Journal of Antimicrobial Chemotherapy (2002) **50**, 625–627
DOI: 10.1093/jac/dkf194

JAC

Probiotics in human infections

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Keywords: probiotics, human infections

At the beginning of the last century, the Russian immunologist Elie Metchnikoff argued that life-long intake of yoghurt containing lactic acid-producing microorganisms could explain the differences in length of life between ethnic groups. The idea was that the bacteria in the fermented products competed with microorganisms that are injurious to health.[1] Today it is known that the normal human microflora is important as a barrier against colonization by exogenous pathogenic microorganisms and potentially pathogenic bacteria already present in small numbers in the microflora.[2] The normal microflora influence several biochemical, physiological and immunological features of the host, particularly the gastrointestinal flora, which consists of the most dense and diverse collection of bacteria.[3] Disturbances in the normal microflora can be caused by several things, one being the administration of antimicrobial agents.[4] Probiotic microorganisms are thought to counteract disturbances and thereby reduce the risk of colonization by pathogenic bacteria.[5] Studies on strains of microorganisms used in probiotic dietary supplements have demonstrated that several strains produce antimicrobial substances such as organic acids, bacteriocins and peptides. *In vitro* and animal studies have further shown inhibitory effects of probiotic bacteria to be mediated by their interference with the adhesion of gastrointestinal pathogens or with toxins produced by the pathogenic microorganisms. Adjuvant-like effects on intestinal and systemic immunity have also been demonstrated for some strains.[6] However, it is important to remember that even closely related strains have heterogeneous qualities.

A number of clinical studies have been performed on the ability of probiotic strains to prevent or treat gastrointestinal infections. The most common strains belong to the two genera *Lactobacillus* and *Bifidobacterium*, but other microorganisms including *Enterococcus*, *Streptococcus*, *Escherichia coli* and *Saccharomyces* species have also been used. The results from well-performed, double-blind, placebo-controlled studies suggest that *Lactobacillus* strain GG and *Saccharomyces boulardii* are the two most promising species in the prevention of diarrhoea. *Lactobacillus* GG has been effective in reducing the frequency and duration of rotavirus-induced diarrhoea in children. Recently, it was shown that in children admitted to hospital the risk of acquiring nosocomial diarrhoea was reduced from 33% to 7% in the group receiving prophylactic therapy with *Lactobacillus* GG.[7] However, the same strain was used in the prevention of diarrhoea in undernourished children with inconsistent results. Only for non-breast-fed children in one of three age groups was the probiotic strain of any advantage.[8] *Lactobacillus* GG has further been shown to have a preventive effect on antibiotic-associated diarrhoea (AAD) in children.[9,10] This is in contrast to the results from a study in adult patients receiving antimicrobial agents.[11] No differences in the incidence of diarrhoea were observed between patients treated with placebo or active probiotic. *S. boulardii* has been evaluated for prevention of AAD, also with inconsistent outcomes. In two double-blind, placebo-controlled studies the incidence of diarrhoea was reduced,[12,13] but no preventive effect was observed in a study of elderly subjects.[14] Combinations of standard treatment for *Clostridium difficile* infection combined with *S. boulardii* have been shown to reduce the risk of recurrence in patients experiencing renewed infection.[15] In a follow-up study, however, the preventive effect was limited to treatment with a combination of a high dose of vancomycin (2 g/day) and *S. boulardii*.[16] No beneficial effects were observed when *S. boulardii* was combined with a lower dose of vancomycin or with metronidazole.

The effects of probiotic strains in the prevention of diarrhoea caused by enterotoxinogenic microorganisms have been studied in subjects travelling to a number of destinations. Generally, the pathogens have not been identified and even though statistically significant differences between groups of individuals receiving active substance and placebo products

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have been achieved, the clinical effects have been moderate.[17] Furthermore, the same probiotic strain had variable effects depending on the travel destination of the subject.

Probiotic strains have further been tested for their clinical effect on *Helicobacter pylori* infection. In two studies a reduction of urea breath test values was demonstrated after treatment with *Lactobacillus gasseri* OLL 2716 (LG21) and *Lactobacillus acidophilus* (*johnsonii*) La1.[18,19] Strain LG21 reduced the gastric inflammation measured by means of serum pepsinogens, but in none of the studies could the eradication of *H. pylori* be confirmed in gastric biopsies. This is in contrast to the results of two earlier studies on *L. acidophilus*, where an improved eradication rate was observed.[20,21]

Furthermore, the benefits of probiotic microorganisms have been evaluated in double-blind, placebo-controlled studies in patients suffering from inflammatory bowel diseases. *E. coli* (Nissle 1917), *S. boulardii*, and a formula consisting of species of *Bifidobacterium*, *Lactobacillus* and *Streptococcus salivarius* subsp. *thermophilus* (VSL#3) have been reported as being as effective as standard treatment in preventing relapses in ulcerative colitis, chronic pouchitis or in Crohn's disease.[22–25]

Several *Lactobacillus* species have been used in the prevention and treatment of urinary tract infections, with mixed results.[26] *Lactobacillus* species have also been reported as effective in the treatment of bacterial vaginosis.[27] An important characteristic of bacteria that are beneficial for urogenital health is the production of lactic acid and H_2O_2. Recently, several other metabolic traits of probiotic strains have been identified *in vitro*, but *in vivo* studies on expressed properties are still lacking.[26,27]

The majority of clinical studies on probiotics have been performed with regard to the prevention or treatment of disturbances in the normal gastrointestinal microflora. However, increased awareness of the importance of the indigenous microflora has resulted in the assessment of potential benefits of probiotics in new areas, such as the prevention of recurrences of acute and secretory otitis media, and streptococcal pharyngotonsillitis in children. Sprays containing α-haemolytic streptococci isolated from healthy children have been tested in placebo-controlled studies. α-Haemolytic streptococci had previously been tested for their ability to inhibit growth of pathogens. Spray application following treatment with antimicrobial agents was found to reduce the incidence of recurrence and thereby the need for further treatment with antimicrobial agents.[28,29] The microflora of the nasopharynx and the nasal cavity has been shown to differ between sinusitis-prone children and children not prone to sinusitis.[30] The microflora of non-sinusitis-prone children contains more of both aerobic and anaerobic microorganisms with the capability of interference, and lower numbers of potential pathogens. Interfering microorganisms play an important role in preventing recurrence of diseases in the upper respiratory tract.[31]

The probiotic concept has been regarded as attractive also in the prevention of dental caries. Dairy microorganisms have been tested *in vitro* for their ability to become a part of the supragingival dental biofilm and for their ability to compete with cariogenic microorganisms, and promising results have been obtained for some strains.[32] In addition, milk fermented with *Lactobacillus* GG was recently shown to reduce the adherence of *Streptococcus mutans* to saliva-coated hydroxyapatite beads.[33] The preventive effect of *Lactobacillus* GG in milk has been evaluated in a clinical study of caries involving nearly 600 pre-school children over a period of 7 months.[34] Statistically significant differences were found in the development of caries between children treated with the probiotic strain compared with those given a placebo milk product. However, children in the active group developed caries in 13 new teeth and six new initial carious lesions, while the corresponding figures in the placebo group were 16 and eight. Clinically, the effect must be considered to be minimal, and the use of fluoride has probably been more cost-effective.

The use of probiotics to maintain health must be considered promising, although much remains to be elucidated. The universal use of dairy strains seems less reasonable from an ecological point of view than selection of strains from their natural habitat where they are adapted to the ecological niche. In addition, the pharmacokinetic and the pharmacodynamic properties, the safety and the risks of acquisition of resistance to antimicrobial agents should be considered. Double-blind, placebo-controlled clinical trials are needed.

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