A probiotic should be delivered in a formulation that is stable when stored. The colony number of bacteria and viability need to be reliable and they must survive the acid and bilious environment in the upper GI tract before they reach the small intestine and colon. Since the quality and content of probiotics have not been regulated, it is difficult to accurately assess their efficacy and safety.

Efficacy

Many questions related to efficacy, viability, most optimal dose, and method of delivery remain:

(1) The optimal number of colony forming units (CFUs) for each bacterial strain delivered remains unknown. Doses in human trials are based on those used in animal studies despite the differences in intestinal surface area. Dose–response studies are generally lacking. Commercially available probiotic formulations typically have at least 10^6 CFUs, but they may range up to 10^{12} CFUs.

(2) Very few studies have actually documented survival of an administered probiotic as it transits the gut, by means of fecal recovery studies. One probiotic may not necessarily be translatable to other probiotic(s): for example, different Bifidobacterium species have different tolerances to acid and growth requirements and will have different fecal recovery rates [Matto *et al.* 2004; Takahashi *et al.* 2004].

(3) The method of delivery, i.e. yogurt *versus* milk, may have an impact on the viability and number of bacterial colonies. Furthermore, only one strain of *B. longum* could survive in fermented milk for 2 weeks [Takahashi *et al.* 2004].

(4) Probiotics may produce their effects with viable as well as nonviable bacteria, suggesting that metabolic or secreted factors or structural or cellular components may mediate their immunomodulatory activities [Borchers *et al.* 2009]. Furthermore, several experiments indicate that the ability to induce secretion of various cytokines is mediated by and large by cell wall components [Borchers *et al.* 2009].

(5) Different probiotic species and genuses may have different immunological and physiological effects in different disease states. Wagner and colleagues showed that different Lactobacillus species have different efficacy in preventing fungal sepsis in mice [Wagner *et al.* 1997].

(6) The composition of colonic bacterial microflora appears to change with aging (age >60 years). It is unknown whether elderly patients should be treated with different probiotics than young patients [Enck *et al.* 2009].

(7) Combination probiotics may interact and have an impact on host intestinal flora differently than single probiotic preparations.

(8) Optimal duration of probiotic treatment and durability of response are unknown. How long a given probiotic will take to colonize, alter the microflora, and have an impact on immune function remains uncertain. There is significant heterogeneity in treatment duration in the human studies, likely contributing to the differences in reported results.

It is not, therefore, possible to extrapolate the results of one study with one species of a probiotic, one dose, and one formulation in one

disease state to other probiotic(s) as a whole. It is for these reasons that clinical trials using probiotics have yielded very inconsistent and difficult to interpret data.

Safety

Probiotics have been consumed by humans in one form or another for over 100 years, with a good safety record generally. A Finnish epidemiological study has shown no increase in Lactobacillus infections in healthy individuals in areas with documented large rises of use of Lactobacillus-containing products [Saxelin *et al.* 1996]. Probiotic supplementation has been studied in healthy volunteers, and the data suggest that several probiotic strains may enhance nonspecific immune responses, but the effects on adaptive cellular and humoral immune responses appear to be negligible [Borchers *et al.* 2009].

Questions and concerns have been raised, however, about the safety of probiotic administration in the setting of a severe illness. Probiotic sepsis is the most feared complication related to probiotic administration [Boyle *et al.* 2006]. Lactobacillus is a rare but documented cause of endocarditis in adults [Cannon *et al.* 2005]. There are several reports in the literature of bacteremia in adults and children in the setting of probiotic administration [De Groote *et al.* 2005; Land *et al.* 2005; Kunz *et al.* 2004, 2005; Mackay *et al.* 1999; Rautio *et al.* 1999]. In addition, several cases of *Saccharomyces boulardii* fungemia have been reported in the literature [Cherifi *et al.* 2004; Henry *et al.* 2004; Cassone *et al.* 2003; Lestin *et al.* 2003; Riquelme *et al.* 2003; Lherm *et al.* 2002; Cesaro *et al.* 2000; Hennequin *et al.* 2000; Perapoch *et al.* 2000; Rijnders *et al.* 2000; Niault *et al.* 1999; Bassetti *et al.* 1998; Fredenucci *et al.* 1998; Pletincx *et al.* 1995], including two series in which the fungi spread to neighboring patients who were not taking the probiotic [Cassone *et al.* 2003; Perapoch *et al.* 2000]. This spread was thought to be due to contamination of central catheters in patients who had intestinal surgery (jejunostomy) or chronic illnesses (valvular heart disease), and who were immunocompromised. Only one case of probiotic sepsis was thought to have been directly fatal [Lestin *et al.* 2003]. A randomized, double-blind, placebo-controlled trial was performed using probiotic prophylaxis (six different strains of viable bacteria: *L. acidophilus, L. casei, L. salivarius, L. lactis, B. bifidum*, and *B. lactis*) in a total daily dose of 10^{10} bacteria orally twice daily for 28 days in patients hospitalized with severe acute pancreatitis. This showed no decrease in infectious complications but increased mortality (16%) in the probiotics group in comparison with the placebo group (6%, relative risk [RR] 2.53, 95% confidence interval [CI] 1.22–5.25). Nine of the 152 patients in the probiotics group developed bowel ischemia, eight of whom died, compared with none in the placebo group [Besselink *et al.* 2008].

Other safety concerns relate to the unpredictability of immune modulation through change in intestinal flora in certain disease states. For example, worsening of Crohn's disease (CD) in patients taking some probiotic formulations [Rolfe *et al.* 2006] or exacerbation of indomethacin-induced enteropathy in animal models by Lactobacillus GG [Kamil *et al.* 2007]. As rare as these complications appear to be, probiotic safety profile needs to be specifically studied, particularly in hospitalized patients. There are no formal clinical trials assessing the safety of probiotics as there are safety data on regulated medications. At this time, we can only rely on case reports, which is without a doubt suboptimal.

Gastrointestinal disorders for which studies of probiotics have shown some benefit

Ingested probiotics are thought to alter deranged bowel flora or to change patients' tolerance to their own commensal flora and thus play a role in the pathogenesis of many GI disorders. The following disorders have been most commonly studied with regard to probiotic interventions.

Antibiotic-associated diarrhea (AAD) may be prevented by coadministration of probiotics, as suggested by several randomized controlled trials (RCTs). Several comprehensive meta-analyses, recently published, all show that probiotics significantly decreased incidence of AAD (RR 0.39–0.43) [McFarland, 2006; Szajewska and Mrukowicz, 2005; Cremonini *et al.* 2002; D'Souza *et al.* 2002]. The effects were similar across all categories and formulations of probiotics and treatment durations. The most commonly used probiotics were *S. boulardii*, LABs, and several combinations of LABs, given in doses from 10^7 to 10^{11}, for durations of 5–49 days, generally paralleling the duration of antibiotic therapy. One of the meta-analyses found that *S. boulardii, L. rhamnosus*, and multiple mixtures of two different probiotics were the most protective against AAD [McFarland, 2006]. Other

specific preparations have been studied to a lesser extent and that may be why their efficacy has been found to be less significant. One randomized, double-blind, placebo-controlled trial in individuals over the age of 50 using combination *L. casei*, *L. bulgaricus*, and *S. thermophilus* twice daily during a course of antibiotics and for 1 week after the completion of antibiotic therapy showed reduction in the incidence of AAD [Hickson *et al.* 2007].

Clostridium difficile colitis (CDC) has not consistently been shown to be prevented by probiotic cotreatment in a number of studies [Pillai and Nelson, 2008; McFarland, 2006]. In the largest study to date *S. boulardii*, at a dose of 2×10^{10} per day, in combination with vancomycin and metronidazole was associated with a significant decrease in risk of CDC recurrence [McFarland *et al.* 1994]. In addition, the study by Hickson and colleagues above showed efficacy in preventing CDC [Hickson *et al.* 2007]. Other studies, however, have not confirmed this benefit. A recent Cochrane review, limited by the small number of quality studies, concluded that there was insufficient evidence to recommend probiotic use even in combination with vancomycin and metronidazole [Pillai and Nelson, 2008]. In practice, however, many clinicians tend to recommend probiotics after antibiotic treatment, particularly in patients who have had CDC relapse.

Infectious diarrhea in both adults and children may be shortened by the use of probiotics [Allen *et al.* 2004]. The duration of symptoms is decreased by about 30 hours as suggested by a systematic review of trials in active infectious diarrhea. In this Cochrane review, 23 studies including almost 2000 participants (352 of which were adults), it was concluded that probiotics reduced the risk of persistent diarrhea compared with placebo or no probiotics at 3 days with a RR of 0.66 (95% CI 0.55–0.77) [Allen *et al.* 2004]. The majority (18 out of 23 studies) of the probiotics tested were LABs with two studies using *S. boulardii*.

Inflammatory bowel disease (IBD) treatment with antibiotics is fraught by variable efficacy. Recent discovery of genetic polymorphisms (NOD2/CARD15) in CD which play a role in bacterial peptidoglycan recognition [Inohara *et al.* 2003; Kobayashi *et al.* 2005], may be responsive to alterations in enteric flora and thus be important in the pathogenesis and maintenance of IBD [Sartor, 2004].

(1) *Ulcerative colitis* (UC). Several trials have been published examining probiotics in the induction and remission of UC, however, only few of these are RCTs. Most are with different probiotic formulations and overall have been performed in a relatively small number of patients (Table 3). For induction of remission, the first and largest controlled trial to date published by Remnacken showed no additional efficacy of *E. coli* Nissle 1917 than steroids, mesalazine, and antibiotics [Rembacken *et al.* 1999]. Three additional trials, all small in number of patients and of short duration of therapy and with variable standard of care, showed improvement in various measures of disease activity and even cytokine profiles [Furrie *et al.* 2005; Kato *et al.* 2004; Tursi *et al.* 2004]. Mallon and colleagues performed a Cochrane database systematic review, but no formal meta-analysis was possible due to differences in probiotics, outcomes and methodology, and concluded that probiotics when combined with other therapies did not improve remission rates [Mallon *et al.* 2007]. However, this analysis showed a reduction in disease activity in mild to moderately severe UC. A second systematic review published recently also suggested a similar efficacy profile between probiotics and anti-inflammatory agents [Zigra *et al.* 2007].
With regard to maintenance of UC remission, probiotics have been tested in a larger number of patients (Table 3). One trial by Kruis and colleagues tested *E. coli* Nissle 1917 and found no difference in relapse rates in patients on a probiotic *versus* mesalamine [Kruis *et al.* 2004]. A trial by Zocco and colleagues also found no difference in relapse rates at 6 or 12 months when comparing Lactobacillus GG with mesalamine with a combination of the two [Zocco *et al.* 2006]. Those patients who took the probiotic did appear to have a longer time to relapse. All of these studies support the idea that probiotics may be as effective as mesalamine in maintaining remission in the short-term trials.
(2) *Crohn's disease*. The literature on the induction and maintenance of remission in CD is heterogeneous and difficult to interpret (Table 4). Partly, this is due to the unclear definition of extent of inflammatory involvement in patients who were studied and a small number of patients included in the trials. Furthermore, very few studies

Table 3. Controlled trials of probiotics for the induction and maintenance of remission in adults with ulcerative colitis.

Study	Study design	*n*	Regimen	Duration (months)	Outcomes
Induction of Remission					
[Rembacken *et al.* 1999]	RCT	120	ECN 1×10^{11} daily *versus* mesalazine 2.4 g daily (both with prednisone and gentamicin)	3	No difference in induction rates
[Tursi *et al.* 2004]	RCT	90	VSL #3 9×10^{11} daily + 2.25 balsalazide daily *versus* 4.5 g balsalazide or 2.4 g mesalamine daily	2	Probiotic with significantly more induction of remission
[Kato *et al.* 2004]	RCT	20	100 ml daily probiotic milk (BBr, BBi and LA 1×10^{10}) *versus* placebo	3	Significantly better change in clinical activity index, histological score in the probiotic group
[Furrie *et al.* 2005]	RCT	18	Symbiotic (2×10^{11} *Bifidobacterium longum* and 6 g fructooligosaccharide/ inulin mix) plus SD *versus* SD	1	Improved sigmoidoscopy scores and cytokines compared with controls
Maintenance of Remission					
[Kruis *et al.* 1997]	RCT	120	ECN 1917 5×10^{10} daily *versus* mesalazine 500 mg PO TID	3	Relapse rates 16% *versus* 11.3%, statistically equivalent
[Ishikawa *et al.* 2003]	RCT	21	100 ml daily probiotic milk (BBr, BBi and LA 1×10^{10}) with SD *versus* SD alone	12	Statistically fewer relapses in the probiotic group
[Kruis *et al.* 2004]	RET	327	ECN 1917 200 mg ($2.5–25 \times 10^{9}$) daily *versus* mesalazine 500 mg TID	12	Relapse rates 36.4% and 33.9%, statistically equivalent
[Zocco *et al.* 2006]	RCT	187	LGG 18×10^{9} daily *versus* mesalazine 2400 mg daily *versus* both	12	No difference in relapse rate at 6 or 12 months, but LGG significantly prolonged time to relapse

RCT, randomized controlled trial; RET, randomized equivalence trial; LGG, Lactobacillus GG; ECN, *Escherichia coli* Nissle 1917; SD, standard treatment; BBr, Bifidobacterium breve; BBi, Bifidobacterium bifidum; LA, Lactobacillus acidophillus; PO, by mouth; TID, three times daily.

Table 4. Controlled trials of probiotics for the induction and maintenance of remission in adults with Crohn's disease.

Study	Study design	*n*	Regimen	Duration (months)	Outcomes
Induction of Remission					
[Schultz *et al.* 2004]	RCT	11	LGG 2×10^{9} daily *versus* placebo (both with tapering steroids and antibiotics)	6	No difference in induction of remission
Maintenance of Remission					
[Malchow, 1997]	RCT	28	ECN $\times 10^{10}$ daily *versus* placebo	12	No significant difference
[Guslandi *et al.* 2000]	RCT	32	*Saccharomyces boulargii* 1g daily + mesalamine 1 g BID *versus* mesalamine 1 g TID	6	Probiotics with mesalamine superior in CDAI
[Schultz *et al.* 2004]	RCT	11	LGG 2×10^{9} daily *versus* placebo (both with tapering steroids and antibiotics)	6	No difference in maintenance of remission
Prevention of Relapse Following Surgery					
[Prantera *et al.* 2002]	RCT	45	LGG 12×10^{9} daily *versus* placebo	12	No difference
[Marteau *et al.* 2006]	RCT	98	*Lactobacillus johnsonii* LA1 4×10^{9} daily *versus* placebo	6	No difference in recurrence
[Van Gossum *et al.* 2007]	RCT	70	*Lactobacillus johnsonii* LA1 10^{10} *versus* placebo	3	No difference in endoscopic recurrence
[Chermesh *et al.* 2007]	RCT	30	Symbiotic 2000 *versus* placebo	24	No difference in endoscopic or clinical relapse rates

RCT, randomized controlled trial; LGG, Lactobacillus GG; ECN, *Escherichia coli* Nissle 1917; SD, standard treatment; BID, twice daily; TID, three times daily; CDAI, Crohn's disease activity index.

examined the additive effect probiotics may have on active CD. In one study with only 11 patients, probiotics provided no additional benefit to steroids and antibiotics in inducing remission [Schultz *et al.* 2004]. An open-label study with 10 patients who were refractory to prednisolone and aminosalicylates, were tried on a combination of probiotics (*B. breve*, *B. longum*, and *L. casei*) and a prebiotic (psyllium) simultaneously. A complete response was found in 6 of 10 patients without any adverse consequences [Fujimori *et al.* 2007].

More controlled studies have been performed on the maintenance of remission in adults with CD (Table 4), but in general these studies fail to show any benefit of probiotic administration [Schultz *et al.* 2004; Guslandi *et al.* 2000; Malchow, 1997]. Data are even more robust on the prevention of relapse following surgical intervention, but again probiotics fail to prevent endoscopic or clinical recurrence (Table 4) [Chermesh *et al.* 2007; Van Gossum *et al.* 2007; Marteau *et al.* 2006; Prantera *et al.* 2002]. Several meta-analyses and systematic reviews have shown that probiotics were ineffective in maintenance of remission in CD [Rahimi *et al.* 2008; Rolfe *et al.* 2006].

(3) *Pouchitis*. The strongest evidence for the use of probiotics in IBD is in prevention and treatment of pouchitis (Table 5) [Mimura *et al.* 2004; Kuisma *et al.* 2003; Gionchetti *et al.* 2000, 2003]. After proctocolectomy with ileal pouch–anal anastomosis, pouchitis or acute and chronic inflammation of the ileal reservoir is the most frequent long-term complication of this operation, occurring in up to 20% of patients at 1 year. Studies of the microflora in the pouch have revealed deficiency of Streptococcal species [Komanduri *et al.* 2007]. This has led to a number of prospective controlled clinical trials of a probiotic, VSL#3 for 9–12 months, in the prevention and treatment of pouchitis [Gionchetti *et al.* 2000, 2003; Mimura *et al.* 2004]. These studies show consistently a decrease in incidence and relapse of inflammatory response. One uncontrolled trial in patients with mild active pouchitis who were treated with VSL#3, showed a remission rate of 69% [Gionchetti *et al.* 2007]. In contrast, a single species of Lactobacillus GG failed to show efficacy in a 3-month trial [Kuisma *et al.* 2003].

Irritable bowel syndrome (IBS) is a multisymptom GI disorder with unclear etiology and pathogenesis. Changes in GI microflora in IBS patients have been reported by a number of investigators [Kassinen *et al.* 2007; Shanahan, 2007]. Recently, reports on variable prevalences of small intestinal bacterial overgrowth (SIBO) in IBS have been published [Posserud *et al.* 2007; Lin, 2004]. IBS symptoms such as bloating or flatulence have been attributed to possible alterations in the intestinal microflora and probiotics have been used empirically to treat these difficult symptoms [Kim *et al.* 2003, 2005]. Postinfectious IBS may begin after a bout of acute gastroenteritis suggesting that altered microflora or induction of an altered inflammatory or immune state in the bowel may lead to altered bowel function and IBS symptoms [Collins *et al.* 2009]. An increase in lymphocytes and an increase in pro-inflammatory cytokines have been described [Spiller *et al.* 2000].

Recently Brenner and colleagues analyzed 16 RCTs in IBS patients who were defined either

Table 5. Controlled trials of probiotics for the prophylaxis and remission of pouchitis.

Study	Study design	*n*	Regimen	Duration (months)	Outcomes
Prophylaxis					
[Gionchetti *et al.* 2003]	RCT	40	VSL#3 (9×10^{11}) daily *versus* placebo	12	Significant reduction in the onset of acute pouchitis with probiotic group
Maintenance of Remission					
[Gionchetti *et al.* 2000]	RCT	40	VSL#3 6 g daily *versus* placebo	9	Significant decrease in relapse in the probiotic group
[Kuisma *et al.* 2003]	RCT	20	LGG 0.5–1 $\times 10^{10}$ daily *versus* placebo	3	No difference in disease activity
[Mimura *et al.* 2004]	RCT	36	VSL#3 6 g daily *versus* placebo	12	Significantly decreased relapse in the probiotic group ($p < 0.0001$)

RCT, randomized controlled trial; LGG, Lactobacillus GG.

by Rome II or Manning Criteria and who received either single or a combination probiotics *versus* placebo [Brenner *et al.* 2009]. *Bifidobacterium infantis* 35624 demonstrated efficacy in two appropriately designed RCTs. Both global as well as individual IBS symptoms (abdominal pain, bloating, incomplete evacuation, intestinal gas, straining, and bowel function) were significantly improved without evidence to suggest an increase in adverse events. No other probiotic, including isolated Lactobacillus species, showed significant improvement in IBS symptoms in appropriately designed RCTs [Brenner *et al.* 2009].

Another systematic review of the literature evaluating efficacy of probiotics in the treatment of IBS revealed that probiotics had a statistically significant effect in reducing IBS symptoms with a number needed to treat (NNT) of 4 (95% CI 3–12.5) [Moayyedi *et al.* 2010]. Almost all probiotic combinations contained both Bifidobacteria and Lactobacilli; the latter had no effect as assessed by continuous data meta-analysis. This raises the possibility that Bifidobacter may be the active treatment in probiotic combinations.

Elevated levels of interleukin 6 (IL-6), IL-6R, IL-1Beta and tumor necrosis factor alpha (TNF-α) [Dinan *et al.* 2006; Liebregts *et al.* 2007] and a lower IL-10/IL-12 ratio [O'Mahony *et al.* 2005] have been reported in IBS patients in comparison to controls, suggesting that IBS may be associated with increased pro-inflammatory cytokine secretion. However, plasma cytokine levels may not necessarily reflect the expression or levels of cytokines in the mucosa of the bowel wall, but may come from activated immune cells in the spleen or liver [Nance and Sanders, 2007]. The imbalance between IL-10 and IL-12, observed in peripheral blood mononuclear cells, was confirmed at the mucosal level in a recent study by Macsharry and colleagues suggesting that this finding may be an underlying phenotype in IBS and a potential biomarker for a subset of IBS patients [Macsharry *et al.* 2008]. *B. infantis* was shown to increase IL-10/IL-12 ratio in IBS patients [O'Mahony *et al.* 2005] suggesting a possible mechanism by which this probiotic may exert its effect.

The effect of probiotics on *other GI disorders* have also been studied, including lactose intolerance, *Helicobacter pylori* infection, microscopic colitis, prevention and treatment of diverticulitis, and even colon cancer prevention. The studies have been small and meta-analyses are too variable to draw firm conclusions of benefit.

Summary and conclusions

Probiotics are a therapeutic class being increasingly used for a variety of GI disorders. Probiotics appear to alter intestinal microflora and may exert their effect(s) by a variety of mechanisms. Many species of probiotics exist and it is generally accepted that all probiotics are not created equal. Efficacy may be due to a single strain or multiple strains or a combination of different probiotics. There is good evidence to support the efficacy of *S. boulardii* and LABs and the combination of the two for AAD, VSL#3 for pouchitis, and *B. infantis* 35624 for IBS. Probiotics decrease the duration of symptoms in acute infectious diarrhea. Probiotics, including *E. coli* Nissle 1917, LGG, and VSL#3 are as effective as standard therapy (mesalamine) in inducing or maintaining remission in UC or CD. When added to standard therapy, probiotics do not provide additional benefit compared with standard therapy alone. Most probiotics tested to date are not more effective than placebo in inducing or maintaining IBD remission.

Probiotics have been shown to be safe in immunocompetent hosts in an outpatient setting. However, administration of probiotics to immunocompromised, chronically ill, hospitalized patients with GI disorders, and indwelling catheters may predispose them to probiotic sepsis. Specifically, in GI disorders in which gut permeability and gut immunity may be compromised, adding probiotics may increase translocation of bacteria into the bloodstream. Until further studies become available on safety of probiotics in hospitalized patients, we caution their use in this setting.

Future studies should address many of the remaining questions related to the basic knowledge of probiotics, such as the composition of human intestinal flora, viability and fecal recovery rates, physiological and immunological effects. Furthermore, most optimal doses, duration of treatment, comparison of different strains and different probiotics, single *versus* combination probiotics, combination of probiotics with prebiotics, efficacy of various probiotics in different disease states, and safety of probiotics in debilitated patients or in patients with compromised gut epithelial integrity need to be evaluated.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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