



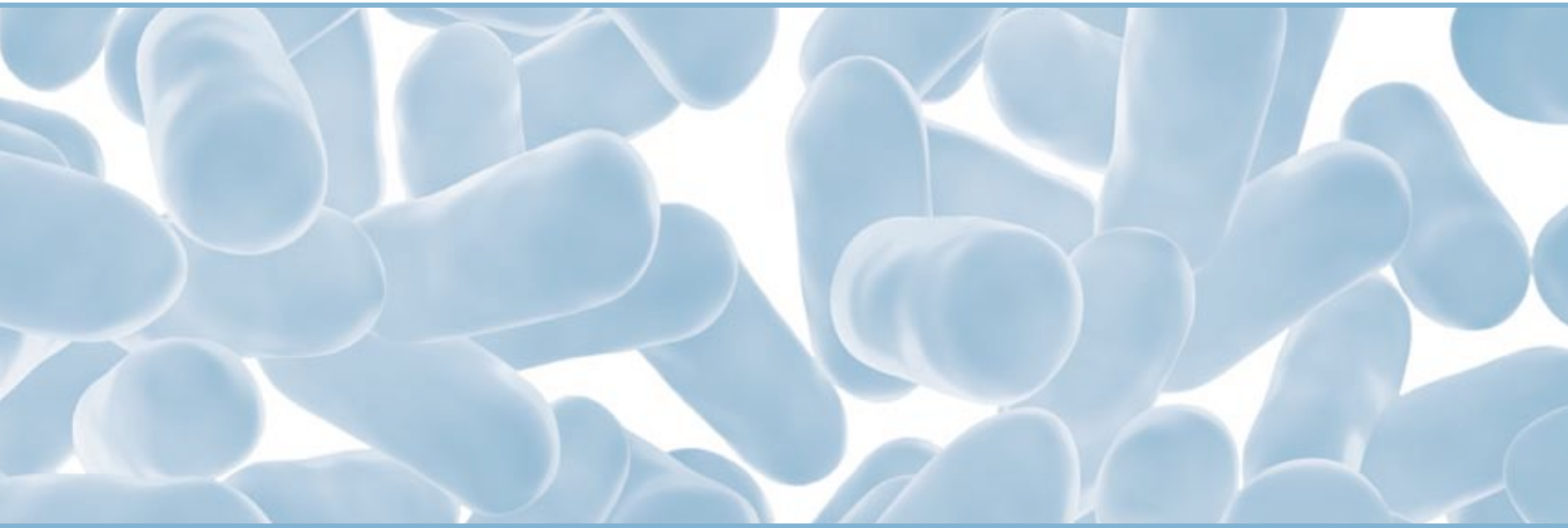
**Symposium**  
in conjunction with  
American College of Gastroenterology  
Annual Scientific Meeting

# Probiotics

Applications in  
Gastrointestinal Health & Disease



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## a note from **Dr. Martin Floch**

Clinical Professor of Medicine &  
Director of Ambulatory Gastrointestinal Services,  
Yale University School of Medicine  
Master of the American College of Gastroenterology

Dear Colleagues,

Probiotics are living microbial organisms that can benefit our health when they are administered in the right amounts. There are many different types of probiotic cultures which can provide various benefits.

Recent research shows positive affects from certain probiotics on intestinal microflora and/or different intestinal functions such as improving intestinal motility and managing diarrhea. The intestinal tract ecology contains at least 10<sup>14</sup> bacteria. The probiotic organisms live within this ecology and help maintain health by stimulating immune responses and controlling pathogenic mechanisms.

Probiotics are now becoming more widely used, usually in the forms of foods or supplements. In other countries, probiotics are frequently recommended by physicians and, as supportive evidence continues to accumulate, the concept of

using probiotics is gaining further recognition in the United States as well.

This past October, in conjunction with the American College of Gastroenterology (ACG) 72<sup>nd</sup> Annual Scientific Meeting, a world-class panel of speakers came together to share insights in a program entitled, “Probiotics: Applications in Gastrointestinal Health and Disease.” This symposium discussed some of the cutting-edge science on how probiotics can play a role in promoting gut health.

We hope you will find this summary useful.

*With Regards,*

Martin Floch, MD

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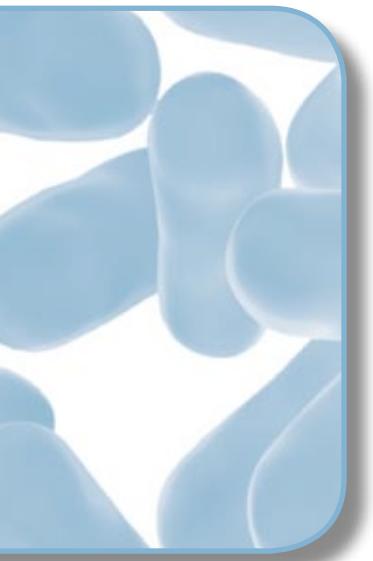
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# why Probiotics?

Various cultures around the world have historically used probiotics for health promotion and preventive purposes. In the past decade, scientific evidence on the health benefits of probiotics is quickly emerging. New research suggests that these “beneficial” bacteria can be incorporated in the diet and have beneficial effects on gut microflora, intestinal motility, and mucosal barrier dysfunctions, including diarrhea, constipation and immune response.

The majority of published data involves the use of probiotics to prevent and treat gastrointestinal infections. New research is giving insight into additional potential functions of these microorganisms. As supportive evidence accumulates, the concept of probiotics continues to gain recognition and is becoming more popular.

This executive proceedings shares background information on probiotics as well as knowledge of the latest research on the role of probiotics in various conditions of the gastrointestinal tract. In addition, the summary shares an understanding of clinical applications for current preventive practices, treatments, and health promoting approaches.



Executive Proceedings  
from Symposium in conjunction with  
American College of Gastroenterology  
72<sup>nd</sup> Annual Scientific Meeting  
Philadelphia PA • October 16, 2007

# Gut Flora and the Impact of Probiotics on Human Health

Mary Ellen Sanders, PhD

Executive Director, International Scientific Association for Probiotics and Prebiotics (ISAPP)

Probiotics have been defined by an FAO working group as live microorganisms that when administered in adequate amounts confer a health benefit on the host. Inherent in this definition is that these microbes have to be shown through human studies to have a health effect. Thus, all live microorganisms or live cultures like those in fermented foods are not necessarily probiotics.

We usually think of probiotics of having an impact on gut function, but any colonized site in the human body could be a potential target for a probiotic. Some evidence for more systemic effects, likely mediated through circulating immune factors, exists. For example, a recent study showed that a probiotic decreased duration of colds.

It's been estimated that about  $10^{14}$  microbial cells are associated with the human body, most being in the colon. Interestingly, 80% have never been cultured and so not much is known about the majority of microbes that colonize the intestinal tract. Between 800 and 1000 different microbe phylotypes might reside in a single individual, so there is a great diversity of microbes associated with us as well.

An individual's microbiota is considered to be a fingerprint. The microbiota is largely stable once a child is weaned all the way through adulthood, and remains stable until old age when there starts to be some transformations. Even though there are opportunities during a lifecycle for alterations, for example, with antibiotic therapy or with certain dietary changes, the microbiota tends to rebound and return to a stable population that is unique to an individual. Our colonizing microbes also have a sizable metabolic potential and they are not static residents: they actively communicate with their host and with other microbes.

Studies with germ-free animals have shown that colonizing organisms play an important role in immune system development and prevention of infection. For example, germ-free animals succumb to infections when exposed with much lower levels of pathogens than colonized animals would. There are also several diseases or disorders that are known or suspected to be due to gut flora alterations or inappropriate host responses to normal colonizing microbes.

Commensal flora play an important role in colonization resistance through pathogen displacement, production of antimicrobial factors, and potentially through nutrient and receptor site competition. They also have structural functions and can effect immune system development. In addition, they play a role in epithelial cell differentiation and proliferation. Furthermore, they metabolize certain types of dietary carcinogens and have been known to synthesize vitamins, such as biotin and folate, and are involved in the fermentation of non-digested substances that make it into the colon.

In humans there are unknowns concerning the ideal composition of colonizing bacteria, how the composition of our microflora is determined, or how it impacts health and disease. It's likely that the host genotype has a significant impact on initially selecting which bacterial groups colonize the intestine and that diet affects the metabolic activities of microbes that are present.

A fundamental premise behind probiotics assumes that adding microbes to a colonized system can have an influence on health. Studies have shown that probiotics can down regulate inflammation and responses to allergens, and interfere with pathogen infections either directly or through enhancing gut barrier

## Mary Ellen Sanders, PhD

was founding President of the International Scientific Association for Probiotics and Prebiotics (ISAPP) from 2002-2006, and is currently the Executive Director. She is also an internationally recognized consultant in the area of probiotic microbiology. She serves on the Product Quality Working Group of the NIH National Center for Complementary and Alternative Medicine. Her past research has focused on strain development of lactic acid bacteria with a primary emphasis on genetic improvement of lactic acid bacteria used as starter cultures, *in vitro* characterization and identification of probiotic *Lactobacilli* and *Bifidobacteria* for commercial applications, evaluation of the effect of probiotics on fecal microecology and tracking specific probiotics through the gastrointestinal tract.

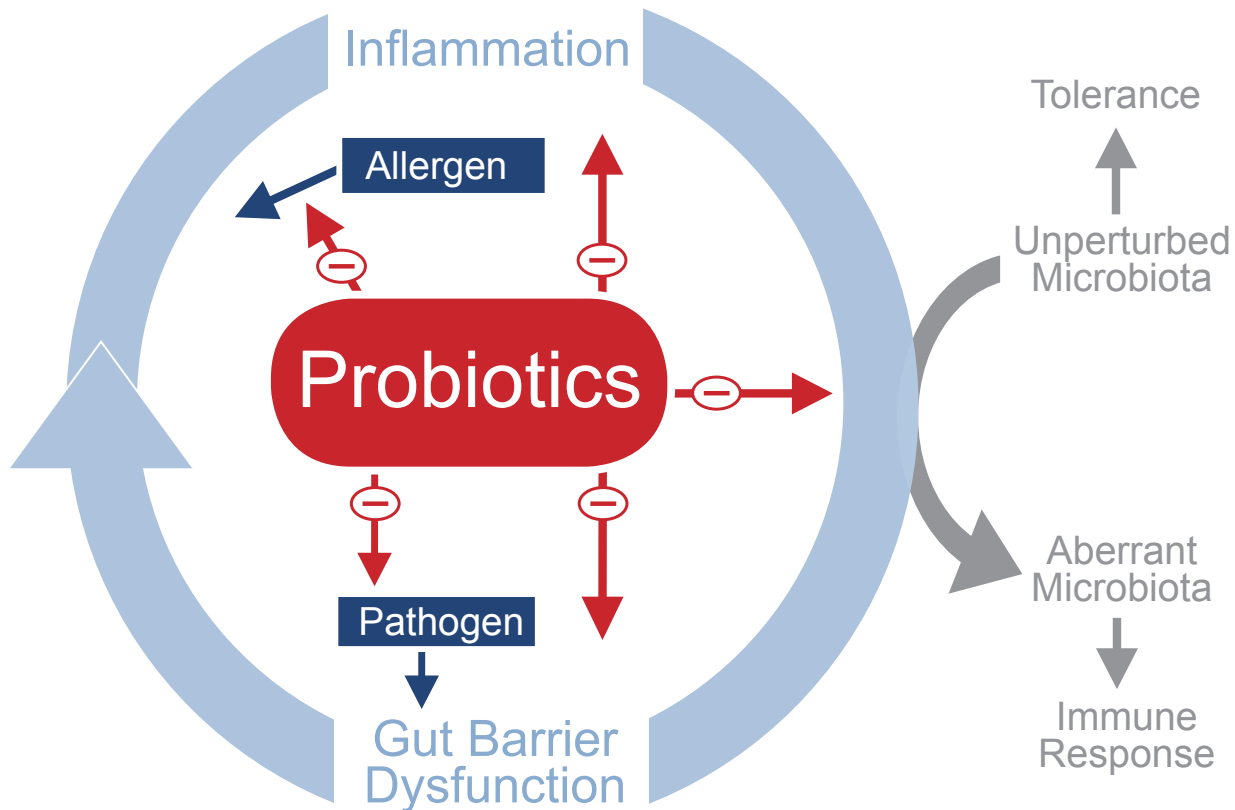


# Mechanisms by which Probiotics Influence Human Health

Probiotics can down regulate:

- inflammation
- responses to allergens
- pathogen infections (interference); and
- alterations in the gut.

They can do this directly or through enhancing gut barrier function.



function. Probiotics can also serve a role for stabilizing the intestinal microflora. Many of the mechanisms are similar to the roles that our normal colonizing microflora play.

Many different health targets have been studied with probiotics. One probiotic should not be expected to do all of these things, however. In general, the best evidence for probiotic health effects is in the area of decreasing duration or incidence of certain diarrheal diseases and in immune enhancement. Emerging evidence exists for probiotics in the areas of dental caries, prevention of allergy, intestinal infections, vaginal infections, colds and respiratory infections, improved growth parameters in undernourished children and improvements in quality of life indicators.

In terms of the microbiology of probiotics, microbes that are the same genus and the same species, but are a different strain of that genus and species, may not have the same clinical effects. There are many different *in vitro* and animal studies that have compared strains head to head to show that their physiological characteristics are different from each other. The effects are also dose specific – studies have shown that as the dose of probiotic went up, the effectiveness also went up. Controlled, human studies are still limited, but until otherwise demonstrated, documented health effects must be considered to be specific to the probiotic strain or strain blend studied at the dose that was studied.

On the market, there are a variety of different formats of probiotics, which

include foods, supplements, medical foods, and pharmaceuticals, all of which are regulated differently by the Food and Drug Administration. In the US, we don't currently have approved human drugs that are comprised of probiotics, but data on endpoints like pouchitis, IBS, bacterial vaginosis, and *C. difficile* associated diarrhea indicate that probiotic drugs may be on the horizon.

In terms of labeling probiotic products, the only standard required by the FDA for foods, supplements, and medical foods, is that the labeling be truthful and not misleading. Sometimes there is a disconnect between what's studied in published papers and what is actually available commercially on the market, but there are some well-validated, properly labeled products out there and those are the ones that should be utilized.

# Probiotics for Antibiotic-Associated Diarrhea and *C. difficile*

Stefano Guandalini, MD

Professor and Chief, Division of Pediatric Gastroenterology, Hepatology and Nutrition,  
University of Chicago Comer Children's Hospital

The definition that WHO gives for antibiotic-associated diarrhea (AAD) is three or more abnormally loose bowel movements per 24 hours. In adult and pediatric trials, this is defined as one to three abnormally loose stools per 24 to 48 hours. It is thought that the prevalence of AAD is 5 to 62%. Diarrhea can start at any point from the beginning of therapy to two months after discontinuation of antibiotics, although, it most commonly occurs within 1-2 weeks.

*C. difficile* contributes to some, but not all AAD. The problem of *C. difficile* associated diarrhea (CDAD) results from preceding antibiotic use and is very common in health care institutions. The only approved treatment by the FDA currently is vancomycin, although the statements from the American Gastroenterological Association (AGA) supported by the CDC also endorses the use of metronidazole.

Disturbingly, there has been a rising incidence of CDAD over the past few years. In addition, CDAD has been found more and more in patients with minimal or no exposure to health-care institutions or antibiotics but, for instance in those who use chronic proton pump inhibitor antacid therapy. There has also been recognition of outbreaks associated with a new hyper-virulent *C. difficile* strain called NAP1, which is more aggressive than traditional strains. Reports of poor clinical response and rising relapse rates involving at least 20% of patients treated with metronidazole have also been shown. Better options are needed to prevent or possibly treat this condition.

The combination of old drugs, the testing of new drugs, and the use of probiotics for prevention are three different strategies that have been used. One study that was

recently published combining drugs added rifampin to metronidazole. It showed small improvements in patients who had relapse, but there was no significant difference. There were also significantly more deaths in the metronidazole and rifampin group, versus the metronidazole group alone.

Netazoximide, an anti-parasitic agent, has been used for many years in Europe and has gained popularity in the US since it has shown *in vitro* activity against *C. difficile*. It has been studied and verified against metronidazole, but showed no improvement in the percentage of patients who had the continuing illness.

Several species of probiotics have been tested as a means to prevent *C. difficile*. A very recent meta-analysis published this year specifically addressed the issue of AAD and probiotics in children. Ten randomized clinical trials were included in the analysis. Two of the studies were in hospitalized patients; four were in private primary care practice, and two were in outpatient university teaching hospitals. The antibiotic usage in all trials was between 5 and 15 days provided orally, and between 2 and 10 billion CFU/day of *Lactobacillus* probiotics strains were utilized.

A statistically significant reduction in the incidence of diarrhea was seen in children that received certain probiotics versus placebo. In addition, it was found in such a meta-analysis that better conducted studies, based on "Jadad" scores, showed the probiotics to be more efficacious in preventing the incidence of diarrhea.

Probiotics are not created equal: they may have different pathophysiological mechanisms and therefore different clinical indications. Some have shown efficacy in preventing the incidence of diarrhea, and some have

## Stefano Guandalini, MD

is Professor of Pediatrics and Chief, Division of Gastroenterology, Hepatology and Nutrition, University of Chicago Comer Children's Hospital. Dr. Guandalini is an internationally recognized expert on celiac disease and is also known for his expertise in the research and treatment of other diarrheal diseases in children. His clinical and research efforts have greatly influenced the way celiac disease is diagnosed and treated today. Dr. Guandalini created the University of Chicago Celiac Disease Center in response to the low rate of celiac disease detection in the United States. His recent research interest is focused on the use of probiotics in diarrheal diseases of children. Dr. Guandalini has been the first and currently is the past President of FISPGHAN (The Federation of the International Societies for Pediatric Gastroenterology, Hepatology, and Nutrition).



not. Data from the meta-analysis showed that *Lactobacillus GG* and *Saccharomyces boulardii*, when used in concentrations equal to or more than 5 billion CFU/day, were efficacious.

A recent study published in the *British Medical Journal* looked at adults older than 50 in 3 London hospitals. They took a probiotic dairy drink which contained *Lactobacillus casei* DN-114-001, at the concentration  $1 \times 10^8$  (100 million) CFU per ml. Participants took 100 grams of the probiotic-containing drink twice a day within 48 hours of the antibiotic treatment for one week. In the patients who consumed the probiotics, 7 (12%) developed diarrhea and 88% did not. This was statistically significant from the control group, in which 34% developed diarrhea. Additionally, patients who had *C. difficile* toxin in their stools as part of their AAD were sub-analyzed. None of the patients who received the probiotic drink had *C. difficile* in their stool.

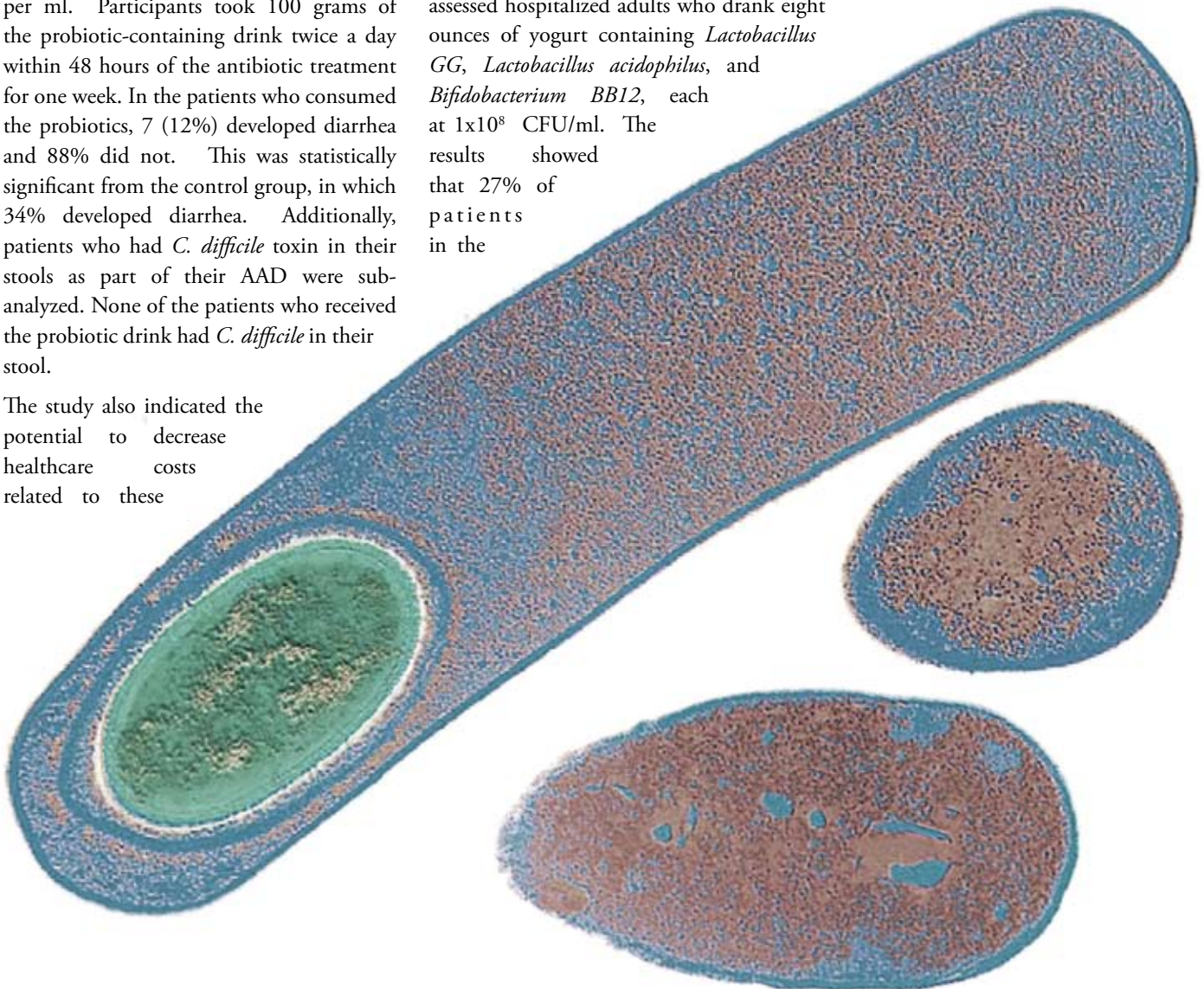
The study also indicated the potential to decrease healthcare costs related to these

conditions by showing that the use of probiotics to prevent one case of diarrhea would cost about \$100, whereas the cost to prevent one case of *C. difficile* would be about \$120, both of which are much less than the cost that could accrue with conventional treatments (\$3669) mainly because of increased hospital stays, but also because of the use of vancomycin.

Another promising article in the *European Journal of Clinical Nutrition* recently assessed hospitalized adults who drank eight ounces of yogurt containing *Lactobacillus GG*, *Lactobacillus acidophilus*, and *Bifidobacterium BB12*, each at  $1 \times 10^8$  CFU/ml. The results showed that 27% of patients in the

placebo group versus 6% in the probiotic group experienced AAD.

Thus, we can conclude that there is growing, solid evidence that choosing the right probiotics in the right amounts can be effective in preventing AAD in both children and adults. Clearly substantial savings could be made by routine use of certain probiotics.



Representation of colored transmission electron micrograph of *Clostridium difficile* forming an endospore (green)

# Probiotics and IBS, Constipation and Intestinal Motility

Eamonn Quigley, MD

Professor of Medicine and Human Physiology, Alimentary Pharmabiotic Centre, University College Cork

There is now some interesting data to confirm disturbances in the gut flora in Irritable Bowel Syndrome (IBS). Some believe that bacterial overgrowth is common in IBS; others feel that the disturbance lies more in the colonic flora where there may be either qualitative or quantitative changes in the microbiota. There's also increasing evidence for a role for inflammation, or immune activation, in some patients with IBS.

Promising evidence is showing that in a variety of experimental studies probiotics have anti-inflammatory effects. Furthermore, probiotics could affect stool consistency or frequency, and gas related symptoms.

A recent study looking at the fecal flora in IBS patients found significant differences between the bacterial population in IBS subjects versus controls. There is also evidence of increased mast cells, both in the ileum and in the colon in those with IBS. More recently, evidence of degranulating mast cells has been found, and data shows that the greater the proximity between the mast cell and the enteric neuron, the greater the pain experienced by the patient.

Evidence of inflammation and immune activation has been demonstrated by increased interepithelial lymphocytes, or increased CD3 or CD25 positive lymphocytes. Studies have also found elevated levels of IL-6 and the soluble receptor for IL-6 in patients with IBS. Other groups have looked at peripheral blood mononuclear cells and have seen an increase in TNF *alpha*, IL-1 *beta*, and IL-6 at baseline. Cells stimulated by lipopolysaccharide have shown a further increase in IL-6 levels.

Accepting that there is some disturbance in the flora in IBS, therefore, it's not unreasonable to suggest that this could lead to immune dysfunction in the mucosa. Evidence in a

variety of animal models demonstrates that immune phenomena in the mucosa can lead to significant changes in motility, sensitivity, and in more distal sites in gut-brain axis function.

Various parameters in the immune response might interact. In certain circumstances, such as emotional or physical stress, or following an enteric infection or disturbances in the microbiota, changes in the flora occur. These stimuli can result in changes in intestinal permeability, and in doing so; they can allow access for bacteria or bacterial products to the subepithelial compartment. This, in turn, leads to immune activation, mast cell activation, and through the release of various neuromodulators and inflammatory mediators -- to activation of sensory neurons. A variety of factors can alter permeability, but probiotics can fortify the epithelial barrier so that its barrier function is restored.

The scientific basis to link the flora to the subepithelial compartment and finally to neuronal signaling is presently based on a variety of animal model studies and some clinical studies. If elevated levels of cytokines in serum or peripheral blood mononuclear cells turn out to be validated in these studies, it is possible that they could act as biomarkers for IBS or for subgroups of patients with IBS.

In regards to constipation and motility disorders, certain probiotics seem to stimulate intestinal transit. Studies on a specific strain of *Bifidobacterium animalis* showed shortened colonic transit time in healthy women and in the elderly. This effect was seen independent of changes in fecal mass or bile acid content, suggesting a more direct rather than indirect effect. In another recent study, a more direct effect in stimulating motility was seen for probiotics combined with inulin.

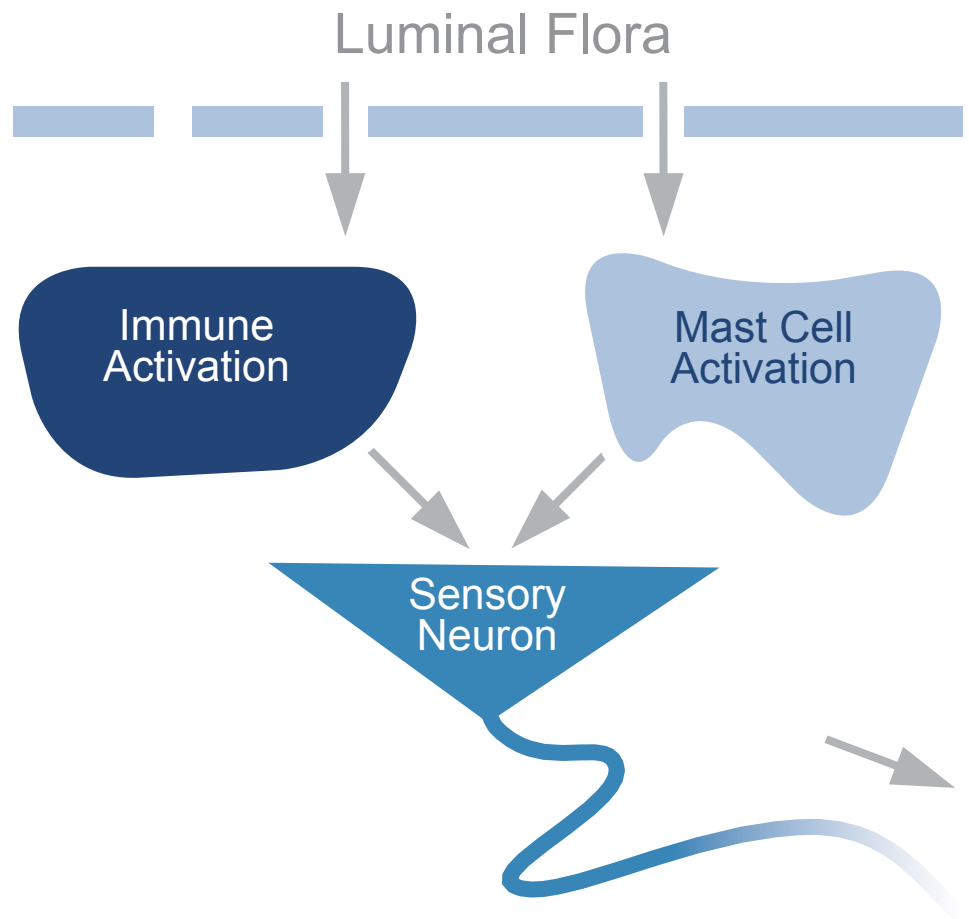
## Eamonn Quigley, MD is

Professor of Medicine and Human Physiology at National University of Ireland, Cork, Ireland and was appointed as the first Head of the Medical School there in 2000. He previously served as Chief of Gastroenterology and Hepatology at the University of Nebraska Medical Center from 1991 to 1998. Dr. Quigley is the President-Elect of the American College of Gastroenterology (ACG) as well as the President of the World Gastroenterology Organization (WGO). He has also served as Editor-in-Chief of the American Journal of Gastroenterology from 1997-2003. Dr. Quigley has published over 400 articles, including original manuscripts, editorials, review articles, book chapters and case reports mostly in the areas of motility, functional gastrointestinal disorders (FGIDs) and gastro-oesophageal reflux disease (GERD or GORD).



# Probiotics can fortify the epithelial barrier so that barrier function is restored

1. Emotional or physical stress and enteric infection can lead to changes in the gastrointestinal flora
2. These stimuli can result in changes in intestinal permeability, allowing bacteria access to the subepithelial compartments
3. This leads to immune activation, mast cell activation, and activation of sensory neurons



A review by Hamilton-Miller summarized evidence on probiotics in IBS prior to 2000. Up to that time there had been several small trials, which were almost universally underpowered. They used a variable condition of IBS, differed in trial design and in endpoints, and many were uncontrolled. Furthermore, they used variable organisms and concentrations, and viability was usually not assessed. Despite all of these caveats, Hamilton-Miller concluded that overall the trends were positive.

Over the next five years, studies were inconsistent, but somewhat improved. A more recent study with a *Lactobacillus* and *Bifidobacterium infantis* strains found that pain and the other cardinal IBS symptoms improved significantly with the *Bifidobacterium* administration.

The study also assessed peripheral blood mononuclear cells and the ratio between an anti-inflammatory cytokine, IL-10 and a pro-inflammatory cytokine, IL-12. In the three IBS groups at baseline, the ratio was significantly lower indicating a pro-inflammatory state. But upon treatment with *Bifidobacterium infantis*, the ratio normalized, suggesting an anti-inflammatory effect. This effect was not seen with placebo or the *Lactobacillus* strains.

*Bifidobacterium infantis* has also proven efficacious in a larger study again providing significant reductions in pain and the other IBS symptoms and was the only organism to demonstrate significant benefit in an appropriately designed study outlined in a recent systematic review of probiotics and IBS.

Another recent study, which treated primary care patients with fermented milk containing a specific strain *Bifidobacterium animalis* or a heat-treated yogurt for 6 weeks, saw no difference between the placebo and treatment groups. At 3 weeks, however, they did find significant benefit in discomfort and bloating scores, and an increase in stool frequency in those who were constipated at the outset.

In summary, immune activation and various disturbances in the flora have been variably and, for the most part, separately described in IBS and need to be linked. It is clear that specific probiotics might reverse these changes and improve the cardinal symptoms of IBS.

# Probiotics Probiotics Prob

## Frequently Asked Questions

**Q** Are probiotics safe?

**A** There is a lot of evidence supporting the safety of organisms such as *Lactobacillus* and *Bifidobacterium*, as well as other starter bacteria. Certain organisms, such as *Enterococcus*, may not be best to give immunocompromised patients as they could theoretically be opportunistic depending on the condition of the host, but overall there have not been safety issues.

**Q** At what point should probiotic use start in the treatment of the *C. difficile* diarrhea when antibiotics are in use?

**A** There is no published evidence one way or another. One opinion is to start the probiotic at the same time as the antibiotic. Whether or not this would improve the rate of recurrences has not been proven, but since probiotics are safe products, waiting would not be necessary.

**Q** Does the intestinal microflora change when using probiotics?

**A** There are studies that have shown stool culture changes indicating that luminal bacterial changes occur, but it is unclear what is related to the mucosal population. Early studies using biopsies have also shown changes in inflammatory cytokines.

**Q** Since resident colonic bacteria have been there for years or decades, and its not easy for probiotics to get a foothold, are there studies looking at Irritable Bowel Syndrome (IBS) where antibiotics are given to weaken the resident bacteria prior to giving probiotics?

**A** Sequential therapy, first with an antibiotic, followed by a probiotic has some attractiveness, but before sequential therapy is considered more data and long-term studies are needed regarding the use of antibiotics in IBS.

**Q** How should probiotics be consumed?

**A** Probiotics have to be nurtured. Therefore, it is best to take them with foods that they enjoy such as with dietary fiber or dairy products.

**Q** Are probiotics on the market regulated or standardized?

**A** There is currently no standardization or third party evaluation of the amount and type of probiotics in a product. Product statements are to be truthful and not misleading, but no action is currently taken if they don't contain the amounts that are claimed.

# Antibiotics Probiotics Probiotics

## Suggested Reading

Aslam, S. et al. Treatment of Clostridium difficile-associated disease: old therapies and new strategies. *The Lancet Infectious Diseases*. 2005; 5: 549-557.

Barbara G, et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. *Gastroenterology*. 2004 Mar;126(3):693-702.

Bausserman M and Michail S. The use of Lactobacillus GG in irritable bowel syndrome in children: a double-blind randomized control trial. *J Pediatr*. 2005 Aug;147(2):197-201.

Beaugerie L and Petit JC. Microbial-gut interactions in health and disease. Antibiotic-associated diarrhoea. *Best Pract Res Clin Gastroenterol*. 2004 Apr;18(2):337-52. Review.

Chadwick VS, et al. Activation of the mucosal immune system in irritable bowel syndrome. *Gastroenterology*. 2002 Jun;122(7):1778-83.

De Vrese M, et al. Effect of Lactobacillus gasseri PA 16/8, Bifidobacterium longum SP 07/3, B. bifidum MF 20/5 on common cold episodes: a double blind, randomized, controlled trial. *Clinical Nutrition*. 2005 Aug; 24(4): 481-491.

Dinan TG, et al. Hypothalamic-pituitary-gut axis dysregulation in irritable bowel syndrome: plasma cytokines as a potential biomarker? *Gastroenterology*. 2006 Feb;130(2):304-11.

Floch, MH and Montrose, DC. Use of probiotics in humans: an analysis of the literature. *Gastroenterol Clin N A* 2005;34:547-570.

Gill et al. Enhancement of immunity in the elderly by dietary supplementation with the probiotic Bifidobacterium lactis HN019. *American Journal of Clinical Nutrition*. 2001 Dec; 74(6): 833-839.

Guyonnet D, et al. Effect of a fermented milk containing Bifidobacterium animalis DN-173 010 on the health-related quality of life and symptoms in irritable bowel syndrome in adults in primary care: a multicentre, randomized, double-blind, controlled trial. *Aliment Pharmacol Ther*. 2007 Aug 1;26(3):475-86.

Hamilton-Miller, JMT and Shah, S. Deficiencies in microbiological quality and labelling of probiotic supplements. *International Journal of Food Microbiology*. Volume 72, Issues 1-2, 30 January 2002, Pages 175-176.

Hamilton-Miller JM. The role of probiotics in the treatment and prevention of Helicobacter pylori infection. *Int J Antimicrob Agents*. 2003;22:360-366.

Hickson M, et al. Use of probiotic Lactobacillus preparation to prevent diarrhoea associated with antibiotics: randomized double blind placebo controlled trial. *BMJ*. 2007 Jul 14;335(7610):80.

Ishikawa H, et al. Randomized controlled trial of the effect of bifidobacteria-fermented milk on ulcerative colitis. *J. Am. Coll. Nutr.*, 2003; 22(1): 56-63.

Isolauri E, et al. Probiotics: a role in the treatment of intestinal infection and inflammation? *Gut*. 2002 May;50 Suppl 3:III54-9. Review.

Johnston BC, et al. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. *Danish Cochrane Database Syst Rev*. 2007 Apr 18;(2):CD004827.

Kajander K, et al. A probiotic mixture alleviates symptoms in irritable bowel syndrome patients: a controlled 6-month intervention. *Aliment Pharmacol Ther*. 2005 Sep 1;22(5):387-94.

Kassinen A, et al. The fecal microbiota of irritable bowel syndrome patients differs significantly from that of healthy subjects. *Gastroenterology*. 2007 Jul;133(1):24-33. Epub 2007 Apr 14.

Kato K, et al. Randomized placebo-controlled trial assessing the effect of bifidobacteria-fermented milk on active ulcerative colitis. *Aliment. Pharmacol. Ther*. 2004; 20(10): 1133-1141.

Kim HJ, et al. A randomized controlled trial of a probiotic combination VSL# 3 and placebo in irritable bowel syndrome with bloating. *Neurogastroenterol Motil*. 2005 Oct;17(5):687-96.

Kim HJ, 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 Apr 1;17(7):895-904.

Koebnick C, et al. Probiotic beverage containing Lactobacillus casei Shirota improves gastrointestinal symptoms in patients with chronic constipation. *Can. J. Gastroenterol.*, 2003; 17(11): 655-659.

Lagrotteria D, et al. Prospective, randomized inpatient study of oral metronidazole versus oral metronidazole and rifampin for treatment of primary episode of Clostridium difficile-associated diarrhea. *French Clin Infect Dis*. 2006 Sep 1;43(5):547-52. 25.

Liebrechts T, et al. Immune activation in patients with irritable bowel syndrome. *Gastroenterology*. 2007 Mar;132(3):913-20. Epub 2007 Jan 26.

Lesniewska V, et al. Relationship between dietary-induced changes in intestinal commensal microflora and duodenal myoelectric activity monitored by radiotelemetry in the rat in vivo. *Exp Physiol*. 2006 Jan;91(1):229-37.

Majamas, H and Isolauri, E. Probiotics: a novel approach in the management of food allergy. *J Allergy Clin Immunol* 1997;99:179-185.

Marteau P, et al. Bifidobacterium animalis strain DN-173 010 shortens the colonic transit time in healthy women: a double-blind, randomized, controlled study. *Aliment Pharmacol Ther*. 2002 Mar;16(3):587-93.

Matsumoto K, et al. The effects of a probiotic milk product containing Lactobacillus casei strain Shirota on the defecation frequency and the intestinal microflora of sub-optimal health state volunteers. *Bioscience Microflora*, 2006; 25(2): 39-48.

Meance S, et al. A fermented milk with Bifidobacterium probiotic strain DN-173 010 shortened oro-fecal gut transit time in elderly. *Microb Ecol Health Dis* 2001; 13(4):217-222.

Meance S, et al. Recent advances in the use of functional foods: Effects of the commercial fermented milk with Bifidobacterium animalis strain DN-173 010 and yoghurt strains on gut transit time in the elderly. *Microb Ecol Health Dis*. 2003;15(1):15-22.

McFarland, LV. Meta-analysis of probiotics in the prevention of antibiotic associated diarrhea and the treatment of Clostridium difficile disease. *Am J Gastroenterol* 2006;101:812-822.

Musher DM, et al. Nitazoxanide for the treatment of Clostridium difficile colitis. *Clin Infect Dis*. 2006 Aug 15;43(4):421-7.

Niedzielin K, et al. A controlled, double-blind, randomized study on the efficacy of Lactobacillus plantarum 299V in patients with irritable bowel syndrome. *Eur J Gastroenterol Hepatol*. 2001 Oct;13(10):1143-7.

Niv E, et al. The efficacy of Lactobacillus reuteri ATCC 55730 in the treatment of patients with irritable bowel syndrome—a double blind, placebo-controlled, randomized study. *Clin Nutr*. 2005 Dec;24(6):925-31.

Nobaek S, et al. Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome. *Am J Gastroenterol*. 2000 May;95(5):1231-8.

O'Hara AM and Shanahan F. Gut microbiota: mining for therapeutic potential. *Clin Gastroenterol Hepatol*. 2007 Mar;5(3):274-84. Review.

O'Hara AM and Shanahan F. The gut flora as a forgotten organ. *EMBO Rep*. 2006 Jul;7(7):688-93. Review.

Olivares M, et al. Oral intake of Lactobacillus fermentum CECT5716 enhances the effects of influenza vaccination. *Nutrition*. 2007 Mar;23(3):254-60.

O'Mahony L, et al. Lactobacillus and bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. *Gastroenterology*. 2005 Mar;128(3):541-51.

O'Sullivan MA and O'Morain CA. Bacterial supplementation in the irritable bowel syndrome. A randomized double-blind placebo-controlled crossover study. *Dig Liver Dis*. 2000 May;32(4):294-301.

Penders J, et al. The role of the intestinal microbiota in the development of atopic disorders. *Allergy*. 2007 Nov;62(11):1223-36. Epub 2007 Aug 17.

Sanders, ME. Probiotics: Their Potential to Impact Human Health Issue Paper. <http://www.cast-science.org/>

Sazawal S, et al. Efficacy of probiotics in prevention of acute diarrhoea: a meta-analysis of masked, randomized, placebo-controlled trials. *Lancet Infect Dis*. 2006 Jun;6(6):374-82.

Seksik P, et al. Review article: the role of bacteria in onset and perpetuation of inflammatory bowel disease. *Aliment Pharmacol Ther*. 2006 Oct;24 Suppl 3:11-8. Review.

Sen S, et al. Effect of Lactobacillus plantarum 299v on colonic fermentation and symptoms of irritable bowel syndrome. *Dig Dis Sci*. 2002 Nov;47(11):2615-20.

Tubelius P, et al. Increasing work-place healthiness with the probiotic Lactobacillus reuteri: a randomized, double-blind placebo-controlled study. *Environmental Health*. 2005 Nov 7; 4: 25.

Turnbaugh PJ, et al. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature*. 2006 Dec 21;444(7122):1027-31.

van Niel et al. Lactobacillus therapy for acute infectious diarrhea in children: a meta-analysis. *Pediatrics*. 2002 Apr; 109(4): 678-684.

Whorwell PJ, et al. Efficacy of an encapsulated probiotic Bifidobacterium infantis 35624 in women with irritable bowel syndrome. *Am J Gastroenterol*. 2006 Jul;101(7):1581-90.

Zoetendal, EG, et al. The Host Genotype Affects the Bacterial Community in the Human Gastrointestinal Tract. *Journal Microbial Ecology in Health and Disease*, Vol13, Issue 3, August 2001 , pages 129 – 134.

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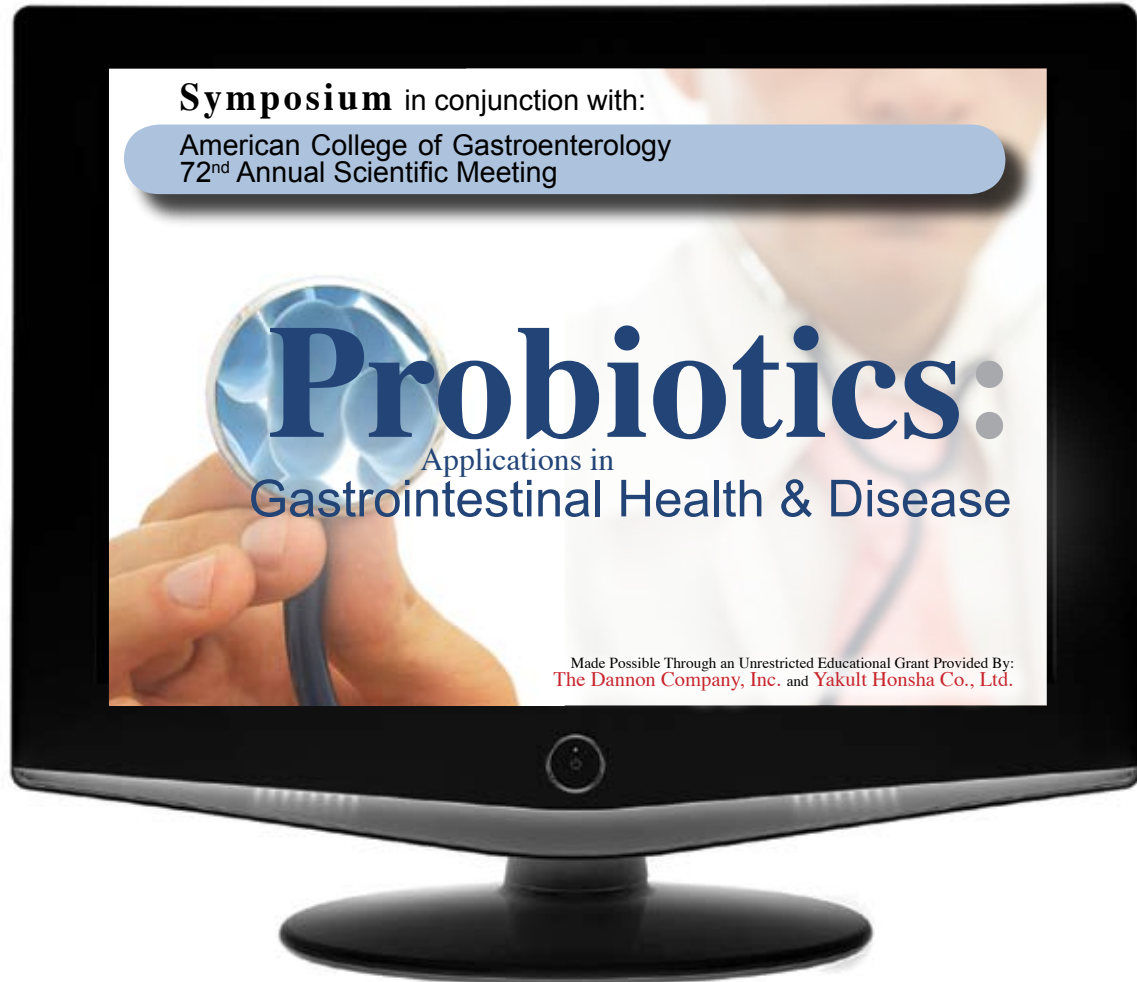
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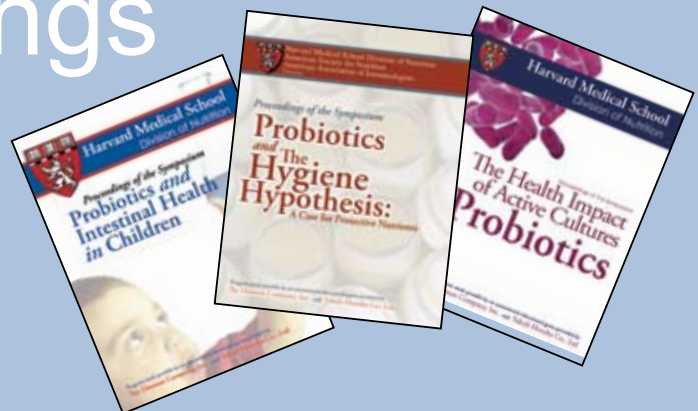
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