
Editorial

Yogurt as Oral Bacteriotherapy for Diarrhea: Back to the Future?

Diarrhea continues to plague the developing world, resulting in more than 3 million deaths annually. Children, especially malnourished children, remain at greatest risk. In addition to the grim mortality data, the morbidity of diarrheal episodes is substantial, affecting the child through the loss of "catch-up" growth after recurrent episodes. The problem and solutions involve issues related to both infectious diseases and nutrition.

The last twenty years has seen a rise in the use of oral rehydration solution (ORS) for treating the severe volume loss of infectious diarrhea, and its potential contribution cannot be understated. Unfortunately, the global impact of ORS remains limited for a variety of reasons, including its incomplete utilization and its failure to diminish stool output. In addition to improving availability, investigators are searching for a "super"-ORS that will shorten the course of diarrhea, and also alleviate dehydration. While this quest continues, other anti-diarrheal therapies are needed. Improved treatment and, more importantly, prevention are critical and merit new approaches.

An effective anti-diarrheal agent for the developing world would not only curtail the complications of acute diarrheal episodes, but would shorten the clinical course and limit the sequelae. Prevention of childhood diarrhea altogether remains the ideal. Interventions for a preventive approach must be inexpensive, readily available, and palatable to the population for whom it is

intended; the agent should also have minimal or no adverse effects. While unproven, the possibility of manipulating enteric flora through the administration of live bacteria, as in curd (yogurt), is a concept which may meet these criteria and holds enough promise to deserve further evaluation.

Long claimed to have health-promoting properties, fermented milk products have become a staple to many native diets worldwide. Like all milk products, yogurts are rich in calcium, protein and other important nutrients. The presence of active cultures, though, distinguishes yogurt from ordinary milk. The live bacteria present in these foods are believed to impart additional health benefits. The use of yogurts for either remedial or prophylactic health purposes far antedates the advent of controlled clinical trials. As such, many well-intentioned, knowledgeable physicians have dismissed this potentially valuable substance as nothing more than an untested folk remedy. Others have argued that yogurts are true probiotics, limiting or inhibiting disease by effecting colonic microbial balance.

Yogurt's direct effects on the colonic microflora have been extensively examined, due in part to difficulties in studying this outcome. Nevertheless, different investigators have shown that live-culture yogurt has *in vitro* inhibitory effects to many known diarrhea pathogens, including strains of *Campylobacter*, *Shigella*, *Salmonella* and *E. coli*. The mechanism for this remains unclear, with a variety of effects postulated as being responsible, including altered levels of luminal lactic acid, hydrogen peroxide, luminal pH, competitive inhibition of pathogenic organisms, production of

bactericidal enzymes and increased secretion of IgA. Most of these studies have used yogurts containing *Lactobacillus* and *Streptococcus thermophilus*; yogurts containing some *Bifidobacter spp.* have also been promising. Unfortunately, most *in vivo* studies investigating the digestive tract survival of these bacteria following routine yogurt ingestion (once to three times daily) have failed to demonstrate colonization, as measured by persistent fecal excretion of the orally delivered organism after discontinuation. Whether this is truly a prerequisite for a biotherapeutic effect remains unclear, though it might be reasonable to expect this to be the case. In addition, some clinical results in treatment of diarrheal illnesses appear rapidly, well before bacterial colonization would be likely to alter colonic microflora.

In recent years, investigators have looked into the therapeutic efficacy of fermented milk products and their constituent bacteria in a number of diarrheal illnesses. In using a human *Lactobacillus* strain (*Lactobacillus GG*) that has been shown to colonize the gut, Isolauri and co-workers demonstrated an accelerated recovery from rotavirus in a pediatric population in Finland⁽¹⁾. Raza *et al.* showed similar results in a prospective study in Pakistan, though this was only demonstrated on a sub-group analysis of patients who had non-bloody diarrhea⁽²⁾. This same *Lactobacillus* species has shown promising preliminary results in treating refractory *C. difficile* diarrhea, as well⁽³⁾. Yogurt containing *Bifidobacterium longum* was shown to reduce by about 50% erythromycin-induced diarrhea and abdominal complaints in a small, blinded crossover trial⁽⁴⁾. Although initial trials suggested that *Enterococcus faecium* SF68 (a lactic acid producing organism that inhibits the growth of enterotoxigenic *E. coli*, *Salmonella*, *Shigella* and *Clostridia*), might

have role in the treatment of acute diarrhea, a large, randomized trial showed no antidiarrheal effect for this therapy in treating adults with diarrhea secondary to *Vibrio cholera* and enterotoxigenic *E. coli*⁽⁵⁾. Dietary therapy comparing a traditional khitchri and yogurt diet with a soy formula in infants and toddlers with persistent diarrhea has yielded conflicting results^(6,7). In controlled trials in developing countries, *Lactobacillus* has demonstrated an effect in diminishing rotavirus associated diarrhea, in particular⁽⁸⁾. Studies with *Lactobacillus GG* have also demonstrated an increase in the immunogenicity of an oral rotavirus vaccine, suggesting that the mechanism of action is not through modification of intestinal flora alone but through immunomodulatory effects as well⁽⁹⁾.

In a more significant and perhaps more relevant study, a seventy-five per cent reduction in hospital acquired diarrhea was noted in pediatric population fed an infant formula supplemented with *Bifidobacterium bifidum* and *Streptococcus thermophilus*⁽¹⁰⁾. This prophylactic effect is what holds promise for a preventive approach through administration of probiotics (in the form of live bacteria) in yogurt. Whether these findings can be translated into successful therapies using *Lactobacillus* and *Streptococcus thermophilus* remains unclear.

These results show some promise for yogurt, or at least certain strains of bacteria delivered in yogurt, as a legitimate therapy in the prevention or treatment of diarrheal illness. Although challenges facing the developing world may limit the immediate use of yogurt as an anti-diarrheal, fermented milk products are already incorporated into many diets and in many developing countries, are made cheaply at home. The possibility that a

common food vehicle, with its own nutritional advantages, could deliver a prophylactic or remedial agent demands attention and investigation.

Researchers will need to carefully design both clinical and *in vitro* studies to better delineate the mechanism of action of these biotherapeutic agents and the clinical scenarios in which they will and will not work. Surely, the prevention of diarrheal diseases is an area ripe for study. The role of colonic flora, often referred to as the neglected organ, has been inadequately investigated in health and disease. The manipulation of the colonic flora to take advantage of potentially important properties of nonpathogenic bacteria may yield a valuable tool for the prevention of childhood diarrhea. Recently, the World Health Organization announced its desire to promote investigation of microbial interference therapy, stating that "several older forms of therapy, including bacterial interference may be worth reconsidering(11)". A recent investigation has evaluated the effect of adding fructooligosaccharide (FOS), non-digestible carbohydrate known to alter the gut flora, to experimental oral electrolyte solution in a pig model; the results indicate that FOS accelerates the recovery of the normal flora(12). Perhaps in an effort to stimulate thought and research, Gut recently committed its lead article to a review of probiotic theories and therapies(13).

We expect this recent awareness and curiosity to generate a number of investigations into the manipulation of gut flora to limit disease. Yogurt delivery of *Lactobacillus* and other probiotic organisms is certain to be studied. We eagerly anticipate the results.

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