

Probiotics in Childhood

Allergic Illness and Respiratory Infections

Michele Miraglia del Giudice, MD,* Salvatore Leonardi, MD,† Giorgio Ciprandi, MD,‡
 Francesca Galdo, MD,* Adelmo Gubitosi, MD,* Mario La Rosa, MD,† Carmelo Salpietro, MD,§
 Gianluigi Marseglia, MD,|| and Laura Perrone, MD*

Abstract: Over the last decade, there has been a growing interest in the use of probiotics for allergic diseases. In the last years, some studies showed a significant improvement for atopic eczema by the administration of probiotics during pregnancy and postnatally. About food allergy, probiotics administration seems to be effective in the management of food allergy symptoms but has no effect on the prevention of sensitization. In the international literature, there are few studies that evaluated the probiotic effect on allergic rhinitis, and authors reported that probiotics might have a beneficial effect in AR by reducing symptom severity and medication use. Another major potential benefit of probiotics has been suggested in patients with asthma. On this topic, several studies have been carried out using different probiotics and the results have not been univocal. Indeed, probiotics seems to be able to offer protection about common cold and respiratory infections in healthy and hospitalized children.

Key Words: probiotics, food allergy, atopic dermatitis, allergic rhinitis, asthma, respiratory infections

(*J Clin Gastroenterol* 2012;46:S69–S72)

The United Nation's Food and Agricultural Organization and the World Health Organization define *Probiotics* as "live microorganisms which when administered in adequate amounts confer a health benefit on the host."¹ The beneficial effects of probiotics on gastrointestinal diseases, inflammatory diseases in particular, have long been known.

Recently, a great deal of literature has been published demonstrating the health effects of probiotics in the treatment of inflammatory diseases affecting other organs too.

PROBIOTICS AND ALLERGIC DISEASES

Over the last decade, there has been a growing interest in the use of probiotics for allergic diseases.^{2,3} The reason for this lies in the discovery of the major immune-modulating role played by gut microbiota in the gastrointestinal tract, lactobacilli and bifidobacteria, in particular. Some studies have shown that allergic children in Estonia and Sweden are less often colonized with lactobacilli ($P < 0.01$),

as compared with the nonallergic children in the 2 countries.⁴ Current evidences seem to point to a different composition of gut microbiota between children with and without allergic diseases.⁵

Application of nonpathogenic probiotic bacteria during early infancy might protect from allergic disorders.^{6–9}

PROBIOTICS AND ATOPIC ECZEMA

About atopic eczema, Kalliomaki et al^{10–13} administered *Lactobacillus rhamnosus* GG (LGG) prenatally to mothers who had at least 1 first-degree relative (or partner) with atopic eczema, allergic rhinitis (AR), or asthma, and postnatally for 6 months to their infants. During the second year of follow-up the incidence of atopic eczema in the probiotic group was half that of the controls. This beneficial effect did not persist until the fifth year of follow-up. In another study, Wickens et al¹⁴ showed that prenatal supplementation with LGG reduced the cumulative prevalence of eczema by about 50% as compared with placebo. Instead, *Bifidobacterium lactis* showed no effect on prevention of eczema or of atopy.

As far as treatment is concerned, a recent study by Gore et al¹⁵ assessed the effect of dietary supplementation of *Lactobacillus paracasei* and *B. lactis* in 208 infants aged 3 to 6 months with eczema. Three months after the beginning of the study, eczema severity decreased significantly over time both in the probiotics and the placebo group.

To confirm the efficacy of different species of probiotics, Wu et al¹⁶ compared the effects of *Lactobacillus salivarius* plus fructooligosaccharide (synbiotic) with fructooligosaccharide alone (prebiotic) in 60 children (2 to 14 y old) with moderate to severe atopic dermatitis. At 8 weeks, the scoring atopic dermatitis, a clinical tool for assessing the severity of atopic dermatitis, were significantly lower in the treatment group than those of the controls treated with only placebo. Also, eosinophil cationic protein levels were significantly reduced in the treatment group at 8 weeks as compared with 4 weeks.

In 2012, a meta-analysis¹⁷ collecting studies published between 2001 and 2009 assessed the impact of probiotics intake on the development of atopic dermatitis and showed a significant risk reduction for atopic eczema in children aged 2 to 7 years by the administration of probiotics during pregnancy. However, this effect was only significant for lactobacilli, but not for a mixture of various probiotics bacterial strains.

PROBIOTICS AND FOOD ALLERGY

Regarding the use of probiotics in food allergy, in a very recent study Zuercher et al¹⁸ investigated the intrinsic antiallergic potential of the *Lactococcus lactis* NCC 2287

From the *Department of Pediatrics, "F.Fede," Second University of Naples, Naples; †Department of Pediatrics, University of Catania, Catania; ‡Department of Internal Medicine, AOU San Martino, Genoa; §Department of Pediatrics, Genetics and Immunology Unit, University of Messina, Messina; and ||Department of Pediatrics, Foundation IRCCS Policlinico San Matteo, University of Pavia, Pavia, Lombardy, Italy.

The authors declare that they have nothing to disclose.

Reprints: Michele Miraglia del Giudice, MD, Department of Pediatrics "F.Fede," Second University of Naples, Via De Crecchio 4-80138-Naples, Italy (e-mail: michele.miraglia@unina2.it).

Copyright © 2012 by Lippincott Williams & Wilkins

strain in mice that were sensitized at weekly intervals with ovalbumin plus cholera toxin orally for 7 weeks. Results showed that oral administration of *L. lactis* NCC 2287 is effective in the management of food allergy symptoms but has no effect on the prevention of sensitization. In the mice that had been given *L. lactis*, there was a significant decrease in relative expression levels of Th2 cytokines, interleukin (IL)-13, and associated chemokines CCL11 (eotaxin-1) and CCL17 (TARC) in the ileum. No effect was observed in the jejunum. On the basis of these results, these authors consider *L. lactis* NCC 2287 effective for the management of allergic symptoms. This underlines that certain probiotic strains may be “specialized” in modulating different phases of the allergic response.¹⁹ Of course, these new results will have to be confirmed in a human model.

Another study on a murine model by Schiavi et al²⁰ evaluated the effect of VSL#3 (a probiotic mix) on the specific immune responses and anaphylactic reactions induced by the major food allergen shrimp tropomyosin (ST). The cytokine production by spleen cell from ST-sensitized mice upon allergen restimulation in the presence of VSL#3 was analyzed. Next, the effects of oral administration of VSL#3 on allergen-induced anaphylaxis and Th2 response in the murine model of food allergy to ST was investigated by evaluating symptom score and histamine content in the feces after allergen challenge, antibody response in serum and feces, and cytokine and transcription factor expression in the jejunum. The *in vitro* studies on mouse spleen cells indicate that the VSL#3 preparation was able to shift the Th2 response to a Th1/T regulatory-type profile. Oral therapeutic administration of VSL#3 to ST-sensitized mice significantly reduces symptom score and histamine release in the feces after allergen challenge, as well as specific immunoglobulin (Ig)E response. In the jejunum, IL-4, IL-5, and IL-13 tissue content was significantly reduced, whereas FOXP3 and IL-27 mRNA expression, IL-10, transforming growth factor beta (TGF- β), and interferon (IFN)- γ tissue content were upregulated. These results suggest that the oral therapeutic treatment with the probiotic mixture VSL#3 may have beneficial effects in a murine model of food allergy, but further studies are needed in humans.

PROBIOTICS AND AR

In the international literature, there are few studies that evaluated the effect of probiotics on AR. The first study that suggests a role of probiotics in children with AR was published in 2007. The study aimed to investigating whether the long-term daily (12 mo) consumption of fermented milk containing specific *Lactobacillus casei* may improve allergic symptoms in children aged 2 to 5 years with allergic asthma and/or AR.²¹ The results showed that children receiving fermented milk containing *L. casei* had 33% lower occurrence of AR episodes than the control group. More recently, Koyama et al²² evaluated the effect of a mixture of *L. rhamnosus* GR-1 plus *Bifidobacterium adolescentis* in 36 subjects with AR over 2 pollen seasons in a double-blind, placebo-controlled (DBPC) trial. The probiotics did not have any significant effect on quality of life scores, use of antihistamines, or eosinophil cationic protein concentration in nasal lavage. However, at the end of the grass pollen season, serum IL-10 and IL-12 levels were increased in the probiotic group as compared with the controls. During the ragweed season, the serum TGF- β

levels were also significantly higher in the probiotic group than in the controls.

A meta-analysis in 2008²³ evaluated all the results of randomized controlled trials (RCTs) studying the effect of probiotics on AR. Nine of the 12 RCTs that evaluated clinical outcomes in AR showed an improvement with probiotics. All the RCTs studying perennial AR showed lower symptom scores and medication use of probiotics as compared with placebo. Nine RCTs that reported various immunologic measurements of allergy found no significant probiotic effects. The authors reported that probiotics might have a beneficial effect in AR by reducing symptom severity and medication use, even if many more good-quality studies are needed to resolve this issue.

According to the concept of united airway diseases,²⁴ AR and asthma often recognize common mechanisms. For this reason the study by Chen et al²⁵ assessed the effects of *Lactobacillus gasseri* in school children suffering from AR and asthma. This randomized, DBPC study was conducted only in school children (aged 6 to 12 y) receiving either *L. gasseri* or a placebo daily for 2 months. The results showed the clinical symptom scores for AR and asthma decreased in the probiotic-treated patients as compared with the control. Further, there was a significant reduction in the TNF- α , IFN- γ , IL-12, and IL-13 production by the peripheral blood mononuclear cells after the probiotic treatment.

PROBIOTICS AND ASTHMA

Another major potential benefit of probiotics has been suggested in patients with asthma.²⁶ On this topic several studies have been carried out using different probiotics, and the results have not been univocal.

In a murine model of asthma, it has been shown that the oral administration of LGG or *B. lactis*, starting from birth for consecutive 8 weeks, during systemic sensitization (days 29 to 40) and airway challenge (days 54 to 56) with ovalbumin, leads to a suppression of all the characteristics of the asthma phenotype, including specific IgE production, airway hyperresponsiveness, and pulmonary eosinophilia. Furthermore, this effect is associated with the suppression of allergen-induced Th2 responses together with the induction of TGF- β in the intestine.⁶ Several studies analyzed the role of probiotics in the treatment and prevention of asthma in humans. Recently, Chen et al²⁷ conducted a randomized, DBPC study in school children (aged 6 to 12) with mild to moderate persistent asthma and AR. The aim of this study was to highlight if the daily administration of *L. gasseri* A5, for 8 weeks, could improve the of asthma and AR clinical symptoms and if it had immune-modulating effects. The results of this study showed significant improvements in forced expiratory volume in one second (FEV₁), forced expiratory vital capacity, FEV₁/forced expiratory vital capacity (%), and MEF25-75 after the treatment period in the probiotic group. Moreover, the response to bronchodilator dilatation test decreased significantly in the probiotic-treated group as compared with the control group ($P < 0.001$); this suggested that probiotic treatment may decrease airway hyperresponsiveness in asthmatic children and not only in mice. There was a statistically significant improvement in daytime asthma and AR symptoms score and in childhood asthma control test score only in the probiotic group. About the immune-modulating effect, after the treatment with *L. gasseri*, there was a reduction in the production of Th1-related cytokines

as IFN- γ and IL-12, as compared with the control group. The decrease in the values of IL-10 before and after the treatment was not statistically significant in both the groups.

More recently, we evaluated the effect of oral *Lactobacillus reuteri* administration (1×10^8 cfu) on airways allergic inflammation in 50 children (6 to 14 y old), affected by mild persistent asthma (Global Initiative for Asthma step 2) and allergic to house dust mite in a randomized DBPC study. At the end of the study (after 60d) the exhaled breath condensate (FeNO) values showed a significant reduction ($P = 0.045$) only in *L. reuteri* group. Cytokine examination showed an increase in IL-10 levels ($P < 0.05$) and a significant reduction in IL-2 levels ($P < 0.05$) only in the probiotic group. No significant differences in FEV₁ values and childhood asthma control test score were found in both groups. Our data show that *L. reuteri* (108 cfu) was effective in reducing bronchial inflammation in asthmatic children.²⁸

PROBIOTICS AND RESPIRATORY INFECTIONS

Probiotics seems to be able to offer protection about bacterial and viral infections in the gastrointestinal and respiratory systems.²⁹ Indeed medication by probiotics has been associated with minor incidence of pneumonia,³⁰ with a reduction in the number of respiratory infections both in healthy and hospitalized children.^{31,32} Probiotics also reduce the duration of common cold.³³ Several data suggest that respiratory infections contribute to the worsening of asthma and the development of wheezing.³⁴ Indeed, it has been suggested that the potential beneficial effect of probiotics in asthma could be also determined by the capacity of reducing the viral infections in the first years of life.³⁵ The protective effect of probiotics on respiratory infections may be related to IgA increase³⁶ and through the upregulation of the natural killer cells and macrophages in the airway mucosa.^{37,38} In a randomized, DBPC study, Rautava and colleagues administered infant formula supplemented with the probiotics LGG and *B. lactis* Bb-12 or placebo in infants requiring formula before the age of 2 months. The formula was administered daily until the age of 12 months. The results showed that 28% infants receiving probiotics and 55% infants receiving placebo encountered recurrent respiratory infections in the first year of age. These data suggest that probiotics may offer a safe means of reducing the risk of early acute otitis media and antibiotic use, and the risk of recurrent respiratory infections during the first years of life.³⁹ Analogous results emerged from a study conducted on a population of 326 children aged 3 to 5, showing a decrease by >65% in the incidence of the use of antibiotics and a reduction by <25% of the days of absence from the school among children treated with probiotics.⁴⁰ Further clinical trials are required to corroborate these results.

CONCLUSIONS

In conclusion these data show that the potential field of application of probiotics is wide and not thoroughly clarified. Certainly the international literature has confirmed a real beneficial and immune-modulating effect of probiotics in several allergic and respiratory illnesses. The efficacy of probiotic interventions seems to be strongly dependent to the specific strain used and the appropriate

timing. Further, scientific confirmations are required to include them in the therapeutic plans.

REFERENCES

1. FAO/WHO Expert Consultation. Health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria. 2001. Available at: <http://www.fao.org>. Accessed 2, April 2012.
2. Miraglia del Giudice M, Brunese FP. Probiotics, prebiotics, and allergy in children: what's new in the last year? *J Clin Gastroenterol*. 2008;42(suppl 3Pt 2):S205–S208.
3. Miraglia del Giudice M, Rocco A, Capristo C. Probiotics in the atopic march: highlights and new insights. *Dig Liver Dis*. 2006;38(suppl 2):S288–S290.
4. Björkstén B, Naaber P, Sepp E, et al. The intestinal microflora in allergic Estonian and Swedish 2-year-old children. *Clin Exp Allergy*. 1999;29:342–346.
5. Ly NP, Diane AL, Gold Juan R, et al. Gut microbiota, probiotics, and vitamin D: interrelated exposures influencing allergy, asthma, and obesity? *J Allergy Clin Immunol*. 2011;127:1087–1094.
6. Feleszko W, Jaworska J, Rha RD, et al. Probiotic-induced suppression of allergic sensitization and airway inflammation is associated with an increase of T regulatory-dependent mechanisms in a murine model of asthma. *Clin Exp Allergy*. 2007;37:498–505.
7. Forsythe P. Probiotics and lung diseases. *Chest*. 2011;139:901–908.
8. Miraglia del Giudice M, De Luca MG. The role of probiotics in the clinical management of food allergy and atopic dermatitis. *J Clin Gastroenterol*. 2004;38(suppl 6):S84–S85.
9. Miraglia del Giudice M Jr, De Luca MG, Capristo C. Probiotics and atopic dermatitis. A new strategy in atopic dermatitis. *Dig Liver Dis*. 2002;34(suppl 2):S68–S71.
10. Kalliomaki M, Salminen S, Arvilommi H, et al. Probiotics in primary prevention of atopic disease: a randomised placebo controlled trial. *Lancet*. 2001;357:1076–1079.
11. Rautava S, Kalliomaki M, Isolauri E. Probiotics during pregnancy and breast-feeding might confer immunomodulatory protection against atopic disease in the infant. *J Allergy Clin Immunol*. 2002;109:119–121.
12. Kalliomaki M, Salminen S, Poussa T, et al. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. *Lancet*. 2003;361:1869–1871.
13. Kalliomaki M, Salminen S, Poussa T, et al. Probiotics during the first 7 years of life: a cumulative risk reduction of eczema in a randomized, placebo controlled trial. *J Allergy Clin Immunol*. 2007;119:1019–1021.
14. Wickens K, Black PN, Stanley TV, et al. A differential effect of 2 probiotics in the prevention of eczema and atopy: a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2008;122:788–794.
15. Gore C, Custovic A, Tannock GW, et al. Treatment and secondary prevention effects of the probiotics *Lactobacillus paracasei* or *Bifidobacterium lactis* on early infant eczema: randomized controlled trial with follow-up until age 3 years. *Clin Exp Allergy*. 2012;42:112–122.
16. Wu KG, Li TH, Peng HJ. *Lactobacillus salivarius* plus fructo-oligosaccharide is superior to fructo-oligosaccharide alone for treating children with moderate to severe atopic dermatitis: a double-blind, randomized, clinical trial of efficacy and safety. *Br J Dermatol*. 2012;166:129–136.
17. Doege K, Grajecki D, Zyriax BC, et al. Impact of maternal supplementation with probiotics during pregnancy on atopic eczema in childhood—a meta-analysis. *Br J Nutr*. 2012;107:1–6.
18. Zuercher AW, Weiss M, Holvoet S, et al. *Lactococcus lactis* NCC 2287 alleviates food allergic manifestations in sensitized mice by reducing IL-13 expression specifically in the ileum. *Clin Dev Immunol*. 2012;2012. article ID 485750: 1–10.

19. Miraglia del Giudice MM, Leonardi S, Maiello N, et al. Food allergy and probiotics in childhood. *J Clin Gastroenterol*. 2010;44(suppl 1):S22–S25.
20. Schiavi E, Barletta B, Butteroni C, et al. Oral therapeutic administration of a probiotic mixture suppresses established Th2 responses and systemic anaphylaxis in a murine model of food allergy. *Allergy*. 2011;66:499–508.
21. Giovannini M, Agostoni C, Riva E, et al. A randomized prospective double blind controlled trial on effects of long-term consumption of fermented milk containing *Lactobacillus casei* in pre-school children with allergic asthma and/or rhinitis. *Pediatr Res*. 2007;62:215–220.
22. Koyama T, Kirjavainen PV, Fisher C, et al. Development and pilot evaluation of a novel probiotic mixture for the management of seasonal allergic rhinitis. *Can J Microbiol*. 2010;56:730–738.
23. Vliagoftis H, Kouranos VD, Betsi GI, et al. Probiotics for the treatment of allergic rhinitis and asthma: systematic review of randomized controlled trials. *Ann Allergy Asthma Immunol*. 2008;101:570–579.
24. de Benedictis FM, Miraglia del Giudice M, Bonifazi F. Rhinitis, sinusitis and asthma: one linked airway disease. *Paediatr Respir Rev*. 2001;2:358–364.
25. Chen YS, Jan RL, Lin YL, et al. Randomized placebo-controlled trial of lactobacillus on asthmatic children with allergic rhinitis. *Pediatr Pulmonol*. 2010;45:1111–1120.
26. Cocurullo G, Campana G, Valenti N, et al. Probiotics and asthma, new insight. *The Child*. 2012;1:2–3.
27. Chen Y-S, Jan R-L, Lin Y-L, et al. Randomized placebo-controlled trial of lactobacillus on asthmatic children with allergic rhinitis. *Pediatr Pulmonol*. 2010;45:1111–1120.
28. Miraglia del Giudice M, Maiello N, Decimo F, et al. Airways allergic inflammation and *L. reuterii* treatment in asthmatic children. *J Biol Regul Homeost Agents*. 2012;26:35–40.
29. Goldin BR, Gorbach SL. Clinical indications for probiotics: an overview. *Clin Infect Dis*. 2008;46:S96–S100.
30. Morrow LE, Kollef MH, Casale TB. Probiotic prophylaxis of ventilator-associated pneumonia: a blinded, randomized, controlled trial. *Am J Respir Crit Care Med*. 2010;182:1058–1064.
31. Hatakka K, Savilahti E, Pönkä A, et al. Effect of long term consumption of probiotic milk on infections in children attending day care centres: double blind, randomised trial. *BMJ*. 2001;322:1–5.
32. Hojsak I, Abdović S, Szajewska H, et al. *Lactobacillus* GG in the prevention of nosocomial gastrointestinal and respiratory tract infections. *Pediatrics*. 2010;125:e1171–e1177.
33. de Vrese M, Winkler P, Rautenberg P, et al. Probiotic bacteria reduced duration and severity but not the incidence of common cold episodes in a double blind, randomized, controlled trial. *Vaccine*. 2006;24:6670–6674.
34. Holtzman MJ, Byers DE, Benoit LA, et al. Immune pathways for translating viral infection into chronic airway disease. *Adv Immunol*. 2009;102:245–276.
35. Yoo J, Tcheurekdjian H, Lynch SV, et al. Microbial manipulation of immune function for asthma prevention: inferences from clinical trials. *Proc Am Thorac Soc*. 2007;4:277–282.
36. Perdigon G, Alvarez S, Medina M, et al. Influence of the oral administration of lactic acid bacteria on IgA producing cells associated to bronchus. *Int J Immunopathol Pharmacol*. 1999;12:97–102.
37. Izumo T, Maekawa T, Ida M, et al. Effect of intranasal administration of *Lactobacillus pentosus* S-PT84 on influenza virus infection in mice. *Int Immunopharmacol*. 2010;10:1101–1106.
38. Harata G, He F, Hiruta N, et al. Intranasal administration of *Lactobacillus rhamnosus* GG protects mice from H1N1 influenza virus infection by regulating respiratory immune responses. *Lett Appl Microbiol*. 2010;50:597–602.
39. Rautava S, Salminen S, Isolauri E. Specific probiotics in reducing the risk of acute infections in infancy—a randomised, double-blind, placebo-controlled study. *Br J Nutr*. 2009;101:1722–1726.
40. Leyer GJ, Li S, Mubasher ME, et al. Probiotic effects on cold and influenza-like symptom incidence and duration in children. *Pediatrics*. 2009;124:e172–e179.