



THE SUPPLEMENT

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PROBIOTICS AND CYSTIC FIBROSIS

Foods containing beneficial bacteria, now referred to as probiotics, date back to ancient times. (1) People in many cultures attributed their long lives to frequent consumption of fermented dairy products such as yogurt and kefir. Currently, worldwide attention is directed towards the various roles probiotics play in overall health promotion, and in disease prevention and treatment. Limited evidence is available describing probiotics and CF. This newsletter summarizes the topic of probiotics and their potential roles in the care of persons who have CF.

FEATURED PAPERS:

Probiotics and prebiotics in dietetics practice.

Douglas LC, Sanders ME. J Am Diet Assoc.

108:510-521, 2008. This is a comprehensive overview of both prebiotics and probiotics, including definitions; products with indications for their use; regulatory recommendations; professional practice considerations; questions and answers; and sources of additional information.

Effect of *Lactobacillus* GG supplementation on pulmonary exacerbations in patients with cystic fibrosis: A pilot study. Bruzzese E, Raia V, Spagnuolo MI, Volpicelli M, DeMarco G, Maiuri L, Guarino A. Clin Nutr. 26:322-28, 2007. Objective:

To determine the effects of *Lactobacillus* GG (LGG) on pulmonary exacerbations in CF. **Study design:** A prospective, randomized, placebo-controlled, cross-over study. **Subjects:** 38 pancreatic insufficient CF patients; 17 homozygous for Delta F508; 16 male; mean age 13.25 yrs (range 5-18). **Methods:** 19 subjects received *Lactobacillus rhamnosus* GG (LGG) (6×10^9 CFU/day) in an oral rehydration fluid (ORF) for 6 months, then after washout of 4 weeks, shifted to plain ORF; 19 received plain ORF for 6 months, then washout, then LGG in ORF. **Results:** While receiving LGG, subjects showed reduction in pulmonary exacerbations and hospital admissions, increased FEV₁, and increased weight. **Conclusions:** LGG provided positive outcomes in patients with CF. Results may suggest a relationship between intestinal and pulmonary inflammations.

Intestinal inflammation is a frequent feature of cystic fibrosis and is reduced by probiotic administration. Bruzzese E, Raia V, Gaudiello G, Polito G, Buccigrossi V, Formicola V, Guarino A. Aliment Pharmacol Ther. 20:813-19, 2004. Objective: To assess the incidence of intestinal inflammation in children with CF and to determine if probiotics decrease it.

Study design: Two-phase, case-controlled, prospective, open study. **Subjects:** 30 CF patients, 13 male; mean age 10.7±5.5 yrs (range 1-16). 15 IBD, 9 male; mean age 10.6±3.7. 30 control, 12 male; mean age 7.3±2.8. **Methods:** Fecal calprotectin (indicator of intestinal inflammation) measured in all children; 10 children with CF received LGG (5×10^9 CFU/day) for 4 weeks with fecal calprotectin remeasured. Rectal nitric oxide production (indicator of distal intestine inflammation) was measured in 20 children with CF, 5 received LGG for 4 weeks. **Results:** 27 of 30 CF subjects had significantly higher fecal calprotectin than controls; 8 of 10 CF children had reduced fecal calprotectin after 4 weeks on LGG. Compared to controls, 18 of 20 CF subjects had elevated rectal nitric oxide production; 4 of 5 children treated with LGG had reduced nitric oxide production. **Conclusions:** Intestinal inflammation was present in CF and was reduced by LGG, perhaps by modifying the intestinal microflora.

SPECIAL POINTS OF INTEREST:

- Consumer, clinical, and scientific interest in prebiotics and probiotics has been gaining momentum as a method of enhancing health, and preventing or treating diseases.
- Evidence-based recommendations for the general public are evolving.
- Research related to probiotics and cystic fibrosis is limited but promising.

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REVIEW

People have trillions of bacteria both in and on their bodies. The majority of the bacteria live in the GI track, with the greatest number in the colon. Beneficial bacteria often are referred to as commensal bacteria. Some of their identified activities are: degrade toxins, synthesize nutrients, form barriers against infective agents, repair GI mucosal membrane, and contribute to the body's immune system. (2) In the gut many factors, including antibiotics, reduce the number of beneficial bacteria. Probiotics may replenish the type and amount of beneficial microflora.

Consumer, clinical, and scientific interest in prebiotics and probiotics has been gaining momentum as a method of enhancing health, and preventing or treating diseases. For example, a Newsweek (December 10, 2007) article addressed the role of probiotics and health. For a comprehensive review of the topic the reader is referred to: The February, 2008 supplement to the journal Clinical Infectious Diseases which was devoted to the "Scientific and Regulatory Challenges of Development of Probiotics as Foods and Drugs" and the September, 2005 issue of Gastroenterology Clinics of North America, which targeted the basic science and clinical applications of commensal bacteria in health and disease. Overviews of probiotics can be found at:

<http://nccam.nih.gov/health/probiotics/> and www.usprobiotics.org.

In 2002, a joint United Nations and World Health Organization Working Group provided a working definition for probiotics: "Live microorganisms which, when administered in adequate amounts, confer a health benefit on the host." (3) Probiotics are identified by their genus, species, and strain. Two of the most common genus are: *Lactobacillus* and *Bifidobacterium*, with examples of species as *Lactobacillus acidophilus* and *Bifidobacterium bifidus*. One extensively studied specific genus, strain and species is *Lactobacillus rhamnosus* GG, often abbreviated as LGG. Research which identifies specific health benefits of one genus, strain, and species of bacterium cannot be generalized to any other microorganism, nor to all probiotics as a class of therapeutic agents. *Saccharomyces boulardii*, a non-pathogenic yeast, often is included in reviews of probiotics.

Related to probiotics, but different, are prebiotics. A prebiotic is defined as "a selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microflora that confers benefits upon host wellbeing and health." (4) Prebiotics enhance the growth of naturally occurring gut bacteria or of probiotics consumed in

food or as a dietary supplement. Examples of prebiotics include dietary fiber, fructooligosaccharides, fructan and inulin. Some food products contain naturally occurring prebiotics, and others are added by the manufacturer. (Douglas, 2008)

Probiotics are available both in foods and as dietary supplements. In the USA, they are found in a limited number of foods including some yogurt, kefir, and baby formulas. The beneficial effect of the food or supplement is dependent on the overall number of CFUs (colony-forming unit) that remain in the product following manufacturing, storage, and transit through the GI track. Similar to pancreatic enzymes, microencapsulation may protect probiotic viability within the GI track until it reaches its target location of action. (5)

Numerous claims have been made regarding the beneficial effects of probiotics, but limited supportive research is available. Goldin, et al. found strong evidence for probiotics in the treatment of acute and antibiotic associated gastroenteritis; substantial evidence for atopic dermatitis and promising evidence in several other medical challenges.(6) Floch, et al. graded the evidence and found: A-level evidence in adults for the use of probiotics in the treatment of diarrhea, antibiotic-associated diarrhea, and pouchitis; B-level evidence for immune response; and C-level for other diseases including Crohn's disease, vaginosis, and *H pylori*. (7) Szajewske, et al. performed a meta-analysis for the pediatric age range and found evidence for use of probiotics in the treatment of diarrhea and antibiotic-associated diarrhea, and prevention of some GI and respiratory infections, necrotizing enterocolitis, and food allergies.(8) An evidence-based table of indications for use and product source of specific probiotic strains was provided by Douglas (2008). The National Center for Complementary and Alternative Medicine of the NIH is supporting research and providing guidance for probiotic use. Additionally, in 2007, the NIH added the Human Microbiome Project to its roadmap, with the goal of evaluating "the relationships among the entire microbial flora that exist within the

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REVIEW (CONT.)

body and the relationship of the flora to health, disease, and response to therapy.” (9)

There is a paucity of information describing the use of probiotics in the care of persons who have CF. Claims include: reduction of antibiotic-associated diarrhea, prevention of *Clostridium difficile*, reduction of intesti-

**RESULTS OF A PILOT STUDY FOUND THAT
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INCREASED WEIGHT.”
BRUZZESE, 2007.**

nal inflammation, and reduction of respiratory infection. In 1998 Sidhu described the increased risk for persons who have CF developing kidney stones as a result of decreased *oxalobacter formigenes* (OF) in the GI track. (10) OF, the main bacterial species involved in oxalate degradation, is destroyed by antibiotics. In non-CF subjects urinary oxalate excretion was reduced by providing OF. (11) Bruzzese et al. (2004, 2007) published two papers specific to CF; both are featured in this newsletter. The 2004 paper investigated the use of probiotics in the reduction of intestinal inflammation and accompanying pain in children who have CF. The genesis of chronic inflammation was not clear and a number of causes, including modification of intestinal microflora, have been proposed. The results of the study, using LGG (5x10⁹cfu/day), for four weeks, supported the intestinal microflora hypothesis. This pilot study had promising results that need further investigation. In the second study, Bruzzese (2007) investigated the effect of LGG on pulmonary exacerbation. Following use of LGG (6x10⁹ cfu/day) for six months, children with CF demonstrated fewer pulmonary exacerbations, improved FEV₁, and increased weight.

CLINICAL APPLICATIONS

Probiotic research is in its infancy and nearly nonexistent in CF. Probiotics are generally safe, and although the evidence is limited, may not be indicated for premature infants or for persons who are immunocompromised, severely ill, or have a central line.(1) When considering probiotics for the person who has CF, the RD assesses the individual patient’s age, gastrointestinal status, antibiotic use, and usual diet. When selecting a probiotic, the product must meet minimal criteria of having: scientific evidence of efficacy for specific strain, record of overall safety, documented availability in sufficient dose and active form for desired effect, and be labeled with the probiotic content and dose through the end of shelf life. This may be a challenge due to current label regulations regarding probiotics. (12) Based on currently published peer-reviewed research papers, only one genus, species, and strain (*Lactobacillus rhamnosus* GG) appears to have been studied in CF. For specific food products and dietary supplements containing this bacterium, refer to the Douglas, 2008 paper or www.mesanders.com, “Quick Reference Guide to Probiotics.” The RD is encouraged to attend the presentation on probiotics at the 2008 North American CF Conference.

ABOUT EURAND

We are a specialty pharmaceutical company that develops, manufactures and commercializes enhanced pharmaceutical and biopharmaceutical products using our proprietary drug formulation technologies. We are dedicated to the continued development and commercialization of breakthrough products that better satisfy patients’ needs. Our research efforts are focused on the development of treatment options with enhanced efficacy, superior safety and convenient dosing. We have a pipeline of products in development for ourselves and our co-development collaborators.

REFERENCES

1. Boyle RJ, Robins-Browne RM, Tang MLK. Probiotic use in clinical practice: what are the risks? *Am J Clin Nutr.* 83:1256-64, 2006.
2. Yan F, Polk DB. Commensal bacteria in the gut: Learning who our friends are. *Curr Opin Gastroenterol.* 20 (6):565-71, 2004.
3. Joint FAO/WHO Working Group on Drafting Guidelines for the Evaluation of Probiotics in Food. London, Ontario, Canada, April 30 and May 1, 2002. Available at : www.who.int/foodsafety/fs_management/en/probiotc_guidelines.pdf. Accessed March 21 2008.
4. Gibson GR, Probert HM, Loo JV, Rastall RA, Roberfroid MB. Dietary modulation of the human colonic microbiota: Updating the concept of prebiotics. *Nutr Res Rev.* 17:259-75, 2004.
5. Champagne CP, Fustier P. Microencapsulation for the improved delivery of bioactive compounds into foods. *Curr Opin Biotechnol.* 18(2):184-90, 2007.
6. Goldin BR, Gorbach SL. Clinical indications for probiotics: An overview. *CID.* 46(Suppl 2):S96-100, 2008.
7. Floch MH, Madsen, KK, Jenkins DJA, Guandalini S, Katz JA, Onderdonk A, Walker WA, Fedorak RN, Camilleri M. Recommendations for probiotic use. *J Clin Gastroenterol.* 40:275-8, 2006.
8. Szajewska H, Setty M, Mrukowicz, Guandalini S. Probiotics in gastrointestinal diseases in children: Hard and not-so-hard evidence of efficacy. *JPGN.* 42:454-75, 2006.
9. Hoffman FA, Heimbach JT, Sanders ME, Hibberd PL. Executive summary: Scientific and regulatory challenges of development of probiotics as foods and drugs. *CID.* 46:(Suppl 2):S53-57, 2008.
10. Sidhu H, Hoppe B, Hesse A, Tenbrock K, Bromme S, Rietschel E, Peck AB. Absence of *Oxalobacter formigenes* in cystic fibrosis patients: a risk factor for hyperoxaluria. *Lancet.* 352:1026-29. 1998.
11. Duncan SH, Richardson AJ, Kaul P, Holmes RP, Allison MJ, Stewart CS. *Oxalobacter formigenes* and its potential role in human health. *Appl Environ Microbiol.* 68:3841-47. 2002.
12. Saldanha LG. US Food and Drug Administration regulations governing label claims for food products, including probiotics. *CID.* 46(Suppl 2):119-21. 2008



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