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Probiotics in infectious diarrhoea: are they indicated? A review focusing on *Saccharomyces boulardii*

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Infectious gastroenteritis continues to be a leading cause of mortality and morbidity worldwide and, while rotavirus vaccination will certainly reduce the incidence, it is unlikely to make a significant impact on this condition. The cornerstone of treatment remains replacement of water and electrolyte losses with oral rehydration solution (ORS). In areas with low vitamin A status, supplementation of the latter may be of benefit and, in time, the addition of zinc may become routine.

A few years ago, probiotics were discussed primarily in the context of alternative medicine. Probiotics are now entering mainstream medical practice since they have been shown to decrease the severity and shorten the duration of infectious gastroenteritis by approximately 24 hours and are therefore a potent add-on therapy. Curtailing the duration of diarrhoea as well as reducing hospital stays, emphasises the social and economic benefits of probiotic treatment in adjunction to ORS in acute infectious gastroenteritis in children. Evidence in viral gastroenteritis is more convincing than in bacterial or parasitic infection. Mechanisms of action are strain specific, and only those probiotic strains for which there is evidence of clinical efficacy should be recommended. In acute gastroenteritis, there is evidence of efficacy of some strains of lactobacilli (*Lactobacillus caseii* GG and *L. reuteri*) and *Saccharomyces boulardii*. Although probiotics are 'generally regarded as safe', side-effects such as septicaemia have very rarely been reported.

Acute infectious diarrhoea remains the most common cause of diarrhoea worldwide and is a leading cause of childhood deaths. In the developed world, despite its greater wealth and improvements in public health, the incidence of intestinal infection remains high and continues to be a significant clinical problem with attendant morbidity.[1] The risk of diarrhoeal disease is increased in specific groups, such as young infants, the elderly, immune-deficient individuals (HIV, cancer, chemotherapy, malnutrition), and people with a high exposure to pathogens (informal settlements, travellers, contaminated food, medications buffering gastric acid).

Probiotics are non-pathogenic micro-organisms that resist normal digestion to reach the colon alive, where they have a beneficial effect on the health of the host. The number of published articles about the benefits of probiotics in different diseases and conditions has virtually exploded during recent years, especially in the area of acute infectious gastroenteritis. The authors of this paper reviewed and discussed evidence from the international literature and its applicability to health care in South Africa.

Prevention of acute infectious gastroenteritis

The longer an infant is breastfed and the longer that breastfeeding is the sole food source, the better the protection that the infant enjoys from infectious diseases such as gastroenteritis. As such, promotion of exclusive breastfeeding should be maximally endorsed. During recent years, attempts have been made to adapt the composition of second-choice infant feed, such as cow's milk-based formulas, so as to better mimic the immune development of breastfed infants. To recreate these benefits, probiotics and prebiotics have been added to infant formula. Saran *et al.* showed that feeding fermented milk to Indian infants over a 6-month period resulted in significantly better weight gain and a 50% reduction in infectious diarrhoea.[2] In contrast, the prophylactic beneficial effects of probiotic-enriched formula is less manifest in the developed world. While most trials show a beneficial trend, these are not consistent.[3] No studies have suggested side-effects of probiotic formula in healthy infants.

Although prebiotic oligosaccharides also have a positive effect on the immune system, data on the prevention of infectious gastroenteritis are limited. In an open-label trial, Bruzesse showed a decrease of infectious gastroenteritis in infants fed for 9 months with a prebiotic-enriched formula.[4]

Viral pathogens are the major causative organisms of infectious diarrhoea, accounting for up to 70 - 80% of all episodes. Rotavirus is the most prevalent pathogen; as a consequence, rotavirus vaccination may to some extent alter the epidemiology of infectious gastroenteritis. Initial trials show good efficacy; however, long-term follow-up is needed, and it is still unclear to what extent repeat vaccinations will be necessary. Furthermore, vaccination is expensive (about R114.00 per dose), making this option unaffordable for lower socio-economic classes. Additionally, rotavirus accounts at most for only 50% of cases of infectious diarrhoea. Athough attractive, systematic vaccination of all infants is therefore likely to remain unaffordable; and even if 100% vaccination rates were achieved, infectious gastroenteritis would at best be reduced by 50%.

Although some studies suggested that *Streptococcus thermophilus*, *Bifidobacterium bifidum* and *Lactobacillus* GG reduce nosocomial infection (especially for rotavirus gastroenteritis), a recent review concluded that there was not enough evidence to recommend the routine use of probiotics to prevent nosocomial diarrhoea.[5]

Treatment of infectious gastro-enteritis

Treatment of acute infectious gastroenteritis should focus on the pathophysiological consequences of the condition: loss of water and electrolytes, and disturbance of the gastrointestinal ecosystem.

The cornerstone of therapy is rapid rehydration and re-alimentation. The use of ORS has significantly reduced mortality. Experience has shown that rapid rehydation with ORS with re-alimentation to prevent (further) malnutrition, plus extra ORS for every watery stool, is the best form of therapy. Re-alimentation should commence after 4 - 6 hours with normal feeding at normal concentration. While a discussion on the optimal composition of ORS and re-alimentation is beyond the focus of this review, more effort is needed to instruct caregivers who may pay too much attention to fluid intake, and neglect the importance of electrolyte replacement. Many well-designed studies have failed to show additional benefit of improved ORS, evaluating the addition of glycine, alanine, glutamine and oligosaccharides, or the use of rice instead of glucose as a carbohydrate.

Administration of vitamin A has been shown to reduce the severity of acute shigellosis in children living in areas with a high incidence of vitamin A deficiency, but was not associated with reduction in prolonged diarrhoea.[6] In contrast, the combination of zinc and vitamin A synergistically reduced the prevalence of persistent diarrhoea and dysentery. Zinc supplementation may be associated with an increase in acute lower respiratory tract infection, but this adverse effect is reduced by concurrent vitamin A supplementation. The addition of zinc to ORS shortens the duration and decreases the mortality of acute gastroenteritis, even in HIV-positive individuals. Zinc reduces ion secretion and nitric oxide synthesis; improves appetite, absorption and regeneration of enterocytes; and restores enteric enzymes and humoral and cellular immunity.[7,8]

Zinc also reduces stool output, persistence of episodes of diarrhoea and fluid requirement because of its antioxidant properties and effects on growth through growth hormone and insulin-like growth factor-1.[7,8]

Probiotics address the second patho-physiological aspect of acute gastroenteritis – abnormal gastrointestinal flora – and per definition need to be prepared, preserved and administered in a viable form, and to survive in the intestinal ecosystem. There are a multitude of foods and food supplements that contain micro-organisms. Fermented alimentation features in most traditional cuisines, often as fermented milk products such as *amasi*. Furthermore, the food industry makes use of selected micro-organisms, primarily in milk-based drinks and yoghurts. Data on the mechanisms of action and efficacy of many bacterial micro-organisms are largely derived from fundamental research in laboratory settings but lack clinical evaluations of the commercialised products. Most probiotic products in capsule form are registered only as food supplements. In contrast, a biotherapeutic agent is a probiotic with proven therapeutic efficacy, and therefore considered as medication. The legislation of food supplements differs from that of medication, and biotherapeutics are therefore subject to more stringent regulation and quality control. Although some probiotic food supplements are of good quality, others are not and, unfortunately, the consumer has no way to differentiate. Analyses of commercial food supplements have illustrated the poor quality of many of these products. According to the literature, more than a third of commercial food supplements do not contain one viable strain, and only about 10% of the products in fact contain the strains claimed on the label.[9]

Strain specificity is of utmost importance. About 10 000 different strains are known to colonise the human gastrointestinal tract, and both bacterial and non-bacterial probiotic strains exist. Bacterial biotherapeutic strains comprise different lactobacilli and bifidobacteria, but to a certain extent also non-pathogenic *Escherichia coli* (*E. coli* Nissle 1917) and some strains of enterococci (although relevant transfer of plasmid-induced resistance was reported with enterococci). The yeast *Saccharomyces boulardii* is the only non-bacterial biotherapeutic strain known. Effects demonstrated for one strain cannot be extrapolated to other strains, even if they belong to the same species. Since some commercial products are combinations of different strains, laboratory and clinical testing of combinations of products is mandatory, as concurrent combinations of strains may have an antagonistic effect. *Lactobacillus acidophilus* LB has been shown to have antibacterial activity against *E. coli*. However, if the *E. coli* is present in the gastrointestinal tract of the host prior to the *L. acidophilus* LB (as occurs in acute gastroenteritis), its antibacterial activity is greatly reduced by nonspecific steric hindrance of the receptor sites.[10] Adherence of *Bifidobacterium* Bb12 improves in the presence of *L. casei* GG, both in healthy infants and during episodes of diarrhoea, suggesting that synergism may well occur.[11] Only those probiotics can be recommended for which the commercial product has been extensively evaluated in well-designed clinical trials.

One of the first trials performed in acute gastroenteritis was a multi-centre prospective, randomised trial of *L. casei* GG as additional therapy to ORS in acute diarrhoea, showing a decrease of the duration of diarrhoea by about 10% in the intervention group (a mean duration of diarrhoea of 123 hours in the placebo group versus 110 hours in the intervention group).[12] A more detailed analysis showed that the difference was greatest in the rota-positive, but that there was no efficacy in the group with invasive pathogens (about one-fifth of

all inclusions).[12] More recently, trials of lactobacilli with negative results have been published.[8,13] Lack of success in shortening the duration of diarrhoea was also reported for a mixture of *L. acidophilus, Bifidobacterium bifidum* and *L. bulgaricus*, while the volume of stool output was not reduced with *L. paracasei* ST11.[8,13]

While numerous clinical trials have been published, evaluating different probiotics in the treatment of acute gastroenteritis, they vary in relation to strains tested, dosage, methodological quality, diarrhoea definitions and outcomes. In general, meta-analyses of published trials in acute infectious gastroenteritis demonstrate a reduction of diarrhoeal duration of approximately 24 hours for selected strains of lactobacilli (such as *L. casei* GG and *L. reuteri*) and *S. boulardii*.[5,8,13,14] This benefit seems to be dose dependent and is magnified if the probiotic is given in the early stages of illness.

The first double-blind, prospective, randomised trials of *S. boulardii* were performed more than 15 years ago: diarrhoea persisted for more than 7 days in 12% of the placebo group, and in 3% of the *S. boulardii* group.[15] Since then, several double-blind, prospective, randomised trials performed with *S. boulardii* in children with acute gastroenteritis have systematically shown a significant improvement in comparison with placebo. A consecutive series of 130 Mexican children, aged 3 months to 3 years, with acute infectious diarrhoea were treated with ORS and placebo, or *S. boulardii* (600 mg/d), for 5 days.[8,13,16] A significant decrease in the number of stools was apparent from day 2 onward.[8,13,16] After 48 hours, the percentage of children considered cured was almost 50% in the *S. boulardii* group, compared with 8% in the placebo group; on day 4, resolution was up to 95% in the *S. boulardii* group, compared with just short of 50% in the placebo group.[8,13,16]

Kurugol treated 200 children with acute diarrhoea with 250 mg *S. boulardii* or placebo for 5 days; duration of both diarrhoea and hospital stay decreased in the *S. boulardii* group over approximately 24 hours.[8,13,16] Villaruel and co-workers showed similar results in ambulatory care in Argentina; diarrhoea persisted for more than 7 days in 27% of a placebo group compared with 7% of a group treated with *S. boulardii* for 6 days.[17] The efficacy of *S. boulardii* was also demonstrated in acute amoebiasis; the addition of *S. boulardii* to antibiotic treatment resulted in significantly more rapid healing and more rapid disappearance of the amoebic cysts.[18]

Shortening the duration of diarrhoea, as well as reduced hospital stays, suggests social and economic benefits from probiotic treatment in adjunction to ORS in acute infectious gastroenteritis in children. Furthermore, an open-label trial in Pakistani children with acute infectious gastroenteritis showed that administration of 500 mg of *S. boulardii* for 5 days resulted 2 months later in a 50% decrease in re-infection rates and 30% improved weight gains.[19]

Szajewska and co-workers concluded in two recent meta-analyses that the use of *L. casei* GG and *S. boulardii* are associated with moderate clinical benefits in the treatment of acute diarrhoea in children.[16,20] These findings should be interpreted with caution due to the important methodological limitations and heterogeneity of most of the studies.[16,20]

Rapid rehydration and re-alimentation are the cornerstones of treatment of acute gastroenteritis.

Traveller's diarrhoea can be considered as a high-risk form of infectious gastroenteritis. At least 3 placebo-controlled studies with lactobacilli have been performed, all with negative results. One trial with *S. boulardii* reported a small but significant preventive effect in a subgroup. According to a recent meta-analysis, several probiotics (*S. boulardii* and a mixture of *L. acidophilus* and *Bifidobacterium bifidum*) had significant efficacy. No serious adverse reactions were reported in 12 trials. Probiotics may offer a safe and effective method of preventing traveller's diarrhoea.[21]

Very few trials have been performed in chronic persistent infectious diarrhoea. Castaneda showed an improved tolerance of feeding after eradication of *Giardia lamblia*.[8,13] Saint-Marc showed efficacy of *S. boulardii* in HIV-diarrhoea.[22]

Side-effects

Probiotics are 'generally regarded as safe', and side-effects in ambulatory care are rarely seen. *Lactobacilli* have been reported exceptionally to cause cases of sepsis, meningitis and localised infections in organs. Probiotic enterococci may be a higher risk, given possible plasmid transfer in immunocompromised patients. Fungaemia with *S. boulardii* has been reported in about 50 patients.[23] A central venous catheter is the main risk factor.[23] Translocation from the gastrointestinal tract in the systemic circulation has not been reported.

Mechanisms of action

A probiotic organism needs to withstand gastric acid, pancreatic secretions and bile. Most micro-organisms present in naturally fermented dairy products do not survive contact with gastric acid and bile. Per definition, a probiotic needs to be detectable alive throughout the entire digestive system. Only 1.5% of *L. acidophilus* and 37.5% of bifidobacteria present in food reach the ileum alive.[24] Probiotics do not colonise the gastrointestinal tract, and become undetectable a few days after stopping the administration. This results in the absence of any risk for long-term side-effects. More studies are needed on pharmacodynamic and pharmacokinetic aspects, as dose-related efficacy studies are lacking.

Strain specificity is of utmost importance. Because the vast majority of probiotic products are commercial food supplements or dairy products, information regarding the strains is often limited. However, one lactobacillus is not the same as another, so one *Saccharomyces* does not have the same effect as another. While adherence of a probiotic to the gastrointestinal mucosa is reported as one of the major mechanisms of action, most beneficial effects are likely to be immune mediated, and *S. boulardii* is known to influence inflammatory pathways (NF-κB, MAPK) mediated through soluble factors.[25] The polyamine increase induced by *S. boulardii* in humans results in a maturation of brush border disaccharidases and enzymes (lactase, sucrase, maltase and aminopeptidase), increased immunoglobulin A secretion, and an increase in the number of glucose carriers in the enterocyte-membrane.[26]

Conclusion

Rapid rehydration and re-alimentation are the cornerstones of the treatment of acute gastroenteritis. Biotherapeutic agents administered as add-on medication decrease the duration of acute infectious gastroenteritis by about 24 hours. Furthermore, with *S. boulardii*, a 24-hour reduction in hospital stay has been documented, and this holds obvious notable benefits for the patient and the economy alike. Because of strain-specificity, only those organisms that have been clinically tested can be recommended, *Lactobacillus* GG and *S. boulardii* being the best studied. The number of strains tested in randomised, prospective, double-blind trials is limited. At present, evidence of shortening the duration of infectious acute (viral) gastroenteritis has been established for some strains. However, there are many questions that still need to be answered. The literature shows a statistically significant but clinically moderate benefit for some probiotic strains, mainly in infants and young children in the treatment of acute watery diarrhoea, especially in rotavirus gastroenteritis. With lactobacilli and *S. boulardii*, greater efficacy has been shown if treatment is started early.

In general, most studies evaluating the efficacy of probiotics in acute gastroenteritis have been performed in developed countries. However, the majority of the trials with *S. boulardii* in acute gastroenteritis have been performed in developing countries.

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