Epidemiologic risks for food allergy

Gideon Lack, MD  London, United Kingdom

This article reviews possible risk factors and theories for the development of food allergy. It is noted that previous strategies to prevent food allergy through allergen avoidance during pregnancy, breast-feeding, and infancy have more recently been called into question. Alternative hypotheses are examined with respect to food allergy, namely the hygiene hypothesis, the dietary fat hypothesis, the antioxidant hypothesis, and the vitamin D hypotheses. An alternative hypothesis is proposed, suggesting that sensitization to allergen occurs through environmental exposure to allergen through the skin and that consumption of food allergen induces oral tolerance. This hypothesis provides a possible explanation for the close link between eczema and the development of food allergies. It also suggests novel intervention strategies to prevent the development of food allergies. (J Allergy Clin Immunol 2008;121:1331-6.)

Key words: Risk factors, food allergy, allergen

Although our understanding of food allergies has increased in the past decade, knowledge about the epidemiology and causes of food allergy remains limited. Although there are numerous studies documenting the prevalence of peanut, egg, and milk allergies in childhood in Western countries, there are no international surveys defining the prevalence of food allergies in different populations at a global level. The International Study on Allergies and Asthma in Childhood asks specifically about symptoms of asthma, eczema, and rhinitis in children but does not focus on food allergies. Knowledge about food allergies in the developing world is even more limited and relies mainly on case series derived from tertiary allergy clinics in different countries. Despite egg and milk allergy being the leading food allergies across the globe, there are marked geographic variations. Certain food allergies seem to be specific for certain regions or countries, such as bird nest soup allergy in Singapore, royal jelly allergy in Hong Kong, and mustard allergy in France.

More recently, a meta-analysis of 51 articles from different countries examined the prevalence of food allergies by using different criteria. The self-reported prevalence of allergy varied from 1.2% to 17% for milk, 0.2% to 7% for egg, 0% to 2% for peanut and fish, 0% to 10% for shellfish, and 3% to 35% for any food. Challenge-proved food allergies provided lower estimates: 0% to 3% for milk, up to 1.7% for egg, 0.2% to 1.6% for peanut, and 1% to 10.8% for any food. In a second study of plant food allergies (wheat, soya, tree nut, fruits, and seeds), the authors found marked heterogeneity between studies. There are a number of methodological explanations for the differences in prevalence observed in the different studies. Research in the area is hampered by the difficulty in defining food allergies; double-blind, placebo-controlled challenges are the gold standard and are used in a minority of studies. Consequently, many studies define food allergies based on history, which is inaccurate. Other studies use IgE positivity or skin test positivity to specific foods as a marker of food allergy. The difficulty with this latter approach, especially the adoption of specific IgE serology to foods as the sole determinant of food allergy, is that between 50% and 75% of patients with specific IgE to food tolerate the food. Therefore examination of risk factors for positive specific IgE to particular foods will not necessarily elucidate risk factors for food allergy but might define protective factors for tolerance to foods in individuals who, despite having IgE to a particular food antigen, are able to eat that food without problems. It is therefore not surprising that our knowledge on risk factors for the development of food allergies is even more limited.

GENETIC AND MOLECULAR RISK FACTORS

Individual food allergies, such as peanut allergy, have been shown to have increased in certain parts of the world in the past decade, and there clearly is the impression that new food allergies are increasing in prevalence, particularly kiwi allergy and sesame seed allergy. Although it is unlikely that genetic risk factors could account for this recent increase in food allergies, it is nevertheless likely that there are genetic predisposing factors for the development of food allergies, just as there are genetic factors that predispose toward other atopic diseases (asthma and eczema). Whether the same genetic polymorphisms that are associated with asthma and eczema exist in patients with food allergy and whether there are unique polymorphisms associated with food allergies remains to be seen.

In the case of peanut allergy, a child has a 7-fold increase in the risk of peanut allergy if he or she has a parent or sibling with peanut allergy. In the case of monozygotic twins, a child has a 64% likelihood of peanut allergy if his or her twin sibling has peanut allergy. This indicates a strong genetic contribution to peanut allergy.

There has been little research on HLA background and the development of individual food allergies. There is conflicting literature showing links between HLA background and peanut and nut allergies. A signal transducer and activator of transcription 6 polymorphism has been shown to be associated with nut

Abbreviations used
AAP: American Academy of Pediatrics
OR: Odds ratio
PG: Prostaglandin

From Kings College London, St Thomas’ Hospital, Children’s Allergies Department. Disclosure of potential conflict of interest: G. Lack has received conference expenses from SBS Nutricia and ALK-Abelló and has served as a research project investigator for the Immune Tolerance Network (NIH). Food Standards Agency, National Peanut Board, and the Food Allergy and Anaphylaxis Network. Received for publication April 9, 2008; revised April 28, 2008; accepted for publication April 28, 2008.

Reprint requests: Gideon Lack, MD, Kings College London, St Thomas’ Hospital, Children’s Allergies Department, 2nd Floor, South Wing, St Thomas’ Hospital, London SE1 7EH, United Kingdom. E-mail: gideon.lack@kcl.ac.uk.

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allergies in one study. Recently, an IL10 gene polymorphism has been associated with food allergy in a Japanese population, and an IL13 polymorphism has been identified in association with food allergy in another study. These studies will need to be replicated in different populations.

**FOOD ALLERGIES AND OTHER ATOPIC DISEASES**

Eczema is the first manifestation of the allergic march, occurring in the first few months of life, with food allergies presenting at between 1 and 3 years of age. There is a well-documented link between the presence of early eczema in childhood and the development of food allergy, especially peanut, egg, and milk allergies. Between 33% and 81% of children with infantile eczema have IgE-mediated food allergy. Eczema severity in the first year of life is associated with the development of egg, milk, and peanut allergies. The presence of eczema in the first 6 months of life was associated with an increased risk of peanut allergy, and this risk increased with more severe eczema. More recently, a study of 2184 infants showed that the risk of egg, milk, or peanut allergy was approximately twice as high if eczema was present in the first 6 months of life compared with the second 6 months of life.

**EXPOSURE TO FOOD ALLERGENS**

Currently, important questions remain about exposure to food allergens both in the infant's diet and in the maternal diet. Until very recently, the American Academy of Pediatrics (AAP) recommended that families with an infant at increased risk of atopy based on family history should avoid peanuts in the infant's diet during the first 3 years of life and common food allergens until the first (milk), second (egg), or third (tree nuts and fish) years of life. It was also recommended that mothers avoid peanuts during pregnancy and breast-feeding and additional allergens during lactation. In the United Kingdom similar recommendations are still in place with respect to peanut avoidance.

More recently, the AAP has changed its position, acknowledging that we do not know whether certain aspects of avoidance prevent allergies, and recommendations about avoidance of specific food allergens have been withdrawn and replaced by comments about the lack of current evidence on these topics. A recent expert committee statement by the Section on Paediatrics of the European Academy of Allergology and Clinical Immunology is in close agreement with the revised AAP position.

We have little evidence-based guidance about when to introduce allergens in the diet and whether to introduce these foods in large or small quantities regularly or irregularly. This reflects a profound lack in our evidence base for weaning infants. At a global level, the World Health Organization strategy to prevent allergy is to promote exclusive breast-feeding during the first 6 months of the infant's life and thus delay weaning onto solids and milk formulas. However, there is no compelling evidence that exclusive breast-feeding beyond 4 months of age has any effect on reducing atopic disease. Indeed, more recently, observational cohort studies show that breast-feeding and prolonged breast-feeding are associated with an increased risk of asthma and eczema. Although such studies do not eliminate the possibility of reverse causality as an explanation for this finding (high-risk infants with eczema are deliberately breast-fed longer), they raise the question as to whether exposure to solids in infancy might have a role in preventing allergic disease.

The purpose of this review is not to analyze in detail the numerous studies that have assessed the effect of early versus delayed introduction of allergenic foods in the diet of the infant. This has been carefully reviewed in recent publications. The conventional wisdom has always been that early exposure to allergenic food proteins during pregnancy or lactation could lead to food allergies and that prevention strategies should aim to eliminate allergenic food proteins during pregnancy, breast-feeding, and early childhood. More recent analyses reflect a shift in our thinking. This shift is not so much a departure from the original theories but a realization that, on further analysis of the existing data, the evidence to support food allergen avoidance is currently lacking.

**CHANGES IN DIETARY COMPOSITION**

There is a growing body of research on the relationship between diet and the development of allergies. In the past 3 decades, there have been marked changes in diet, and it has been suggested by researchers that differences in macronutrient and micronutrient dietary content could explain the geographic differences seen in the prevalence of allergies and asthma in different parts of the world and the increase in allergies. There are 3 theories that deserve discussion. The first is the dietary fat and allergy hypothesis. The second is the antioxidant hypothesis, and the third is the vitamin D hypothesis.

**Dietary fat hypothesis**

The dietary fat hypothesis argues that reduction in consumption of animal fats and corresponding increase in the use of margarine and vegetable oils has led to the increase in allergies. The argument is that there has been an increase in the consumption of ω-6 polyunsaturated fatty acids, such as linoleic acid, and similarly that through reduced consumption of oily fish, there has been a reduction in ω-3 polyunsaturated fatty acids, such as eicosapentaenoic acid. ω-6 Fatty acids lead to the production of prostaglandin E2 (PGE2), whereas ω-3 fatty acids inhibit synthesis of PGE2. PGE2 reduces IFN-γ production by T lymphocytes, thus resulting in increased IgE production by B lymphocytes. This has been proposed to explain the increase in the prevalence of asthma, eczema, and allergic rhinitis.

There are few data to refute or support this hypothesis with respect to food allergy. Thus in an interventional study the early introduction of fish did not change the prevalence of fish and citrus fruit allergies compared with that seen in the groups avoiding fish and citrus. In contrast, a large birth cohort study, after controlling for confounding factors (parental atopy, early onset of eczema, and wheeze), found that regular fish consumption during the first 12 months of life was associated with a decreased risk for allergic sensitization to foods by 4 years of age. This was an observational birth cohort study, and therefore the association between increased oily fish consumption and reduced IgE allergic sensitization to foods is not necessarily causal. Second, in this study food allergy was defined by sensitization but not by history of reactions or food challenges. As discussed earlier, sensitization to foods and allergy are not the same, and the majority of children with IgE to foods do not react to the foods. It is interesting, however, that there was a decrease in IgE levels to all the food groups and not only to fish, suggesting a nonspecific immune effect.

**Antioxidant hypothesis**

It has been argued that the decrease in consumption of fresh fruit and vegetables in the United Kingdom in the Western diet...
might account for allergies, particularly asthma. The idea is that certain antioxidants, such as vitamin C and β-carotene, could have anti-inflammatory protective effects in asthma. There is no biologic explanation as to how this could affect IgE sensitization to foods. There is some evidence from observational studies that a Mediterranean diet is associated with lower rates of asthma and hay fever. No such data exist for food allergies.

**Vitamin D hypotheses**

The vitamin D hypothesis is one of the more interesting hypotheses to have been advanced in recent years as an explanation for the increase of asthma and allergies. The vitamin D hypothesis takes 2 forms: the vitamin D excess hypothesis argues that increases in vitamin D levels have led to increased allergies. The vitamin D deficiency hypothesis argues the opposite. Wüst et al. was the first to argue the vitamin D excess hypothesis and noted that in farming communities in Germany there was less vitamin D supplementation used in foods, which could explain the lower prevalence of allergies in children. The argument was also promoted that the increase in allergies in Bavaria was a post-1960 phenomenon coinciding with vitamin D supplementation intervention programs to prevent rickets in childhood.

Supporting this is the cohort observational study by Milner et al. showing that infants who had vitamin D supplementation were at increased risk of food allergy. Similarly, in a cohort study of 1258 infants, the odds ratio (OR) for atopy was 1.7 if babies were treated with regular rather than irregular vitamin D supplementation. In contrast, proponents of the vitamin D deficiency hypothesis argue that inadequate vitamin D (mainly as a result of inadequate sunlight) is responsible for the increase in asthma and allergies. Ecologic evidence is cited, namely that countries furthest from the equator have some of the highest rates of asthma. The argument is that a Western way of life and prosperity is associated with more time indoors, less exposure to sunlight, and less vitamin D.

The most interesting study linking the vitamin D deficiency hypothesis to food allergy was performed by Camargo et al. They found a strong north-south gradient for EpiPen (Dey, Napa, Calif) prescriptions in the United States. Northernmost states were prescribing 8 to 12 EpiPens per 1000 population, whereas the Southern states were prescribing 3 per 1000 population. This gradient persisted despite a multivariate analysis, and importantly, the number of allergists per population did not explain this gradient. There was an inverse association between EpiPen prescription and the incidence of melanoma in the population, suggesting that this north-south effect was due to sunlight exposure.

Just as the vitamin D hypothesis can be articulated both ways (deficiency vs excess), there are immunologic arguments that can be used to support both hypotheses. Vitamin D has been shown to inhibit in vitro T-cell proliferation and production of the Th2 cytokines IL-2, IFN-γ, and IL-12. However, there is also literature showing that vitamin D promotes the development of regulatory T cells in vitro and in vivo, and this could downregulate allergic inflammation.

Therefore the vitamin D controversy remains unresolved, and it will be helpful in the future to look at interventional studies with vitamin D supplementation during both pregnancy and infancy.

**THE HYGIENE HYPOTHESIS**

Despite the large body of literature examining the hygiene hypothesis, especially the sibling effect in prevention of allergies, little work has been done with respect to the hygiene hypothesis and food allergy. It is, however, worth noting that these studies have attempted to look at the hygiene hypothesis in relation to eczema, which is closely related to the development of food allergies. Eczema can frequently be a manifestation of food allergy. Although the effect of sibling size is inconsistent between various studies, overall, a higher number of older siblings seems to protect infants against the development of eczema. The results of such studies have been variable. Of 11 studies that reported results on eczema and family size, 10 such studies reported an inverse association with the number of siblings, of which only 5 were statistically significant. For the 11 studies, the weighted average OR for having eczema was 0.66 when having 3 or more siblings. Furthermore, there is some evidence that frequent use of antibiotics can predispose to eczema, and the early presence of furry pets in the infant’s environment can also protect against eczema. This might provide indirect evidence for the role of microbial exposure in the prevention of food allergies.

Limited evidence for the hygiene hypothesis exists with respect to food allergy. A Norwegian birth cohort study showed that birth through a cesarean section was associated with a 7-fold increased risk of parental perceived reactions to eggs, fish, or nuts. For infants whose mothers were allergic, there was also a 4-fold increased risk of confirmed egg allergy in this study. A recent meta-analysis on the relationship between cesarean delivery and atopic outcome found 6 studies that confirmed a mild effect of cesarean delivery, increasing the risk of food allergy or food atopy (OR, 1.32; 95% CI, 1.12-0.55). One explanation is that early colonization of the infant by colonic microflora protects against the development of allergic disease. However, other explanations are possible: cesarean sections are more common in firstborns (therefore a sibling effect); alternatively, the primary effect might be on reducing eczema rather than food allergy. Another possible explanation for the effect of cesarean sections is that they are associated with higher maternal age, and this latter factor has been shown to be a possible risk factor for food allergy in a case-control study.

Such observations have led to strategies to alter commensal gut floral either directly through the administration of probiotics or indirectly through the administration of prebiotics. Although the small number of probiotic prevention studies done suggests a small protective effect against development of eczema, there is no evidence that probiotics prevent the development of food allergies; indeed, probiotic studies that looked at IgE sensitization to foods did not show any reduction.

**FOOD ALLERGEN EXPOSURE REVISITED**

As discussed earlier, there is no convincing evidence that allergen avoidance in the infant beyond 4 months of age is beneficial in preventing allergies. It is indeed surprising that studies eliminating food allergens during pregnancy, lactation, and infancy have consistently failed to reduce long-term IgE-mediated food allergy in children. There are 4 possible explanations for this failure. First, exposure to allergens is irrelevant for the development of food allergy. Second, allergen reduction measures have not been sufficient in previous studies, and dietary elimination was not sufficiently stringent. Third, sensitization to food allergens does not occur as a result of consumption but can occur through other routes of exposure. Finally, the paradigm of allergen avoidance is flawed, and early oral exposure can be required to prevent the development of allergy.
The first explanation can be immediately discounted. Food allergy is an antigen-specific immunologic disease, and antigen exposure is necessary for T-cell maturation, affinity maturation, and isotype switching.

The second explanation, that allergen reduction measures might have been insufficient, is certainly plausible. However, even if this explanation is correct, it seems very unlikely that “complete” allergen avoidance could successfully prevent food allergies as a public health measure, given that careful elimination studies have failed, despite rigorous dietary supervision, to achieve a reduction in food allergies.25

The third explanation of “environmental food exposure” is supported by a number of murine studies that show that allergic sensitization to antigen occurs after cutaneous exposure. Exposure of mice to ovalbumin or peanut on abraded skin led to significant food-specific IgE responses.29,40 In human subjects there is more limited evidence for cutaneous sensitization. There are studies, for example, in which food allergen–specific T cells have been isolated from lesional skin in patients with eczema.41 In a prospective birth cohort study it was found that low-dose exposure to peanut in the form of arachis oil applied to inflamed skin on infants was associated with increased risk of peanut allergy at age 5 years.16 The use of such oils is not widespread in different countries, but it is worth noting that food allergens can be measured in the environment, and cutaneous sensitization to a variety of foods could occur through environmental exposure.42

There are animal data supporting the fourth explanation, that oral tolerance induction rather than dietary elimination is required to prevent the development of food allergies. In animal models an early high dose of oral protein antigen induces oral tolerance to the respective antigen. A single dose of food allergen in mice (β-lactoglobulin, ovalbumin, or peanut) is effective in preventing the development of subsequent IgE-mediated responses. In a murine model of peanut exposure, a single high dose of peanut flour (100 mg) was sufficient to promote oral tolerance and prevent subsequent IgE sensitization and T-cell proliferation.43

Ecologic explanations from African and Asian countries suggest that there is little peanut allergy where peanuts are consumed throughout pregnancy and early childhood (Table 1).44-47 In Western industrialized societies where peanuts are avoided in pregnancy and infancy, the rate of peanut allergy is higher.44 A recent study demonstrated that delaying initial exposure to cereal grain after 6 months of life was associated with an increased risk of IgE-mediated food allergy.48 This important observation will need to be further studied in observational and interventional studies for different food allergens.

**DUAL-ALLERGEN-EXPOSURE HYPOTHESIS**

The long-held view that allergic sensitization to food occurs through oral exposure and prevention of food allergies is best accomplished through elimination diets is now challenged. It is proposed instead that allergic sensitization to food can occur through low-dose cutaneous sensitization and that early consumption of food protein induces oral tolerance (Fig 1).

It is argued that low-dose exposure to environmental foods (on tabletops, hands, and dust) penetrates the skin barrier and is taken up by Langerhan’s cells. This leads to Th2 responses and IgE production by B cells. In contrast, early high-dose oral consumption induces tolerance, and it is proposed that Th1 and regulatory T-cell responses occur in the gut-associated lymphoid tissue. The timing and balance of cutaneous and oral exposure determine whether a child will have allergy or tolerance.

This hypothesis explains the association between the presence of early severe eczema in infancy and the subsequent development of food allergies. There is indeed a molecular basis for the increased skin permeability in eczema, and it has been shown that loss-of-function variants of the epidermal barrier protein filaggrin are a predisposing factor for eczema.49 Furthermore, there is evidence that Th2 inflammation in the skin of patients with eczema reduces filaggrin gene expression.50 The hypothesis also can explain different rates of food allergies in different parts of the world and changes in food allergy over time. Thus in societies in which a food is not consumed, there is no environmental exposure, and therefore allergy to that food will not occur. Allergy to kiwi was not a problem in the United Kingdom before it entered the food market in the 1970s through 1980s. In countries where consumption of peanut is high and peanut is therefore present in the environment but infants are avoiding peanuts, one would expect to see allergic sensitization (United Kingdom, United States, Australia, and Canada; Table 1). In countries where consumption and therefore environmental exposure are high but infants are eating peanut regularly, one would not expect to see peanut allergy (southern/western Africa/Asia).

There are several predictions that can be made on the basis of this hypothesis, which can in turn be tested. One prediction is that prompt intensive treatment of eczema in early infancy will decrease inflammation in the skin, reduce skin permeability, and prevent allergic sensitization to foods. This could be tested in future clinical trials. The second prediction is that reduction of food allergens in the child’s environment will lead to a reduction in sensitization. However, there is doubt as to whether it is practical and feasible to reduce levels of exposure to proteins in home environments, such as kitchens, and this approach could be extremely difficult to test. Indeed, approaches to reduce respiratory allergens in the environment have not met with uniform success. Nevertheless, it ought to be possible to prospectively measure food allergens in the homes of high-risk infants during the first 6 months of life and relate those levels to the subsequent risk of food allergies. The third prediction is that early introduction of allergenic foods to the infant’s diet (in the first 6 months of life) can reduce the development of food allergies through oral tolerance induction. This approach is currently being tested in the Learning Early About Peanut Allergies study in a randomized controlled trial in which half the infants are avoiding peanut and the other half are consuming peanut.51

**CONCLUSIONS**

We have reviewed nonspecific factors that might be involved in immune modulation, as well as food exposure, which is an antigen-specific effect. There is limited support for the hygiene...
hypothesis having a role in the development of food allergies, although evidence is stronger for a role in eczema than in food allergies. However, there is a close association between food allergies and eczema. Furthermore, cesarean sections appear to increase the risk for the development of food allergy, suggesting that early colonization of the gastrointestinal tract with microflora might be important in establishing tolerance. There are other non–antigen-specific dietary factors (both macronutrients and micronutrients) that might modulate the immune system and influence the establishment of tolerance or allergy. There is no direct evidence that antioxidants, vitamin supplementation, or ω-3 fatty acids prevent food allergies. However, the role of vitamin D in the development of tolerance or allergy to foods might be relevant, and the observed association of the north-south gradient in the United States for EpiPen prescriptions is intriguing. Vitamin D is a potent immunomodulator produced mainly in the skin from sunlight exposure. The vitamin D deficiency hypothesis could explain the association between Western urban environments and the development of allergies through decreased exposure to sunlight.

Elimination diets have achieved limited success in the past several decades, whereas food allergies have continued to increase. Nevertheless, it is proposed, on the basis of animal studies and limited human observations, that allergen exposure is critical in the cause of food allergies. The dual-allergen-exposure hypothesis suggests that exposure through the skin leads to sensitization, whereas consumption of allergenic proteins results in the induction of oral tolerance. This hypothesis could in part explain the distribution of certain food allergies (e.g., peanut) in different regions of the world and the more recent increase in food allergies as a result of prolonged exclusive breast-feeding and the delayed introduction of allergens into the diet. If environmental exposure to food predominates in the absence of infant consumption, allergy is more likely to occur, whereas if the infant is allowed to consume the food, tolerance is more likely to occur. This hypothesis also explains the critical association between the early development of severe eczema and the subsequent development of food allergies. Although the dual-allergen-exposure hypothesis stipulates the importance of both allergen and the route of exposure to allergen, other factors can modulate immunologic responses to the food and participate in shaping the clinical outcome. Thus, for example, high levels of vitamin D or the presence of microbial organisms might be necessary for oral tolerance induction to occur. It is noteworthy, for example, in animal models that oral tolerance induction can only occur in the presence of normal gastrointestinal microflora, and oral tolerance induction cannot be achieved in germ-free mice.

A number of interventional approaches have been suggested, including the early rigorous treatment of eczema and studies looking into the possibility of oral tolerance induction. It is critical that such studies be randomized, controlled interventional studies (ideally placebo controlled) with careful determination of food allergy on the basis of a double-blind, placebo-controlled food challenge. Intervventional studies on vitamin D supplementation in the future would also be worthwhile, although it is unclear whether this should take the form of nutritional intervention or exposure to sunlight. Furthermore, maternal intervention during pregnancy might be equally important with respect to the vitamin D hypothesis.

In summary, it is argued that antigen exposure through inflamed skin or through the gastrointestinal mucosa might be involved in the establishment of allergy and tolerance. Immune responses to such allergen exposures are likely to be modulated by nonspecific factors, such as gastrointestinal microflora, infectious exposure, other dietary factors, and possibly sunlight exposure. It is hoped that interventional trials in the next few years will help determine the relative contribution of these different factors and allow us to reduce the burden caused by food allergies.

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**REFERENCES**