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EDITORIAL

Probiotics and the gastrointestinal tract: Where are we in 2005?

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Abstract

Probiotic agents are live microbes or components of microbes that have a positive effect on the host. They exert their action through interplay with the immune system of the host. Some of this effect is local and some is systemic. The full story is yet to be discovered. Probiotics have a definite positive effect on rotavirus diarrhea, post antibiotic diarrhea and pouchitis. Their exact role in inflammatory bowel disease, irritable bowel syndrome, other forms of infectious diarrhea, and prevention of cancer is yet to be determined. This review summarizes the data about probiotics in these conditions.

Keywords: Probiotics; Inflammatory bowel disease; Crohn's disease; Lactose intolerance; Antibiotic associated diarrhea; Rotavirus; Pseudomembranous colitis; Clostridium dificile; Irritable bowel syndrome; Toll like receptor 9

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INTRODUCTION

The modern term 'probiotic'was first used by Fuller [1], describing a live microbial feed supplement which beneficially affects the host animal by improving its microbial balance. Later it was demonstrated that heat-inactivated bacteria or fragments of bacterial DNA have positive effects as well. Marteau *et al* [2] in 2002 defined probiotics as 'microbial cell preparations or components of microbial cells that have a beneficial effect on the health and well-being'. The mechanisms by which probiotics beneficially affect the host are multiple. Probiotics can prevent or ameliorate diarrhea and inflammation through their local effects and/or their effect on the immune system. In the gut, probiotic bacteria are thought to occupy binding sites on the gut mucosa, preventing pathogenic bacteria from adhering to the mucosa [3, 4]. Lactobacilli produce proteinaceous compounds, namely bacteriocins, that act as local antibiotics against more pathogenic organisms [5, 6] and decrease production of pro-inflammatory cytokines such as IFN-γ, TNF-α and IL-12 [7-9]. Probiotics stimulate IgA production [10]. Lactobacilli produce acetic and lactic acid and inhibit the growth of bacterial pathogens [3]. It has been postulated that probiotics compete with pathogens for nutrients and modify toxins produced by pathogens or toxin receptors found in the gut wall. Rachmilewitz *et al* [11] have shown that specific DNA repeats isolated from probiotics (VSL #3) can attenuate experimental colitis in various animal models. This is true even with inactivated bacteria. By using toll-like receptor 9 (TLR-9) deficient mice, they have proved that TLR9 signaling is essential in mediating the anti-inflammatory effect of probiotics [12].

Prerequisites for probiotics are to be effective and safe. The characteristics of an effective probiotic as defined by Saavedra [11] are resistance to digestion by enteric or pancreatic enzymes, gastric acid and bile, ability to prevent the adherence, establishment and/or replication of pathogens in the gastrointestinal tract.

Examples of probiotic bacteria are members of the Lactobacilli family such as Lactobacillus rhamnosus GG, bifidobacteria and the yeast saccharomyces boulardii. There are many candidate bacteria which can be qualified as probiotics, but different bacteria have different actions in different disease states, taking into account that some disease states are better treated with a combination of bacteria and that there is an issue of dosing and viable vs. non viable components of the bacteria. Treatment with probiotics is relatively safe, but not risk free. Probiotics are potentially pathogenic [13]. A recent report describes 3 patients with fungemia in whom the probiotic origin was proven by DNA fingerprinting [14]. Reports of infections of probiotic origin emphasize the fact that these patients are usually immunosupressed with multiple ports of entry, such as venous and urinary catheter.

This article reviews the use of various probiotics in the treatment of infectious diarrhea, inflammatory bowel disease and lactose intolerance.

PROBIOTICS AND DIARRHEAL DISEASE

Probiotics have been proved to be beneficial to four types of diarrhea: rotavirus diarrhea, antibiotic-associated diarrhea, clostridium difficile diarrhea, and traveler's diarrhea.

Trials of probiotics for other infectious diarrhea diseases have not been consistent in terms of efficacy so far. Paton *et al* [15] have produced toxin binding probiotics in a breakthrough study using a toxin-binding recombinant probiotic for the treatment and prevention of enterotoxigenic Escherichia coli diarrhea. If these probiotics can be proved effective, it might open a whole new era in the treatment of different kinds of diarrhea.

ACUTE VIRAL DIARRHEA

One of the established benefits of probiotics is that they are effective in the treatment of children with acute viral enteritis [16,17] . Lactobacillus reuteri can shorten the course of acute diarrhea in infants from 2.5 days to 1.5 days [18]. Lactobacillus casei GG is effective in treating acute diarrhea as well [19]. Different strains of probiotics exhibit different efficacy. Kaila *et al* [20] studied different lactic acid bacteria for their effect on the immune response to rotavirus in children with acute rotavirus gastroenteritis and found that Lactobacillus casei subsp. casei strain GG (LGG) is most effective on disease duration and produces the highest titers of IgA antibodies. It has been postulated that IgA specific Ab confers immunity against future infectious diarrhea, a higher level of such Ab is desired. Allan *et el* [21] systematically reviewed 23 papers concerning probiotic treatment of infectious diarrhea and concluded that probiotics appear to be a useful adjunct to rehydration therapy in treating acute infectious diarrhea in adults and children.

ANTIBIOTIC-ASSOCIATED DIARRHEA AND PSEUDOMEMBRANOUS COLITIS

Antibiotic-associated diarrhea (AAD) is seen in up to 39% of hospitalized patients treated with antibiotics [22] and varies from uncomplicated diarrhea to colitis and pseudomembranous colitis. The pathogenic factors include any one or all the followings: use of antibiotics causing changes in the normal gut flora, pathogenic bacteria taking advantage of the situation and causing inflammation and diarrhea, change in bacterial flora causing changes in carbohydrate metabolism and changes in short chain fatty acid metabolism and absorption. The latter is interfered and osmotic diarrhea ensues. The well-known syndrome of pseudomembranous colitis characterized by high levels of toxin forming Clostridium difficile may take a fulminate course with a high recurrence and mortality rate. AAD can be prevented or treated with probiotics. A meta-analysis summing the results of nine controlled trials indicates that both Lactobacilli and S boulardii are effective in preventing AAD [23]. Various probiotics have been used to prevent and treat Clostidium difficile-associated pseudomembranous colitis, including S. boulardii, Lactobacillus GG, B. longum and B. longum with L. acidophilus. S. boulardii and fecal transplantation can be used through a naso-enteric tube or as an enema [24]. S. boulardii seems to be a choice in prevention and treatment of recurrent Clostridium difficile pseudomembranous colitis [24].

INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) has a complex etiology. Environmental as well as genetic factors play a role. It has been established that microbes play a crucial role in IBD though search for an infectious agent has been futile so far. It was reported that Lactobacillus and bifidobacteria counts are significantly reduced in feces of patients with Crohn's disease compared to those with ulcerative colitis and controls and continuous interplay exists between the immune system and intestinal flora, suggesting that normalization of gut flora is a logical means of treatment [25, 26]. Venturi *et al* [25] treated 20 ulcerative colitis patients with VSL#3 and it is able to change the gut microflora because the faecal concentrations of Streptococcus salivarius ssp. thermophilus, Lactobacilli and bifidobacteria were significantly increased in all patients, compared to their basal level which remained stable throughout study. As mentioned before, probiotics have local and systemic effects. Lactobacillus casei strain GG given to pediatric Crohn's patients results in increased serum titers of IgA [27]. It was also reported that murine colitis was successfully treated with Lactococcus lactis secreting interleukin-10 [28].

Probiotics can achieve and maintain remission, prevent post surgical recurrence of Crohn's disease and pouchitis, and treat pouchitis, but an established role of probiotics exists only in the latter two indications. Gosselink *et al* [29] treated 39 patients with L. rhamnosus GG and proved that it had a better effect on these patients than on those not treated with it. Gionchetti *et al* [30, 32] demonstrated that pouchitis episode was reduced by 30% using VSL#3 in a double blind placebo-controlled study. Mirura *et al* [31] and kuisma *et al* [33] showed that remission of chronic pouchitis can be achieved with antibiotics. S. boulardii has no efficacy on ulcerative colitis [34].

Treatment of active ulcerative colitis has been extensively investigated in clinical trials [34-37]. All the studies proved that probiotics are effective at least on one of the followings: clinical and endoscopic improvement or decrease in proinflammatory cytokine expression. One additional report described six active refractory patients treated with human probiotic infusions and symptoms were abolished in all within four months [38]. These data support using probiotics in mild to moderate active disease. Three trials showed probiotics can be used as a maintenance treatment of UC [39-41].

Clinical trials have also been conducted in Crohn's disease patients [42-45]. Campieri *et al* [45] compared mesalazine with VSL#3 in 40 patients and found that endoscopic recurrence was significantly reduced noted in probiotic-treated patients, but Lactobacillus GG and L. Jonhsonii effect cannot prevent post surgical recurrence of Crohn's disease. Treatment of active Crohn's disease has been assessed in some studies [46, 47], no definite conclusion could be reached due to methodological drawbacks.

LACTOSE MALABSORPTION

Lactase deficiency is a frequent condition causing intolerance to lactose due to maldigestion. Kolars *et al* [48] and Savaiano *et al* [49] in 1984 showed that absorption of lactose from yogurt is improved compared with milk, presumably due to digestion of lactose by lactase released from the yogurt microorganisms [50]. Shermak *et al* [51] examined the effect of yogurt or milk on symptoms and hydrogen breath concentration in children with lactose intolerance and found that symptoms as well as exhaled hydrogen concentration were lower in children challenged with yogurt.

IRRITABLE BOWEL SYNDROME

Evidence for benefit of probiotic treatment in irritable bowel syndrome (IBS) has not been consistent. Nobaek *et al* [52] conducted a double-blind, randomized placebo-controlled study in 60 unselected patients with IBS, and found that probiotic treatment resulted in improvement of flatulence only. Recently, O'Mahony *et al* [53] reported patients taking B infantis had improvement in their symptoms, but no difference was observed between patients treated with L. salivarius and those treated with placebo. An interesting finding was that the basal ratio of IL-10/IL-12 was lower in IBS patients than in matched healthy controls. Treatment with B. infantis but not L. salivarius or placebo led to normalization of the ratio, suggesting that inflammation plays a role in the pathogenesis of IBS.

PROBIOTICS AND CANCER

It is assumed that cancer is the outcome of genetic and environmental conditions. In each individual the interplay between the two is different. Cancer is the endpoint of a series of events. Various studies have shown the effect of probiotics on some of the enzymatic pathways and intermediates assumed to precede cancer [54-56]. Brady *et al* [54] have summarized the data concerning the use of probiotics in the prevention of cancer in their review. Other studies reported that the use of probiotics is inversely related with aberrant crypts or tumor development [55, 56]

POTENTIAL BENEFIT OF PROBIOTICS

Treatment of constipation with probiotics has yielded confusing results [57, 58]. Probiotic *E. coli* strain has been found to be effective on collagenous colitis [59].

CONCLUSION

Probiotics are a large group of microbes. Different microbes have different actions in different situations. Probiotics play a definite role in a number of clinical situations, namely rotavirus diarrhea, post antibiotic diarrhea and pouchitis. Their role in other clinical situations is yet to be defined.

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