Probiotics: sorting the evidence from the myths

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ABSTRACT

- Probiotics consist of yeast or bacteria, especially lactic acid bacteria. They are available as capsules, powder, fermented milks or yoghurts.
- Probiotics exhibit strain-specific differences in their resistance to acid and bile, ability to colonise the gastrointestinal tract, clinical efficacy, and benefits to the health of the host.
- There is level I evidence for the use of probiotics in treating acute infectious diarrhoea and preventing antibiotic-associated diarrhoea, with *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii* having the most evidence to support their use for these conditions.
- There is level II evidence that *S. boulardii* combined with high-dose vancomycin is more effective than the antibiotic alone in preventing recurrent *Clostridium difficile* diarrhoea.
- There is level I evidence that probiotics prevent traveller's diarrhoea.
- There is level I evidence for use of the high-potency probiotic VSL#3 in preventing pouchitis, and level II evidence for this agent in preventing relapse in patients with ulcerative colitis.
- Probiotics are generally regarded as safe and well tolerated. Some probiotics may be contraindicated in patients who are immunocompromised or have severe underlying illness, as they have been reported to cause fungaemia and bacteraemia.

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The mucosa of the gastrointestinal tract is constantly presented with antigens from microorganisms or ingested foods. Over 500 bacterial species are resident in the adult gastrointestinal tract, principally the colon. This community of microbiota not only lives in peaceful coexistence with the human host but also plays a significant role in the host's wellbeing.[1] There is a constant and complex interaction among these commensal bacteria, the intestinal epithelial cells, and the immune system.[2]

Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer a beneficial effect on the health of the host (Box 1).[3] The most commonly used probiotic agents are bacteria from the *Lactobacillus* and *Bifidobacterium* genera, which form part of the normal healthy intestinal microbiota. Other probiotics include the yeast *Saccharomyces boulardii*, which is now regarded as a separate cluster located within the species *Saccharomyces cerevisiae*.[4]

Probiotics exhibit strain-specific differences in their resistance to acid and bile, ability to colonise the gastrointestinal tract, and clinical efficacy.[5] The effects of probiotics may be due to various mechanisms of action, including suppressing growth of pathogenic bacteria, blocking epithelial attachment by pathogens, enhancing mucosal function, and modulating host immune response.[6]

Probiotics are now widely marketed in the form of capsules, powder and functional foods such as fermented milks and yoghurts. Here, we review the evidence for the role of probiotics in treating both gastrointestinal and extragastrointestinal diseases in children and adults. Levels of evidence designated here as E1, E2, E3 and E4 are based on the National Health and Medical Research Council (NHMRC) levels of evidence I, II, III (including III-1, III-2, III-3) and IV, respectively.[7]

Efficacy of probiotics for diarrhoeal disease

Infectious diarrhoea

Infectious diarrhoea is the most widely investigated area for probiotic use in children, with several meta-analyses published.[8-11] Most of the randomised controlled trials included in these meta-analyses involved children in developed countries in a health care setting. All meta-analyses were challenged by a lack of heterogeneity between studies. However, despite the variability between probiotics tested, dose and duration of treatment, participant groups, and definitions of diarrhoea and outcome, all reviews concluded that probiotics, coadministered with standard rehydration therapy, decrease the duration of acute diarrhoea (E1).

A Cochrane review[11] comprised 23 studies with a total of 1917 participants (1449 children). Pooled results showed that probiotics reduced the risk of diarrhoea at 3 days (relative risk [RR], 0.66; 95% CI, 0.55–0.77; random effects model, 15 studies) and the mean duration of diarrhoea by 30.5 hours (95% CI, 18.5–42.5 hours; random effects model, 12 studies) (E1). None of the studies reported adverse effects.

Lactobacillus rhamnosus GG (LGG) is the most investigated probiotic strain for this condition. A meta-analysis of paediatric studies contained a subgroup analysis restricted to LGG therapy, which comprised 10 study arms.[10] The pooled estimate showed that LGG reduced the duration of diarrhoea by 1.2 days (95% CI, –1.6 to –0.8 days; $P < 0.001$) (E1).

The Cochrane review[11] suggested that LGG may be particularly effective for rotaviral diarrhoea (E1). Rotavirus is the most common cause of severe diarrhoea in children worldwide.[12]

From these meta-analyses,[8-11] it appears that probiotics are more effective if given early in the course of illness and at daily doses of at least 10 billion colony-forming units (CFU). Thus, there is good evidence to support the use of probiotics in infectious diarrhoea of viral aetiology, when given early in the illness. There is no evidence to support the efficacy of probiotics in diarrhoeal illnesses of bacterial origin.

Antibiotic-associated diarrhoea

Antibiotic-associated diarrhoea (AAD) is defined as otherwise unexplained diarrhoea that occurs in association with antibiotic administration.[13] It is a common problem, occurring in up to 25% of patients receiving antibiotics, with rates varying depending on the population studied and the antibiotic used.[13] While *Clostridium difficile* is the most common infectious agent isolated, in most cases of AAD a causative organism is not found. AAD can begin after a single antibiotic dose or occur up to 6 weeks after the commencement of treatment.[14] Oral antibiotic agents, such as cephalosporins, clindamycin and broad-spectrum penicillins, are more likely to cause AAD than parenteral antibiotics.[14] The rationale for using probiotics in AAD rests on the assumption that antibiotics alter the normal

1 Drug profile of probiotics

Action: Probiotics are thought to suppress the growth of pathogenic bacteria, block epithelial attachment or invasion by pathogens, enhance mucosal function and modulate host immune response.

Preparation: Available in capsule and powder form, and as fermented dairy foods. Stability is an issue with non-yeast preparations and therefore most probiotics require refrigeration.

Dosing: There is significant variation in the number of bacteria between different preparations, as production is not standardised. There has been considerable variability between probiotic strains and doses used in clinical trials for a range of gastrointestinal and extraintestinal disorders. Appropriate doses of specific probiotics for specific clinical uses have not been established.

Metabolism: Probiotics exhibit strain-specific differences in their resistance to acid and bile, and ability to colonise the colonic mucosa. They are not metabolised.

Adverse effects: Probiotics are generally safe and well tolerated. They are contraindicated in patients with severe underlying illnesses or those who are immunocompromised; these patients are at risk of bacteraemia and fungaemia.

Regulation: In Australia, probiotics that are marketed for a specified health benefit require review by the Therapeutic Goods Administration and are regulated as complementary medicines. ◆

intestinal flora. Several probiotics have been evaluated in treating or preventing AAD, including *Lactobacillus acidophilus*, *Lactobacillus casei*, LGG, and *S. boulardii*.

In a meta-analysis on the role of *S. boulardii* (strains not reported) in preventing AAD, five randomised controlled trials (1076 participants) were included.[15] The largest of these studies was conducted in 269 children[16] and concluded that for every 10 patients receiving *S. boulardii* with antibiotics, one fewer will develop diarrhoea (E1). This meta-analysis supported the results from two prior meta-analyses,[17,18] involving *S. boulardii* and *Lactobacillus* species (E1).

A systematic review evaluating the efficacy of LGG in preventing AAD[19] suggested that additional research was needed to clarify its effectiveness (E2). A randomised controlled trial undertaken in children[20] showed that LGG, in doses of at least 10–20 billion CFU daily, has a beneficial role in preventing AAD (E2).

A recent study of 135 patients over the age of 50 years compared the effects of a drink containing *L. casei*, *Lactobacillus bulgaricus* and *Streptococcus thermophilus* with placebo in preventing AAD. Twelve per cent of treated patients developed diarrhoea compared with 34% in the control group ($P = 0.007$).[21] Notwithstanding these results, judicious use of antibiotics should remain the first step in preventing AAD.

Clostridium difficile diarrhoea

There is little evidence to support the routine use of probiotics to prevent or treat *C. difficile* diarrhoea, according to two systematic reviews.[22,23] One trial reported that *S. boulardii* combined with high-dose vancomycin was more effective than the antibiotic alone in preventing recurrent *C. difficile* diarrhoea (E2).[24]

Traveller's diarrhoea

The results from trials studying the role of probiotics in preventing traveller's diarrhoea are inconsistent, possibly reflecting the variation in probiotic strains used. However, meta-analysis of 12 studies showed that probiotics decreased the risk of traveller's diarrhoea (RR, 0.85; 95% CI, 0.79–0.91; $P < 0.001$) (E1).[25] One placebo-controlled trial showed a beneficial prophylactic effect of LGG[26] (E2), while another failed to demonstrate any benefit[27] (E2).

Probiotics in Crohn's disease and ulcerative colitis (inflammatory bowel disease)

Although the precise aetiologies of two of the inflammatory bowel diseases — Crohn's disease (CD) and ulcerative colitis (UC) — are unknown, there is evidence that intestinal microflora play major roles, along with host genetic makeup and innate immune responses. The importance of the intestinal flora is illustrated in animal models of gut inflammation, where the absence or modification of flora prevents or delays development of inflammation. Consequently, it has been hypothesised that probiotic therapy may have a significant role in the management of inflammatory bowel disease in humans.

Studies have examined the role of probiotics in inducing or maintaining remission of CD, and in preventing postoperative recurrence. A small pilot study showed that LGG given to four children with active CD led to decreased disease activity scores and improved gut barrier function (E4).[28] A subsequent randomised controlled trial showed that LGG did not maintain remission in children with CD (E2).[29] *S. boulardii* has been evaluated in maintaining remission of CD: 32 patients with quiescent CD were given aminosalicylic acid alone or with probiotics for 6 months in a blinded fashion.[30] The relapse rate was substantially lower in patients receiving probiotics (6/16 v 1/16; $P = 0.04$) (E2).

Studies using two different probiotic agents (LGG and *Lactobacillus johnsonii* LA1) have shown that probiotics are not effective in preventing postoperative recurrence of CD.[31,32] Another study with negative results assessed Synbiotic 2000 (Medipharm, Kågeröd, Sweden), which comprises a combination of four probiotic and four prebiotic components.[33] (Prebiotics are compounds that enhance the growth of beneficial bacteria.)

Probiotics may have roles in both initiating and maintaining remission of UC, with several studies suggesting that probiotics may help to induce remission. The first of these used a synbiotic, combining a probiotic (*Bifidobacterium longum*) and a prebiotic (Synergy 1; Orafti, Tienen, Belgium), for 1 month in 18 adults with active UC (E3).[34] Patients receiving the synbiotic had decreased endoscopic severity scores, clinical activity scores and levels of key pro-inflammatory proteins. A second study of 32 adults with acute UC used the high-potency probiotic VSL#3 (Sigma-Tau, Pomezia, Italy), which contains eight separate bacterial strains in large numbers, in an open-label design over 6 weeks (E4).[35] Remission or response was seen in 77% of patients following therapy.

A further study investigated the probiotic yeast *S. boulardii* in 25 patients who had a flare of UC while on maintenance therapy.[36] Seventeen patients attained remission after 4 weeks of therapy. However, in a separate study, non-pathogenic *Escherichia coli* Nissle 1917 was compared with aminosalicylic acid to induce remission in 120 patients with active UC (E2).[37] Remission occurred at an equivalent rate in the two groups.

Other studies have assessed probiotic agents in maintaining remission of UC. When comparing *E. coli* Nissle 1917 with standard maintenance therapy over 12 weeks in 120 adults, investigators showed no difference in relapse rates (E2).[38] A preliminary open-label study assessed VSL#3 in 20 adults with UC in remission; 15 patients remained in remission after 12 months of observation.[39]

Probiotics also have well defined roles for treating pouchitis, an inflammatory condition involving the pouch created after colectomy

for UC. VSL#3 is effective both in preventing pouchitis[40] and in treating established inflammation (E2).[41] A study using a single agent (LGG) did not show any benefit as primary therapy.[42]

Probiotics and irritable bowel syndrome

Clinical studies employing various probiotic agents in adults with irritable bowel syndrome have evaluated different outcomes.[43] Although some of these studies suggest relief of symptoms such as bloating or flatus, others show no benefit. For instance, in a study evaluating VSL#3 in a small group of 25 adults with diarrhoea-predominant irritable bowel syndrome,[44] subjects treated with the probiotic had less bloating than those given placebo ($P = 0.046$), but there was no impact on other symptoms.

Only two published studies have included more than 100 patients. One used a mixture of four probiotics and resulted in improvements at 6 months,[45] while the other study assessed an encapsulated form of *Bifidobacterium infantis* 35624 in 362 adults and found that all cardinal symptoms abated, compared with subjects treated with placebo.[46] Further studies of the benefits of probiotics in treating irritable bowel syndrome are required to define the expected roles and to elucidate which probiotic agents are optimal.

Probiotics and necrotising enterocolitis

Two recent studies suggest that probiotics may have a role in preventing necrotising enterocolitis in neonates.[47,48] However, there have been case reports of bacteraemia and sepsis in this age group as a result of probiotic administration,[49] which may make further investigation of these agents in this setting problematic.

Probiotics and allergic disorders

Probiotic agents may have a role in preventing and treating atopy, although this remains controversial. Two Scandinavian studies showed that provision of probiotics alone (LGG)[50] or as synbiotics[51] to pregnant mothers and infants after birth reduces rates of eczema at 2 years of age. Other studies using different probiotics (*L. acidophilus* LAVRI-A1[52] or *Lactobacillus reuteri* ATCC 55730[53]) did not confirm these findings (E2). One of these studies, which involved Western Australian infants at high risk of developing atopy receiving probiotics for the first 6 months of life, showed that the rates of atopic dermatitis in treated children were not lower than those in infants who received placebo at 6 and 12 months of age.[52]

Probiotics may have a role in treating established atopic dermatitis. A double-blind randomised controlled trial evaluated *Lactobacillus fermentum* in 53 infants and toddlers with moderate or severe atopic dermatitis (E2).[54] The children received probiotic or placebo for 8 weeks and then were assessed after a further 8 weeks. The subjects provided with probiotics had reduced severity and extent of dermatitis compared with controls ($P = 0.03$). However, this conclusion was not confirmed in a subsequent randomised controlled trial involving children in early infancy.[55]

Probiotics and other non-gastrointestinal disorders

Several lines of evidence support a role for probiotics in preventing recurrent urinary tract infections (UTIs) in women. *L. rhamnosus* GR-1 and *L. reuteri* RC-14 (formerly *L. fermentum* RC-14) seem to be the most effective among the studied lactobacilli for UTI prevention, but are only commercially available in Austria.[56] These agents are efficacious when taken orally or when applied intravaginally. There is some evidence for efficacy of other agents, including *L. casei* Shirota and *Lactobacillus crispatus* CTV-05, but conflicting evidence for LGG. Additional studies are required to fully define the role of probiotics in managing UTIs in women, as well as in other female urogenital conditions (candidiasis and bacterial vaginosis).

Adverse effects of probiotics

Probiotics are generally regarded as safe. Side effects are rarely reported and generally amount to little more than flatulence or change in bowel habit. A study of long-term consumption of *Bifidobacterium lactis* and *S. thermophilus*-supplemented formula in children aged less than 2 years showed the product was well tolerated (E2).[57] The use of LGG, which has increased markedly since its introduction in Finland in 1990, has not led to a significant change in the incidence of *Lactobacillus* bacteraemia.[58]

Complications of treatment with probiotics have been observed in patients who are immunocompromised or in the intensive care setting. *S. cerevisae* fungaemia[59] and *Lactobacillus* bacteraemia[49,60] have been reported in patients with severe underlying illnesses.

As with variations in efficacy, there are likely to be differences in adverse effects between different strains, and this should be taken into consideration for the probiotic strain being used.

Conclusions

Probiotics, which encompass numerous bacterial and fungal species, have become increasingly popular in the past few decades. In many cases, the marketing and use of probiotic agents has preceded firm scientific evidence to support their efficacy. Furthermore, there are likely variations between what is claimed for some products and what they actually do.

At present, there is convincing evidence for using probiotics in managing acute viral diarrhoeal disease, AAD and pouchitis. There is developing evidence for their role in other conditions, such as irritable bowel syndrome, necrotising enterocolitis, inflammatory bowel disease, and atopy. Some of these findings, however, remain controversial.

It is clear that although one probiotic agent may have a role for a specific condition, this does not mean that all probiotics are useful for that indication — there are clear agent-specific effects. Other factors, such as the quantity of organisms in the probiotic, are also important.

Probiotics promise to have important roles in human health. Current data support use of probiotics for only a few indications, and detailed studies are required to further define the roles of these therapies in children and adults. Important messages for patients are shown in Box 2.

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2 Important messages for patients

- Probiotics consist of yeast or bacteria.
- Probiotics can be beneficial in some gastrointestinal disorders.
- The efficacy of a probiotic agent is specific to a condition; therefore, the role of different probiotics cannot be generalised.
- The number of bacteria present in the probiotic agent is important.
- Probiotics are generally safe and well tolerated.
- Probiotics should be avoided in patients who are severely ill or immunocompromised. ◆

Competing interests

Andrew Day attended a probiotics meeting in Rome in 2004 as a guest of VSL#3 Pharmaceuticals. Daniel Lemberg and Andrew Day are investigators on several projects examining the roles of probiotics in inflammatory bowel disease: these projects are supported by VSL#3 Pharmaceuticals by the provision of product only. No other funding has been received.

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References

1 Isolauri E, Salminen S. Probiotics, gut inflammation and barrier function. *Gastroenterol Clin North Am* 2005; 34: 437-450.
2 Meier R, Steuerwald M. Place of probiotics. *Curr Opin Crit Care* 2005; 11: 318-325.
3 Food and Agriculture Organization of the United Nations, and World Health Organization. Report of a Joint FAO/WHO Expert Consultation on evaluation of health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria. Cordoba, Argentina: FAO/WHO, 2001.
4 Mitterdorfer G, Mayer HK, Kneifel W, Viernstein H. Clustering of *Saccharomyces boulardii* strains within the species *S. cerevisiae* using molecular typing techniques. *J Appl Microbiol* 2002; 93: 521-530.
5 Madsen K. Probiotics and the immune response. *J Clin Gastroenterol* 2006; 40: 232-234.
6 Sartor RB. Probiotic therapy of intestinal inflammation and infections. *Curr Opin Gastroenterol* 2005; 21: 44-50.
7 National Health and Medical Research Council. A guide to the development, implementation and evaluation of clinical practice guidelines. Canberra: NHMRC, 1999.
8 Szajewska H, Mrukowicz JZ. Probiotics in the treatment and prevention of acute infectious diarrhea in infants and children: a systematic review of published randomized, double-blind, placebo-controlled trials. *J Pediatr Gastroenterol Nutr* 2001; 33 Suppl 2: S17-S25.
9 Van Niel CW, Feudtner C, Garrison MM, Christakis DA. *Lactobacillus* therapy for acute infectious diarrhea in children: a meta-analysis. *Pediatrics* 2002; 109: 678-684.
10 Huang JS, Bousvaros A, Lee JW, et al. Efficacy of probiotic use in acute diarrhea in children: a meta-analysis. *Dig Dis Sci* 2002; 47: 2625-2634.
11 Allen SJ, Okoko B, Martinez E, et al. Probiotics for treating infectious diarrhoea. *Cochrane Database Syst Rev* 2004; (2): CD003048.
12 Cunliffe NA, Kilgore PE, Bresee JS, et al. Epidemiology of rotavirus diarrhoea in Africa: a review to assess the need for rotavirus immunization. *Bull World Health Organ* 1998; 76: 525-537.
13 Bartlett JG. Antibiotic-associated diarrhea. *N Engl J Med* 2002; 346: 334-339.
14 Wiström J, Norrby SR, Myhre EB, et al. Frequency of antibiotic-associated diarrhoea in 2462 antibiotic-treated patients: a prospective study. *J Antimicrob Chemother* 2001; 47: 43-50.
15 Szajewska H, Ruszcyski M, Radzikowski A. Probiotics in the prevention of antibiotic-associated diarrhea in children: a meta-analysis of randomised controlled trials. *J Pediatr* 2006; 149: 367-372.
16 Kotowska M, Albrecht P, Szajewska H. *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhoea in children: a randomized double-blind placebo-controlled trial. *Aliment Pharmacol Ther* 2005; 21: 583-590.
17 D'Souza AL, Rajkumar C, Cooke J, Bulpitt CJ. Probiotics in prevention of antibiotic-associated diarrhoea: meta-analysis. *BMJ* 2002; 324: 1361-1367.
18 Cremonini F, Di Caro S, Nista EC, et al. Meta-analysis: the effect of probiotic administration on antibiotic-associated diarrhoea. *Aliment Pharmacol Ther* 2002; 16: 1461-1467.
19 Hawrelak JA, Whitten DL, Myers SP. Is *Lactobacillus rhamnosus* GG effective in preventing the onset of antibiotic-associated diarrhoea: a systematic review. *Digestion* 2005; 72: 51-56.
20 Vanderhoof JA, Whitney DB, Antonson DL, et al. *Lactobacillus* GG in the prevention of antibiotic-associated diarrhea in children. *J Pediatr* 1999; 135: 564-568.
21 Hickson M, D'Souza AL, Muthu N, et al. Use of probiotic *Lactobacillus* preparation to prevent diarrhoea associated with antibiotics: randomised double blind placebo controlled trial. *BMJ* 2007; 335: 80-84.
22 Dendukuri N, Costa V, McGregor M, Brophy JM. Probiotic therapy for the prevention and treatment of *Clostridium difficile*-associated diarrhea: a systematic review. *CMAJ* 2005; 173: 167-170.
23 Segarra-Newnham M. Probiotics for *Clostridium difficile*-associated diarrhea: focus on *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii*. *Ann Pharmacother* 2007; 41: 1212-1221.
24 Surawicz CM, McFarland LV, Greenberg RN, et al. The search for a better treatment for recurrent *Clostridium difficile* disease: use of high-dose vancomycin combined with *Saccharomyces boulardii*. *Clin Infect Dis* 2000; 31: 1012-1017.
25 McFarland LV. Meta-analysis of probiotics for the prevention of traveler's diarrhea. *Travel Med Infect Dis* 2007; 5: 97-105.
26 Oksanen PJ, Salminen S, Saxelin M, et al. Prevention of travellers' diarrhoea by *Lactobacillus* GG. *Ann Med* 1990; 22: 53-56.
27 de dios Pozo-Olano J, Warram JH Jr, Gómez RG, Cavazos MG. Effect of a lactobacilli preparation on traveler's diarrhea. A randomized, double blind clinical trial. *Gastroenterology* 1978; 74: 829-830.
28 Gupta P, Andrew H, Kirschner BS, 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.
29 Bousvaros A, Guandalini S, Baldassano RN, 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.
30 Guslandi M, Mezzi G, Sorghi M, Testoni PA. *Saccharomyces boulardii* in maintenance treatment of Crohn's disease. *Dig Dis Sci* 2000; 45: 1462-1464.
31 Prantera C, Scribano ML, Falasco G, 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.
32 Marteau P, Lémann M, Seksik P, 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.
33 Chermesh I, Tamir A, Reshef R, et al. Failure of Synbiotic 2000 to prevent postoperative recurrence of Crohn's disease. *Dig Dis Sci* 2007; 52: 385-389. DOI: 10.1007/s10620-006-9549-7.
34 Furrie E, Macfarlane S, Kennedy A, 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.
35 Bibiloni R, Fedorak RN, Tannock GW, et al. VSL#3 probiotic-mixture induces remission in patients with active ulcerative colitis. *Am J Gastroenterol* 2005; 100: 1539-1546.
36 Guslandi M, Giollo P, Testoni PA. A pilot trial of *Saccharomyces boulardii* in ulcerative colitis. *Eur J Gastroenterol Hepatol* 2003; 15: 697-698.
37 Rembacken BJ, Snelling AM, Hawkey PM, et al. Non-pathogenic *Escherichia coli* versus mesalazine for the treatment of ulcerative colitis: a randomised trial. *Lancet* 1999; 354: 635-639.
38 Kruis W, Fric P, Pokrotnieks J, 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.
39 Venturi A, Gionchetti P, Rizzello F, 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.
40 Gionchetti P, Rizzello F, Helwig U, et al. Prophylaxis of pouchitis onset with probiotic therapy: a double-blind, placebo-controlled trial. *Gastroenterology* 2003; 124: 1202-1209.
41 Gionchetti P, Rizzello F, Venturi A, et al. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000; 119: 305-309.
42 Kuisma J, Mentula S, Jarvinen H, et al. Effect of *Lactobacillus rhamnosus* GG on ileal pouch inflammation and microbial flora. *Aliment Pharmacol Ther* 2003; 17: 509-515.
43 Quigley EM, Flourie B. Probiotics and irritable bowel syndrome: a rationale for their use and an assessment of the evidence to date. *Neurogastroenterol Motil* 2007; 19: 166-172.
44 Kim HJ, Camilleri M, McKinzie S, et al. A randomized controlled trial of a probiotic, VSL#3, on gut transit and symptoms in diarrhoea-predominant irritable bowel syndrome. *Aliment Pharmacol Ther* 2003; 17: 895-904.
45 Kajander K, Hatakka K, Poussa T, et al. A probiotic mixture alleviates symptoms in irritable bowel syndrome patients: a controlled 6-month intervention. *Aliment Pharmacol Ther* 2005; 22: 387-394.
46 Whorwell PJ, Altringer L, Morel J, et al. Efficacy of an encapsulated probiotic *Bifidobacterium infantis* 35624 in women with irritable bowel syndrome. *Am J Gastroenterol* 2006; 101: 1581-1590.
47 Bin-Nun A, Bromiker R, Wilschanski M, et al. Oral probiotics prevent necrotizing enterocolitis in very low birth weight neonates. *J Pediatr* 2005; 147: 192-196.
48 Lin HC, Su BH, Chen AC, et al. Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants. *Pediatrics* 2005; 115: 1-4.

49 Land MH, Rouster-Stevens K, Woods CR, et al. *Lactobacillus* sepsis associated with probiotic therapy. *Pediatrics* 2005; 115: 178-181.
50 Kalliomäki M, Salminen S, Poussa T, et al. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. *Lancet* 2003; 361: 1869-1871.
51 Kukkonen K, Savilahti E, Haahtela T, et al. Probiotics and prebiotic galacto-oligosaccharides in the prevention of allergic diseases: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2007; 119: 192-198.
52 Taylor AL, Dunstan JA, Prescott SL. Probiotic supplementation for the first 6 months of life fails to reduce the risk of atopic dermatitis and increases the risk of allergen sensitization in high-risk children: a randomized controlled trial. *J Allergy Clin Immunol* 2007; 119: 184-191.
53 Abrahamsson TR, Jakobsson T, Böttcher MF, et al. Probiotics in prevention of IgE-associated eczema: a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2007; 119: 1174-1180.
54 Weston S, Halbert A, Richmond P, Prescott SL. Effects of probiotics on atopic dermatitis: a randomised controlled trial. *Arch Dis Child* 2005; 90: 892-897.
55 Brouwer ML, Wolt-Plompen SA, Dubois AE, et al. No effects of probiotics on atopic dermatitis in infancy: a randomized placebo-controlled trial. *Clin Exp Allergy* 2006; 36: 899-906.
56 Reid G, Bruce AW. Probiotics to prevent urinary tract infections: the rationale and evidence. *World J Urol* 2006; 24: 28-32.
57 Saavedra JM, Abi-Hanna A, Moore N, Yolken RH. Long-term consumption of infant formulas containing live probiotic bacteria: tolerance and safety. *Am J Clin Nutr* 2004; 79: 261-267.
58 Salminen MK, Tynkkynen S, Rautelin H, et al. *Lactobacillus* bacteraemia during a rapid increase in probiotic use of *Lactobacillus rhamnosus* GG in Finland. *Clin Infect Dis* 2002; 35: 1155-1160.
59 Riquelme AJ, Calvo MA, Guzmán AM, et al. *Saccharomyces cerevisiae* fungemia after *Saccharomyces boulardii* treatment in immunocompromised patients. *J Clin Gastroenterol* 2003; 36: 41-43.
60 Salminen MK, Rautelin H, Tynkkynen S, et al. *Lactobacillus* bacteremia, clinical significance, and patient outcome, with special focus on probiotic *L. rhamnosus* GG. *Clin Infect Dis* 2004; 38: 62-69.

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