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# Infant Food Allergy: Where Are We Now?

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For many years, the prevailing maxim for prevention of food allergy in at-risk infants was to reduce allergic sensitization by avoiding exposure to highly allergenic foods until the baby's immune and digestive systems were sufficiently developed to cope with the allergen. Current thinking is completely different: exposure to food in the early stages of development may be the way to induce tolerance. Exclusive breastfeeding until 4–6 months, followed by introduction of complementary foods individually, is recommended. Any restrictions on mother's diet, other than avoidance of her own allergens during pregnancy and breastfeeding, are contraindicated. If a baby at high risk for allergy (defined as having 1 first-degree relative with diagnosed allergy) cannot be exclusively breastfed to 4–6 months of age, the preferred method of feeding for the prevention of atopic disease is an extensively hydrolyzed formula. There

appears to be no value in delaying the introduction of any food beyond 6 months of age. Most food allergy is outgrown in childhood, but allergy to some foods tends to persist. Induction of tolerance to foods to which a child is allergic may be achieved by low-dose exposure in a process known as specific oral tolerance induction (SOTI). Early results indicate that some probiotic strains of bacteria, such as *Lactobacillus rhamnosus* GG or *Lactobacillus F19*, may reduce allergic sensitization. (*JPEN J Parenter Enteral Nutr.* 2012;36:49S-55S)

**Keywords:** food allergy prevention; pediatric food allergy management; probiotics in food allergy prevention; allergy nutrition; specific oral tolerance induction (SOTI)

One of the most significant changes in pediatric food allergy management in recent years has been in strategies to prevent food allergy in early infancy. Previously, the idea prevailed that if the most highly allergenic foods are withheld from the infant until the immune and digestive systems were more mature, allergic sensitization would be prevented or significantly reduced. Frequently, the advice regarding introduction of the most highly allergenic foods was “the later the better.” It was hoped that this would in turn prevent allergy not only to food but to inhalant and contact allergies in later life. However, new research seems to indicate the very opposite—that *exposure* to allergens in early life may actually tolerize the infant's immune system and prevent allergic sensitization to food.\*

## Early Allergy Predictors

Allergic diseases result from a strong relationship between genetic and environmental factors. Various definitions of

high-risk infants have been used; the prevailing definition, published as a joint statement of the European Society of Paediatric Allergology and Clinical Immunology (ESPACI) and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)<sup>1</sup> and the American Academy of Pediatrics,<sup>2</sup> defines high-risk infants as those with at least 1 first-degree relative (parent or sibling) with documented allergic disease, and most authorities rely on this definition as the basis of their assessment of the at-risk-for-allergy pediatric population.

Sensitization to food allergens occurs mainly in the first year of life, and cow's milk allergy is often the first food allergy to appear in susceptible infants. The incidence of allergy in children of allergic parents is significantly greater than in children of nonatopics; it is estimated that genetic factors account for 50%–70% of asthma and allergy.<sup>3</sup> However, many children who develop atopic diseases during the first years of life come from families without any history of allergy.

The potential to develop allergy is thought to be inheritance of the Th2 response to allergens, not inheritance of allergy to a specific allergen. Allergic sensitization

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\*Allergic sensitization involves an immunological response to the allergen with the production of allergen-specific IgE; Immunological tolerance indicates that consumption of the allergenic food does not result in an allergic response.

depends on the baby's exposure to the allergen and the response of his or her immune system at the time of exposure, although some foods are more likely than others to lead to allergy.

### Food Allergy and Other Allergic Diseases

For many years, it was assumed that if the early onset of allergy could be prevented or delayed, the child might avoid what allergists like to call the "allergic march"—the progression from food allergy to inhalant-triggered respiratory allergy and asthma, which usually have their onset at a later age. It was assumed that the early expression of allergy in the form of allergic reaction to foods "primed" the immune system to take the Th2 route, and once started, like a train starting from a station along a track, the Th2 response would progress to respiratory allergy and asthma. However, newer research has demonstrated that this is not necessarily the case. Prevention of food allergy in early infancy prevents or reduces *food allergy*; the direct effect of food allergy in the development of allergy to airborne and environmental allergens has yet to be identified by scientific studies. Nevertheless, it is extremely important to prevent, reduce, or relieve food allergy as early as possible because of the central role of allergy to foods in many allergic diseases (particularly eczema), its contribution to asthma and allergic rhinitis, and the real danger of life-threatening anaphylactic reactions.

This leads to an extremely important question: how can we implement strategies to promote tolerance and avoid sensitization of the baby to allergens? Clearly, the first difficulty is in determining exactly when allergic sensitization is likely to occur.

### Does Atopic Disease Start in Fetal Life?

During pregnancy, immune responses in the uterus are skewed to the Th2 (allergic) rather than the Th1 (protective) response because the fetus must be protected from rejection by the mother's system.<sup>4</sup> The fetus, having inheritance from both father and mother, has a different cellular composition from its mother. Therefore, the developing baby might be at risk of rejection by the mother's immune system, which would be a Th1 response. To avoid this rejection, the fetal environment is thought to develop a predominantly Th2 milieu, which suppresses the mother's protection/rejection response. This effectively bathes the fetus in Th2-type cytokines that keep it safe in its environment.

Because the fetus is enveloped by Th2-type cytokines in the womb, it is logical to question whether allergens from the mother's diet might gain access to the developing baby's system and thereby start allergic sensitization even

before birth. Allergens have been detected in amniotic fluid, indicating that allergenic material to which the mother has been exposed can cross the placenta.<sup>5</sup> However, there is no real evidence to suggest that the fetal immune system is primed to respond to these allergens.<sup>6</sup> In fact, some authorities suggest that exposure to food antigens in utero may promote fetal tolerance<sup>7</sup>—that is, the immune system is "educated" to recognize the food as "foreign but safe" and not to mount a defensive action against it when the food is encountered at any time in the future. So, in utero exposure to food molecules may mark the beginning of the ability to consume food with impunity.

At birth, all neonates have low levels of interferon (INF)- $\gamma$  and produce the cytokines associated with the Th2 response, especially interleukin (IL)-4, and newborns of both atopic and nonatopic inheritance have a predominantly Th2 response to antigens. As the baby matures, there is a switch from the Th2 to the "protective" Th1 response, except in atopic babies, where the Th2 response continues to predominate and sets the stage for allergen sensitization and allergy.<sup>8</sup> So here the important question is, why do all neonates not have allergy? New research is indicating that the answer may lie with the immune system of the mother, which plays a significant role in the *expression* of allergy in her baby.<sup>9</sup>

The only antibody that crosses the placenta from mother to fetus is IgG. There are 4 subtypes of IgG, designated IgG1, IgG2, IgG3, and IgG4. IgG4 is frequently associated with IgE in allergy. The nonatopic mother produces abundant IgG1 and IgG3, which cross the placenta to protect her fetus in utero. Because food proteins can cross the placenta, it is thought that fetal exposure to these antigens in the environment of the uterus protected by the mother's IgG1 and IgG3 may promote fetal tolerance to these foods, and this continues in the neonatal period. In contrast, the allergic mother tends to produce IgE and IgG4; IgG4 is very poor at crossing the placenta, and it is thought that the IgE/IgG ratio of the mother has the greatest consequences for the offspring.<sup>9</sup> In allergic mothers, there is likely to be insufficient IgG1 and IgG3 to downregulate fetal IgE, and thus at birth, her baby may be primed to become sensitized to allergens and to develop allergic symptoms very early.

Although there is no evidence that the fetus of the allergic mother can mount an IgE-mediated response to specific allergens in utero, the potential to produce allergen-specific IgE predominates at birth. The only defence against this at present is to reduce the allergic mother's exposure to *her own allergens* throughout pregnancy in an attempt to decrease her production of IgE and IgG4 and, it is hoped, enhance production of the protective IgG1 and IgG3. The mother should avoid foods to which she is allergic at all times and obtain complete balanced nutrition from alternate sources. There is no evidence to suggest that maternal avoidance of any foods other than her own allergens (and not

those of the baby's father) during pregnancy will improve the allergic status of her baby. A 1988 report<sup>10</sup> indicated that excluding highly allergenic foods from the mother's diet from week 28 to the end of pregnancy did not affect the atopic status of the infant in any way.

## Breastfeeding and Allergy

Breast milk provides the ideal nutritional, immunologic, and physiologic nourishment for all newborns. Components of human milk enhance the baby's natural defences and promote maturation of the immune system.<sup>11</sup> Ninety percent of antibodies in human colostrum and milk are secretory IgA, which provide the baby with protection at mucosal surfaces until the infant is producing adequate quantities of its own sIgA at about 6 months of age.<sup>12</sup> However, the effect of breastfeeding on the development of allergic diseases in the breastfed infant remains controversial.

Several studies report that breastfeeding is protective against allergy, with a definite improvement in infant eczema and associated gastrointestinal complaints, as well as a reduced risk of asthma in the first 24 months, when the baby is exclusively breastfed and the mother eliminates highly allergenic foods from her diet.<sup>13</sup> A recent (2010) report indicates that IgG immune complexes found in breast milk are potent inducers of tolerance to aerosolized antigens to which the mother was sensitized, providing antigen-specific protection from asthma in their babies.<sup>14</sup>

However, other studies seem to indicate that breastfeeding has no effect on the infant's symptoms of allergy or, worse, may be associated with an increased prevalence of atopic eczema.<sup>15,16</sup> One of the reasons for this apparent contradiction may be explained by data that indicate that the breast milk of atopic mothers differs immunologically from that of the nonallergic.<sup>17-19</sup>

Atopic mothers tend to have a higher level of the cytokines and chemokines associated with allergy in their breast milk and also have a lower level of the cytokine known as transforming growth factor (TGF)- $\beta$ 1 that promotes tolerance to food components in the intestinal immune response. A normal level of TGF- $\beta$ 1 in the mother's colostrum and breast milk is likely to facilitate tolerance to food encountered by the infant in the mother's breast milk and later to formulas and solids.<sup>20</sup> Evidence seems to suggest that breastfeeding is protective against allergies when the mother is nonatopic<sup>21</sup> but that babies of allergic mothers may be at risk of developing allergies, especially to foods, during breastfeeding.

In view of the large amount of evidence regarding the role of breast milk in promoting the well-being of all babies, on the basis of careful analysis of all research data on the topic, ESPACI and ESPGHAN strongly recom-

mend exclusive breastfeeding for 4–6 months, and the American Academy of Pediatrics (AAP)<sup>2,22</sup> recommends at least 4 months, with introduction of complementary foods no earlier than 4–6 months as the hallmark for allergy prevention.<sup>2,23</sup>

## Prevention of Food Allergic Sensitization During the First 6 Months

From the results of epidemiological studies, it is thought that initial sensitization to food allergens in the exclusively breastfed baby occurs predominantly from external sources, such as a single feeding of infant formula or perhaps by accident. In an important study of 1749 newborns in Odense, Denmark, 39 (2.2%) were identified as being sensitized to cow's milk proteins soon after birth. Of these, 9 developed symptoms of cow's milk allergy before 3 months of age, despite being exclusively breastfed. Review of records from the newborn nursery revealed that all 9 infants had been exposed to cow's milk formula in amounts corresponding to approximately 0.4–3.0 g of  $\beta$ -lactoglobulin (BLG) during the first 3 days of life. Similar proteins were detected in their mother's breast milk, to which the allergic infants reacted with the development of symptoms. The authors conclude that early inadvertent and occasional exposure to cow's milk proteins may initiate sensitization in predisposed neonates; subsequent exposure to minute amounts of bovine milk proteins in human milk may then act as booster doses eliciting allergic reactions.<sup>24</sup>

The current directives from position papers and consensus documents from many countries now recognize that restriction of the maternal diet during pregnancy and lactation is probably contraindicated in allergy prevention.

- The AAP<sup>2</sup> suggests that antigen avoidance during lactation does not prevent atopic disease, with the caveat that more data are needed to substantiate this conclusion.
- The European Academy of Allergology and Clinical Immunology states that "no conclusive evidence for protective effect of maternal exclusion diet during pregnancy or lactation has been documented."<sup>1</sup>
- The Australasian Society of Clinical Immunology and Allergy states, "Dietary restrictions in pregnancy are not recommended," and "Maternal dietary restrictions during breast feeding are not recommended."<sup>25</sup>

In summary, professional groups do not recommend the elimination of any specific foods from the maternal diet during breastfeeding, except for the mother's own allergens, unless the baby has been diagnosed with allergy

to 1 or more foods, in which case the baby's allergenic food should be avoided by its mother as long as she is breastfeeding.

### Formula Feeding

It is not always possible for a baby to be breastfed, and when the infant is at risk for or has developed allergies, making the best choice of formula is extremely important.

Most authorities suggest that if a baby has no signs or symptoms of cow's milk allergy, a conventional cow's milk-based formula is safe for infant feeding.

However, in high-risk-for-allergy babies, there is emerging evidence that hydrolyzed infant formulas provide a measure of protection against the development of atopic disease<sup>26</sup> compared to conventional milk-based formulas. Hydrolysis of cow's milk breaks the protein into smaller, potentially less allergenic proteins.

On the basis of evidence from a variety of studies,<sup>27-29</sup> the AAP, in its position paper published in 2008,<sup>2</sup> states that "in studies of infants at high risk of developing atopic disease who are not breast-fed exclusively for 4 to 6 months or are formula fed, there is modest evidence that atopic dermatitis may be delayed or prevented by the use of extensively hydrolyzed or partially hydrolyzed formulas, compared with cow's milk formula, in early childhood." The AAP further stated that "extensively hydrolyzed formulas may be more effective than partially hydrolyzed in the prevention of atopic disease." However, the authors of a more recent research study (2011) stated that, "Despite current dietary guidelines, we found no evidence to support recommending the use of pHWF (partially hydrolyzed whey formula) at weaning for the prevention of allergic disease in high-risk infants."<sup>30</sup>

There is good consensus among pediatric groups worldwide that no evidence exists for the use of soy-based infant formula for the purpose of allergy prevention.<sup>2,25,31</sup>

So in summary, it is fair to state that if a baby at high risk for allergy cannot be exclusively breastfed to 4-6 months of age, the preferred method of feeding in the prevention of atopic disease is an extensively hydrolyzed formula.

### Introducing Solid Foods

The first consensus document on the introduction of solid foods for the food-allergic infant was published in July 2006 by the Adverse Reactions to Foods Committee of the American College of Allergy, Asthma and Immunology.<sup>32</sup> It recommended that introduction of the multiple allergens in solid foods to the allergic infant is preferably delayed until after 6 months of age. Until this age, the authors suggest that the infant's immature diges-

tive tract and immune system may increase the risk of sensitization and development of allergy. Furthermore, it was recommended that the most highly allergenic foods should not be introduced until after 1 year of age or later. Specific times of introduction were suggested as follows: cow's milk at 12 months; egg at 24 months; and peanut, tree nut, and fish at 3 years.

However, more recent research has demonstrated that these recommendations were neither supported by evidence-based research nor were effective in practice. Newer position papers reflect this change in approach. The AAP paper, published in 2008,<sup>2</sup> states, "The evidence . . . does not allow one to conclude that there is a strong relationship between the timing of the introduction of complementary foods and development of atopic disease."

According to the published guidelines of all pediatric societies and consensus committees, solid foods should be introduced individually and gradually, starting at about 4-6 months of age. Each food should be introduced, ideally over a 4-day period, with careful monitoring of the baby for the development of signs of allergy. No mixed foods should be given until each food in the mixture has been given to the baby and is tolerated.

### Prognosis for Infant Food Allergy

Many children outgrow their early allergies to foods spontaneously. A few examples are as follows.

#### *Cow's Milk Allergy*

Most children with early cow's milk allergy outgrow their allergy by 3 years of age. A 1990 study reported that 56% of the infants with cow's milk allergy outgrew their allergy at 1 year, 77% at 2 years, and 87% at 3 years.<sup>33</sup> However, a 2007 study<sup>34</sup> reported that 19% of their patients with cow's milk allergy developed tolerance by age 4 years, 42% by age 8 years, 64% by age 12 years, and 79% by age 16 years. Those children with the highest level of cow's milk-specific IgE were least likely to outgrow their cow's milk allergy. Furthermore, children with asthma, atopic rhinoconjunctivitis (hay fever), and atopic dermatitis (eczema) are reported to be less likely to outgrow their early cow's milk allergy, suggesting that the most highly allergic individuals are most at risk for persistent food allergies.<sup>35</sup>

#### *Egg Allergy*

It has been reported that 80% of infants with egg allergy are able to consume egg by 5 years of age.<sup>36</sup> Other more recent reports using predicted resolution of egg allergy are more pessimistic: 4% of egg-allergic children were predicted to outgrow their allergy by 4 years, 12% by 6 years, 37% by 10 years, and 68% by 16 years of age.<sup>37</sup> The

persistence of egg allergy was related to the presence of asthma and allergic rhinitis and higher levels of egg-specific IgE. Nevertheless, the consensus from published studies concludes that most patients with egg allergy are likely to develop tolerance to egg by late childhood, with the exception of patients with an egg IgE  $>50$  kU<sub>A</sub>/L, in whom egg allergy is likely to persist into adulthood.

### ***Peanut Allergy***

Recent reports suggest that at least 21% of peanut-allergic children will outgrow their peanut allergy over time<sup>38</sup> (median age 6 years). Traditionally, allergy to peanut was considered to be lifelong and unlikely to be outgrown. Those children with lower peanut-specific IgE ( $<5$  kU<sub>A</sub>/L at time of challenge) and lower rates of asthma and allergic rhinitis were reported to be more likely than those with high levels to outgrow their peanut allergy. An earlier report from the United Kingdom indicated that 9.8% of their peanut-allergic patients outgrew their peanut allergy<sup>39</sup> in childhood.

### ***Tree Nut Allergy***

Allergy to tree nuts is another condition that traditionally has been considered to be rarely outgrown. However, a study of 278 tree nut allergic patients reported that 9% outgrew their tree nut allergy, including some who had previous severe reactions.<sup>40</sup> The authors suggested that patients aged 4 years or older with tree nut-specific IgE levels of 5 kU<sub>A</sub>/L or less should be considered for challenge of tree nuts under medical supervision to determine whether they remain allergic to tree nuts.

It is important that children who have outgrown their early allergy to foods should be identified so that the previously allergenic food can be included in their diet. This is important for several reasons:

- The diet becomes easier to formulate and maintain.
- The vigilance previously exerted to avoid the culprit food can be relaxed, which reduces the stress associated with maintaining restricted diets, especially those that contain foods that may be considered “life-threatening.”
- Including the now-tolerated food in the diet on a regular basis reduces the likelihood of recurrence of the allergy because maintenance of tolerance reduces this risk.<sup>41</sup>

## **Oral Tolerance in the Management of Established Food Allergy**

In some cases, desensitization or tolerance to a food allergy can be achieved even if the child has not sponta-

neously outgrown the allergy. This is a relatively new concept as previous directives for food allergy management emphasized strict avoidance of the culprit allergen. Now specific desensitization protocols are being developed that expose the allergic child to the offending allergen by the oral route in a safe environment in order to induce tolerance to it.

Several studies have reported achievement of tolerance to cow's milk by starting with minute quantities of milk and increasing the dosage over time, a process termed specific oral tolerance induction (SOTI). Examples include the following:

- One study reported that starting with 1 drop of milk and increasing to 120 mL over a period of 136 days, 13 of 16 children achieved tolerance to 120 mL milk in 3–12 months.<sup>42</sup>
- Starting with an initial dose of 0.05 mL cow's milk, reaching 1 mL on the first day, and increasing the dosage weekly until a dose of 200–250 mL of milk taken once a day was tolerated, 16 of 18 patients 4 years and older achieved tolerance after a median length of 14 weeks (range, 11–17 weeks). Thirteen children continued to tolerate 200–250 mL per day of milk after more than a year.<sup>43</sup>
- Another study<sup>44</sup> reported achievement of tolerance to cow's milk in 7 of 10 children with established milk allergy, starting with 1 drop of milk and increasing weekly over a period of 4 months until a dose of 200 mL was tolerated.

A similar tolerance to foods other than milk have been achieved, for example, to egg<sup>45,46</sup> and peanut.<sup>47,48</sup> Undoubtedly, successful SOTI to other allergenic foods will be achieved over time.

## **Probiotics and Allergy**

Studies in the past decade have indicated that the intestinal microflora might be the major source of microbial stimulation that promotes maturation of the immune system in early childhood.<sup>49</sup> The appropriate microbial stimulus soon after birth may be extremely important in balancing the Th1/Th2 response of the immune system, which is skewed to the Th2 (allergy) type at birth.<sup>50</sup>

Lactic acid bacteria and bifidobacteria are found more commonly in the intestinal flora of nonallergic children, and atopic children appear to have a different microflora composition than nonatopics, with higher levels of clostridia and lower levels of bifidobacteria.<sup>51</sup> These observations may pave the way for selecting probiotic strains that might promote the intestinal environment most beneficial in developing tolerance rather than sensitization to

allergens in the immature infant. A number of studies suggest that the appropriate selection of the bacterial strains used in probiotics may help in certain allergic conditions, but at the present time, we have insufficient evidence to recommend probiotics as a therapy for allergy prevention in regular clinical practice.<sup>52,53</sup>

The use of probiotic therapy to prevent allergic disease has been demonstrated in a few studies using the probiotic strain *Lactobacillus rhamnosus* GG in neonates. This seemed to be particularly effective in reducing the incidence and severity of atopic eczema.<sup>54</sup>

In a Finnish study, infants with milk allergy and atopic dermatitis had milder symptoms and fewer incidences of intestinal infections if their milk formula was fortified with lactobacilli.<sup>55</sup> However, a similar study from Singapore reported that administration of a cow's milk formula supplemented with probiotics (*Bifidobacterium longum* and *L rhamnosus*) for the first 6 months showed no effect on prevention of eczema or allergen sensitization in the first year of life in Asian infants at risk of allergic disease.<sup>56</sup> Another study using the probiotics *L rhamnosus* or *Lactobacillus* GG in infant formula for 3 months in children younger than 5 months as prevention or management of atopic dermatitis (AD) concluded that the results "indicate that oral supplementation with these probiotic bacterial strains will not have a significant impact on the symptoms of infantile AD."<sup>57</sup>

A positive effect of probiotics on symptoms of allergy was reported in a study from Sweden that evaluated the effects of feeding *Lactobacillus F19* in cereals during weaning on the incidence of eczema in children aged between 4 and 13 months (89 in the study group; 90 in the control group). At 13 months of age, the incidence of eczema was reported as 11% in the study group and 22% in the placebo group. The authors conclude that "feeding *Lactobacillus F19* during weaning could be an effective tool in the prevention of early manifestations of allergy, e.g. eczema."<sup>58</sup>

The problem with comparing such studies at the present time is that there are so many variables to consider before any conclusions can be made as to the effectiveness of probiotics, prebiotics, and synbiotics on childhood allergy—for example:

- The specific species and strains of the micro-organisms
- The number of micro-organisms required to be delivered orally (dosage) as colony-forming units (CFU)
- The number of micro-organisms surviving in their movement through the digestive tract
- The number colonizing (implantation and multiplication in) the bowel, usually measured as live organisms in the feces
- The age at which the probiotic is administered, whether prenatally or postnatally

- The duration of consumption of the probiotic
- The means of administering the probiotic (in milk, formula, cereal, or other)
- The selection of an appropriate prebiotic (milk, oligosaccharides [eg, fructo-oligosaccharide], inulin) or other appropriate substrates

It is hoped that evidence-based studies will begin to answer these questions, possibly offering an additional method for managing pediatric food allergies in the future.

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