

Food Allergy and Probiotics in Childhood

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Abstract: Food allergy is a frequent problem in childhood and its prevalence is increasing. In most cases food allergy is an IgE-mediated hypersensitivity response that cause skin reactions as urticaria. Subacute or chronic disorders have generally a not IgE mediated mechanism. Milk is the most common food allergen in USA and UK followed by egg, peanut and walnuts. Sensitization to milk or egg in infancy is associated with an increased risk to develop house dust mite sensitization and asthma later in childhood. Commensal gut flora play a role in induction of oral tolerance and the importance of the intestinal microbiota in the development of food allergy is essential in early ages, when the mucosal barrier and immune system are still immature. Probiotics interact with the mucosal immune system by the same pathways as commensal bacteria. Recent study show that probiotic bacteria induced in vivo increased plasma levels IL-10 and total IgA in children with allergic predisposition. Many clinical studies reporting significant benefits by probiotics supplementation in food allergy prevention and management but not everyone agree on their effectiveness. These differences are probably related to differences in selected populations and in probiotic strains used.

Key Words: food allergy, probiotics, childhood

(*J Clin Gastroenterol* 2010;44:S22–S25)

Food allergy is a common problem in childhood, 4 of every 100 children have a food allergy.¹ CDC data show that in 2007, 3 million children under the age of 18 years (3.9%) had reported a food allergy and those children younger than 5 years had the highest rate.¹ Recent data show that hospital admissions with a diagnoses related to food allergies have increased among children.² The average number of discharges for food allergies increased from 2.615 (1996 to 2000) to 9.537 (2004 to 2006).² Food allergy in children is the most common cause of anaphylaxis and fatalities that occur more often in children suffering of asthma.³

FOOD ALLERGY CLASSIFICATION

The term food allergy is generally used to describe adverse immune responses to foods. On the basis of the immunologic mechanism involved, adverse reaction to food may be classified as toxic and nontoxic. Among the nontoxic there are nonimmune-mediated reactions (intolerance: enzymatic, pharmacologic, and undefined) and immune-mediated (allergy: non-IgE-mediated and IgE-mediated).⁴

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The authors confirm that there is no financial support.

The authors declare no conflict of interest.

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Respiratory reactions to food hypersensitivity are divided into IgE-mediated (allergic rhinitis, acute bronchospasm, generalized anaphylaxis, food-associated, exercise-induced anaphylaxis) and non-IgE-mediated (food-induced pulmonary hemosiderosis). Asthma may have a mechanism that is IgE-mediated and non-IgE-mediated.

Cutaneous reactions to food hypersensitivity are IgE-mediated (acute urticaria and angioedema, and chronic urticaria) and non-IgE-mediated (dermatitis herpetiformis). Atopic dermatitis may have a mixed mechanism that is IgE-mediated and non-IgE-mediated.

Gastrointestinal reactions to food hypersensitivity are IgE-mediated (immediate gastrointestinal hypersensitivity, oral allergy syndrome) and non-IgE-mediated (dietary protein enterocolitis, dietary protein proctitis, dietary protein enteropathy). Allergic eosinophilic esophagitis, gastritis, and gastroenteritis may have a mechanism that is IgE-mediated and non-IgE-mediated. Disorders with an acute onset of symptoms after ingestion are usually mediated by an IgE antibody. Subacute or chronic disorders are T-cell-mediated and a third group of chronic disorders attributed to food allergy are mixed IgE-mediated and cell-mediated.^{5,6}

FOOD ALLERGY: NATURAL HISTORY

Foods involved in food allergy depend on age, local diet, and culture.

In United States and Britain milk is the most common food allergen followed by egg, peanut, and walnuts.⁷ Sesame is an important allergen in Israel and Australia⁸ and allergy from the bird's nest is the most common in Singapore.⁸

Food allergies traditionally resolved by 3 years but recent data show that only 11% of children resolved egg allergy and 19% resolved milk by 4 years.^{9,10} Most patients with milk and egg allergy are likely to develop tolerance to milk and egg by late childhood.^{9,10} Peanut allergy is more persistent; only 20% of children by school age became tolerant.¹¹

Food allergy is the first step in the atopic march. The atopic march refers to the natural history of allergic reaction characterized by a typical sequence of clinical symptoms and conditions.¹¹ In general, the clinical features of food allergy and atopic eczema precede the development of asthma and allergic rhinitis.¹²

Sensitization to milk or egg in infancy is associated with an increased risk of developing house dust mite sensitization and asthma later in childhood.^{13,14}

PATHOGENESIS OF FOOD ALLERGY

Food allergy in most cases is an IgE-mediated hypersensitivity response. Dietary allergenic proteins are taken up by dendritic cells and are presented to naive CD4⁺ T cells in the mesenteric lymph node or Peyer's

patch. In nonallergic individuals these T cells differentiate into regulatory T cells, which produce IL-10 and/or T-helper (Th)3 cells, which in turn produce TGF- β . These cytokines stimulate local IgA production, further expansion of CD4⁺ CD25⁺ T regulatory cells, and suppression of CD4⁺ effector (Th1 and Th2) cell development leads to oral tolerance.¹⁵

In contrast, in allergic individuals the naive T cells differentiate into CD4⁺ Th2 effector cells and lead to elevated levels of Th2 cytokines, IL-4, IL-5, IL-9, and IL-13. Elevated levels of these cytokines stimulate IgE production, mast cell and eosinophil recruitment and activation, and onset of food allergy and anaphylaxis.¹⁵

Genetic and environmental factors influence this aberrant immune response. Some evidence suggests that genetic factors may play a role in food allergy. A twin study shown that the expression of peanut allergy has a substantial genetic basis.¹⁶ Atopic constitution polymorphisms in 9 genes were associated with the incidence of food allergy but the specific genetic loci that may modulate individual risk of food allergy must be further identified.¹⁷

Environmental influence includes maternal age, mode of delivery, maternal ingestion of potential allergens, and breast-feeding. Other environmental factors include exposure to endotoxin and bacterial DNA in house dust, and the timing and route of exposure to allergenic foods.¹⁸

The intrinsic properties of food allergens, the dosage, and the frequency of exposure may contribute to promoting an allergic immune response.⁵ Major food allergens are water-soluble glycoproteins, 10 to 70 kD in size, relatively stable to heat, acid, and proteases.⁵

Recent studies have shown that patients with food allergies have an increased intestinal permeability, which correlates with the severity of clinical symptoms.¹⁹ However, in childhood there is a physiological immaturity of the gastrointestinal mucosal barrier with a reduction in the secretory IgA system. Consequently, this immaturity may play a role in the increased prevalence of food allergies seen in the first years of life.⁵

FOOD ALLERGY, INTESTINAL MICROBIOTA, AND PROBIOTICS

The importance of the intestinal microbiota in the development of food allergy is essential in early age, when the mucosal barrier and immune system are still immature. Commensal gut flora play a role in the induction of oral tolerance; mice raised in a germ-free environment do not have a normal tolerance²⁰ and a mixture of an oral probiotic can reduce anaphylactic symptoms induced by oral challenge in sensitized mice.²¹

The mode of delivery and the type of care have a great impact on the acquisition of the intestinal bacteria. Intestinal microbiota after cesarean delivery are characterized by an absence of bifidobacteria species that are the predominant species in newborn that are vaginally delivered.²²

The complex mixture of oligosaccharides present in human breast milk induces the predominance of beneficial bacteria in the gut microflora of infants that are breast-fed, such as bifidobacteria and lactobacilli.²³ Allergic mothers had significantly lower amounts of bifidobacteria in their breast milk compared with nonallergic mothers and their infants had concomitant lower counts of bifidobacteria in their feces.²⁴ *Bifidobacterium adolescentis* is the most

common species in infants with allergic diseases.²⁵ A recent study showed that only the infants of allergic mothers were colonized with *B. adolescentis*.²⁴ The authors speculated that allergic mothers may transfer *B. adolescentis* to their infants and that *B. adolescentis* may predispose infants toward allergic diseases.²⁴

Probiotics interact with the mucosal immune system by the same pathways as commensal bacteria.²⁶ A recent study showed that probiotic bacteria induced in vivo increased plasma levels IL-10 and total IgA in children with an allergic predisposition.²⁷ A cohort of 237 allergy-prone infants received a combination of 4 probiotic strains or placebos prenatally and during 6 months from birth. The highest fecal IgA in the probiotics group was a marker of immune maturation, which was associated with reduced risk for atopic diseases during the first 2 years of life.²⁸ Probiotic colonization of the gut is temporary²⁹ but it may guide subsequent colonization and immunologic development.^{30–31}

Since 1997, probiotics have been used in management of food allergy. In the Majamaa study,³² the clinical and immunologic effects of cow's milk elimination without and with the addition of the *Lactobacillus GG* (LGG) in an extensively hydrolyzed whey formula in infants with atopic eczema and cow's milk allergy were evaluated. The second part of the study involved 10 breast-fed infants who had atopic eczema and cow's milk allergy; in this group LGG was given to nursing mothers. The results showed a significant improvement in the SCORAD score after intervention in children receiving LGG but not in the other group. In the breast-fed infants the SCORAD score improved statistically after 1 month of treatment. To test the effect of probiotics in the primary prevention of atopic disease, Kalliomaki et al³³ assigned 159 mothers to receive placebo or LGG daily for 4 weeks before expected delivery. After delivery, LGG or placebo were taken postnatally for 6 months. In children aged 2 years, the frequency of atopic eczema in the probiotic group was half that of the placebo group. The 7-year follow-up visit confirmed that the cumulative risk of developing eczema during the first 7 years of life was significantly lower in the LGG group than in the placebo group. However, atopic sensitization was similar between the groups, suggesting that the preventive effect on eczema was not IgE-mediated.³⁴

It has been suggested that human breast milk oligosaccharides could lead to the development of gastrointestinal bacterial flora. Recent studies have shown that early dietary intervention with the administration of a mixture of prebiotic oligosaccharides, galacto oligosaccharides/fructo oligosaccharides, was associated with a significantly higher number of fecal bifidobacteria,³⁵ reducing the incidence of allergic reactions³⁶ and the plasma level of total IgE, IgG1, IgG2, and IgG3.³⁷ The authors concluded that oral galacto oligosaccharides/fructo oligosaccharides supplementation is a safe method to restrain the atopic march.³⁷

Not all clinical studies agree with the efficacy of probiotics in allergic diseases. In the Abrahamsson study³⁸ the cumulative incidence of eczema was similar in babies receiving *Lactobacillus reuteri* before delivery and up to 12 months old and the control group. The *L. reuteri* group had lesser IgE-associated eczema during the second year and therefore possibly ran a reduced risk of developing allergic diseases later. No differences in the frequency of allergic diseases and sensitization were shown between the probiotic mixture (LGG, *Lactobacillus rhamnosus*, *Bifidobacterium*

breve, and propionibacteria) and placebo groups after 5 years of follow-up in Kuitunen study.³⁹ In this study, 1223 mothers with infants at high risk for allergy were randomized to receive the probiotic mixture or placebo during the last month of pregnancy and their infants to additionally receive prebiotic galactooligosaccharide from birth until the age of 6 months. However, less IgE-associated allergic disease occurred in cesarean-delivered children receiving a probiotics mixture. The study by Taylor et al⁴⁰ showed an opposite effect; in 178 newborns of allergic women, *Lactobacillus acidophilus* supplementation for the first 6 months of life failed to reduce the risk of atopic dermatitis and increased the risk of allergen sensitization.

Finally, probiotics and allergic disease and/or food hypersensitivity outcomes were assessed by 6 studies enrolling 2080 infants in a recent review of the Cochrane library.⁴¹

All studies reporting significant benefits used probiotic supplements containing *L. rhamnosus* and enrolled infants at a high risk of allergy. No other benefits were reported for any other allergic disease or food hypersensitivity outcome. The authors concluded that there is insufficient evidence to recommend the addition of probiotics to infant feeds for the prevention of allergic disease or food hypersensitivity.⁴¹ However, the results of this review should be treated with caution due to an excess loss in patient follow-up (17% to 61%).

CONCLUSIONS

The gastrointestinal tract represents a barrier against antigens derived from food and oral tolerance depending on an intact and immunologically active gastrointestinal barrier.^{5,42}

Differences between the studies about the benefits of probiotics in food allergic disorders are related probably to differences in the populations selected and probiotic strain.^{43,44}

The age of the host is very important; probiotics may aid the direction of the development of the immune system during infancy but not later.⁴³ The diet of the host may influence the probiotic effect, particularly the quality of protein in the diet seems to affect the induction of oral tolerance.⁴³

The importance of using viable probiotic strains was clearly shown.⁴⁵ Probiotics are a specific strain and there are differences in probiotic strain performance. Each probiotic strain is a unique organism in itself with specific properties that cannot be extrapolated from other, even closely related, strains.⁴³

Combining probiotic strains does not always enhance their clinical efficacy.⁴⁶ Competitive exclusion and interference in adhesion and aggregation between probiotic strains may reduce their activity.

Further studies are needed to better understand the mechanisms of food allergic disorders and the role of probiotics in food allergy.

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