Early-Life Allergen Exposure and Its Influence on Risk of Atopic Disease

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Learning objectives:

1. Identify patterns of allergen exposure in the home, school, and outdoor settings.
2. Describe how allergen exposure can lead to allergic sensitization and disease.
3. Explain two potential mechanisms for early life allergen exposure to have health benefits.
4. Be aware of new clinical practice recommendations on allergen exposure in early life for allergy disease prevention.

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Childhood allergic diseases and asthma have their origins in early life, and allergen exposures during this period could be a critical determinant of the progression to tolerance versus disease. Mechanisms for sensitization may be different but overlapping for food and aeroallergen sensitization in children. This suggests differences in how exposure to food and aeroallergens influence allergic sensitization. For food allergy, introducing foods such as peanut and egg proteins into the diet at an early age reduces the risk of peanut and egg allergy, respectively, across a broad demographic, whereas evidence is less established for other foods. The relationship between allergen exposure and sensitization to aeroallergens is more complex but critical, given the close relationship between specific immunoglobulin E and respiratory disease. Several factors could mediate the progression from allergen exposure and allergic sensitization versus tolerance, including epithelial barrier function and altered immune development at the skin and mucosal surfaces, exposure to irritants and pollutants, and

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Abbreviations used
AD- Atopic dermatitis
BEAT- Beating Egg Allergy Trial
FA- Food allergy
HEAP- Hen's Egg Allergy Prevention
IgE- Immunoglobulin E
IL-4- Omterleukin 4
LEAP- Learning Early About Peanut Allergy
PETIT- Prevention of Egg allergy with Tiny amount InTake
STAR- Solids Timing for Allergy Research
STEP- Starting time of egg protein
Th2- T helper 2
TLR4- Toll-like receptor 4

genetic susceptibility. Collectively, the current evidence base provides a compelling rationale for the primary prevention of food allergy by introducing common allergens such as peanut and egg early. In contrast, primary prevention of aeroallergen sensitization is more complex and perhaps more challenging to achieve by manipulating allergen exposures. Even so, recent advances in understanding how the microbiome and environmental toxins and irritants modulate the mucosal immune response have identified potential new strategies for primary prevention of food and aeroallergen sensitization.

Key words: *Allergic sensitization; IgE; Children; Risk factors; Asthma; Food allergy; Aeroallergens; Prevention; Allergen exposure*

INTRODUCTION

Whereas exposure to allergens in early life is ubiquitous, these exposures can vary in quantity, route, adjuvants, and physical formats. Following contact with epithelial surfaces, local factors such as barrier function, host genetics or epigenetics, inflammation, and the microbiome help to initiate and shape epithelial downstream mucosal immune responses. Given that most allergen exposures and some cofactors are modifiable, it is critical to understand how exposure patterns to food and environmental allergens and cofactors related to the host mucosal and skin immune responses modulate allergic health outcomes. The following sections review evidence related to these concepts and the results of interventional studies, highlighting unresolved questions that could lead to future advances in disease prevention.

EXPOSURE TO FOODS IN EARLY LIFE AND FOOD ALLERGY

Epicutaneous sensitization and food allergy

The strong causal relationship between atopic dermatitis (AD) and food allergy (FA)[1-3] is underpinned by mechanistic evidence suggesting that an impaired epithelial barrier (such as in AD) can cause epicutaneous sensitization to food allergens.[4] In the setting of a disrupted skin barrier, food allergens in the environment encounter resident dendritic cell subsets in the dermis, which present these antigens to naive CD4+ T cells in draining lymph nodes that differentiate into allergen-specific CD4+ T cells. Secretion of T helper 2 (Th2)—proinflammatory cytokines (interleukin 4 [IL-4], IL-13) induces B-cell isotype class switching to immunoglobulin E (IgE), and differentiation into specific IgE-producing plasma cells.[5,6] In the effector phase, oral exposure to offending allergens crosslinks serum IgE antibodies and high-affinity receptor for the Fc region of IgE (FcεRI) receptors on mast cells and basophils, causing degranulation and release of histamine, leukotrienes, and proinflammatory cytokines, which manifest clinical symptoms.[7,8]

Loss-of-function mutations in skin barrier genes such as filaggrin *(FLG)* and *SPINK5* have also been linked to skin barrier impairment and concomitant increased risks of food sensitization and FA.[9,10] Cohort studies have also demonstrated that early skin barrier disruption, such as high transepidermal water loss in the neonatal period; and early-onset AD, could increase the risk of FA development by 1 to 2 years of age.[11-13]

Dual allergen exposure hypothesis and FA prevention

Food allergens are ubiquitous in the indoor environment.[14,15] Food enters the environment during processing or preparation and can become airborne or coat environmental surfaces, to the extent of inducing reactions on inhalation[16] or skin contact. Higher environmental allergen levels also correlate with increased risk of allergen sensitization. For example, household peanut exposure increases the risk for peanut allergy, particularly in children with more severe AD and *FLG* mutations.[17-19] Likewise, applying peanut-containing skin preparations to inflamed skin is associated with infant peanut allergy.[20] Repeated skin exposures to high concentrations of food antigens, with or without eczema, may also increase the risk of FA.[21-23]

The dual-allergen exposure hypothesis, proposed in 2008, postulated that food exposure through a disrupted skin barrier in AD caused sensitization, whereas early oral exposure to food allergens promoted tolerance and prevented FA.[24-26] Observational studies indicated that avoiding consumption of allergenic foods in early life could increase the risk of FA, especially in high-risk infants with AD, in whom transcutaneous sensitization to food allergens frequently leads to development of clinical FA.[27,28] Conversely, earlier oral introduction of food allergens between 4 and 6 months of age could mitigate this pathway and protect against FA by inducing gastrointestinal tolerance (Table I).[29-39]

Subsequently, several randomized controlled trials found that early introduction of peanut or egg to high-risk infants with severe AD or preexisting food sensitization reduced the risk of developing allergies to those foods (Table I). The landmark Learning Early About Peanut Allergy (LEAP) trial found that high-risk infants who consumed 6 g of peanut protein in a week, or 2 g 3 times a week, had an 81.4% lower risk of developing challenge-proven peanut allergy by age 5 years, compared with those who completely avoided peanut.[32] This effect was sustained for up to 72 months.[40] Many scientific organizations subsequently released consensus statements recommending the early introduction of peanut in high-risk populations for the prevention of peanut allergy.[41-43]

Several other trials on the early introduction of egg and milk have also since been performed in other countries (Table I).[44] The earlier trials left doubt about whether early egg consumption reduced the risk of FA in normal or high-risk infants.[33-37] Subsequently, the PETIT (Prevention of Egg allergy with Tiny amount InTake) study confirmed that early

TABLE I. Studies on early food-allergen exposure and FA risk.

Food	Year Country Author (Study name)	Study population	Study type	I C	FA outcome	FA outcomes in relation to allergen-consumption patterns
Observational studies						
Wheat	2006 United States Poole[27]	n = 1,612 normal-risk infants	Longitudinal observational study	NA	Parent reported wheat allergy up to age 4 y	0.41% if wheat introduced before 6 mo 1.8% if wheat introduced after 6 mo OR 3.8; 95% CI 1.18−12.28; $P = .025$
Cow's milk	2010 Israel Katz[28]	n = 13,019 normal-risk infants	Longitudinal observational study	NA	OFC or suggestive history up to age 3−5 y	0.05% if CMP formula started in first 14 d 1.75% if CMP formula started between 105 and 194 d OR 19.3; 95% CI 6.0−62.1; $P < .001$
Cow's milk	2022 United States Switkowski[29] (Project Viva)	n = 1,484 normal-risk infants	Longitudinal observational study	NA	Parent reported cow's milk allergy up to age 13 y	5.3% if CMP introduced < 2 wk of age 7.1% if CMP introduced between 2 wk and 6 mo of age OR 1.4; 95% CI 0.8−2.4 10.8% if CMP introduced > 6 mo of age OR 2.1; 95% CI 1.2−3.7
Peanut	2008 Israel and United Kingdom Du Toit[30]	n = 5615 Israel n = 5,171 United Kingdom Normal-risk infants	Cross-sectional study	NA	Parent reported peanut allergy at age 4−18 y	69% of Israeli infants consumed peanut by age 9 mo 7.1 g median monthly peanut consumption in first year of life 10% of UK infants consumed peanut by age 9 mo 0g median monthly peanut consumption in first y of life Peanut allergy 0.17% in Israel vs 1.85% in United Kingdom RR 5.8; 95% CI 2.87−11.8
Egg	2010 Australia Koplin[31] (HealthNuts)	n = 2,589 normal-risk infants	Cross-sectional study	NA	Egg allergy by OFC at age 15−18 mo	5.6% if egg introduced at 4−6 mo 7.8% if egg introduced at 7−9 mo (OR 1.3; 95% CI 0.8−2.1) 10.1% if egg introduced at 10−12 mo [OR 1.6; 95% CI 1.0−2.6) 27.6% if egg introduced after 12 mo (OR 3.4; 95% CI 1.8−6.5); $p < .001$
Randomized controlled trials						
Peanut	2015 United Kingdom Du Toit[32] (LEAP)	n = 640 infants Moderate to severe eczema and/or egg allergy Peanut SPT ≤ 4 mm	Randomized controlled trial	I: 6 g peanut protein/wk from 4 to 11 mo C: avoidance	Peanut allergy by OFC at age 5 y	I: 10 of 312 (1.9%) Cl: 54 of 313 (13.7%) OR 0.19; 95% CI 0.10−0.36; $P < .001$

(continued)

TABLE I. *(Continued)*

Food	Year Country Author (Study name)	Study population	Study type	I C	FA outcome	FA outcomes in relation to allergen-consumption patterns
Multiple foods*	2016 United Kingdom Perkin[33] (EAT)	n = 1,303 normal-risk infants Exclusively breastfed	Randomized controlled trial	I: 6 allergenic foods = 4 g protein/wk/food* from 3 mo C: standard guidelines, introduce from 6 mo	Food allergy by OFC at 1 y and 3 y	Peanut I: 7 of 571 (1.2%) C: 15 of 597 (2.5%) OR 0.49 (0.20 − 1.19) p=0.11 Egg I: 21/569 (3.7%) C: **32/596 (5.4%)** OR 0.69; 95% CI 0.40−1.18; $P = .17$
Egg	2017 Australia Palmer[34] (STEP)	n = 820 Infants of atopic mothers No known allergic disease	Randomized controlled trial	I: pasteurized raw whole egg powder (0.4 g protein) daily from 4 to 6 mo C: placebo	Egg allergy by positive SPT and OFC at 12 mo	I: 26 of /371 (7%) C: 39 of 377 (10.3%) OR 0.75; 95% CI 0.48−1.17; $P = .20$
Egg	2013 Australia Palmer[35] (STAR)	n = 86 Moderate to severe eczema	Randomized controlled trial	I: pasteurized raw whole egg powder (0.9 g protein) daily 4−8 mo and cooked egg from 8 mo onward C: placebo	Egg allergy by OFC at age 12 mo	I: 14 of 42 (33%) C: 18 of 35 (51%) OR 0.65; 95% CI 0.38−1.11; $P = .11$
Egg	2017 Germany Bellach[36] (HEAP)	n = 406 Normal-risk infants with egg-specific IgE < 0.35 kU_A/L	Randomized controlled trial	I: pasteurized egg white powder (2.5 g protein) 3 times a week from 4 to 6 mo C: placebo	Egg sensitization by sIgE ≥ 0.35 kU_A/L at 12 mo	I: 3 of 142 (2.1%) C: 1 of 156 (0.6%) OR 3.30; 95% CI 0.35−31.32; $P = .35$
Egg	2017 Australia Tan[37] (BEAT)	n = 319 high-risk infants with first-degree relative with history of atopy, and egg white SPT < 2 mm	Randomized controlled trial	I: pasteurized whole egg powder (0.35 g) from 4 mo and cooked egg from 8 mo onward C: placebo	Egg sensitization by egg white SPT ≥ 3 mm at 12 mo	I: 13 of 122 (10.7%) C: 25 of 122 (20.5%) OR 0.46; 95% CI 0.22−0.95; $p = 0.03$
Egg	2017 Japan Natsume[38] (PETIT)	n = 121 high-risk infants with atopic dermatitis	Randomized controlled trial	I: 50 mg heated egg powder (6−9 mo) then 250 mg heated egg powder (9 −12 mo) C: placebo	Egg allergy by OFC at 12 mo	I: 5 of 60 (8.3%) C: 23 of 61 (37.7%) OR 0.221; 95% CI 0.090−0.543; $P = .0013$
Milk	2021 Japan Sakihara[39]	n = 504 normal-risk infants	Randomized controlled trial	I: 10 mL CMP formula daily C: avoidance	Cow's milk allergy by OFC at 6 mo	I: 2 of 242 (0.8%) Cl: 17 of 249 (6.8%) RR 0.12; 95% CI 0.01−0.50; $P < .001$

C, Control; *CMP,* cow's milk protein; *I,* intervention; *OFC,* oral food challenge; *NA,* not available; *sIgE,* serum immunoglobulin E; *SPT,* skin prick test.
*Cow's milk, peanut, egg, sesame, fish, wheat.

introduction of heated egg from 6 to 12 months of age reduced the risk of egg allergy at age 1 year, even in infants without AD.

An updated systematic review and meta-analysis concluded that there was high-certainty evidence (9 trials, n = 4,811) that egg introduction between 3 to 6 months of age was associated with a 40% reduction in the risk of egg allergy (relative risk [RR] = 0.60; 95% confidence interval [95% CI] 0.46−0.77); high-certainty evidence (4 trials, n = 3,796) that peanut introduction between 3 to 10 months of age was associated with a 69% reduction in the risk of peanut allergy (RR = 0.31; 95% CI 0.19−0.51); but the evidence linking the timing of cow's milk introduction to the risk of cow's milk allergy was of very low certainty.[45]

This field of research demonstrates the juxtaposition of the opposing pathways; environmental food allergen exposure through the skin in active AD induces FA and early oral food allergen exposure can effectively mitigate this adverse outcome, offering protection against FA.

ALLERGIC RHINITIS AND ASTHMA

Common patterns of indoor and outdoor allergen exposure

House dust mites, particularly *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, are among the most common allergens worldwide.[46] Their presence is largely influenced by humidity and temperature, with variations in distribution depending on geographical regions and seasons.[47] Within the same region, dust mites are more prevalent in private homes, especially those associated with higher socioeconomic and educational levels, lower population densities, older homes, and the absence of air conditioning.[48-51]

Cockroaches are significant indoor environmental allergens, particularly in inner-city areas.[52] Cockroach allergens are excreted through feces or released from their bodies.[53-55] Indoor and outdoor mold exposure has been linked to allergic diseases in children.[56] Atmospheric mold levels are generally higher than indoor levels.[56,57] Indoor molds comprise a combination of outdoor mold influx and those generated from indoor sources.[58] Indoor mold levels are higher in water-damaged homes, where exposure might involve other harmful substances.[59] Mouse allergens are also a significant concern owing to their association with allergic diseases, particularly in urban areas with concentrated poverty.[60] Mouse allergen levels can be substantial not only in households but also in schools.[61,62] The major mouse allergens are synthesized in the mouse liver and secreted in the urine.[63] Aerosolization of mouse allergens serves as a significant route of exposure.[61]

Global pet ownership varies widely, with an average of 23% of people owning cats and 33% owning dogs.[64] In a study conducted in the United States, over 50% of households owned pets, and 12% of the population demonstrated sensitization to pet allergens.[65] Whereas pet allergens are high in households with pets, they are also frequently detected in schools, day cares, and homes without pets.[65-67]

The types of outdoor pollens and molds and their concentrations vary by region and season,[68,69] and atmospheric pollen levels and allergen concentrations fluctuate in similar patterns.[70] Aeroallergens can attach to other fine particles that have adjuvant properties, including diesel combustion by-products, pollutants, and submicron biological particles.[71]

Aeroallergen exposure should be evaluated not only in terms of the exposure itself but also by considering various factors that can influence aeroallergen concentrations, such as climate and geographic region. Furthermore, the distribution of indoor and outdoor allergens is anticipated to evolve due to ongoing changes in urbanization, climate change, and lifestyle shifts. Climate change might expand the geographic range of pollen and mold spores, and increasing urbanization and indoor living could elevate exposure to indoor allergens such as dust mites and pet dander. In addition, changes in environmental policies and advancements in housing and ventilation systems could further influence allergen exposure patterns.

Inner-city environments have frequently been the focus of studies on allergen exposure and allergic diseases, because they provide critical insights into the interplay between environmental and socioeconomic factors shaping health outcomes.[72] The neighborhoods disproportionately house Black and Hispanic/Latinx communities, who are more likely to face structural inequalities that further increase their exposure to environmental allergens.[73] These conditions contribute to significant disparities in allergic diseases by increasing exposure to prevalent environmental allergens such as mouse and cockroach allergens as well as mold.[74]

Aeroallergen exposure in early life and allergic sensitization and disease

Early-life allergen exposure can modify allergic sensitization versus tolerance and the development of allergic diseases through immune system modulation, barrier function disruption, microbiome alterations, and environmental factors, which vary with genetic susceptibility.[75-77] The timing of exposure (prenatal, lactational, or postnatal periods), the amount of allergen exposure, and interactions with factors such as air pollution further influence these associations (Figure 1).[75-81]

Cockroach exposure in children with asthma is associated with cockroach sensitization and acute exacerbations of asthma.[82,83] For example, high-level cockroach exposure in children with asthma and cockroach allergy is associated with increased asthma morbidity,[82] and similar relationships exist for other indoor allergens such as mouse and cat.[62,84] However, in a multicenter birth cohort study of children in disadvantaged neighborhoods, cockroach, mouse, and cat allergen levels in house dust obtained during infancy were inversely associated with recurrent wheezing.[85] Notably, preschoolers with concurrent exposure to rich house dust microbiomes had the lowest rates of allergic sensitization and respiratory symptoms.[86] The sum of exposure to 3 common allergens (cockroach, cat, and mouse) was also related to reduced asthma at ages 7 and 10 years.[87,88]

Similar paradoxical relationships have been described for pets. Exposure to elevated levels of pet allergens in the home is associated with increased asthma attacks in children sensitized to these allergens.[65] Conversely, early-life exposure to dogs reduces rates of recurrent wheezing and early onset of asthma, without affecting the risk of allergic sensitization.[89-91] Similarly, studies designed to dissect which farm exposures are associated with reduced allergic diseases and asthma indicate that exposure to farm animals, as well as barns and farm milk, are related to reduced risk.[92]

These findings suggest that the relationships between early-life allergen exposure, allergic sensitization, and symptoms depend on personal characteristics or other environmental factors.[93,94]

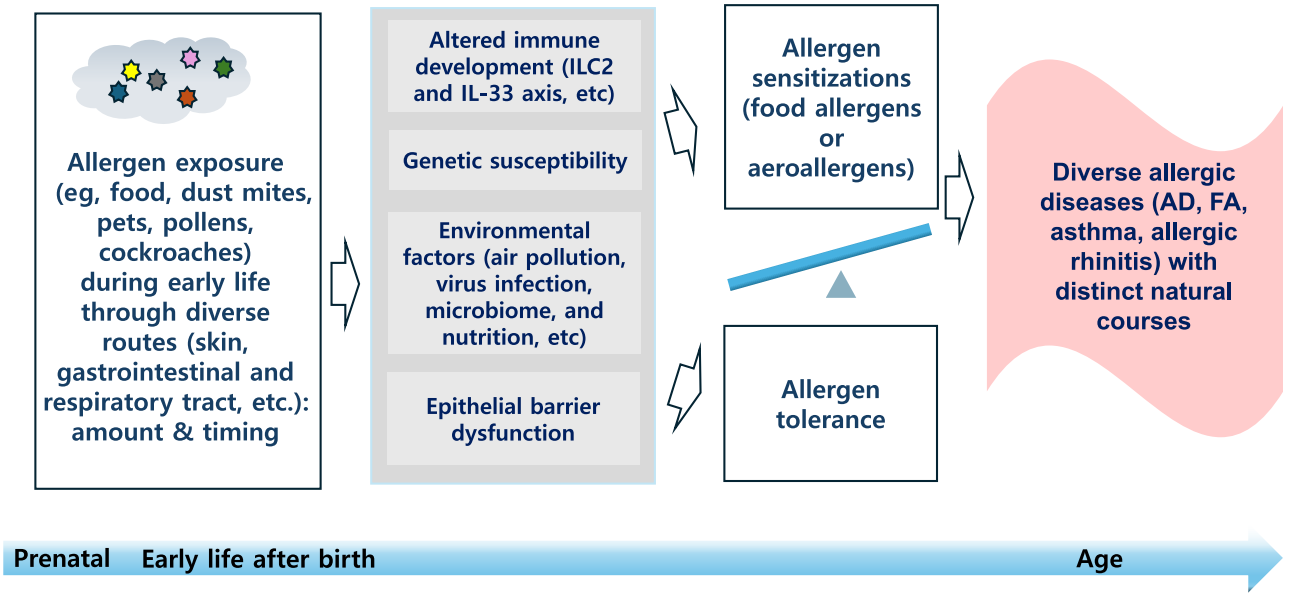

FIGURE 1. How early-life allergen exposure influences the development of allergic sensitization and the progression of allergic diseases. *ILC2,* innate lymphoid type 2 cells.

Epithelial barrier dysfunction could be pivotal in allergic sensitization by facilitating allergen penetration and modulating downstream immune responses. Barrier dysfunction could result from internal factors, such as type 2 inflammation, hormones, and genetic variation, or external factors, including injury, pollutants, proteases, and dietary and microbial factors.[95,96] Environmental tobacco smoke exposure during the first few months of life increases the risk of allergic sensitization, potentially through mucosal damage and inflammation.[80,97] The composition of environmental bacteria encountered during infancy can also affect allergic outcomes.[85] For instance, reduced exposure to *Firmicutes* and *Bacteroidetes* in infancy has been associated with a higher risk of allergic sensitization and atopic wheezing later in childhood.[85] A meta-analysis showed that early-life antibiotic exposure is associated with an increased risk of hay fever, eczema, and food allergies later in life, but no significant association was found with atopy based on skin prick test or specific IgE levels.[98] Early-life antibiotic exposure can influence the development of allergic diseases, such as AD and childhood asthma, by altering the diversity of the gut microbiome in early life.[99,100]

Toxic or immunostimulatory properties of some allergens might also increase their ability to promote sensitization. Some studies have associated cockroach allergen exposure in early life with allergic sensitization. This relationship is influenced by polycyclic aromatic hydrocarbon levels and genetic factors, such as glutathione-S-transferase μ 1.[101] Cockroach allergen exposure in mouse airways can damage airway epithelial cells and induce allergic inflammation.[102] Components of cockroach allergens, including glycans and serine protease activity, can drive allergic inflammation.[52,103]

Effects of aeroallergen exposure on immune development

Newborns typically exhibit low interferon responses, which may contribute to a Th2-skewed immune pattern.[104-106] House dust mite allergens contribute to the development of allergic diseases by directly activating group 2 innate lymphoid cells via the Toll-like receptor (TLR4)—mediated ERK/p38/NF-κB (NF-κB) nuclear factor kappa B) signaling pathway.[107] In addition, house dust mite sensitization interacts with the TLR4 rs1957911 polymorphism, influencing the development of allergic rhinitis, which highlights the interactions of genetic and innate immune mechanisms in the development of allergic diseases in exposure to house dust mite.[108]

Environmental molds and their components, including proteases and chitin, promote IL-25, IL-33, and thymic stromal lymphopoietin and activating type 2 innate lymphoid cells, leading to Th2-mediated allergic inflammation.[109,110] Mold components can activate immune cells through pattern recognition receptors, triggering immune responses involving innate and adaptive immune cells, as well as airway epithelial cells.[109]

Exposure to allergens in early life could modulate immune development. For example, allergens in house dust such as dog (suburban homes),[111] cockroach (urban homes),[112] and farm exposures (which are complex)[113] have been related to increased peripheral blood mononuclear cell cytokine responses. Farm exposures during prenatal and early life are associated with increased T regulatory cells and enhanced innate immune responses.[114,115] Also, dust from protective dairy farm environments contains increased quantities of lipocalins, such as Bos d 2 (a major cow allergen). Lipocalins can bind free fatty acids and other molecules, and these complexes can exert immunomodulatory effects and enhance epithelial barrier function.[116]

In summary, early-life exposure to aeroallergens may play a dual role in immune development, with the potential to promote either Th2-mediated responses or protective immunoregulatory effects, depending on the nature, timing, amount, and context of allergen exposure, as well as host susceptibility, including genetics and barrier function. These findings underscore the complex

interplay between environmental exposures, genetic factors, and immune mechanisms in shaping the risk of atopic sensitization and allergic diseases. These findings suggest that early-life allergen exposure alone might not significantly affect the risk of allergic sensitization and diseases.[93,94]

Allergen exposure and the atopic march

The sequential occurrence of allergic diseases during childhood, often termed the "atopic march," remains a topic of debate. Some argue it represents a genuine progression of allergic conditions, whereas others suggest it reflects the co-occurrence of these diseases owing to shared genetic and environmental factors.[117-122] For some children, allergen exposure could facilitate sensitization and also drive the progression of allergic diseases, especially in individuals with epithelial barrier dysfunction, highlighting its pivotal role in this relationship. The AD could increase the risk of allergic rhinitis and asthma by facilitating epicutaneous sensitization to aeroallergens due to epidermal barrier dysfunction.[4]

CLINICAL IMPLICATIONS: ALLERGEN AVOIDANCE AND DISEASE PREVENTION

AD and FA

Clinical trials typically recruit well-defined populations who follow a strict research protocol. In a real-world setting, other considerations that impact efficacy include clinical heterogeneity, optimal window for intervention, treatment adherence, and feasibility of intervention at scale.

A subanalysis from the LEAP cohort found that the protective effect of early peanut consumption was allergen-specific and early peanut introduction also did not accelerate resolution of AD or egg allergy.[123] Pooled data from LEAP and Enquiring About Tolerance (EAT) also showed that the allergen-specific benefit was consistent despite eczema severity and ethnicity.[124]

The Peanut Allergy Sensitization (PAS) cohort was an observational cohort comprising children from LEAP who did not fulfill the original enrollment criteria: who had either very mild eczema or highly sensitized (peanut skin prick test wheal sizes > 4 mm) and, thus, were probably peanut-allergic at the screening visit. They were also followed up to age 60 months and evaluated for peanut allergy using the same LEAP protocol.[125] A combined analysis (LEAP, EAT, and PAS) found that early peanut introduction by 6 months of age across the entire population, with even earlier intervention at age 4 months in those with eczema, would have the greatest benefit on reduction of peanut-allergy burden.[125]

The ability to regularly consume high doses of allergenic foods in infancy limits the efficacy of this intervention. The EAT study (Table I)[33] was a demanding protocol in which the criteria for adherence was defined as "consumption of at least five of the allergenic foods (peanut, cooked egg, cow's milk, sesame, white fish, and wheat) in at least 75% of the recommended amount (3 g of allergen protein/wk) for at least 5 weeks between 3 and 6 months of age." Only 42% of infants were able to fully adhere to this criteria,[126] Although the intention-to-treat analysis did not meet efficacy criteria, early-food introduction was efficacious in the per-protocol analysis, and in a secondary intention-to-treat analysis in high-risk infants (moderately severe eczema or sensitized to 1 or more foods).[127]

Factors associated with nonadherence included increased maternal age, non-White ethnicity, lower maternal quality of life at baseline, food-related allergy symptoms, and reported feeding difficulties by 4 months of age.[126] Furthermore, caregivers struggled with infants' refusal of the allergenic food (causing a sense of defeat), and difficulties with adhering to the complicated regimen.[128] Clinicians advocating for early introduction of allergenic foods in infants for FA prevention should balance these considerations according to each family's specific needs and provide tailored support to promote successful outcomes.

Implementation in the real-world setting is difficult. The Australian EarlyNuts found that, although peanut consumption during the first year of life increased from 28.4% (2,007−2,011) to 88.6% (2,016−2,018) after the rollout of new Australian infant feeding guidelines recommending early peanut introduction, there was no significant decline in peanut-allergy prevalence.[129,130] This could be partly explained by the relatively looser recommendation for the timing of peanut introduction: before the first year of life, compared with the 4- to 6-month age proposed by LEAP/EAT/PAS.

Allergy screening before early-allergen introduction may be neither cost-effective nor feasible across the general population,[131] particularly in low-resourced countries, and could potentially delay allergen introduction while awaiting evaluation. It might be more practical to recommend early-allergen introduction by the age of 4 months for infants with adequate health care provider support to promote adherence, and limit allergy screening to high-risk infants with severe eczema and/or an existing FA. This approach could be used in high-resource countries with increased FA prevalence. In other populations and low-risk infants, parents should be encouraged to start introducing their children to solid foods at 4 to 6 months of age according to cultural practices while continuing breastfeeding, and to adopt a diverse weaning diet inclusive of allergenic foods without delay.[132]

Reducing allergen exposure to prevent allergic rhinitis and asthma

Several interventional studies have tested whether reducing aeroallergen exposure during the prenatal period or infancy can prevent subsequent allergic diseases or asthma (reviewed in[116] and[133]). For example, 3 controlled studies successfully reducing dust mite exposure levels in the home reported no lessening of either asthma or allergic rhinitis.[134] In the Manchester Asthma and Allergy Study, the intervention group had an early reduction in wheeze but increased dust mite sensitization.[134] Several studies included allergen avoidance measures with multimodal interventions including reducing dietary allergens, and smoking cessation yielding mixed results.[135-137] These studies are difficult to compare owing to differences in study design and interventions used, and the inconclusive results preclude consensus recommendations for primary prevention of aeroallergen sensitivity or asthma.

There are several potential reasons why allergen avoidance studies have not consistently improved health outcomes. Perhaps the amount of allergen exposure needed to prevent sensitization and disease is lower than that achieved by previous interventions, Second, reducing home allergen exposure may be insufficient, given that children are exposed to allergens in daycares and other places outside of the home. Finally, it is possible that the main difference between children who develop allergic disease versus

tolerance is not the level of allergen exposure, but instead individual or neighborhood factors that promote sensitization and allergic diseases.

Besides reducing allergen exposure, there are additional potential approaches to primary prevention of respiratory allergy and childhood asthma. Improving epithelial barrier function and the skin and mucosal immune environment in early life could be critical to achieving immune tolerance versus allergic sensitization.[138] In addition, as AD and FA prevention protocols are implemented, it will be interesting to see whether preventing these early atopic outcomes leads to reduced respiratory allergy or morbidity. Results to date have been mixed.[123] Other potential approaches include minimizing exposure to oral antibiotics, pollutants, tobacco smoke, and epithelial irritants, while promoting breastfeeding and healthy diets. Additional dietary factors (fermented food, fiber, and nutritional supplements), commensal bacteria, and bacterial metabolites are being evaluated for therapeutic use in the gastrointestinal tract, skin, and nasal airways.

There is greater evidence to support recommending targeted or multi-allergen avoidance for older children with established allergic asthma. Still, trials for house dust mite, pet, cockroach, mouse, or multi-allergen avoidance have had variable results. The 2020 updates to the National Asthma Education and Prevention Program (NAEPP) guidelines acknowledged the low certainty of evidence that allergen mitigation in the home is beneficial for asthma and recommended a tailored approach for patients with allergy asthma that considers not only individual characteristics of asthma but also participant burden and social barriers to achieving success with allergen interventions.[139]

CONCLUSIONS

Early-life exposure to certain food allergens reduces the risk of allergy to these foods. There are challenges, such as adding sufficient levels of multiple allergens to the infant's diet to achieve tolerance. More studies are needed to understand the mechanisms and antigen specificity of this effect and to refine current protocols to enhance their feasibility. The effects of allergen exposure during early life on aeroallergen sensitivity are more complex. Whereas increased exposure to some antigens (mold or house dust mites) might promote sensitization owing to their enzymatic or immunological properties, broad exposure to allergens and commensal microbes may have trophic effects on the developing immune system. In sensitized children with asthma, allergen exposure can reduce asthma control and promote exacerbations. Mitigating allergens in the home is difficult but may lead to significant improvement for some children. One common feature in the pathogenesis of food and respiratory allergy is the central role of epithelial barrier dysfunction and T2 inflammation. Designing interventions to improve the epithelial milieu in early life could prevent or treat both types of allergic diseases and perhaps other chronic inflammatory conditions.[140]

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