Annales Nestlé

Nutrition Intervention in Allergy Prevention

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Contents

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Policy Statement

The Nestlé Nutrition Institute was created to provide health professionals with up-to-date information on nutrition and nutrition-related disorders in order to enable them to continuously improve patient care based on the latest medical and scientific developments.

One of the key pillars of the Nestlé Nutrition Institute is *Annales Nestlé*, a pediatric journal that has been published on a regular basis since 1942. It contains review articles on clinical practice and research in all fields of pediatrics with focus on nutrition.

Annales Nestlé comprises 3 issues each year and with around 50,000 copies per issue, it is one of the most widely read pediatric journals in the world.

Annales Nestlé is edited by an independent editorial board of opinion leaders in pediatric research, thus guaranteeing the medical and scientific impartiality of the journal, and hence the high level of respect and appreciation in medical and scientific circles. The editorial board sets the editorial policy, identifies topics to be addressed, selects authors and is in charge of the review process of each publication.

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Editorial

In recent years, parents and healthcare providers have increasingly been faced with dilemmas concerning allergy and food. We all ask ourselves why children nowadays are more likely to develop food allergies. Which is better: avoidance of or exposure to food in the prevention and treatment of food allergy? Will early introduction of peanuts or eggs to the diets of infants at high risk of developing food allergy significantly reduce the risk of peanut or egg allergy? Can early exposure to a food allergen, such as peanuts, through (broken) skin contribute to food allergy development? Breast is best, but does breastfeeding reduce the risk of allergy? What is the role of protein hydrolysates in reducing the risk of eczema and allergies? What are the current recommendations for allergy prevention?

The rising number of children and adults with allergic disorders worldwide is a major public health concern. Traditionally, it was a major problem in populations with a Western lifestyle; however, in recent years, it has also become a problem in less affluent countries. The pathophysiology is multifactorial. In addition to a predisposing genetic background, a number of environmental factors may play a role in the development of allergic disorders, including the mode of birth, antibiotic use, gut microbiota, lack of breastfeeding, and early infant diet. Currently, avoidance of the allergenic protein in any form is the only available treatment. While some allergies (e.g., cow's milk allergy), especially non-IgE-mediated allergies, are generally outgrown during early childhood or, at the latest, during adolescence, others are not. For example, peanut allergy is seldom outgrown. Allergic diseases can be fatal, and, in addition to this uncommon but significant consequence, they may impose a considerable socioeconomic burden and can have a negative impact on the quality of life of both children and their families.

As "prevention is better than cure," this issue of *Annals of Nutrition and Metabolism* was designed to address some of the most pressing issues and questions in the field of allergy prevention through nutrition interventions, which healthcare professionals can use in daily practice. The issue has 4 chapters, with each chapter written by one or more expert(s) in the field. Topics include basic concepts such as current knowledge of the mechanisms of allergen tolerance and clinical issues such as the role of breastfeeding (often hotly debated), the timing of the introduction of complementary feeding (with special emphasis on recent randomized controlled trials evaluating the effects of early versus late introduction of potentially allergenic foods), and finally, the role of protein hydrolysates in allergy prevention, recently challenged by some investigators.

Each chapter focuses on specific issues and stands alone. However, overlap was unavoidable, reflecting the novelty and importance of some recent findings. As black-and-white thinking is uncommon in science and can be dangerous, we believe that nuanced commentaries on the same topic made by the contributing authors may be of special value to the reader.

While some answers to questions on allergy prevention through dietary interventions have become available, there are still many remaining questions. Rapid progress in the field of allergy research is expected and no doubt will bring about a number of exciting discoveries. Thus, in the future, while the questions may remain the same, the answers soon may be different. Stay tuned!

Finally, as editors, we would like to thank all contributing authors for their hard work.

Hania Szajewska
Raanan Shamir

FOCUS

Oral tolerance is a state of active nonresponsiveness to ingested soluble antigens mediated by gut-associated intestinal lymphoid tissue

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Mechanisms of Tolerance Induction

by Anna Nowak-Węgrzyn and Pantipa Chatchatee

Key insights

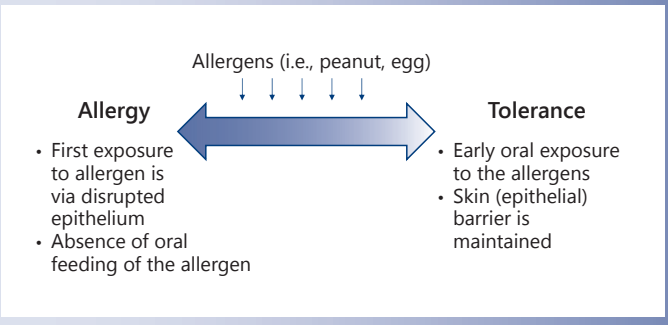
Food allergy arises when oral tolerance fails to develop in early life or is breached at an older age. The initial exposure to food allergens occurs predominantly via the gastrointestinal tract or the skin, and can occur at different pre- and postnatal stages. Exposure to food allergens such as peanut and hen's egg via an inflamed and disrupted epithelial barrier in the absence of oral feeding is an important pathway of allergic IgE sensitization in infants with severe atopic dermatitis. An additional route of allergic sensitization to food could be via the airway tissues.

Current knowledge

Food allergy is defined as an immune-mediated adverse reaction to specific foods. This problem is becoming more widespread and affects up to 8% of children and 5% of adults in Western countries. Currently, there are no effective strategies to induce permanent tolerance: management of food allergies consists of recognizing the adverse reactions and treating the symptoms. Due to the immaturity of their gut barrier and immune system, infants and young children are particularly susceptible to food allergy.

Practical implications

Recent evidence points towards the protective effect of early feeding with peanut and egg in children with eczema, thereby harnessing the pathways that underlie oral tolerance to counteract epicutaneous exposure. An addendum to the NIAID food allergy guidelines recommends the introduction of peanut into the diet of infants with severe eczema or egg allergy, starting at 4–6 months of age. Another approach is to maintain and restore the skin barrier in high-risk infants. Yet another means of inducing gut tolerance is via probiotic and prebiotic supplementation. Despite the promise of oral, epicutaneous, and sublingual methods of food immunotherapy, these have not yet been proven to restore permanent oral tolerance.



A key mechanism of allergic sensitization is the initial exposure to food allergens via an inflamed and disrupted epithelial barrier in the absence of oral feeding.

Recommended reading

Von Berg A, Koletzko S, Grubl A, Filipiak-Pittroff B, Wichmann HE, Bauer CP, et al: The effect of hydrolyzed cow's milk formula for allergy prevention in the first year of life: the German Infant Nutritional Intervention Study, a randomized double-blind trial. J Allergy Clin Immunol 2003;111:533–540.

Du Toit G, Roberts G, Sayre PH, et al; LEAP Study Team: Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med 2015;372:803–813.

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Nutrition Intervention in Allergy Prevention

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Mechanisms of Tolerance Induction

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Key Messages

- **Early introduction of peanut and egg is associated with a decreased risk of development of allergy to these high-risk foods, especially in infants with severe eczema.**
- **Restoration of the skin barrier via meticulous and gentle skin care represents another approach to reducing epicutaneous exposure to a food allergen present in the environment and may contribute to a decreased risk of allergic sensitization.**
- **Interventions aimed at correcting the underlying alterations in the gut microbiota of infants via supplementation with probiotics have potential applications for prevention and treatment of food allergy.**
- **Oral, epicutaneous, and sublingual immunotherapy induce desensitization in the majority of the treated subjects with food allergy, but their capacity to restore permanent oral tolerance remains unclear.**

Keywords

Oral tolerance · Gut-associated lymphoid tissue · Food allergy · Food hypersensitivity · Food allergy prevention · Food allergy treatment · Eczema · Atopic dermatitis · Probiotics · Prebiotics · Microbiota · Desensitization

Abstract

Food allergy results from failure in oral tolerance that usually occurs in infancy or early childhood. Exposure to peanut and hen's egg via the inflamed and disrupted epithelial barrier in children with severe atopic dermatitis is a risk factor for the development of allergy to these foods and supports the hypothesis that epicutaneous exposure in the absence of oral feeding is an important pathway of allergic IgE sensitization in infants. In recent years, the collective evidence has pointed toward the protective effect of an early feeding with peanut and egg in children with eczema, taking advantage of the pathways underlying oral tolerance to counteract epicutaneous exposure. An addendum to the NIAID food allergy guidelines recommends introduction of peanut into the diet of 4- to 6-month-old infants with severe eczema or egg allergy as an effective strategy to prevent peanut allergy. Strategies aimed at restoring the skin barrier are currently explored as an alternative approach of prevention of eczema and allergic sensitization. Manipulation of the diet via sup-

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plementation with probiotics and prebiotics to restore the healthy gut microbiota represents another potential pathway to induction of tolerance in the gut. Oral, epicutaneous, and sublingual routes of food immunotherapy are promising and induce desensitization in the majority of the treated subjects with food allergy but are not proven to restore permanent oral tolerance. Rigorous multicenter randomized clinical trials are necessary to elucidate the optimal timing, dose, duration, as well as the preventive and therapeutic effects of these diverse approaches.

Introduction

Food allergy is defined as an immune-mediated adverse reaction to food [1]. Food allergy has become an important, global public health problem [2]. Overall, food allergy is estimated to affect up to 8% of children and up to 5% of adults in countries with a so-called Western lifestyle, such as the USA, the UK, Canada, Australia, and Western Europe. The prevalence of peanut allergy documented by a physician-supervised oral food challenge in a population-based cohort of 12-month-old infants in Australia was 3%, reaching epidemic proportions [3]. Currently, there are no proven strategies to induce permanent tolerance; the management relies on recognition of adverse reactions and treatment of symptoms [1, 4]. Considering the risk of fatal anaphylaxis, the negative impact on the nutritional status and quality of life, as well as the cost to the individual and the society, finding effective preventive and therapeutic strategies for food allergy has become a focus of many international research efforts [5, 6].

Food Allergy Risk Factors

Food allergy is most common in infants and young children, as a result of the immaturity of the gut barrier and the immune system in these age groups [7, 8]. Immune deficiencies – including selective IgA deficiency, common variable immunodeficiency, and IPEX (immunodysregulation polyendocrinopathy enteropathy X-linked syndrome) – are associated with an increased prevalence of food allergy [9]. Genetic factors play an important role in the development of food allergy; however, epigenetic and environmental factors seem to have more relevance in the recent increase in food allergy prevalence (Table 1) [10–18].

Oral Tolerance

Food allergy results from failure to develop primary oral tolerance or from breach in previously established oral tolerance. Oral tolerance is a state of active nonresponsiveness to ingested soluble antigens mediated by gut-associated intestinal lymphoid tissue. Gut-associated intestinal lymphoid tissue is the largest secondary lymphoid organ in the human body that mounts a protective immune response against a pathogen and ignores a benign antigen, e.g., food or commensal bacteria. Oral tolerance is a highly efficient mechanism that fails in only about 4–8% of the humans who develop food allergy. In mouse models of food allergy, it is very difficult to induce allergic sensitization via oral or parenteral immunization to foods such as cow's milk, egg white, or peanut included in the diet [19]. However, an exposure through the damaged skin (mimicking a skin barrier defect occurring in atopic dermatitis [AD]) is more likely to induce IgE sensitization to ovalbumin in hen's egg white and peanut proteins [20, 21].

Mechanism of Oral Tolerance

T cells have been identified as the pivotal cells in oral tolerance based on the experiments in animal models where tolerance can be transferred to naive animals through the transfer of regulatory T (T_{reg}) cells (Table 2) [8].

Inducible FOXP3$^+$ CD4$^+$ T_{reg} cells are central to the maintenance of immune homeostasis and tolerance throughout the body, particularly in the gut [22, 23]. Intestinal FOXP3$^+$ T_{reg} cells regulate mucosal immune responses at multiple cellular levels [24, 25]. Foxp3$^+$-induced T_{reg} cells are required for oral tolerance and their depletion results in defective oral tolerance in mice and food allergy in humans [26]. Natural development of oral tolerance in food-allergic children is associated with increased Foxp3$^+$ T cells. The resolution of cow's milk allergy (CMA) in children is associated with an increased frequency of peripheral blood CD4$^+$ CD25$^+$ T_{reg} cells after an oral milk challenge and reduced proliferation of milk-specific T cells [27, 28]. Depletion of CD4$^+$ CD25$^+$ T_{reg} cells restores the in vitro proliferative response in milk-tolerant individuals [27].

Another cell type important for oral tolerance are CD103$^+$ dendritic cells in the murine and human mesenteric lymph nodes that express high levels of the enzyme retinal dehydrogenase 2 (RALDH2), which converts retinal to retinoic acid. Retinoic acid derived from CD103$^+$ dendritic cells determines gut-homing activity and reg-

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Table 1. Genetic and environmental risk factors for food allergy

Type	Effect on food allergy risk
Genetic[1]	
Family history, twin studies	2–10× increased risk
Genetic variants in the HLA-DQ locus (HLA-DQB1*02 and DQB1*06:03P)	Increased risk of peanut allergy
Loss of function mutation in filaggrin gene	Increased risk for eczema and peanut allergy in children
Common variant rs1933064 in filaggrin gene	In Japan: associated with increased risk of food IgE sensitization
Interleukin-10 polymorphism – 1082G/A	Increased risk of CMA in Brazilian children
STAT6 polymorphisms	Increased risk of nut allergy
GG genotype of *STAT6* polymorphism rs324015	Significant association with longer persistence of CMA than the AA + AG genotype states
Defects in *FOXP3*	Association with IPEX and food allergy
Lower FOXP3 mRNA expression	Associated with asthma and food allergy
Epigenetic[1]	
Differential DNA methylation profile of $CD4^+$ T-cell MAPK signaling pathways	Increased risk of IgE-mediated food allergy in children
Low methylation level of *FOXP3* CpG sites	Association with increased antigen-induced T_{reg} cell function
Two top-associated SNPs and CpG sites' methylation levels in the genes *HLA-DQB1* and *HLA-DRB1*	Increased risk of food allergy
Environmental	
Treatment with proton pump inhibitors	Increased risk of IgE sensitization to food due to increased pH and impaired digestion of proteins
Diet low in fiber	Effects on commensal probiotic bacteria, changes bacterial metabolites (such as short-chain fatty acids) that are crucial for maintaining mucosal integrity and promoting oral tolerance by epigenetic effects on T_{reg} cells
Alterations in microbiome Birth by cesarean section Lack of microbial exposure (including *Helicobacter pylori* infection) in early life	In vitro alterations in the gut microflora might change Toll-like receptor signalling and integrity of intestinal epithelial cells in children with food allergy

CMA, cow's milk allergy; IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; MAPK, mitogen-activated protein kinases. [1] Reviewed by Li et al. [11].

ulatory activity of responder T cells. $CD103^+$ dendritic cells also promote the development of T_{reg} cells from naive T cells as well as via indoleamine 2,3-dioxygenase and secretion of transforming growth factor β (TGF-β) [29–32].

Allergic Sensitization

Food allergy develops when oral tolerance fails to develop early in life or is breached at an older age. Allergic sensitization refers to the event when, following an initial exposure to an antigen, presentation by antigen-presenting cells leads to antigen-specific immune reactions, including the generation of antigen-specific T lymphocytes and the production of antigen-specific IgE antibodies by plasma cells and subsequent binding to its high-affinity receptors on the surface on mast cells and basophils. The initial exposure to food allergens occurs predominantly via the gastrointestinal tract or the skin. The initial contact and subsequent sensitization with a food allergen can occur at different stages of pre- and postnatal life.

The initial exposure to allergens may occur prenatally [33–35]. The immunologic environment of the placenta likely plays a critical role in the development of the fetal immune system. A recent study examining the influence of in vitro allergen exposure in human placentae showed a distinct cytokine/chemokine milieu in allergic and non-atopic mothers with increased allergen-induced placental IL-6 and TNF-α production in atopic mothers. This might explain the higher incidence of sensitization in off-

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Table 2. Evidence supporting the pivotal role of T regulatory lymphocytes in oral tolerance

T_{reg} cell phenotype	Mechanism of action	Consequence of defect
Intestinal FOXP3$^+$ T_{reg} cells; in the intestinal lamina propria, they constitute a much higher proportion: more than 30% of CD4$^+$ T cells in the colonic lamina propria and about 20% in the small intestinal lamina propria	Constitutive expression of CTLA4, inducible T-cell co-stimulator, IL-10, TGF-β, and IL-35 Inhibition of the bystander T cells to maintain immune tolerance to dietary components and intestinal microbiota Control of expansion of T follicular helper cell (T_{FH} cell) populations Suppression of immunopathology mediated by effector T cells [22]	Mice with fewer numbers or lower suppressive activity of colonic T_{reg} cells are more susceptible to infection and mucosal injury Depletion of Foxp3$^+$-induced regulatory T_{reg} cells results in defective oral tolerance in mice Lack of Foxp3$^+$ T cells leads to enteropathy, eczema, and elevated IgE in both mice and humans (IPEX syndrome) [24–26]
Th3 cells that are CD4$^+$ CD25$^-$ Foxp3$^-$ and express latency associated peptide	Their suppressive effect is dependent on TGF-β [93, 94] Th3 cells promote the development of iT_{reg} cells through the secretion of TGF-β [23]	

IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome.

spring of allergic mothers [36–38]. However, modification of the maternal diet during pregnancy did not influence the development of food allergies in the infant later in life seen in the analysis of multiple interventional studies following children up to 10 years of age [39].

Presence of food allergens in breast milk might trigger sensitization in the infant [40, 41]. For many years, guidelines have recommended avoidance of peanut and tree nuts for the first 3 years of life and some also included avoidance during pregnancy (AAP Committee on Nutrition, 2000). These recommendations have been modified after studies failed to show a correlation between maternal diet and development of atopic disease [42]. In contrast to past recommendations, more recent studies have shown a protective effect of high allergen consumption during pregnancy [43]. High consumption of peanuts and tree nuts during pregnancy was found to be associated with lower rates of food allergy in children [44]. A study investigating associations between maternal consumption of common childhood allergens during pregnancy and childhood outcome of allergic disease and asthma showed a decreased incidence of asthma and atopic disease at the age of 8 years in children whose mothers had a high consumption of peanut, milk, and wheat during early pregnancy [45]. It is likely that other routes of sensitization like transcutaneous exposure are key factors in the development of food allergy.

A clear association has been shown between early onset of AD and the development of food allergies [46]. The impaired skin barrier leads to increased transcutaneous passage of antigens and subsequent sensitization. Children with severe AD who used skin care products containing peanut oil showed higher rates of peanut sensitization, supporting the theory of transcutaneous sensitization [46]. It was found that about 50% of children with moderate-to-severe AD had a loss of function mutation of filaggrin and also showed increased sensitization to peanut [10]. This was also noted in mouse models: filaggrin-deficient mice showed a Th17-dominated skin inflammation and susceptibility to epicutaneous sensitization [47]. In mouse models of egg and peanut allergy, skin exposure to these foods promotes the development of specific IgE sensitization to ovalbumin and peanut, whereas an oral exposure promotes oral tolerance [20, 21]. Cutaneous exposure to food antigens induces thymic stromal lymphopoietin production, activation of basophils that produce IL-4, production of Th2 cytokines, and accumulation of mast cells in the gut [52]. Mutations in genes encoding proteins that determine the integrity of the skin barrier, such as *FLG* encoding filaggrin, are independent risk factors for peanut allergy [52]. Figure 1 describes differential immune responses to food protein in the gastrointestinal tract and skin.

Sensitization via Food Ingestion

The introduction of food proteins as in infant formula or complementary food leads to a change in the infant's gut microbiota, and the relative immaturity of the infant's

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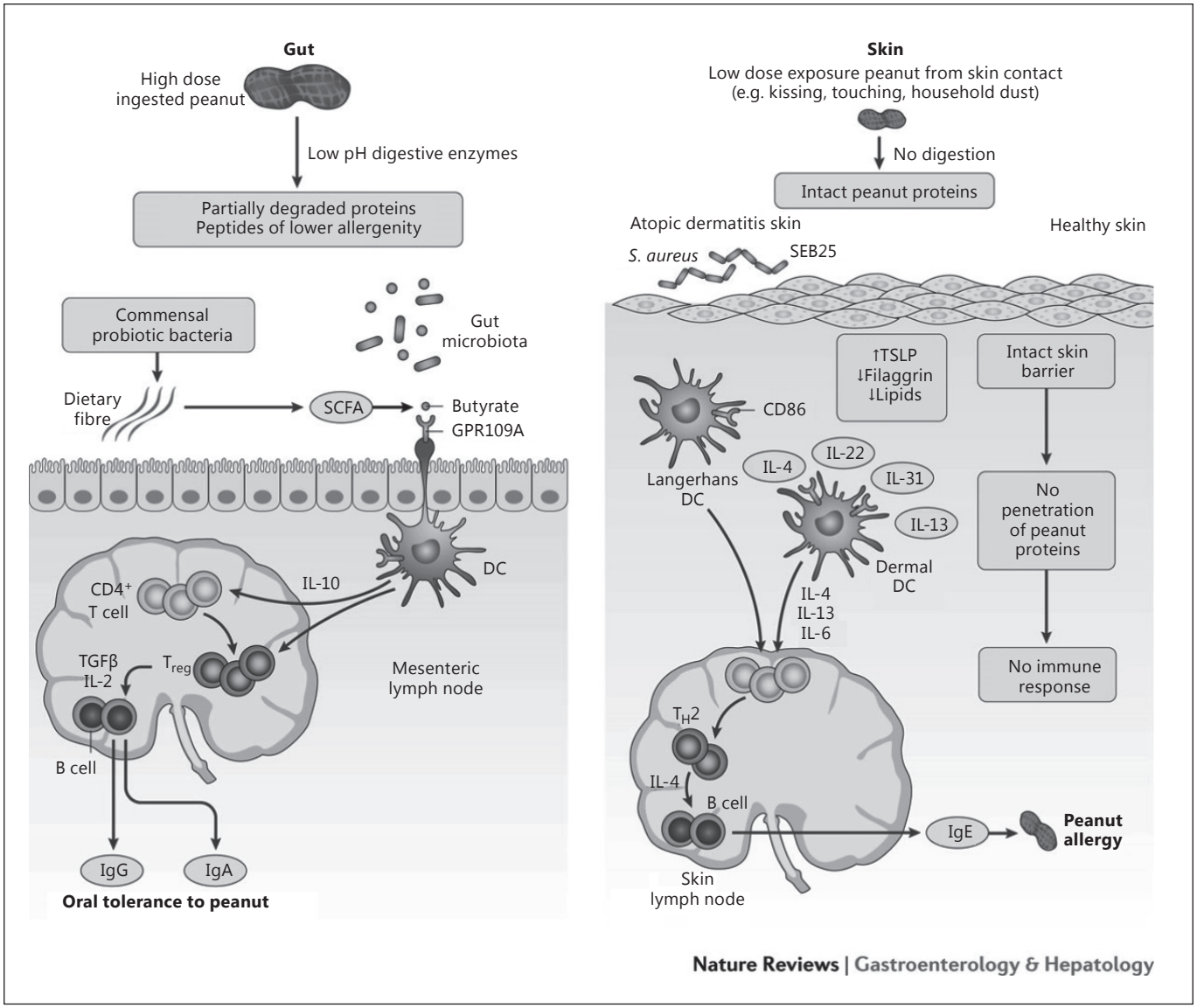

Fig. 1. Differential immune responses in the gut (oral tolerance) and skin (IgE sensitization and food allergy) using peanut allergy as an example. Source: Nowak-Wegrzyn et al. [98].

digestive tract may allow for passage of allergens in a form or amount that will trigger allergic sensitization rather than tolerance (Table 3).

An additional route of allergic sensitization to food could be via the airways, as seen in the occupational settings (e.g., food industry) with exposure to aerosolized food proteins such as wheat and egg [53]. Additionally, systemic reactions to ingested egg can occur in adults exposed to pet bird dander via inhalation due to the presence of a cross-reactive antigen, alpha-livetin in both the dander and egg yolk [54]. It remains to be determined whether primary sensitization via the airways might occur in infants with gastroesophageal reflux through microaspiration of the gastric content.

Tolerance Induction for Food Allergy Prevention

There is no consensus whether food allergies can be prevented and what is the optimal duration of exclusive breastfeeding as well as timing of supplemental formula and solid food introduction.

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Table 3. Mechanisms limiting the access of intact ingested food antigens to the immune system and consequences of their developmental immaturity in infants

Mechanism	Developmental predisposition to food allergy in newborns, infants, and young children
Physical	
Block penetration of ingested antigens	
Intestinal mucus coat (glycocalyx) Intestinal microvillus membrane composition Intestinal peristalsis	Altered antigen binding and transport through mucosal epithelial cells is caused by immaturity of intestinal microvillous membranes in infants
Enzymatic	
Breakdown of ingested antigens	
Gastric acid and pepsins Pancreatic enzymes Intestinal enzymes Intestinal epithelial cell lysozyme activity	Basal acid output is low during the first month of life and the intestinal proteolytic activity is immature until about 2 years of age
Immunologic	
Block penetration of ingested antigens	
Antigen-specific s-IgA in gut lumen	The newborn lacks IgA and IgM in exocrine secretions and salivary s-IgA is absent at birth and remains low during the early months of life
Clear antigens penetrating the gastrointestinal barrier	
Serum antigen-specific IgA and IgG Reticuloendothelial system	Humoral immune system is immature and has low levels of circulating antibodies

Breastfeeding

Human breast milk contains variety of bioactive molecules which are involved in infant growth, actively modulate immune system and gut microbiota, confer passive immunity, and have a positive impact on cognitive development and metabolism [55]. Breast milk contains gut trophic factors (epidermal growth factor, insulin growth factor, and TGF-β), capable of actively stimulating crypt and villi formation, decreasing intestinal permeability in the first week of life. In addition, lactoferrin and vitamin A in breast milk may affect the neonatal gut barrier. Human milk oligosaccharides downregulate CD14 expression in human enterocytes, and epidermal growth factor suppresses TLR4 signaling, leading to attenuation of lipopolysaccharide-induced inflammation [56]. Breast milk is thought to contribute to the diversification of the neonatal microbiota via maternal IgA. Several studies have provided evidence for breast milk to contain bacteria, approximately 103–104 CFU/mL, suggesting that breast milk microbiome may provide a source of commensal bacteria for the infant gut.

Food protein transfer via breast milk is the first exposure to foods for the infant. In a mouse model, mice exposed to nanograms of egg ovalbumin antigen through breast milk were protected from ovalbumin-induced allergic airway disease and TGF-β from breast milk was critical for tolerance induction, suggesting that variability in breast milk allergen content, TGF-β, and allergen-specific immunoglobulin may contribute to heterogeneity of results on allergy prevention by breastfeeding. Presence of peanut in maternal diet was associated with a reduced risk of food allergy in the offspring in both humans and mice [41, 45, 57]. Collectively, there is currently no conclusive evidence that breastfeeding protects from development of food allergy, potentially reflecting the environmental factors that affect the composition of maternal milk. It remains to be determined whether maternal supplementation with probiotic and/or vitamin A might improve the pro-tolerogenic capacities of human breast milk [58, 59]. Currently, the general consensus is that breastfeeding for at least 6 months should be promoted in view of the known and recognized nutritional and immunological benefits of breast milk [60].

Infant Formula

Considering that intact food proteins have the highest allergenicity and the efficacy of hypoallergenic infant formulas in the dietary management of established CMA, a

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variety of hydrolyzed formulas based on cow's milk protein (CMP) have been investigated for the prevention of food allergy and atopic diseases. It has been hypothesized that partially hydrolyzed proteins (whey- or casein-derived peptides of various molecular weights) will result in better oral tolerance induction in a setting of immature gastrointestinal and immune systems, compared to intact CMP. The largest and most rigorous clinical trial to investigate the preventative effect of hypoallergenic formulas, the German Infant Nutritional Intervention Study (GINI Study) reported that infants fed extensively hydrolyzed casein formula (EHCF) for the first 4 months had a reduced rate of AD at 1 year of age compared with infants fed cow's milk formula (CMF) [61]. Feeding with partially hydrolyzed whey or or EHCF was associated with a reduced rate of AD but not of asthma or allergic rhinitis at the ages of 3, 6, 10, and 15 years compared with feeding with CMF [62–65]. However, a meta-analysis of 37 eligible intervention trials of hydrolyzed formula including over 19,000 participants concluded that there was no consistent evidence that partially or extensively hydrolyzed formulas reduce the risk of allergic outcomes in infants at high risk [66]. A limitation of the meta-analysis is that it compared studies using different hydrolyzed formulas within each category. This approach is questionable because different biological effects of various hydrolysates are not only based on molecular mass distribution, but also on different peptide characteristics and sequence profiles.

A large single-center prospective study from Israel examined the prevalence of CMA in 13,019 infants followed up for 2 years [67]. CMP was introduced to healthy infants at a mean age of 61.6 ± 92.5 days and to infants with IgE-mediated CMA at 116.1 ± 64.9 days. The odds ratio (OR) for developing CMA was 19.3 (95% confidence interval [CI] 6.0–62.1) among infants exposed to CMP after more than 15 days compared with those exposed in the first 14 days of life. These findings suggest that early exposure to CMP may be protective against the development of CMA [67].

Timing of Foreign Food Protein Introduction

It was once assumed that the avoidance of allergenic foods and delayed introduction into the diet would prevent allergy by avoiding a so-called "window of physiologic susceptibility" associated with developmental immaturity of the gastrointestinal and immune systems (Table 3). However, the implementation of these expert opinion-based guidelines has been paralleled by a significant increase in the prevalence of peanut allergy in the societies with a so-called Western lifestyle, such as the USA, the UK, Australia, and Western Europe [2]. Subsequent studies determined that risk of peanut allergy is highest in infants with severe eczema, in those with mutations in filaggrin gene resulting in an impaired skin barrier function, and in those not eating peanut but exposed to peanut in the household dust. In addition, the prevalence of peanut allergy was 10-fold higher among Jewish children in the UK compared with Israeli children of similar ancestry [68]. In Israel, peanut-containing foods are usually introduced in the diet when infants are approximately 7 months old and consumed in substantial amounts, whereas in the UK children do not typically consume any peanut-containing foods during their first year of life [68]. These observations inspired a number of clinical trials investigating the early introduction of solid foods for prevention of food allergy [4].

Peanut

A landmark clinical trial (Learning Early About Peanut Allergy, LEAP) randomized 640 infants between the ages of 4 and 11 months with severe eczema, egg allergy, or both (considered at high risk for peanut allergy) to consume or avoid peanut until 60 months of age (Table 4) [48]. Early introduction of peanut dramatically (overall by 81%) decreased the development of peanut allergy among children at high risk for this allergy. Early oral introduction of peanut induces oral tolerance that precedes potential IgE sensitization to peanut via the disrupted skin barrier. Considering the strong protective effect of this intervention and the size of the clinical trial, an addendum to the 2010 NIAID guidelines for food allergy diagnosis and management has been published in 2017 [69]. The guidelines recommend introducing peanut-containing foods in age-appropriate forms to infants at risk (with severe eczema, egg allergy, or both) preferably during breastfeeding, starting at the age of 4–6 months. The document provides practical recommendations on the safe introduction of peanut to such infants. In addition, the guidelines recommend introducing peanut to infants with mild-to-moderate eczema around 6 months of age. For infants without eczema or any food allergy, free introduction of peanut into the diet, together with other solid foods that are age-appropriate, as per family preferences is recommended.

High-Risk Foods (Peanut, Cooked Egg, Cow's Milk, Wheat, Sesame, and Whitefish)

A similar concept has been tested in the EAT trial that evaluated whether the early introduction of allergenic

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Table 4. Clinical trials of early food allergen introduction

Name of trial; author [Ref.] (year); country; food	Target population	Design Number of subjects	Primary outcome	Results	Reactions/risk of early introduction
Peanut					
Learning Early about Peanut Allergy (LEAP); Du Toit et al. [48] (2015); UK; peanut	High risk (infants with moderate/ severe eczema and/or egg allergy)	Open-label RCT – n = 640 (530: negative SPT, 98: SPT 1–4 mm) – Enrolled at 4–11 months of age – Peanut consumption or avoidance until 60 months of age	Peanut allergy at age 60 months confirmed by OFC	Peanut allergy in avoidance vs. consumption – SPT-negative group: ITT: 13.7 vs. 1.9% (95% CI 3.4–20.3; $p < 0.001$) Relative reduction in consumption group: 86.1% PP: 13.9 vs. 0.4% ($p < 0.001$) – SPT-positive group: ITT: 35.3 vs. 10.6% (95% CI 4.9–43.3; $p = 0.004$) Relative reduction in consumption group: 70.0% PP: 34.0 vs. 0.0% ($p < 0.001$)	No significant differences in rates of hospitalization or serious adverse events
Persistence of Oral Tolerance to Peanut (LEAP-On); Du Toit et al. [49] (2015); UK; peanut	High risk (infants with moderate/ severe eczema and/or egg allergy (LEAP participants)	Open-label RCT – n = 556 from LEAP study – Peanut avoidance for 12 months	Peanut allergy determined by OFC after 12 months of peanut avoidance	Rate of peanut allergy after 12 months of peanut avoidance in LEAP peanut-avoidance vs. peanut-consumption group ITT: 18.6 vs. 4.8%, ($p < 0.001$) PP: 19.2 vs. 2.1% ($p < 0.001$)	
Peanut, hen's egg, cow's milk, whitefish, sesame, wheat					
Enquiring about Tolerance (EAT); Perkin et al. [50] (2016); UK; cow's milk, hen's egg, peanut, cod, sesame, wheat	General population (exclusively breastfed infants)	Open-label RCT – n = 1,303 – Enrolled at 3 months of age – Consumption of 6 allergenic foods vs. exclusive breastfeeding until 6 months of age	IgE-mediated food allergy determined by OFC to any of the 6 allergenic foods between 1–3 years of age	Food allergy in early-introduction vs. standard-introduction group ITT: 5.6 vs. 7.1% RR 0.80 (95% CI 0.51–1.25; $p = 0.32$) Peanut allergy: 1.2 vs. 2.5% ($p = 0.11$). Egg allergy: 3.7 vs. 5.4% ($p = 0.17$) PP: 2.4 vs. 7.3% ($p = 0.01$) RR 0.33 (95% CI 0.13–0.83; $p = 0.01$) Peanut allergy: 0 vs. 2.5% ($p = 0.003$) Egg allergy: 1.4 vs. 5.5% ($p = 0.009$)	No cases of anaphylaxis with the introduction of foods at home in the early-introduction group
Egg					
HealthNuts; Koplin et al. [70] (2010); Australia; hen's egg	General population	Population-based cross-sectional study – n = 2,589 – Enrolled at 11–15 months of age	Egg allergy by OFC or parental report of a definite reaction to egg	Egg allergy in infants introduced to egg at 4–6 months vs. after (categorized by age of introduction): 7–9 months: aOR 1.3 (95% CI 0.8–2.1) 10–12 months: aOR 1.6 (95% CI 1.0–2.6) >12 months: aOR 3.4 (95% CI 1.8–6.5) ($p < 0.001$) Egg allergy and type of egg introduced at 4–6 months: cooked vs. baked egg: OR 0.2; 95% CI 0.06–0.71; $p = 0.012$)	

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Table 4 (continued)

Name of trial; author [Ref.] (year); country; food	Target population	Design Number of subjects	Primary outcome	Results	Reactions/risk of early introduction
Solids Timing for Allergy Research (STAR); Palmer et al. [71] (2013); Australia; hen's egg	High risk (infants with moderate/ severe eczema, SCORAD ≥15)	RCT, placebo controlled – $n = 86$ – Enrolled at 4 months of age – Consumption of egg powder or placebo until 8 months of age	IgE-mediated egg allergy at age 12 months defined as positive OFC and positive SPT to egg	IgE-mediated egg allergy in egg vs. placebo group: 33 vs. 51% RR 0.65 (95% CI 0.38–1.11; $p = 0.11$)	31% of infants randomized to receive egg had an allergic reaction to the egg powder and did not continue powder ingestion
Starting Time for Egg Protein (STEP); Palmer et al. [72] (2016); Australia; hen's egg	Infants with atopic mothers but without eczema	RCT, placebo controlled – $n = 820$ – Enrolled at 4–6 months of age – Consumption of egg powder or placebo until 10 months of age	IgE-mediated egg allergy at age 12 months defined as positive OFC and positive SPT to egg	IgE-mediated egg allergy in egg vs. placebo group ITT: 7.0 vs. 10.3% aRR 0.75 (95% CI 0.48–1.17; $p = 0.20$) PP: 3.0 vs. 9.9% aRR 0.32 (95% CI 0.16–0.65; $p = 0.002$)	No anaphylactic reactions to the pasteurized whole egg powder on initial introduction 3 infants (2 in the egg group) experienced anaphylaxis after egg challenge
Hen's Egg Allergy Prevention (HEAP); Bellach et al. [73] (2016); Germany; hen's egg	General population (nonsensitized, hen's egg sIgE <0.35 kU_A/L)	RCT, placebo controlled – $n = 383$ – Enrolled at 4–6 months – Consumption of egg white powder or placebo until 12 months of age	Primary: sensitization to hen's egg by age 12 months Secondary: hen's egg allergy	Sensitization to hen's egg in active vs. placebo Modified ITT : 5.6 vs. 2.6% (RR 2.20; 95% CI 0.68–7.14; $p = 0.24$) PP: 4.8 vs. 2.6% (RR 1.84; 95% CI 0.53–6.37; $p = 0.35$) Hen's egg allergy (secondary outcome) in active vs. placebo ITT: 2.1 vs. 0.6% (RR 3.30; 95% CI 0.35–31.32; $p = 0.35$) PP: 0 vs. 0.7% ($p = 1.0$)	Reported reaction to the study powder in active vs. placebo: 7.1 vs. 0.5% ($p = 0.001$) DBPCFC positive in 3/4 subjects in active group (1 FPIES)
Beating Egg Allergy Trial (BEAT); Wei-Liang Tan et al. [74] (2016); Australia; hen's egg	High-risk infants with at least 1 first-degree relative with allergic disease and SPT to egg white <2 mm	RCT, placebo controlled – $n = 319$ – Enrolled at 4 months of age – Consumption of whole egg powder or placebo until 8 months of age	Sensitization to egg on SPTs at 12 months	Sensitization to egg at 12 months in egg vs. placebo group FAS: 10.7 vs.20.5% OR 0.46 (95% CI 0.22–0.95; $p = 0.03$) Relative risk reduction: 48% (95% CI 3–72%) Absolute risk reduction: 9.8% (95% CI 8.2–18.9%) NNT = 11 (95% CI 6–122) PP: OR 0.24 (95% CI 0.09–0.61; $p = 0.0015$) Probable egg allergy in egg vs. placebo group 6.2 vs.10.5%; $p = 0.20$	No serious adverse events FPIES-type reaction occurred in 1 infant in the placebo group (rice powder)

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Table 4 (continued)

Name of trial; author [Ref.] (year); country; food	Target population	Design Number of subjects	Primary outcome	Results	Reactions/risk of early introduction
Prevention of Egg Allergy with Tiny Amount Intake (PETIT); Natsume et al. [75] (2016); Japan; hen's egg	High risk (infants with atopic dermatitis)	RCT, placebo controlled – n = 147 – Enrolled at 4–5 months – Consumption of egg powder or placebo from 6 until 12 months of age – Egg powder dose increment was given in a two-step approach	Egg allergy confirmed by open OFC at 12 months of age	Study was terminated early because of a large group difference at the interim analysis Egg allergy in egg vs. placebo group Primary analysis: 8 vs. 38% Risk difference 29.4% (95% CI 15.3–43.4) NNT 3.40 (2.30–6.52) Risk ratio 0.221 (0.090–0.543; p = 0.0001) PP: 4 vs. 38% Risk difference 33.7% (95% CI 19.0–48.3) Risk ratio 0.114 (0.028–0.464; p < 0.0001) NNT 2.97 (2.07–5.27) Relative reduction: 89%	No acute reaction after first intake of the trial powder No difference in reported reaction at home

RCT, randomized controlled trial; SPT, skin prick test; OFC, oral food challenge; ITT, intention to treat analysis; PP, per protocol analysis; RR, relative risk; DBPCFC, double-blind placebo-controlled food challenge; FPIES, food protein-induced enterocolitis syndrome; NNT, number needed to treat; FAS, full analysis set (the FAS is the analysis set that is as complete and close as possible to the ITT ideal of having primary outcome data on all randomized subjects).

foods into the diet of breastfed infants would protect against the development of food allergy [49]. The EAT trial recruited 1,303 exclusively breastfed infants from the general population who were 3 months of age. They were randomly assigned to the early introduction of 6 allergenic foods (peanut, cooked egg, cow's milk, sesame, whitefish, and wheat; early-introduction group) or to the current practice recommended in the UK of exclusive breastfeeding to approximately 6 months of age (standard-introduction group). The primary outcome was food allergy to 1 or more of the 6 foods in children between 1 and 3 years of age (Table 4). The trial did not show the efficacy of early introduction of allergenic foods in an intention-to-treat analysis. Further per-protocol analysis raised the question of whether the prevention of food allergy by means of early introduction of multiple allergenic foods was dose dependent. The EAT trials also demonstrated that the early introduction of solids is not easy and may not be practical for many families.

Egg

A number of clinical trials investigated the early introduction of egg (Table 4) [70–75]. The overall effect was that the early introduction of egg may confer a preventative effect, although sensitization to egg occurs early and allergic infants may develop anaphylaxis on a first known ingestion of egg white powder regardless of their eczema status [76]. It is likely that the early introduction of baked or lightly cooked egg is safer.

Potential Pitfalls of Early Food Introduction

While the current cumulative evidence favors the early introduction of highly allergenic foods, there are a number of potential problems that have to be considered. Infants without obvious risk factors such as eczema, other food allergies, or a family history of food allergy may develop food allergy and manifest anaphylaxis on a first known ingestion, in particular of egg. This suggests that an even earlier introduction of egg is necessary but may not be feasible. As demonstrated by the EAT study, early (starting at 3 months) introduction of egg, peanut, sesame, and fish may be challenging because age-appropriate forms of these foods are not easily accessible to families. Regular intake of the food, at least 2–3 times per week, is necessary, and some families struggle with incorporating high-risk foods into the daily diet over prolonged periods of time, especially if the food is not a part of the regular family diet. Finally, the studies focus on prevention of IgE-mediated food allergy, and the effects of early introduction on the development of non-IgE-mediated food allergy is unknown. In the LEAP trial, there was 1 case of peanut food protein-induced enterocolitis syndrome

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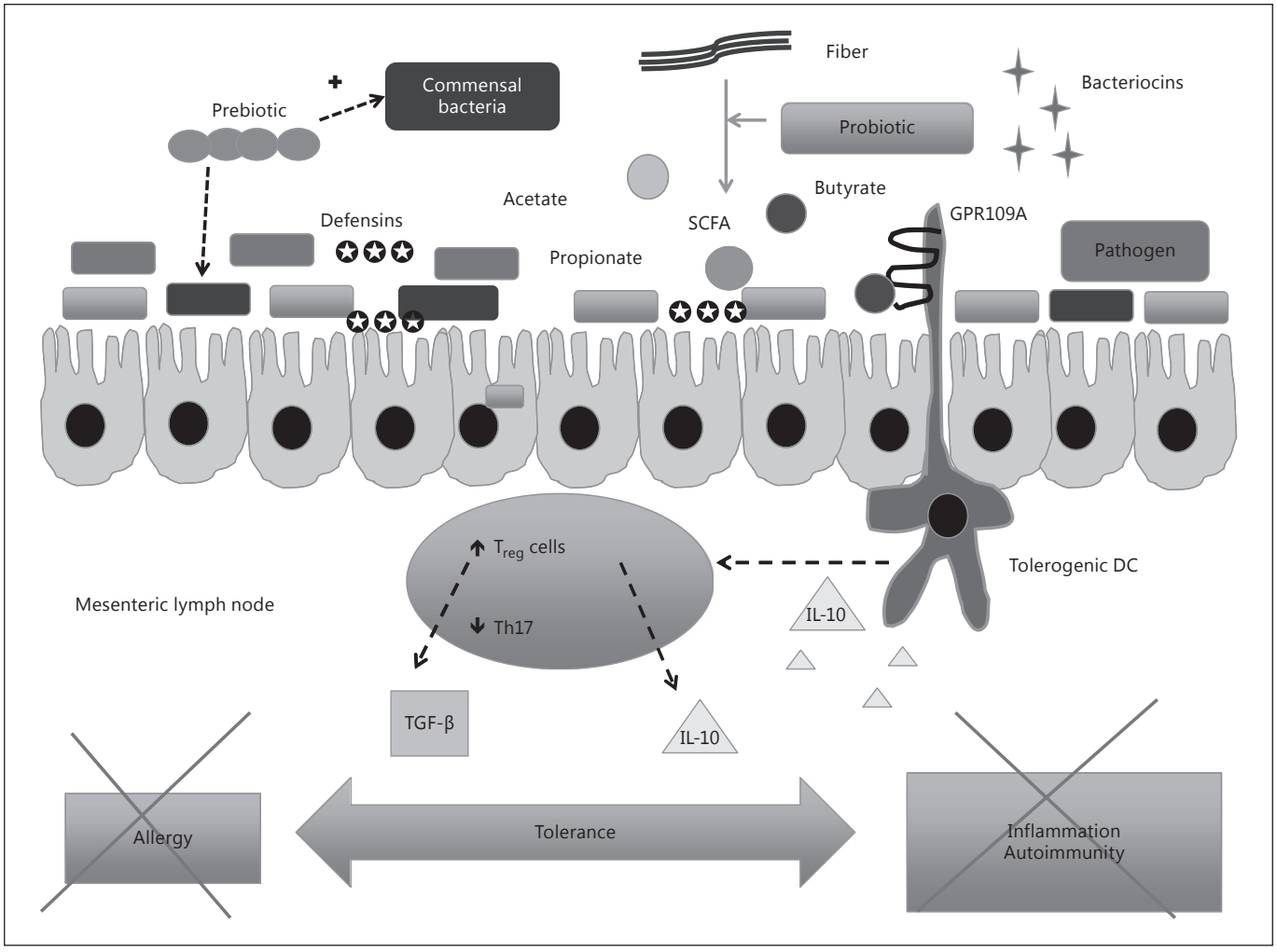

Fig. 2. Probiotics compete with pathogenic organisms for nutrients and binding sites on the intestinal epithelium. Prebiotics support the endogenous colonic commensal bacteria. Probiotics secrete bacteriocins and induce intestinal epithelium to secrete defensins, natural anti-microbial peptides. Probiotics ferment fiber to short-chain fatty acids (SCFA): butyrate, acetate, and propionate. SCFA activate G-protein-coupled receptors (GPCRs) that stimulate colonic dendritic cells and macrophages to secrete IL-10 and promote development of regulatory T lymphocytes (T_{reg} cells) in the mesenteric lymph nodes. T_{reg} cells are a source of tolerogenic cytokines: IL-10 and TGF-β that inhibit allergic and inflammatory responses.

(FPIES). In the EAT trial, there were 10 participants whose families reported FPIES-like reactions (median age, 5 months): 7 in the early-introduction group (6 reporting egg as the trigger, 1 sesame) and 3 in the standard-introduction group (1 fish and prawn, 1 milk, and 1 milk, soya, and rice) ($p = 0.34$). When challenges were undertaken (median age, 16 months) of the 7 early-introduction group participants, 5 had negative challenges, 1 was positive, and 1 did not return for the challenge. Of the 3 standard-introduction group participants, 2 had positive challenges and 1 had a negative challenge. In the HEAP trial, there was 1 case of egg FPIES in the active group, raising concerns about increasing risk for the development of FPIES with early introduction of allergenic foods.

Strategies to Restore the Healthy Gastrointestinal Microbiota

Probiotics

Probiotics are defined as live bacteria that naturally colonize the gastrointestinal tract, and their presence in adequate amounts is associated with health benefits for the host [77]. An altered composition of the gut micro-

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biota might predispose children to food allergy by changing Toll-like receptor signaling and the integrity of intestinal epithelial cells [15]. In a gnotobiotic mouse model, selective colonization of the gut with Clostridia-containing microbiota protects from food allergy via activation of innate lymphoid cells, IL-22 production, and enhancement of intestinal permeability [16]. The gut microbiota may also play a role in the natural history of CMA. Additional potential mechanisms by which probiotics exert pro-tolerogenic effects in the gut are illustrated in Figure 2.

Among 226 children with milk allergy who were enrolled at infancy in the Consortium of Food Allergy observational study of food allergy, the gut microbiome composition at the age of 3–6 months was associated with milk allergy resolution by the age of 8 years (PERMANOVA, $p = 0.047$), with enrichment of Clostridia and Firmicutes in the infant gut microbiome of subjects whose milk allergy resolved [78]. Metagenome functional prediction supported decreased fatty acid metabolism in the gut microbiome of subjects whose milk allergy resolved ($\eta^2 = 0.43$; ANOVA, $p = 0.034$). Therefore, early infancy is a window during which the gut microbiota may determine food allergy outcomes in childhood. Bacterial taxa within Clostridia and Firmicutes could be studied as probiotic candidates for milk allergy therapy.

Supplementation with probiotics has been shown to exert anti-inflammatory properties together with cytokine changes that might skew towards Th1-biased responses and inhibit Th2-biased responses and IgE production. Probiotics were shown to increase secretion of IL-10 and TGF-β by upregulating T_{reg} cells (Fig. 2). A meta-analysis of the randomized controlled clinical trials investigating the use of probiotics in infants for primary prevention of allergies found mild reduction in clinical eczema in infants but insufficient evidence for a general recommendation of probiotic supplementation for prevention of allergic disease or food hypersensitivity [79]. It remains to be determined whether supplementation with probiotic bacteria can correct the underlying alterations in the gut microbiota in children with food allergy [18].

Prebiotics

Prebiotics are food components that are nondigestible and reach the colon where they provide nutrition and stimulate growth and activity of bacteria of the normal gut flora (Fig. 2). They are commonly added as nutritional supplements like oligosaccharides [77]. Pooling of data from multiple studies in a recently updated Cochrane review showed a potential benefit in the prevention of AD, but no conclusive evidence was found regarding the prevention of other allergic diseases or food allergies [80]. In a parallel-group, multicenter, randomized double-blind controlled trial of partially hydrolyzed whey formula containing oligosaccharides (pHF-OS) versus standard CMF, infants with a family history of allergic disease were randomized (stratified by center/maternal allergy) to pHF-OS ($n = 432$) or CMF ($n = 431$) until 6 months of age if the formula was introduced before 18 weeks of age. The primary outcome was cumulative incidence of AD by 12 months in infants randomized at 0–4 weeks (pHF-OS, $n = 375$; control, $n = 383$). At 12 months, there was no difference in AD in the infants fed with study formula (07/347; 30.8%) compared to the infants fed with CMF (112/370; 30.3%; OR 0.99, 95% CI 0.71–1.37; $p = 0.94$). pHF-OS did not change most immune markers including total/specific IgE; however, pHF-OS reduced cow's milk-specific IgG1 ($p < 0.0001$) and increased T_{reg} cell and plasmacytoid dendritic cell percentages [81].

Microbiome Restoration in Infants Born via Cesarean Section

Exposure of newborns to the maternal vaginal microbiota is interrupted with cesarean birthing. Babies delivered by cesarean section (C-section) acquire a microbiota that differs from that of vaginally delivered infants, and C-section delivery has been associated with increased risk for immune and metabolic disorders. In a pilot study, infants delivered by C-section were exposed to maternal vaginal fluids at birth [82]. As in vaginally delivered babies, the gut, oral, and skin bacterial communities of these newborns during the first 30 days of life were enriched in vaginal bacteria – which were underrepresented in unexposed C-section-delivered infants – and the microbiome similarity to those of vaginally delivered infants was greater in oral and skin samples than in anal samples. Although the long-term health consequences of restoring the microbiota of C-section-delivered infants remain unclear, these preliminary results demonstrate that vaginal microbes can be partially restored at birth in C-section-delivered babies [82, 83].

Skin Barrier Restoration

Considering that an impaired and inflamed skin barrier is a hallmark of AD and a risk factor for the development of peanut allergy, strategies aimed at the restoration and protection of the skin barrier represent an alternative approach to prevent food allergy. Two small clinical trials conducted in the USA and Japan reported a reduction in eczema prevalence in infants at risk [84, 85].

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Table 5. Comparison of food allergen immunotherapy in current clinical trials

	OIT	SLIT	EPIT
Daily maintenance dose, food protein[1]; specific foods studied	300–4,000 mg Peanut, cow's milk, hen's egg, wheat OIT with multiple foods is feasible	2–7 mg Peanut, cow's milk, hazelnut, peach Single food treatment has been investigated; multiple food application potentially feasible	50–500 μg, usually 250 μg Peanut, cow's milk Single food treatment
Observed dosing	Up-dosing every 1 or 2 weeks	Up-dosing under observation	Initiation and periodic observation
Safety	Less desirable, common adverse events, frequent gastrointestinal complaints, about 5–8% risk of eosinophilic esophagitis, risk of anaphylaxis <1% of doses; higher risk of adverse events in those allergic to pollen	More desirable; usually mild, local, oro-pharyngo-laryngeal pruritus	More desirable, usually mild, local cutaneous reactions
Efficacy	More desirable	Less desirable; limited by the low total maximum dose	Ongoing investigation
Desensitization	Large effect, 75–80% (usually, the patients who finish the protocol achieve desensitization)	Moderate effect	Ongoing investigation
Long-term tolerance/ sustained unresponsiveness	Variable response, dependent on food (peanut 50%, egg 28%), maintenance dose and duration of therapy Limited evidence	Ongoing investigation	Ongoing investigation
Immunomodulation	Significant; increases in food-specific IgG4 and decreases in food-specific IgE and skin prick test wheal diameters	Present	Present in mice: ongoing investigation in human subjects
Adherence	Suboptimal primarily because of chronic gastrointestinal adverse effects and need for lifestyle modifications[2]	Better than with OIT	Better than with OIT

OIT, oral immunotherapy; SLIT, sublingual immunotherapy; EPIT, epicutaneous immunotherapy. [1] Few studies explored less frequent (every other day of twice a week maintenance dosing therapy with promising results [96, 97]). [2] OIT doses should be taken with meal; physical activity has to be avoided for 1–2 h after ingestion; dosing should be withheld with illness (febrile illness, asthma exacerbation); dose reduction may be necessary during pollen season.

In an Irish birth cohort, transepidermal water loss (TEWL) was measured at birth (day 2) and at 2 and 6 months in 1,903 infants [86]. The prevalence of AD was 18.7% at 6 months and 15.53% at 12 months. In a logistic regression model, upper-quartile TEWL measurement on day 2 of life strongly predicted AD at 12 months (area under the receiver operating characteristic curve, 0.81; $p < 0.05$). Lowest-quartile TEWL on day 2 of life was protective against AD at 12 months. An upper-quartile TEWL at the age of 2 months was also strongly predictive of AD at 12 months (area under the receiver operating characteristic curve, 0.84; $p < 0.05$). At both ages, this effect was independent of parental atopy, filaggrin status, or report of an itchy flexural rash at 2 months. Associations were increased when the parental atopy status or child filaggrin mutation status were added into the linear regression model. Furthermore, food IgE sensitization was present in 6.27%, and food allergy prevalence was 4.45% [86]. Egg was the most prevalent allergen (2.94%), followed by peanut (1.75%) and cow's milk (0.74%). Day 2 upper-quartile TEWL (>9 g water/m^2/h) was a significant predictor of food allergy at the age of 2 years (OR 4.1, 95% CI 1.5–4.8). Day 2 TEWL was in the upper quartile in 75% of children with food allergy at 2 years of age. Even in those without AD, infants with upper-quartile day 2 TEWL were 3.5 times more likely to have food allergy at 2 years than infants in the lowest quartile (95% CI 1.3–11.1; $p = 0.04$). This important study demonstrated that an impairment of skin barrier function at birth and at 2 months precedes clinical manifestations of AD. In addition to providing important mechanistic insights into disease pathogenesis, these findings have practical implications for the optimal timing of interventions for the prevention of AD. Neonatal skin barrier dysfunction predicts food allergy at 2 years of age, supporting the concept of transcutaneous allergen sensitization, even in infants

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who do not have AD. TEWL could be used for stratifying infants in the first few days of life before development of AD or food allergy for targeted intervention studies to potentially alter the atopic march. Currently, large clinical trials are underway to enhance the skin barrier from birth, using emollients and decreasing bathing frequency, to reduce the incidence of AD and food allergy in high-risk neonates.

Tolerance Induction for Food Allergy Treatment

Hypoallergenic Formula with Probiotics in CMA

A nonrandomized study investigated 260 Italian children (median age, 5.92 months) diagnosed with CMA, both IgE-mediated (42.7%) and non-IgE-mediated. Children were fed with: EHCF (n = 55); EHCF + *Lactobacillus rhamnosus* GG (LGG) (n = 71); hydrolyzed rice formula (n = 46); soy formula (n = 55); and amino acid-based formula (n = 33). The formula choice was at the discretion of the managing physician. The rate of children acquiring oral tolerance after 12 months (determined by an oral food challenge) was significantly higher ($p < 0.05$) in the groups receiving EHCF (43.6%) or EHCF + LGG (78.9%) compared with the other groups (hydrolyzed rice formula [32.6%], soy formula [23.6%], and amino acid-based formula [18.2%]). The rate of tolerance acquisition was influenced by 2 factors: (1) IgE-mediated mechanism (B –2.05, OR 0.12, 95% CI 0.06–0.26; $p < 0.001$); and (2) formula choice, such that those receiving either EHCF (B 1.48, OR 4.41, 95% CI 1.44–13.48; $p = 0.009$) or EHCF + LGG (B 3.35, OR 28.62, 95% CI 8.72–93.93; $p < 0.001$). This study suggested that EHCF (especially with added LGG) may accelerate tolerance acquisition in children with CMA compared to other formulas [88]. Feeding with EHCF + LGG led to a significant increase in fecal butyrate levels, suggesting that EHCF + LGG promotes tolerance in infants with CMA, in part, by influencing the strain-level bacterial community structure of the infant gut [18]. In a follow-up study, 40 children (aged 3–18 months) were enrolled: 10 children with active IgE-mediated CMA (group 1), 10 children who outgrew CMA after dietary treatment with an EHCF containing the probiotic LGG (group 2), 10 children who outgrew CMA after treatment with other formulas (group 3), and 10 healthy controls (group 4). FoxP3 TSDR demethylation and expression were measured in mononuclear cells purified from peripheral blood of the 4 groups of children. FoxP3 TSDR demethylation was significantly lower in children with active IgE-mediated CMA than in either children who outgrew CMA or in healthy children. Formula selection influenced the FoxP3 TSDR demethylation profile, suggesting that tolerance acquisition in children with IgE-mediated CMA involves epigenetic regulation of the FoxP3 gene.

A more rigorous parallel-arm randomized controlled trial investigated whether the administration of EHCF containing the probiotic LGG can reduce the occurrence of other allergic manifestations. Children with IgE-mediated CMA were randomly allocated to the EHCF or EHCF + LGG groups and followed up for 36 months [89]. The main outcome was the occurrence of at least 1 allergic manifestation (eczema, urticaria, asthma and rhinoconjunctivitis) diagnosed according to standardized criteria. Tolerance acquisition was evaluated every 12 months. A total of 220 children (147 males, 67%) with a median (IQR) age of 5.0 (3.0–8.0) months were randomized: 110 children were placed in the EHCF group and 110 children were placed in the EHCF + LGG group. In the complete case analysis, the absolute risk difference for the occurrence of at least 1 allergic manifestation over 36 months was –0.23 (95% CI –0.36 to –0.10; $p < 0.001$) and the absolute risk difference for the acquisition of cow's milk tolerance was 0.20 (95% CI 0.05–0.35; $p < 0.01$) at 12 months, 0.24 (95% CI 0.08–0.41; $p < 0.01$) at 24 months, and 0.27 (95% CI 0.11–0.43; $p < 0.001$) at 36 months. This study suggested that EHCF + LGG might reduce the incidence of other allergic manifestations and hasten the development of oral tolerance in children with IgE-mediated CMA. The results are very interesting and should be replicated in different patient populations.

Immunotherapy for Food Allergy

There are no currently approved therapies for food allergy; a number of immunotherapeutic strategies are currently being evaluated for IgE-mediated food allergy [89]. All of them rely on regular exposure to the food allergen via the oral (oral immunotherapy, OIT), sublingual (sublingual immunotherapy), or epicutaneous (epicutaneous immunotherapy) route; subcutaneous vaccines based on modified hypoallergenic major peanut allergens are currently undergoing phase I clinical trials in adults [5, 6]. While OIT induces a temporary state of increased threshold of clinical reactivity to the food allergen, dependent on daily OIT dosing (referred to as desensitization), no food immunotherapy is proven to induce/restore permanent oral tolerance (Table 5). Improvements in safety allowing for the inclusion of patients with severe phenotypes of food allergy and asthma,

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refinements in dose and duration of treatment to enhance efficacy, and understanding of the mechanisms underlying desensitization and tolerance are desirable. Emerging evidence suggests that early initiation of peanut OIT in infants and young children may offer superior efficacy and safety due to lower OIT doses used and a more favorable response to immunomodulation in a developing immune system [91]. Large clinical trials of rigorous design and adequate sample sizes are necessary to fully evaluate the effects of food immunotherapy. Alternative approaches utilizing a combination of several synergistic treatments (e.g., OIT and anti-IgE monoclonal antibody or OIT and probiotics) or modified hypoallergenic molecules combined with adjuvants may be necessary for patients with the most severe phenotypes of food allergy [92, 93].

Summary

Food allergy results from failure in oral tolerance that usually occurs in infancy or early childhood. Exposure to food allergen such as peanut and hen's egg via the inflamed and disrupted epithelial barrier in the absence of oral feeding is an important pathway of allergic IgE sensitization in infants with severe AD. In recent years, the collective evidence has pointed toward the protective effect of an early feeding with peanut and egg in children with eczema, taking advantage of the pathways that underlie oral tolerance to counteract epicutaneous exposure. An addendum to the NIAID food allergy guidelines recommends the introduction of peanut into the diet of infants with severe eczema or egg allergy, starting at 4–6 months of age, as an effective strategy to prevent peanut allergy. Strategies aimed at restoring the skin barrier are currently explored as an alternative approach of prevention of eczema and allergic sensitization. Manipulation of diet via supplementation with probiotics and prebiotics to restore the healthy gut microbiota represents another potential pathway to induction of tolerance in the gut. Oral, epicutaneous, and sublingual routes of food immunotherapy are promising and induce desensitization in the majority of the treated subjects but are not proven to restore permanent oral tolerance. Rigorous multicenter randomized clinical trials are necessary to elucidate the optimal timing, dose, duration, as well as the preventive and therapeutic effects of these diverse approaches.

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FOCUS

Oral tolerance is a state of active nonresponsiveness to ingested soluble antigens mediated by gut-associated intestinal lymphoid tissue

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Breastfeeding, Childhood Asthma, and Allergic Disease

by Wendy H. Oddy

Key insights

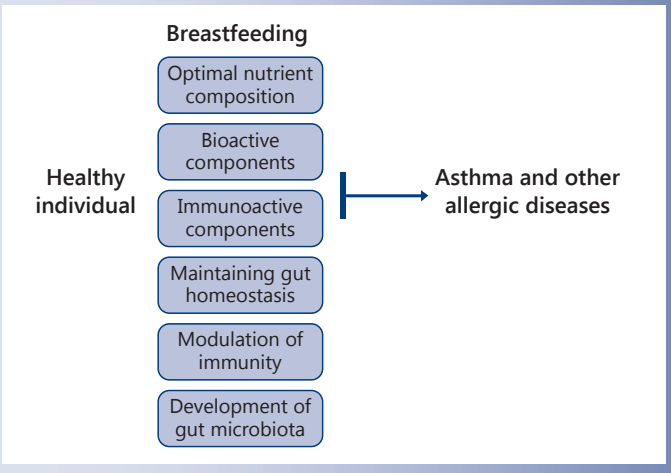
Breastfeeding may protect against childhood asthma and allergic disease, but this is controversial. Breastfeeding is critical for optimum immune development of the infant through bioactivity in milk and through impact on healthy establishment of microbiota. Breast milk is best for babies because of its immunomodulatory effects and protection against early infections. Because early infections are a major risk factor for asthma and allergic disease, protection through breastfeeding may be a pathway that shields against allergic disease.

Current knowledge

Exclusive breastfeeding for the first 6 months of life, and up to 2 years or longer, is encouraged as the "gold" standard for infant feeding because breastfeeding has health benefits for mother and child. Human maternal milk is uniquely suited to the human baby with nutritional composition as well as bioactive and immunological factors that promote healthy development. Breastfeeding has been associated with protection against early respiratory infections, and the observed association between breastfeeding and asthma at early ages may be mediated by the protection of breastfeeding on infections. Compared to formula-fed infants, breastfed infants have a healthier microbiota that may be linked to a reduced risk of allergic disease.

Practical implications

Exclusive or predominant breastfeeding to at least 6 months of age with continued breastfeeding up to 2 years is advised to protect against early infections and strengthen the immune system. Infants should be introduced to "tastes" of allergenic foods, such as egg and peanut, slowly from 4 to 6 months to develop oral tolerance. Lactating mothers should eat a healthy diet to ensure the quality of their breast milk and improve the quality and diversity of their microbiota.



The protective effects of breastfeeding may extend against the development of asthma and allergic diseases.

Recommended reading

Scholtens S, Wijga AH, Brunekreef B, Kerkhof M, Hoekstra MO, Gerritsen J, et al: Breastfeeding, parental allergy and asthma in children followed for eight years: the PIAMA birth cohort study. Thorax 2009;64:604–609.

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Nutrition Intervention in Allergy Prevention

Annales Nestlé

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Breastfeeding, Childhood Asthma, and Allergic Disease

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Key Messages

- Breastfeeding may protect against the development of asthma and allergic disease in children, although this topic has been controversial for more than 8 decades.
- Breastfeeding is recommended for at least the first 6 months of life and up to 2 years for immunological development of the infant.
- Breastfeeding may influence immune responses through the bioactive, immune-modulating properties of breast milk, or through the impact of milk type on intestinal microbiota.
- The composition of breast milk cytokines deserves further investigation, because cytokines may provide protection against wheeze and subsequent asthma in childhood.

Keywords
Breastfeeding · Allergic disease · Childhood asthma

Abstract
The worldwide prevalence of childhood asthma has been increasing considerably, and the protection afforded by breastfeeding in its development has been the subject of controversy for more than 80 years. Previous systematic reviews have generally found a protective effect of breastfeeding on allergic outcomes, although many studies have methodological limitations. Although breastfeeding is protective against lower respiratory tract infection during infancy, such protection has not been demonstrated for asthma in all studies. Breastfeeding has health benefits for the mother and child. Exclusive breastfeeding for the first 6 months of an infant's life, with continued breastfeeding for up to 2 years or longer, is recognized as the "gold" standard for infant feeding because human milk is uniquely suited to the human infant, and its nutritional content and bioactivity promote a healthy development. There is increasing concern that the practice of delaying complementary foods until 6 months may exacerbate the risk of allergic disease. Breast milk contains immunological components that protect against infections and allergic disease in infancy. The composition of human breast milk is complex, containing factors that interact with the infant immune system and intestinal milieu including allergens, cytokines, immunoglobulins, polyunsaturated fatty acids, and chemokines. Transforming growth factor β is a cytokine in human milk involved in maintaining intestinal homeostasis, inflammation regulation, and oral tolerance development. Modern day society, with increased standards of hygiene, has changed the gut flora of Western infants, potentially impacting the risk of developing immune-mediated diseases including allergic disease and

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asthma. Microbial diversity is intrinsic to healthy immune maturation and function. Compared to breastfed infants, formula-fed infants had lower bacterial diversity and an altered intestinal microbiota in the first few weeks of life associated with an increased risk of eczema and asthma. Favorable gut colonization through continued breastfeeding may promote tolerance as well as protection when complementary feeding is initiated.

Introduction

Breastfeeding and Childhood Illness

Breastfeeding has numerous health benefits for the mother and child [1]. Exclusive breastfeeding for the first 6 months of an infant's life, with continued breastfeeding for up to 2 years or longer, is recognized as normal and the "gold" standard for infant feeding [2, 3]. This is because human maternal milk is uniquely suited to the human infant, and its nutritional composition and non-nutritive bioactive factors promote healthy development and ultimately survival. Breast milk contains immune factors such as IgA antibodies protecting against many health problems in infancy, such as necrotizing enterocolitis, overweight and obesity, diabetes, infections, and allergic disease [2, 4], as well as reducing the risk of diseases later in life [5].

In the past 30 years, the evidence for global breastfeeding recommendations has evolved remarkably. Epidemiological studies combined with growing insights from epigenetics, stem cell research, and the "developmental origins of health and disease" hypotheses offer strong and solid support to the concept that breast milk is best for human infants. Never before in science history has so much been known about the complex significance of breastfeeding for mothers and their children.

However, the protection afforded by breastfeeding against the development of childhood asthma and allergic disease has been the subject of controversy in the literature. Although breastfeeding is protective against lower respiratory tract infection during infancy, such protection has not been demonstrated for asthma in all studies. Issues related to study design, analytical methods, and confounding have greatly complicated the interpretation and comparison of studies. Furthermore, asthma has a complex phenotype in which numerous genetic and environmental determinants interact. Consequently, the effect of any single determinant is likely to be small and the independent effects difficult to quantify. Asthma is common at a population level, and breastfeeding is amenable to intervention, so a small effect may have implications for public health. For this reason, it is important to establish whether breastfeeding modifies the risk of childhood asthma, even if the effect is small.

Against this background of breast milk significance, there is evidence that breastfeeding may protect against the development of asthma and allergic disease in children although this has been controversial since it was first observed more than eight decades ago [6, 7].

Definition of Infant Feeding

The World Health Organization [8] defines "exclusive breastfeeding" as feeding with breast milk "only" with no other liquid, solids, or vitamin drops. An infant who receives water or juice but not formula is considered "predominantly breastfed," whereas an infant who receives formula milk, if only for one feed, is considered "partially breastfed," and "never breastfed" refers to a situation where breastfeeding was never initiated. Thereafter, to meet their evolving nutritional requirements, infants should receive nutritionally adequate and safe complementary foods while breastfeeding continues for up to 2 years of age or beyond [9].

Definition of Allergic Disease

The definitions of allergic disease are varied and inconsistent across studies. For example, different studies have used allergen sensitization, self-report, or doctor diagnosis to define presence of food allergy, with the first two definitions correlating poorly with food challenge for diagnosis of food allergy (the gold standard). Similarly, diverse outcome definitions have been applied in studies evaluating the impact of breastfeeding on eczema, asthma, and allergic rhinitis [4].

To limit the scope of this review, the focus is largely on asthma. Asthma represents a chronic, complex, polygenic interaction in individuals with varying environmental exposures [10]. Asthma is the most chronic disease of childhood and the leading cause of morbidity in children globally as measured by emergency department visits, hospitalizations, and days of missed school [11, 12]. Childhood asthma prevalence worldwide has been increasing over decades, and a number of theories are proposed to explain this startling trend. An overview of current thinking in relation to the breastfeeding, asthma, and allergic disease debate is given – from epidemiological, nutritional, immunological, and gut microbial colonization perspectives.

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Determinants of Childhood Asthma and Allergic Disease

The disease has a broad spectrum of possible determinants extending from genetics to lifestyle to environmental factors. Environmental allergens such as smoking in the household, house dust mite, grasses, or pollens may be implicated. Lifestyle and environmental factors including obesity, living in an urban environment, dietary patterns including fast food and poor diet quality, formula milk feeding, gut flora imbalance, smoking, pollution, and infection (viral) have been associated with asthma exacerbations in childhood [12]. Susceptibility to asthma may be increased by early life factors including low birthweight, preterm birth, young maternal age, and male gender. On the other hand, early exposure to respiratory infections may protect, although certain infections may increase the risk [13]. Breastfeeding is implicated because it has been shown to protect against early respiratory and other infections [14].

Breastfeeding has been shown to protect against early respiratory and other infections

Epidemiological Studies on Breastfeeding, Asthma, and Allergic Disease

Epidemiological studies in the debate as to whether breastfeeding can have a role in protecting against allergic disease and asthma in early childhood provide conflicting results. While breastfeeding is recommended for all infants irrespective of allergic heredity [15], with protective effects of breastfeeding on asthma reported in young children [16–18], other studies of children at high [19, 20] or low risk [21] or adults [22, 23] show no protective effects.

Systematic Reviews

Previous systematic reviews have found a protective effect of breastfeeding on allergic outcomes, although most studies have methodological limitations, such as heterogeneity or noncompliant standards. A recent review and meta-analysis aimed to identify and summarize publications on breastfeeding and childhood asthma risk in the general population as well as stratify analyses and meta-regression to explore sources of heterogeneity [24]. Compared with other reviews, this review includes a large number of studies, restricts search and study selection minimally, and includes studies of different methodologies, operational definitions for breastfeeding and asthma, and sets of confounders [24]. These criteria may have increased the variability of effect estimates. Limitations were overcome by performing meta-analyses in standardized subgroups and meta-regressions with a broad array of predictors. An assessment of the methodological quality of the studies using criteria based on Kramer's standards [25] was made and a score based on these criteria was included in the analyses, which addressed heterogeneity between studies. The authors of this review found evidence that children breastfed longer have a lower risk for developing asthma (Fig. 1). Risk reduction was pronounced in children 0–2 years of age, decreasing with age, but still evident at school age with greater effects in early life supporting the theory of protection from early infection. Studies were highly heterogeneous, and results were similar when only longitudinal cohort studies or studies of high methodological quality were included.

Few studies have attempted to assess the association of breastfeeding over the spectrum of allergic conditions: asthma, eczema, allergic rhinitis, and food allergy, which is important because of the substantial overlap in allergic diseases with shared phenotypes. The systematic review of Lodge et al. [26] aimed to analyze current evidence through proven search methods, investigate the heterogeneity and quality of included studies, and contextualize results with respect to the findings related to breastfeeding and allergic outcomes. In this review of various study types, weak evidence that breastfeeding is protective for allergic disease is evident. In spite of heterogeneity in the studies of this review, there is strong evidence that breastfeeding is associated with a reduced risk of asthma (Fig. 2).

Studies were further grouped into those reporting eczema up to or beyond 2 years [26] (Fig. 3). A reduced risk of eczema below 2 years was observed after pooling 6 cohort study estimates comparing exclusive breastfeeding for more than 3–4 months with other feeding types (re OR 0.74, 95% CI 0.57–0.97, I^2 62%). Weak evidence that breastfeeding reduced the risk of eczema up to 2 years was observed.

A review that included all study types published in 2011 considering breastfeeding and wheezing illness beyond 5 years of age only showed no association, highlighting an enormous controversy in this area [27]. The authors of this review recommend that further studies should aim to be of the highest quality and specific diagnostic criteria for asthma to be included.

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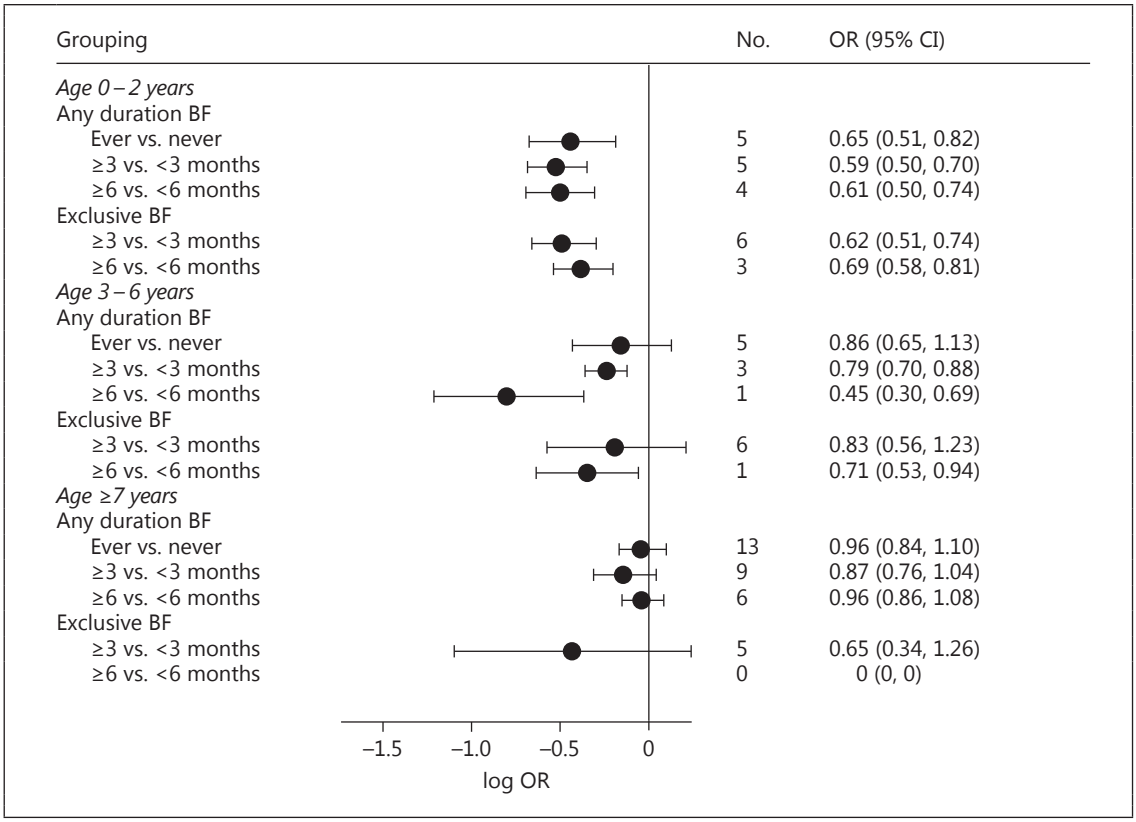

Fig. 1. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) of meta-analyses performed for "recent asthma" in groups determined by age, outcome, breastfeeding (BF) type, and breastfeeding cutoff (stringent categorization). Reproduced from Figure 3 of Dogaru et al. [24] with permission from the authors, December 2016. See [24] for a full list of publications.

A Birth Cohort "Case" Study

One cohort study assessed the association between breastfeeding and asthma from 1 to 8 years and found that breastfeeding for more than 4 months was associated with significantly reduced asthma prevalence regardless of family history and without evidence of attenuation [28]. The study population, 3,963 Dutch children born in 1996/1997 participating in the PIAMA birth cohort study, was followed for 8 years. Asthma was defined as at least one attack of wheeze and/or dyspnoea and/or prescription of inhalation steroids in the previous 12 months. Chronic asthma was defined as asthma diagnosis at 8 years with asthma diagnosis in at least 2 other years. Specific IgE to common airborne allergens and bronchial hyperresponsiveness were measured according to a standard protocol [29]. Breastfeeding was defined as the duration of any breastfeeding (no breastfeeding, breastfeeding for 1–16 weeks, breastfeeding for more than 16 weeks). "Generalized estimating equation" modelling was applied to test for associations between breastfeeding and repeated respiratory outcomes until 8 years adjusting for gender, maternal education, smoking during pregnancy, and current smoking and stratified by parental allergy. Because 10% of baseline data were missing, missing data were imputed. Final imputation, however, made no difference to the study findings.

In this study, asthma risk was shown to be lower in children breastfed for more than 16 weeks compared to those not breastfed [28]. Children breastfed for the longer duration had significantly fewer chronic asthma symptoms. Having an allergic or nonallergic mother did not change these associations. Breastfeeding for more than 16 weeks was inversely associated with sensitization to airborne allergens at 8 years with no association observed for bronchial hyperresponsiveness. Breastfeeding was associated with a lower asthma risk at all

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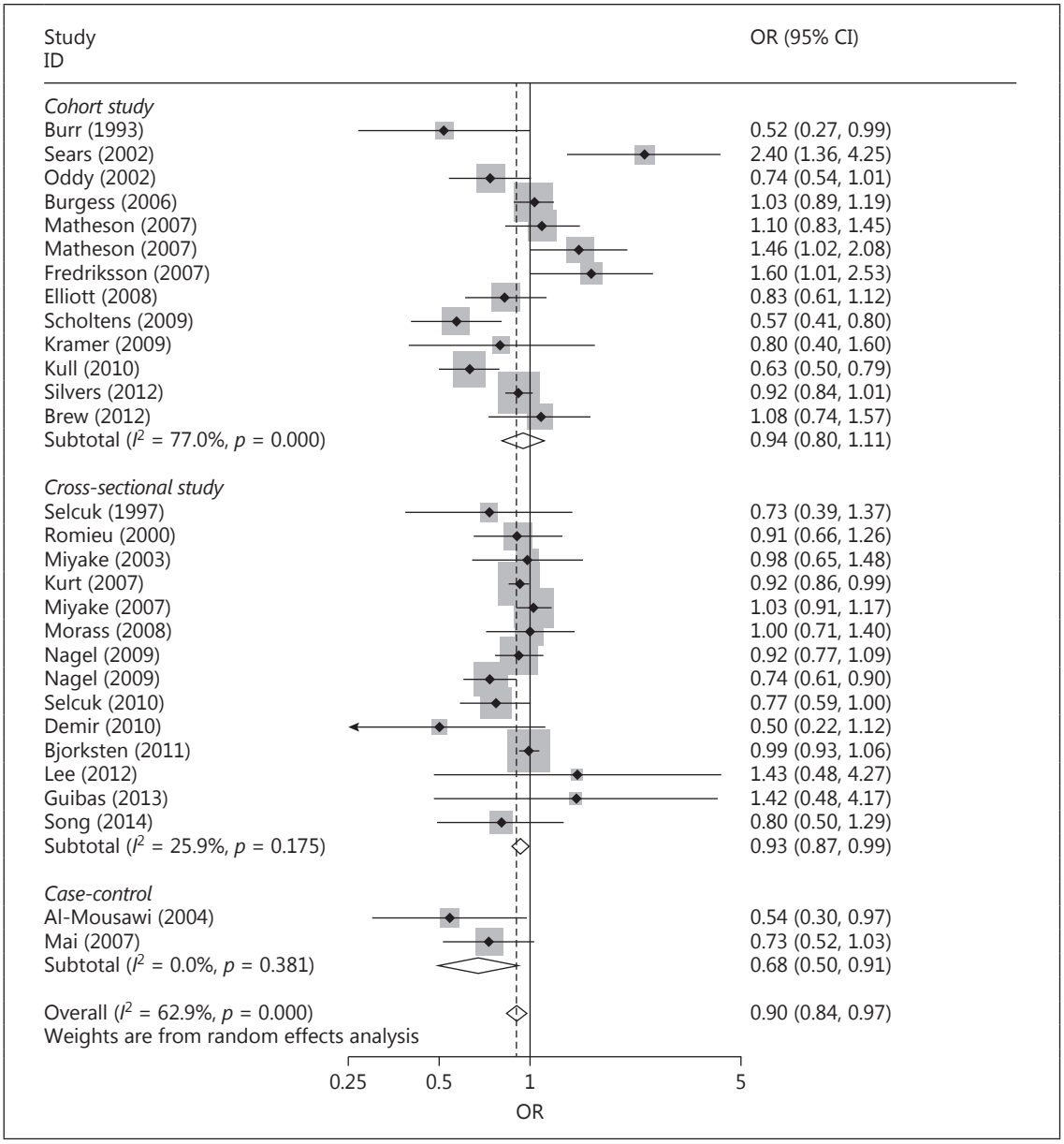

Fig. 2. Meta-analysis: more versus less breastfeeding and risk of asthma in children aged 5–18 years. OR, odds ratio; CI, confidence interval. Reproduced with permission from Lodge et al. [26]. See [26] for a full list of publications.

years regardless of parental history. Repeated measures analysis showed a lower risk of wheeze and asthma from 1 to 8 years in babies breastfed for a longer duration, suggesting that breastfeeding affects long-term outcomes. Strengths of the study include longitudinal design, follow-up until 8 years, repeated measures of data collection, a large study population, low attrition rate, and multiple imputation. The birth cohort design with longitudinal analysis allowed demonstration that breastfeeding protects against asthma throughout childhood both with and without a family history and contributing significantly to the breastfeeding and childhood asthma debate.

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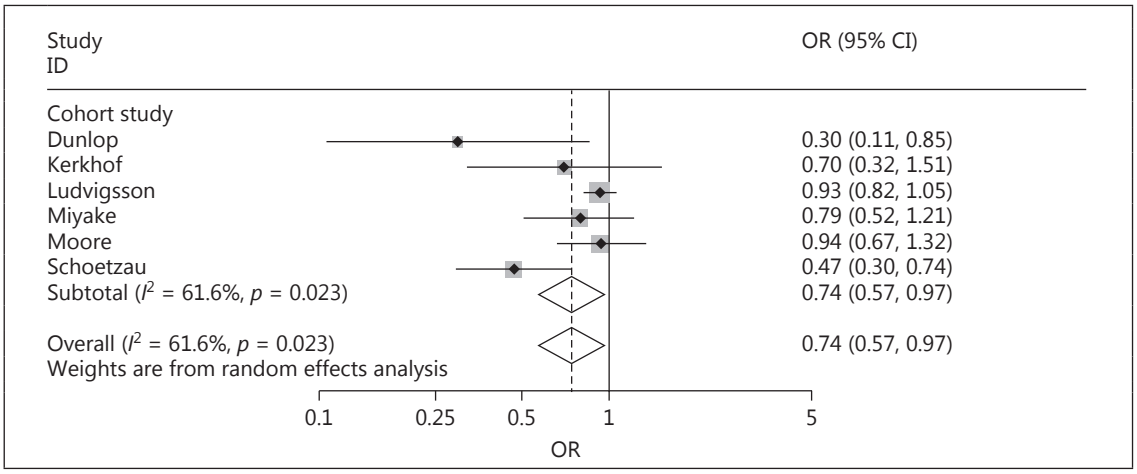

Fig. 3. Meta-analysis: exclusive breastfeeding >3– 4 months compared with less and risk of eczema up to 2 years of age. OR, odds ratio; CI, confidence interval. Reproduced with permission from Lodge et al. [26]. See [26] for a full list of publications.

How May Breastfeeding Protect against Allergic Disease?

Timing of Introduction of Solids

There is increasing concern that the current practice of delaying complementary foods to 6 months of age may exacerbate the risk of immune disorders such as eczema and allergic disease. In addition, evidence suggests that favorable gut colonization through continued breastfeeding may promote tolerance as well as protection when complementary feeding is initiated. Conflict exists between some allergy prevention guidelines that currently recommend delaying the introduction of allergenic foods until at least >12 months, whereas the new recommendations are for the introduction of allergenic foods between 4 and 6 months [30] and not before 6 months [9]. Prescott et al. [31] suggested that early introduction of certain allergenic foods is safe and may build tolerance. Other researchers support the hypothesis that later introduction of foods increases allergenic responses [32]. Koplin et al. [32] showed, following adjustment for confounding, that a later introduction to egg increased rates of egg allergy (OR 3.4, 95% CI 1.8–6.5, at >12 months) compared to introducing egg between 4 and 6 months. These results have major implications for practice and future research as they suggest that the introduction of cooked egg at 4–6 months of age may protect against egg allergy and that delaying introduction to egg may exacerbate it. Confirmation of these findings may result in strong changes to infant feeding guidelines, which currently recommend delaying the introduction of allergenic foods until at least >12 months.

The prevalence of peanut allergy among children in Western countries has doubled in the past 10 years, and therefore a study to evaluate strategies in preventing the development of peanut allergy in infants at high risk for the allergy was conducted [33]. The early introduction of peanut significantly decreased peanut allergy development among high-risk children and modulated immune responses to peanuts. In response to these findings, guidelines have recently changed in relation to peanut allergy in the United States [34].

Bioactive Components in Milk

Breastfeeding protects against wheeze in infancy [14], and several components of human milk have been postulated as conferring this protective effect [35]. Protection may be through a myriad of factors in milk including bioactive enzymes, hormones, growth factors, cytokines, and immunological agents. These findings augment and stimulate host defense development [36, 37], suggesting that bioactive components of milk are important in neonatal development and biologically plausible mechanisms through breastfeeding may impact asthma etiology. Breastfeeding has been associated with protection against early respiratory infections [13], and the observed association between breastfeeding and asthma at early ages may be mediated by the protection of breastfeeding against infections. Breastfeeding may provide an imme-

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Table 1. Factors in breast milk that are being evaluated as inducing or protecting against food allergies

	Inducing	Protective
Antigens	sensitizing allergens	tolerizing allergens
Cytokines	IL-4 IL-5 IL-13	TGF-β soluble CD14
Immunoglobulins		s-IgA to ovalbumin
Polyunsaturated fatty acids	arachidonic acid C22:4n-6 C22:5n-6	eicosapentaenoic acid docosapentaenoic acid docosatetraenoic acid α-linoleic acid n-3 polyunsaturated fatty acids
Chemokines	RANTES IL-8	
Eosinophil-derived granular proteins	eosinophil cationic protein	
Polyamines		spermine spermidine

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diate line of defense against infectious agents, compensating directly for immaturity of the newborn immune system in its ability to resist infection [38]. However, it is not clear which components of this complex biological fluid account for any potential protective effect.

The Composition of Breast Milk

One of the reasons that studies of breastfeeding and allergic disease remain inconclusive could be the complexity of interaction between breast milk, the infant intestinal milieu, and the developing immune system. Some elements in breast milk may protect the infant from developing allergies, whereas others may act in an opposing way (Table 1).

The components of breast milk have immunomodulatory activity, including antigens (allergens), cytokines, immunoglobulins, polyunsaturated fatty acids, and chemokines [18]. It is known that secretory IgA (s-IgA) is passed from mother to infant through breast milk or colostrum. s-IgA may confer passive protection to the infant immune system. Low levels of s-IgA in breast milk are associated with an increased risk of cow's milk allergy in infants. Lower s-IgA levels to ovalbumin have been shown in colostrum and mature milk of allergic mothers compared to mothers without allergy, although the presence of these antibodies was not predictive of allergies in their infants [39].

Cytokines

Cytokines are small soluble glycoproteins acting in an autocrine-paracrine fashion by binding to specific cellular receptors, operating in networks, and orchestrating immune system development and function [40]. Human milk was revealed to contain cytokines more than 20 years ago [41], and early milk has an abundance of cytokines at a time when neonatal organ systems are immature.

Cytokine concentrations may play a role in breast milk immunogenicity. IL-4, IL-5, and IL-13 cytokines intimately involved with IgE production and eosinophil induction exist in higher concentrations in breast milk of atopic mothers compared with nonatopic mothers. Soluble CD-14 may protect against allergy development due to its high concentrations in breast milk and importance in the T_H1 induction response to bacteria [42].

Transforming Growth Factor-β

Transforming growth factor-β (TGF-β) is a cytokine identified in human milk [43], containing TGF-β1, TGF-β2, and other isoforms at mRNA and protein levels with TGF-β2 being the major isoform (95%) [44]. The immunoactive factors in breast milk may influence the development and maturation of the mucosal immune system of the infant [45–50], and mounting evidence suggests that TGF-β, a multifunctional polypeptide, may be a key immunoregulatory factor for the establishment of this response, by promoting IgA production as well as induction of oral tolerance [44, 49, 51–54]. TGF-β increases the infant's ability to produce IgA against β-lactoglobulin, casein, gliadin, and ovalbumin [44]. In an infant

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prone to cow's milk allergy, an increased TGF-β content of mother's milk may be beneficial by promoting IgG-IgA antibody production and inhibiting IgE- and cell-mediated reactions to cow's milk [39, 54].

Original work [55, 56] showed that TGF-β1 was a growth factor exhibiting pleiotropic regulatory effects on developmental and physiological pathways. Disruption of the TGF-β1 gene by homologous recombination in murine embryonic stem cells generated mice that carry the disrupted allele. Homozygotic animals for the mutated TGF-β1 allele showed no gross developmental abnormalities about 20 days after birth, but they then succumbed to a wasting syndrome with a multifocal, mixed inflammatory cell response and tissue necrosis leading to organ failure and death [55]. Letterio et al. [49] observed that TGF-β-deficient mice survived while breastfeeding (i.e., TGF-β1 gene knockout), indicating that maternal sources of TGF-β1 via both placental transfer and milk are essential for normal development and postnatal survival.

The role of milk-borne TGF-β in exposed lactating mice to an airborne allergen assessed the development of asthma in progeny. Breastfeeding-induced tolerance relied on the presence of TGF-β during lactation, was mediated by regulatory CD4+ T lymphocytes, and was dependent on TGF-β signaling in T cells [57]. Airborne allergens transferred from mother to newborn through breast milk induced antigen-specific tolerance in the offspring resulting in protection against allergic disease. Breast milk-mediated transfer of an antigen and TGF-β to the neonate resulted in oral tolerance induction and antigen-specific protection from allergic disease. Further, oral administration of TGF-β in vivo in animal studies results in biological activity sufficient to promote oral tolerance [58].

New insights into the mechanisms underlying tolerance induction in neonates pinpoint maternal influence through "breast milk-mediated antigen transfer" as crucial in the process. Because the amount of TGF-β in maternal milk is less in mothers with atopic disease [59–61], these and other findings [48] suggest that this milk cytokine may influence the development of allergic disease and asthma.

The publication of these reviews relating to TGF-β regulation to immune responses [62, 63] and other studies highlight the importance of milk TGF-β [64], although the mechanistic pathways by which TGF-β modulates development and maintenance of the immune system and its role in regulation of tolerance and immunity has not yet been fully described.

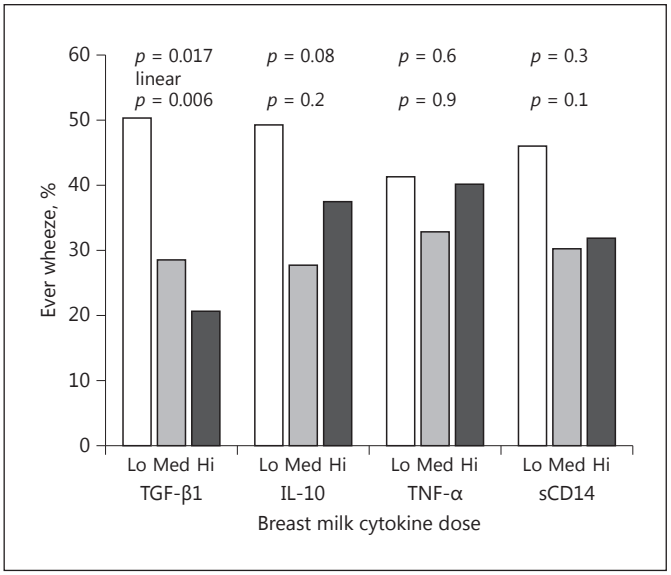

Fig. 4. Percent with ever wheeze at 1 year of age by tertiles of cytokine dose: χ^2 analysis. Reproduced with permission from Oddy et al. [66].

Probiotics

The administration of probiotics may increase human milk TGF-β concentration depending on the probiotic strain. Inverse effects have been seen with *Lactobacillus reuteri* [65], and because concentrations of human milk TGF-β may be critical in determining immune function, more work is needed in this area.

Case Study: Infant Immune Study

Data on breastfeeding and infant wheeze were collected from birth to 1 year from 243 mothers as part of the Infant Immune Study in Tucson, AZ, USA [66]. Breast milk samples obtained at 11 days postpartum (mean age) and assayed by ELISA for concentrations of TGF-β1, IL-10, TNF-α, and soluble form of CD14 as well as cytokine dose and its relationship with wheeze were assessed. An increasing duration of breastfeeding was associated with decreased prevalence of wheeze ($p = 0.039$). A higher TGF-β1 dose was associated with less wheeze ($p = 0.017$) at 1 year, showing a linear trend with wheeze (χ^2 $p = 0.006$) when considered as a dose (Fig. 4). The risk of wheeze decreased (OR 0.22, 95%CI 0.05–0.89, $p = 0.034$) with increasing dose of TGF-β1 (identified from longer duration of breastfeeding and TGF-β1 concentration level, as compared to short duration of breastfeeding and low TGF-β1 concentration level) when adjusted for sex, gestational age, maternal smoking, exposure to other

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children, maternal education, and maternal asthma. The dose of TGF-β1 from breast milk had a significant relationship with infant wheeze at 1 year. Because wheeze is a risk factor for asthma in childhood, this relationship is significant.

The authors concluded that TGF-β from human milk is a family of growth factors involved in maintaining intestinal homeostasis, inflammation regulation, allergy development, and promotion of oral tolerance development. The dose of human milk TGF-β1 and TGF-β2 may modulate or regulate immunological responses of infants in early postnatal life. The composition of breast milk cytokines deserves further investigation, because cytokines may provide protection against wheeze and subsequent asthma in childhood.

Polyunsaturated Fatty Acids and Polyamines

Polyunsaturated fatty acids and polyamines may impact on the allergenicity and/ or immune protectiveness of breast milk. A high arachidonic acid to eicosapentaenoic acid ratio in breast milk may be associated with a higher risk of allergic disease and atopy, although this is controversial [67]. How these various mechanisms of immunomodulation are expressed in mother-infant pairs is not known. Genetic factors may allow better predictability but require future investigation to determine the complex interaction effects of immunomodulatory factors in milk and development of allergic disease [68].

Intestinal Microbiota

Modern day society, with increased standards of hygiene, has changed the gut flora of Western infants, potentially impacting the risk of developing immune-mediated diseases including allergic disease and asthma [69]. In adults, intestinal microbiota consists of several hundred, mostly anaerobic, bacterial species. Formed through successive establishment of different bacteria in infancy and early childhood, this system is complex. Facultative and aerotolerant bacteria establish first, followed by more and more strict anaerobes, and commensal microbes provide major incentive for immune system maturation.

The microbial colonization of the newborn intestine is influenced by delivery and feeding mode, family structure, and other lifestyle behaviors. Gut microbiota are required for normal immune development, regulation of gut inflammatory responses, and oral tolerance induction to new foods [70]. The specific microbial changes associated with protection against allergic disease remain uncertain, and more recent data suggest that microbial diversity may be of relevance [69, 71, 72]. Altered intestinal microbiota in the first few weeks of life is associated with increased risk of eczema and asthma in infancy [7, 73–75]. Mice raised in a germ-free environment failed to develop oral tolerance and had persistent Th2-dependent responses [76]. This immune deviation may be experimentally corrected by *Bacteroides fragilis* seeding, but only during the neonatal period.

Breastfeeding for 4–6 months may assist in the development of a healthy gut microbiota by providing bifidobacteria and lactic acid bacteria that reinforce colonization [77] and by supplying galacto-oligosaccharides that promote a healthy microbiota composition. A wide variety of galacto-oligosaccharides are found in breast milk, exhibiting bifidogenic effects in the infant gut. Breast milk also contains nucleotides, IgA, and antimicrobial factors such as lactoferrin, which can modulate the infant gut microbiota composition.

Breastfeeding facilitates the exchange of microbes between mother and infant, and bacterial diversity could be intrinsic to healthy immune maturation and function. Minor differences are seen in microbial content between breast- and formula-fed infants, reflecting improved infant formulas in the past 30 years [69]. Bifidobacteria and lactobacillus are found in both breast- and formula-fed babies, although formula-fed babies have more prevalent and higher counts of *Clostridium difficile*, *Bacteroides*, enterococci, and Enterobacteriaceae, while staphylococci are more numerous in breastfed infants. Generally, formula-fed infants had lower bacterial diversity. Further research is required to define the microbial stimulus for normal development, investigate the mechanisms involved, and confirm the role of microbiota in protection for allergic disease.

The Debate Continues

The debate whether breastfeeding protects against allergic disease and asthma in children continues, and it is still not possible to make a definitive conclusion regarding this relationship. Much of the difficulty is in the various study designs applied to ask the question. In addition, other factors impact breast milk and its link to allergic disease, such as the mother's diet, the infant's diet, maternal microbiota and exposure to allergens in the environment, timing of introduction to other foods, and composition of the mother's milk (nutritional, immunomodulatory, bioactive). Many of these factors have not been assessed in studies considering the research question "does breastfeeding impact allergic disease?" Research needs to consider confounding, effect modification, and interactions. More research into the bioactive factors

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within breast milk (such as TGF-β) is required to identify possible effect modifiers. Finally, exclusive breastfeeding for 6 months continues to be the keystone for the promotion of allergy health and continues to be recommended by international pediatric societies and academies [78, 79].

Disclosure Statement

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FOCUS

Due to its proximity to food antigens and the microbiome, GALT must continually be able to distinguish nonpathogenic from pathogenic organisms, as well as enable oral tolerance to specific food antigens

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The Role of Hydrolyzed Formula in Allergy Prevention

by Michael D. Cabana

Key insights

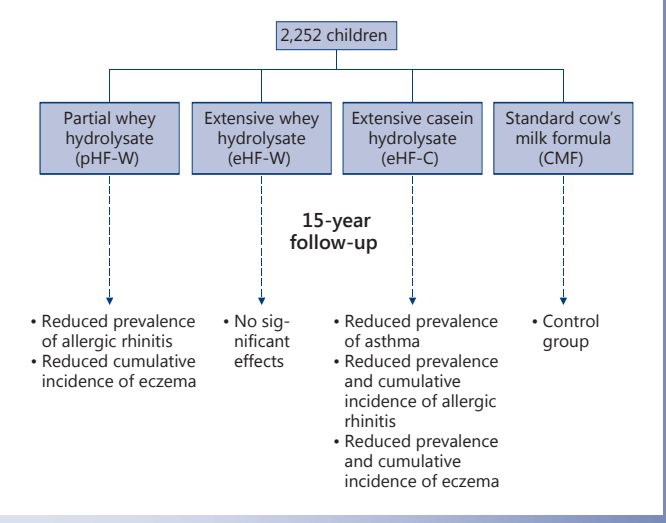
Although breastfeeding is accepted as the optimal way to feed all infants regardless of underlying allergy risk, a large proportion of infants are exposed to infant formula. Initial findings from clinical studies suggest that the use of hydrolyzed formulas may have beneficial effects in reducing the risk of certain allergic diseases, particularly against a background of atopic disease. However, the difficulties in extrapolating these clinical data to general practice arise because different formulas are derived using different hydrolysis methods. These can affect not only the degree of protein hydrolysis but also qualitative changes to the peptides, which in turn can influence the preventive effects of a particular infant formula on the risk of allergic disease.

Current knowledge

Pediatric asthma, eczema, food allergy, and allergic rhinitis incur significant costs to the healthcare system, resulting in missed days of work and school, and affect the quality of life of parents and children. Infant formulas have been developed to mimic human breast milk. Typical infant formulas for full-term infants contain 19–20 calories per ounce and approximately 1.3–1.4 g of protein per 100 mL. Although a variety of protein sources for infant formula exist, the typical protein source is cow's milk proteins. Using various hydrolysis techniques, the intact proteins can be broken down into smaller components or peptides.

Practical implications

The exposure of smaller peptides to gut-associated lymphoid tissue (GALT) is thought to induce oral tolerance without sensitization, as the decreased molecular weight has been associated with decreased allergenicity of the protein. Because of this, hydrolyzed formulas may lower the risk of allergic disease compared to nonhydrolyzed formulas. Some studies suggest that certain partially hydrolyzed whey formulas and extensively hydrolyzed casein formulas may decrease the risk of eczema compared to nonhydrolyzed formulas for children with a background of atopy. In terms of allergic rhinitis, food allergy, and asthma, the evidence for a preventive effect of hydrolyzed infant formula remains inconclusive.



The protective effects of breastfeeding may extend against the development of asthma and allergic diseases.

Recommended reading

von Berg A, et al: Allergic manifestation 15 years after early intervention with hydrolyzed formulas – the GINI Study. Allergy 2016;71:210–219.

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Nutrition Intervention in Allergy Prevention

Annales Nestlé

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The Role of Hydrolyzed Formula in Allergy Prevention

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Key Messages

- **Breastfeeding is the optimal way to feed infants and therefore is recommended for all infants regardless of allergy risk.**
- **For those infants who are exposed to infant formula, some studies suggest that specific partially hydrolyzed or extensively hydrolyzed formulas may decrease the risk of eczema compared to nonhydrolyzed formulas for children with a family history of atopic disease.**
- **The literature to support the preventive effects of hydrolyzed infant formulas for asthma, allergic rhinitis, and food allergy is inconsistent and insufficient.**
- **The qualitative changes to the peptides by the method of hydrolysis, not just the degree of protein hydrolysis, may have a large influence on the preventive effect of a particular infant formula for the potential risk of allergic disease.**

Keywords
Eczema · Atopic dermatitis · Asthma · Food allergy · Whey · Casein · Allergic rhinitis · Hay fever · Prevention

Abstract

Asthma, eczema, food allergy, and allergic rhinitis are some of the most common pediatric, chronic conditions in the world. Breastfeeding is the optimal way to feed all infants. For those infants who are exposed to infant formula, some studies suggest that certain partially hydrolyzed or extensively hydrolyzed formulas may decrease the risk of allergic disease compared to nonhydrolyzed formulas for children with a family history of atopic disease. Overall, there is some evidence to suggest that partially hydrolyzed whey formulas and extensively hydrolyzed casein formulas may decrease the risk of developing eczema for infants at high risk of allergic disease. The evidence for a preventive effect of hydrolyzed formulas on allergic rhinitis, food allergy, and asthma is inconsistent and insufficient. Finally, the qualitative changes to the peptides by the method of hydrolysis, not just the degree of protein hydrolysis, may have a large influence on the preventive effect of a particular infant formula for the potential risk of allergic disease. As a result, it may be difficult to generalize findings from clinical studies using a specific infant formula to other infant formulas from different manufacturers using different methods of hydrolysis. Further clinical studies are needed to help clinicians identify which infants may benefit from early intervention, as well as which specific hydrolyzed formulas are best suited to decrease the risk of future allergic disease.

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Introduction

Asthma, eczema, food allergy, and allergic rhinitis are some of the most common pediatric, chronic conditions in the world. Although mortality from such conditions is relatively rare, there is great impact on healthcare utilization, missed days of work and school, as well as effects on quality of life, for both parents and children. There are currently many treatment strategies for each of these conditions. For example, the use of infant formulas with hydrolyzed proteins is commonly used to treat cow's milk protein allergy.

From a broader, public health perspective, a preventive approach towards these chronic conditions would be more cost-effective and impact a large percentage of the population. Breastfeeding is the optimal way to feed all infants, whether at risk of allergy or not. For those infants who are exposed to infant formula, some studies suggest that hydrolyzed formulas may decrease the risk of allergic disease compared to nonhydrolyzed formulas. This article will review the current evidence regarding the role of hydrolyzed formula in allergy prevention, specifically for eczema, food allergy, asthma, and allergic rhinitis.

Breastfeeding is the optimal way to feed all infants, whether at risk of allergy or not

Hydrolyzed Infant Formulas

In the United States, the Federal Food, Drug, and Cosmetic Act defines an infant formula as "a food which purports to be or is represented for special dietary use solely as a food for infants by reason of its simulation of human milk or its suitability as a complete or partial substitute for human milk" [1]. Although human breastmilk is ideal, a large percentage of infants are exposed to formula in the first year of life. Based on 2013 data, 81% of newborns in the United States initiate breastfeeding; however, by 6 months of age, breastfeeding rates are 52%. By 12 months of age, this percentage drops to 31% [2]. Worldwide, infant formula exposure may be higher as the rates of breastfeeding may be lower. In low- and middle-income countries worldwide, only half of infants younger than 1 month are breastfed. This percentage falls to approximately 30% at 1–5 months of age [3]. As a result, a large percentage of children are exposed to infant formula at an early age.

Infant formulas have been developed to mimic human breast milk. Typical infant formulas for full-term infants have 19–20 calories per ounce and approximately 1.3–1.4 g of protein per 100 mL [4]. Although there are a variety of potential protein sources for infants, the typical protein source is cow's milk proteins. Cow's milk proteins can be separated into 2 general groups, casein and whey. Biochemically, the separation of these 2 proteins can be visualized when cow's milk is acidified or exposed to chymosin (rennin). The casein and whey proteins are present in a 4 to 1 ratio and the specific proteins are listed on Table 1.

Infant formulas can be further classified as intact (or nonhydrolyzed), partially hydrolyzed formulas (pHF), extensively hydrolyzed formulas (eHF), or amino acid formulas. The current classification of infant formula focuses on the degree of hydrolysis; however, different manufacturers employ a number of different proprietary methods of hydrolysis. Using a variety of artificial methods, these intact proteins can be broken down into smaller components or peptides. In general, pHFs have peptides which are <5 kDa with a size distribution of 3–10 kDa, while eHFs have peptides which are <3 kDa [5]. Amino acid-based formulas contain free amino acids for infants who are sensitive to even small peptides of cow's milk protein.

Potential Mechanisms of Action

When these proteins are consumed and enter the gastrointestinal tract, they are exposed to gut-associated lymphoid tissue (GALT), a key component of the mucosal immune system and an extensive immune organ. Due to its proximity to food antigen and the microbiome, GALT must continually be able to distinguish nonpathogenic from pathogenic organisms, as well as enable oral tolerance to specific food antigens [6]. The induction of oral tolerance seems to depend on the timing and the type of exposure [7]. The exposure of the smaller peptides to GALT is thought to induce oral tolerance without sensitization, as the decreased molecular weight has been associated with the decreased allergenicity of the protein. As a result, hydrolyzed formulas may decrease the risk of allergic disease compared to nonhydrolyzed formulas.

The relationship between the allergenicity of infant formulas based on the type of protein and degree of hydrolysis is most likely incomplete. Although this quantitative description is a useful starting point, the qualitative changes to the peptides by the method of hydrolysis may also play a large effect on the potential risk of allergic disease. For example, Lambers et al. [8] described the use of a combination of mass spectrometry-based peptidomics

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Table 1. Percentage and molecular weights of cow's milk proteins

Fraction	Protein	Allergen name	Total protein, %	Molecular weight, kDa
Whey	alpha-lactalbumin	*Bos d 4*	5	14.2
	beta-lactoglobulin	*Bos d 5*	10	18.3
	immunuglobulins	*Bos d 7*	3	160.0
	bovine serum albumin	*Bos d 6*	1	67.0
	lactoferrin		trace	800.0
Caseins	alpha-s1-casein		29	23.6
	alpha-s2-casein		8	25.2
	beta-casein		27	24.0
	gamma1-casein	*Bos d 8*		20.6
	gamma2-casein		6	11.8
	gamma3-casein			11.6
	kappa-casein		10	19.0

Adopted from Tsabouri et al. [44].

and multivariate clustering analyses to create a comprehensive analysis of different hydrolyzed milk protein formulas at the peptide level. The characterization of the specific peptide profiles of an infant formula may provide a better understanding of the likelihood of allergenicity. At least 3 factors, protein source, method of hydrolysis, and degree of hydrolysis, may influence the potential benefit of a hydrolyzed formula in allergy prevention. These observations may help explain why the degree of hydrolysis does not always correlate with the results of clinical trials comparing the effectiveness of pHF with that of eHF, or the lack of consistency of findings within classes of formulas based on the degree of hydrolysis.

Methodologic Issues in Evaluating the Literature

Although double-blind, randomized controlled trials are the gold standard to assess if hydrolyzed formulas decrease the risk of allergic disease, there are several methodologic issues to consider when reviewing and comparing results of studies from across the literature. The main comparison should be breastmilk and breastfeeding; however, it would be unethical to randomize infants into a situation where they were prevented from breastfeeding. In addition to the impossibility of blinding, there is also the issue that the composition of breastmilk differs from mother to mother [9]. As a result, most clinical trials will compare one type of formula versus another type of formula among infants who are not able to breastfeed for various reasons. In addition, if formula exposure is occurring during weaning from breastfeeding or being combined with breastfeeding, the extent of formula exposure may be difficult to control.

There are additional issues of heterogeneity in study design. To increase the likelihood of detecting an effect, studies may only recruit those infants at high risk of allergy based on family history. However, the extent of allergic disease in a family history can vary (e.g., number of relatives affected) and baseline risk can be difficult to determine [10]. In some instances, the use of infant formula is part of a larger environmental intervention. As a result, it is difficult to assess the contributing effect of infant formula exposure. Associated with this issue is the fact that the time to the development of the clinical outcome may be protracted. For example, asthma and allergic rhinitis can be difficult to confirm in a child <5 years of age. During the study period, other environmental, dietary, or medical access factors may confound the association between the exposure and the outcome. A combination of environmental and genetic factors likely plays significant roles in the pathogenesis of allergic disease [11].

Hydrolyzed Formulas and Primary Eczema Prevention

Eczema is a chronic skin disease characterized by pruritic, inflamed skin. It is the most common chronic skin disease in children, affecting approximately 20% of infants and young children [12]. In developed countries,

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the incidence of eczema has steadily increased [13]. Studies have shown a reduced incidence of eczema among infants who are exclusively breastfed [14]. For infants who are not breast fed, cow's milk protein is a common food allergen associated with the development of eczema. It has also been clinically observed that hydrolyzed formulas, used for the treatment of cow's milk protein allergy, have been associated with decreased eczema. Specifically, the chemical and enzymatic hydrolysis reduces the molecular weight and the peptide size of cow's milk protein and can decrease potentially sensitizing allergenic determinants.

Several dozen studies have assessed the effectiveness of early exposure to hydrolyzed formula to decrease the risk of eczema. Two different meta-analyses, both published in 2010, suggest that healthy infants with a family history of allergy who are fed with partially hydrolyzed whey protein (pHF-W) formula have a reduced risk of atopic dermatitis compared with infants fed intact cow's milk protein formula (CMF). Subanalyses conducted in meta-analyses by Szajewska and Horvath [15] and Alexander and Cabana [16] estimate that the risk reduction is 52 and 55%, respectively, at 12 months of age, and 38 and 36%, respectively, at the age of >30 months.

Since the publication of these meta-analyses, more recent analyses have been published that both support and do not support the effectiveness of hydrolyzed formula for eczema prevention. On the negative side, Lowe et al. [17] reported the results of a single-blind (participant) randomized controlled trial that compared allergic outcomes in 620 infants fed CMF, pHF-W, or soy formula at the cessation of breastfeeding. There was no difference in the development of eczema within the first 2 years of life for pHF-W (odds ratio [OR] 1.26, 95% confidence interval [CI] 0.84–1.88) compared to CMF. There was also no difference in the period prevalence at 6–7 years of age for pHF-W (OR 1.08, 95% CI 0.69–1.68) compared to CMF [17].

Studies have shown a reduced incidence of eczema among infants who are exclusively breastfed

In addition, a more recent meta-analysis of 37 eligible intervention trials of hydrolyzed formula by Boyle et al. [18] reexamined the literature and was also less enthusiastic about the preventive effects of hydrolyzed formulas for eczema. The analysis suggested that there was "evidence of conflict of interest and high or unclear risk of bias in most studies of allergic outcomes and evidence of publication bias for studies of eczema and wheeze." This analysis found no consistent evidence that pHF or eHF reduce the risk of allergic disease for infants at high risk [18]. In addition to more data, this analysis differs from others, as the results for different protein hydrolysates based on the degree of hydrolysis were pooled together. This may be inappropriate because the different biological effects of various hydrolysates are not only based on the degree of hydrolysis and peptide size, but also the qualitative characteristics of the peptide [8]. Additional differences include the interpretation of potential conflicts of interest from the studies included. Boyle et al. [18] also included studies in which in the intervention group, but not in the control group, additional interventions were applied such as house dust mite control measures and a smoke-free environment. Furthermore, studies carried out in a high-risk population and in the general population were pooled.

On the other hand, the most recent update of the German Infant Nutritional Intervention (GINI) study suggests a positive benefit from hydrolyzed formula for eczema prevention. The GINI study is a double-blind randomized trial to assess the effectiveness of 3 different types of hydrolyzed formulas: pHF-W and extensively hydrolyzed whey formula (eHF-W), an extensively hydrolyzed casein formula (eHF-C), and regular CMF on the development of allergic disease for children at high risk of developing allergy [19].

From 1995 to 1998, a total of 2,252 infants were enrolled and randomized at birth to receive 1 of the 4 formulas as a supplement to breastfeeding, as needed, during the first 4 months of life. The results from the GINI study suggest that the cumulative incidence of eczema up to 15 years of age was reduced in the pHF-W group (risk ratio [RR] 0.75, 95% CI 0.59–0.96) and the eHF-C group (RR 0.60, 95% CI 0.46–0.77) compared to the CMF group. In addition, eczema prevalence between 11 and 15 years in the eHF-C group was decreased (OR 0.42, 95% CI 0.23–0.79) compared to the CMF group [20]. Cumulative incidence versus prevalence measures slightly different outcomes. Both outcomes are dichotomous; however, cumulative incidence includes anyone with a past or current diagnosis of eczema, while prevalence between 11 and 15 years indicates active disease during that specific time period. It is possible for a child to have developed the disease; however, it may become quiescent during a specific observation period. Further analysis suggests that based on the results of the GINI study, cost-effectiveness analyses suggest

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that both pHF-W and eHF-C can be cost-effective and cost-saving for the prevention of eczema [21].

Based on available evidence, in 2015, the US Food and Drug Administration (FDA) allowed a qualified health claim for pHF-W. Specifically, "for healthy infants who are not exclusively breastfed and who have a family history of allergy, feeding a 100% Whey-Protein Partially Hydrolyzed infant formula from birth up to 4 months of age instead of a formula containing intact cow's milk proteins may reduce the risk of developing atopic dermatitis throughout the 1st year of life and up to 3 years of age. [The] FDA has concluded that the relationship between 100% Whey-Protein Partially Hydrolyzed infant formulas and the reduced risk of atopic dermatitis is uncertain, because there is very little scientific evidence for the relationship" [22, 23].

Hydrolyzed Formulas and Primary Food Allergy Prevention

The estimated prevalence of food allergy in the United States ranges from 2 to 10% [24], and in Europe, food allergy prevalence is estimated at approximately 6%, based on self-report [25]. One of the most common food allergies in children, cow's milk protein allergy, peaks in infancy with an estimated prevalence of 2–6% [26]. Although hydrolyzed formulas are commonly used for treatment and management, there are many studies that have examined the use of hydrolyzed formulas for preventing the development of food allergies.

The development of allergic rhinitis and asthma has been closely associated with the presence of eczema

Using a randomized controlled trial design, Halken et al. [27] enrolled 595 high-risk Danish infants to compare the allergy-preventive effect of 3 different types of hydrolyzed formulas: eHF-C, eHF-W, or pHF-W during the first 4 months of life, as needed. All infants were followed up prospectively and if food allergy was suspected, controlled elimination/challenge procedures were performed. There were no differences in the cumulative incidence of atopic dermatitis or respiratory symptoms. Infants receiving pHF-W were found to be more likely to develop cow's milk allergy (0.6 vs. 4.7%, $p = 0.05$); however, the authors cautioned that "because of the small number of cases the results should be interpreted with caution" [27]. Oldaeus et al. [28] assessed the effectiveness of eHF-C, pHF, or CMF in 155 high-risk infants for the development of allergic disease. Throughout the 18-month period, the infants in the eHF-C group did better than those in the CMF group, and for the first 9 months of age, the eHF group did better than the pHF group in terms of atopic symptoms [28].

These findings were also summarized in a 2009 Cochrane Review. There is some potential benefit for eHF versus pHF for food allergy prevention, based on 2 studies and 341 infants (typical RR 0.43, 95% CI 0.19–0.99). However, overall, there was limited evidence that prolonged feeding with a hydrolyzed formula compared to CMF reduces infant and childhood food allergy, food intolerance, or infant cow's milk protein allergy for high-risk infants [29]. Since this review, there have been additional studies which seem to support these observations.

Kuo et al. [30] investigated whether feeding pHF-W versus CMF (any nonhydrolyzed protein formula) in the first 6 months of life to 1,002 high-risk infants decreased allergic diseases up to 36 months later. The percentage of infants with food sensitization, especially to milk protein, was significantly lower for infants in the pHF-W group compared to infants in the CMF group at 36 months (12.7 vs. 23.4%, $p = 0.048$); however, there was no difference in the prevalence of allergic diseases during the first 3 years of life [30]. Likewise, in the GINI study, no effect on food allergies was noted for infants randomized to hydrolyzed formulas. At 11–15 years of age, there were no differences in food sensitization for the children randomized to any of the hydrolyzed formulas, including pHF-W (OR 1.07, 95% CI 0.61–1.90), eHF-W (OR 1.10, 95% CI 0.63–1.94), or eHF-C (OR 1.20, 95% CI 0.69–2.10), when compared to CMF [20].

Hydrolyzed Formulas and Primary Asthma and Allergic Rhinitis Prevention

Both asthma and allergic rhinitis are common pediatric conditions. Asthma affects approximately 1 in 12 children in the United States [31]. It is associated with increased hospitalizations and emergency department visits, as well as racial and ethnic disparities in outcomes [32]. Globally, asthma is one of the most common, noncommunicable diseases in children [33]. Allergic rhinitis, also known as "hay fever" or allergic rhinoconjunctivitis, is a chronic condition characterized by conjunctivitis, rhinorrhea, nasal congestion, and pruritus. Allergic rhinitis affects 1 in 11 children [34], and although the condition is not associated with frequent emergency department visits or hospitalizations, there are tremendous ef-

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fects on quality of life, quality of nighttime sleep, and the ability to function at school [35]. The development of allergic rhinitis and asthma has been closely associated with the presence of eczema [36]. Similar to eczema, several studies have explored the effect of hydrolyzed formula in decreasing the likelihood of asthma and allergic rhinitis in children.

In the GINI study, although there were no effects on the development of asthma at 10 years of age [37], between 11 and 15 years of age [20], the prevalence of asthma was lower in the eHF-C group than in the CMF group (OR 0.49, 95% CI 0.26–0.89). These results were confirmed by objective spirometric testing. In terms of allergic rhinitis, the GINI study reported that the cumulative incidence of allergic rhinitis was lower in the eHF-C group (RR 0.77, 95% CI 0.59–0.99) than in the CMF group. In addition, the allergic rhinitis prevalence was lower for those children who received pHF-W (OR 0.67, 95% CI 0.47–0.95) and eHF-C (OR 0.59, 95% CI 0.41–0.84) than for those who received CMF [20].

Overall, these results suggest that for those children who are not breastfed, compared to CMF, the early use of specific types of hydrolyzed formulas (pHF-W and eHF-C) may have preventive effects for asthma and allergic rhinitis in children. Of note, eHF-W was not associated with any preventive effect. In addition, these findings from the GINI study are limited to children who are at high risk of allergic disease.

Hydrolyzed formulas have also been used in multipronged interventions. The Isle of Wight prevention study included a variety of interventions, including the use of hydrolyzed formula when breastfeeding was not possible. Starting in 1990, a total of 120 children at high risk of allergic disorders (based on family history and a high cord total IgE), were enrolled in a single-blinded, randomized controlled trial. Infants in the intervention arm were either breastfed with the mother placed on a low-allergen diet or, if not breastfed, they were fed a soy-based protein hydrolysate formula. In addition, exposure to house dust mite allergen was reduced using vinyl mattress covers and acaricide in bedrooms and living rooms. The infants in the control group received routine care and no environmental control was recommended [38]. At the age of 18 years, 114 of 120 (95%) children were assessed and the prevalence of asthma was significantly lower in the prevention group compared with the control group (OR 0.34, 95% CI 0.12–0.96) [39].

The Canadian Childhood Asthma Primary Prevention Study also assessed a multifaceted intervention program for the primary prevention of asthma in high-risk infants. 545 high-risk infants were randomized to an intervention that included avoidance of house dust, pets, tobacco smoke, and encouragement of breastfeeding with delayed introduction of solid foods. pHF-W was provided for the first year of life as needed. At 7 years of age, the prevalence of asthma was lower in the intervention group (adjusted relative risk [ARR] 0.44, 95% CI 0.25–0.79); however, there were no differences in the prevalence of allergic rhinitis (ARR 1.13, 95% CI 0.71–1.81) and atopic dermatitis (ARR 0.92, 95% CI 0.49–1.73) [40].

Summary

Asthma, eczema, food allergy, and allergic rhinitis are some of the most common pediatric, chronic conditions in the world. Although breastfeeding is still regarded as the best approach to reduce the risk of allergy, for those infants who are exposed to infant formula, some studies suggest that certain pHF-W and eHF-C may decrease the risk of eczema compared to nonhydrolyzed formulas for children with a strong family history of atopic disease. However, the clinical interpretation of such studies varies, as do the subsequent clinical recommendations. Different professional medical societies have guidelines with varying levels of enthusiasm regarding the effectiveness of hydrolyzed formulas in preventing allergic disease, as well as which types of formulas are most effective [41–43, 45].

In terms of allergic rhinitis, food allergy, and asthma, the current evidence for a preventive effect of hydrolyzed infant formula on these conditions seems to be inconsistent and insufficient. Finally, the qualitative changes to the peptides by the method of hydrolysis, not just the degree of protein hydrolysis, may have a large influence on the preventive effect of a particular infant formula for the potential risk of allergic disease. As a result, it may be difficult to generalize findings from clinical studies using a specific infant formula to other infant formulas from different manufacturers using different methods of hydrolysis. Further clinical studies are needed to help clinicians identify which infants may benefit from early intervention, as well as which specific hydrolyzed formulas are best suited to decrease the risk of future allergic disease.

Disclosure Statement

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FOCUS

The dual-barrier hypothesis theorizes that avoidance of a specific food (such as egg or peanut) can increase the risk of developing food allergy if the infant is still exposed to the food allergen in the environment and is percutaneously sensitized

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Introduction of Complementary Foods to Infants

by Christina E. West

Key insights

In the past, food allergy prevention strategies focused on the avoidance of allergenic foods in infancy. The current paradigm, however, is shifting from avoidance to controlled exposure. Recent evidence from randomized controlled trials suggests that the early introduction of allergenic foods such as peanuts may reduce the prevalence of food allergies in high-risk infants. In countries where peanut allergy is prevalent, healthcare professionals should recommend the introduction of peanut-containing products into the diets of "high-risk" infants early in life (between 4 and 11 months of age).

Current knowledge

Worldwide, the most common food allergies in children are allergies to cow's milk, hen's egg, soy, peanut, tree nuts, wheat, fish, and seafood. Although a large proportion of those with milk or egg allergies will develop tolerance as they age, certain subgroups remain allergic and are at risk of developing other disorders such as respiratory allergic disease. For instance, the presence of both egg allergy and eczema in infants is a predictor of later respiratory allergies. Those with high levels of IgE antibodies to cow's milk, egg white, wheat, and soy are also more likely to have persistent food allergy.

Practical implications

Current international guidelines state that the introduction of allergenic foods (including egg and peanut) does not need to be postponed beyond 4–6 months of age, but they provide no concrete guidance on whether these foods should be actively introduced within this time frame. The LEAP (Learning Early About Peanut Allergy) trial was the first prospective randomized study regarding early peanut introduction. Results from the LEAP study suggest that early introduction of peanut into the diets of high-risk infants may be beneficial. However, safety and practicality remain key issues when extrapolating the results of this study to the general population. Open questions remain on the optimal timing and doses that should be used, and whether such regimens should be stratified according to the infant's allergy risk.

Introductory foods containing peanuts

- Smooth peanut butter mixed with milk or pureed fruit
- Peanut-containing snacks (for young infants, this may be softened with 20–30 mL water or milk and mixed with pureed fruit or vegetables)
- Peanut soup
- Finely ground peanuts mixed with other foods (i.e., yogurt)

Based on Fleischer DM, et al: Consensus communication on early peanut introduction and the prevention of peanut allergy in high-risk infants. World Allergy Organ J 2015;8:27.

Different types of peanut-containing products that may be introduced to the infant diet.

Recommended reading

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Nutrition Intervention in Allergy Prevention

Annales Nestlé

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Introduction of Complementary Foods to Infants

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Key Messages

- **There is level 1 evidence that early introduction of peanuts (from 4 to 11 months of age) reduces the prevalence of peanut allergy in infants at high risk of allergic disease (infants with severe eczema and/or egg allergy).**
- **The majority of current international guidelines recommend that complementary foods, including allergenic foods, can be introduced from 4 to 6 months of age irrespective of family history risk.**
- **As delayed peanut introduction may increase the risk of peanut allergy, interim guidelines state that healthcare providers should recommend introducing peanut-containing products into the diets of "high-risk" infants early on in life (between 4 and 11 months of age) in countries where peanut allergy is prevalent.**

Keywords
Eczema · Egg · Food allergy · Infant · Peanut · Prevention · Solid foods

Abstract
While earlier food allergy prevention strategies implemented avoidance of allergenic foods in infancy, the current paradigm is shifting from avoidance to controlled exposure. This review focuses on the outcome of recent randomized controlled trials, which have examined the early introduction of allergenic foods for allergy prevention, and discusses the implementation of results in clinical practice. In infants at high risk of allergic disease, there is now direct evidence that regular early peanut consumption will reduce the prevalence of peanut allergy, compared to avoidance. Many international infant feeding guidelines already recommend complementary foods, including allergenic foods, to be introduced from 4 to 6 months of age irrespective of family history risk. Interim guidelines from 10 International Pediatric Allergy Associations state that healthcare providers should recommend the introduction of peanut-containing products into the diets of infants at high risk of allergic disease in countries where peanut allergy is prevalent. Direct translation of the results obtained from a cohort of high-risk infants to the general population has proved difficult, and issues regarding feasibility, safety, and cost-effectiveness have been raised. Five randomized placebo-controlled trials have assessed the effects of early egg exposure in infancy with varying results. In a recent comprehensive meta-analysis, there was moderate-certainty evidence that early versus late introduction of egg was associated with a reduced egg allergy risk. Although promising, optimal timing, doses, and if the feeding regimen should be stratified according to infant allergy risk remain to be determined. The single study that assessed introduction of multiple foods from 3 months whilst breastfeeding compared with exclusive breastfeeding until 6 months of age showed no reduction in food allergy preva-

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lence. Future research should aim at optimizing infant feeding regimens and support a tolerogenic gastrointestinal microenvironment during the period of food allergen introduction.

Introduction

Over the past few decades, we have experienced a rising prevalence of Immunoglobulin E (IgE)-mediated food allergies in the pediatric setting, particularly in developed countries, although the prevalence also appears to be rising in developing countries [1]. Most reports are based on self-reported food allergy, however, and it has been repeatedly shown that self-reported data will overestimate the prevalence as compared with evaluation by an oral food challenge [2–4]. It is estimated that IgE-mediated food allergy affects approximately 6–8% of children in developed countries [1, 3, 4], thereby posing a significant burden on the afflicted children, their families, and the healthcare system. Globally, the by far most common IgE-mediated food allergies in childhood are allergies to cow's milk, hen's egg, soy, peanut, tree nuts, wheat, fish, and seafood [3–5]. Tolerance development is prevalent in milk and egg allergy; and the majority of milk-allergic children [6, 7] and about a half to two-thirds of egg-allergic children [8, 9] will outgrow their food allergy before school age. The rate of peanut allergy resolution is worse; when assessed by oral food challenges both at diagnosis and at follow-up in the Australian HealthNuts cohort study, only 22% of the children outgrew their peanut allergy by 4 years of age [10]. Collectively, a significant proportion of children will remain food allergic and are at risk of developing other comorbidities such as respiratory allergic disease. For instance, infant egg allergy, particularly when coexisting with eczema, has been reported to be a predictor of later respiratory allergies [11], and high levels of IgE antibodies to cow's milk, egg white, wheat, and soy are predictors of persistent food allergy [12].

Avoidance remains the only available treatment in established food allergy. Oral immune therapy, which includes a stepwise dose increase of the food allergen followed by a maintenance phase, is an emerging treatment option. Oral immune therapy has been demonstrated to induce desensitization, i.e., an increase in the amount of offending food that can be ingested as long as it is consumed regularly [13]. It is still undecided if permanent tolerance will develop, and oral immune therapy is not generally recommended unless within a clinical trials protocol. Adherence to an elimination diet is difficult, and there is still risk of accidental exposure and allergic reactions, including anaphylaxis [14]. Allergic children on elimination diets are also at risk of nutritional deficiencies [15, 16], impaired growth [16–18], and reduced quality of life [19]. Collectively, there is urgent need to develop effective strategies to promote tolerance development and prevent food allergy.

While earlier food allergy prevention strategies implemented food avoidance in early infancy, the current paradigm is shifting from avoidance to controlled exposure. The collective evidence from epidemiological studies reporting an association between delayed introduction of complementary foods and allergy risk, and animal models demonstrating that oral tolerance induction is driven by exposure to antigens and allergens [reviewed in 20, 21], led to the first randomized controlled trials (RCTs) to examine the role of early, regular exposure to "allergenic" foods for food allergy prevention. This review focuses on the outcome of these recently published RCTs and discusses the implementation of the results in clinical practice.

While earlier food allergy prevention strategies implemented food avoidance in early infancy, the current paradigm is shifting from avoidance to controlled exposure

Risk Factors for Food Allergy

Both genetic and environmental factors will influence the risk of developing food allergy, and multifaceted changes in our modern environment are a likely driver. The hypotheses proposed to explain the epidemic rise in allergic disease include (a) the biodiversity hypothesis, which theorizes that reduced diversity and intensity of microbial exposures will impair normal development of immunoregulatory networks and increase allergy risk [22], (b) the vitamin D hypothesis that builds on epidemiological evidence that vitamin D deficiency is associated with an increased risk of allergic disease, and (c) the dual-barrier hypothesis [23, 24], which is discussed below. There are also data to suggest that food allergens, specific nutrients, lifestyle factors, and microbial exposures may influence the development of allergic disease through epigenetic mechanisms [25].

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A commonly used definition of allergy risk is based on a history of allergic disease in a first-degree relative [26] and is frequently used in both epidemiological studies and clinical trials. In some of the recently conducted RCTs, however, only infants with an already established allergic phenotype (eczema and/or manifest egg allergy) were included as they are at an even heightened risk [27, 28] (Table 1). For instance, it has been demonstrated that infant eczema is associated with an increased risk of percutaneous sensitization to environmental food allergens, facilitated by an impaired skin barrier [29]. Normally, a food allergen is introduced to and handled by the immune system in the gut to induce a tolerogenic response to the food protein [20, 30]. Accordingly, the dual-barrier hypothesis theorizes that avoidance of a specific food (such as egg or peanut) can increase the risk of developing food allergy if the infant is still exposed to the food allergen in the environment and is percutaneously sensitized [24].

The "Optimal" Window of Introduction of Complementary Foods for Allergy Prevention

Almost 2 decades ago, the American Academy of Pediatrics Committee on Nutrition launched guidelines suggesting a delayed introduction of dairy products in the first year of life in infants with a family history of allergic disease: egg until 2 years, peanuts, nuts, and fish until 2–3 years of age [31]. This recommendation also became integrated in infant feeding guidelines in many other countries at the time. Following the publication of more recent epidemiological studies across the globe, the guidelines were revised to reflect the lack of solid scientific evidence that delayed introduction of complementary foods beyond 4–6 months of age, or avoidance of "allergenic" foods such as cow's milk, egg, peanuts, tree nuts, fish, and seafood, reduce allergy risk [32–36]. Still, the "optimal" time for introduction of complementary food for allergy prevention is not known. There are data to suggest that starting complementary foods before 3–4 months of age may increase the risk of allergic disease [37, 38]. At that age, the gut is more permeable and gastrointestinal colonization is not yet well established, which might contribute to the observed risk increase [39, 40]. Consequently, many international infant feeding guidelines for allergy prevention recommend introduction of any solid food after 4 months of age [32–36].

RCTs for Food Allergy Prevention

Peanuts

In a cross-sectional study, du Toit et al. [41] found that the prevalence of peanut allergy was 10-fold higher in Jewish children in the UK compared with children in Israel. Interestingly, peanut consumption was initiated earlier and in larger quantities in Israel than in the UK. Based on these findings, the Learning Early About Peanut Allergy (LEAP) study was designed to examine if early, regular, controlled peanut consumption, compared with avoidance, could prevent peanut allergy in high-risk infants with severe eczema, egg allergy, or both [42] (Table 1). As part of the screening, a skin prick test (SPT) to peanut was performed, and infants with a wheal size ≥5 mm were excluded. The intervention was initiated between 4 and 11 months and continued until 5 years of age. The study results were pronounced; in the early-introduction group, peanut allergy was reduced with 86% in the group with a negative SPT to peanut at baseline, and with 70% in the group with SPT peanut 1–4 mm at baseline, compared with the avoidance group. Reassuringly, the investigators recently reported that 12-month peanut avoidance in the early-introduction group did not increase the prevalence of peanut allergy at the age of 6 years [43], suggesting that avoidance for a prolonged period will not break tolerance. Still, the long-term consequences of peanut avoidance beyond 12 months are unknown.

Egg

There is also epidemiological evidence to support that delayed introduction of egg to the infant diet increases allergy risk. In the HealthNuts cohort study, delayed introduction of egg at 10–12 months or after 12 months of age was associated with an increased risk of egg allergy compared with egg introduction at 4–6 months of age [44]. To date, 5 RCTs have examined if early versus late introduction of egg can reduce the risk of egg allergy [45–49] (Table 1). In the Solids Timing for Allergy Reduction (STAR) study, high-risk infants with moderate-to-severe eczema were randomized to intake of pasteurized raw whole egg powder or rice powder (placebo) from 4 to 8 months of age [45]. At 12 months of age, 33% in the active group versus 51% in the placebo group had developed egg allergy (relative risk 0.65, 95% CI 0.38–1.11, $p = 0.11$). In the Starting Time of Egg Protein (STEP) study, high-risk infants (based on maternal atopy but no allergic manifestation in the infant at baseline) were randomized to intake of pasteurized raw whole egg powder or rice powder (placebo) from 4 to 10 months of age [46]. At 12 months of age, 7% in the active group versus 10.3% in the placebo

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Table 1. Overview of randomized clinical trials that have assessed early versus late introduction of complementary foods for allergy prevention

Trial name Country	Study population	Intervention	Primary outcome	Ref.
LEAP (Learning About Peanut Allergy) UK	Infants with severe eczema and/or egg allergy (n = 640 randomized, 319 to peanut, 321 to avoidance)	Peanut (snack or peanut butter) from 4 to 11 months to 5 years *or* Peanut avoidance until 5 years	Peanut allergy[1] at 5 years; in the group with negative SPT to peanut (n = 530): 1.9% in the active vs. 13.7% in the avoidance group ($p < 0.001$); in the group with SPT to peanut 1–4 mm: 10.6% in the active vs. 35.3% in the avoidance group ($p = 0.004$)	42
STAR (Solids Timing for Allergy Reduction) Australia	Infants with moderate to severe eczema (n = 86 randomized, 49 to egg, 37 to placebo)	Pasteurized raw whole egg powder *or* Rice powder (placebo) from 4 to 8 months	Egg allergy[1] at 12 months; 33% in the active vs. 51% in the placebo group (relative risk 0.65, 95% CI 0.38–1.11, $p = 0.11$)	45
STEP (Starting Time of Egg Protein) Australia	Infants of allergic mothers (n = 820 randomized, 407 to egg, 413 to placebo)	Pasteurized raw whole egg powder *or* Rice powder (placebo) from 4 to 6 months until 10 months	Egg allergy[1] at 12 months; 7% in the active vs. 10.3% in the placebo group (adjusted relative risk 0.75, 95% CI 0.48–1.17, $p = 0.20$)	46
BEAT (Beating Egg Allergy Trial) Australia	Infants with 1 (or both) parents with a history of allergic disease (n = 319 randomized, 165 to egg, 154 to placebo)	Pasteurized raw whole egg powder *or* Rice powder (placebo) from 4 to 8 months	Egg sensitization[2] at 12 months; 11% in the active vs. 20% in the placebo group (odds ratio 0.46, 95% CI 0.22–0.95, $p = 0.03$)	47
PETIT (Prevention of Egg Allergy with Tiny Amount Intake) Japan	Infants with eczema (n = 147 randomized, 73 to egg, 74 to placebo)	Heated egg powder (50 mg) *or* Squash powder (placebo) from 6 to 9 months, with a dose increase of egg protein from 9 to 12 months	Egg allergy[1] at 12 months; 9% in the active vs. 38% in the placebo group (risk ratio 0.221, 95% CI 0.09–0.543, $p = 0.0001$)	48
HEAP (Hen's Egg Allergy Prevention Trial) Germany	Infants from the general population (n = 406 screened for egg sensitization, 383 nonsensitized randomized, 184 to egg, 199 to placebo)	Pasteurized egg white powder *or* Rice powder (placebo) from 4 to 6 months until 12 months	Egg sensitization[3] at 12 months; 5.6% in the active vs. 2.6% in the placebo group (relative risk 2.20, 95% CI 0.68–7.14, $p = 0.24$)	49
EAT (Enquiring About Tolerance) UK	Exclusively breastfed infants for at least 3 months from the general population (n = 1,303 randomized, 652 to early introduction of 6 foods while breastfeeding, 651 to exclusive breastfeeding and no allergenic foods before 6 months)	Continued breastfeeding with introduction of cow's milk, peanut, hard-boiled egg, sesame, cod, and wheat in a sequential order from 3 months (early introduction) *or* Exclusive breastfeeding for 6 months (standard introduction)	Allergy to any of the 6 foods at 3 years: 5.6% in the early-introduction vs. 7.1% in the standard-introduction group (relative risk 0.80, 95% CI 0.51–1.25, $p = 0.32$)	50

SPT, skin prick test. [1] Confirmed by an oral food challenge. [2] Egg white skin prick test ≥3 mm. [3] Specific IgE to egg ≥0.35 kU/L.

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group had egg allergy (adjusted relative risk 0.75, 95% CI 0.48–1.17, $p = 0.20$). The Beating Egg Allergy Trial (BEAT) also included high-risk infants (based on allergic disease in any or both parents) [47]. Infants were randomized to pasteurized raw whole egg or rice powder (placebo) from 4 to 8 months of age. The primary outcome was egg sensitization at 12 months of age, and 11% in the active group versus 20% in the placebo group were sensitized (odds ratio 0.46, 95% CI 0.22–0.95, $p = 0.03$). Twenty-one infants were classified as having probable egg allergy. Of these, 6.2% were in the active group and 10.5% were in the placebo group ($p = 0.20$).

In the Prevention of Egg Allergy with Tiny Amount Intake (PETIT) study, high-risk infants with established eczema were randomized to intake of either heated egg powder or squash powder (placebo) from 6 to 12 months of age, with an increased dose of egg protein from 9 months [48]. There was a marked effect of the intervention with egg allergy diagnosed at 12 months in 9% in the active group versus 38% in the placebo group (risk ratio 0.221, 95% CI 0.09–0.543, $p = 0.0001$). In fact, the striking effect of the intervention in the preplanned interim analyses led the investigators to terminate the trial prematurely. As discussed by the investigators [48] the difference might be biased, leading to a bigger difference between the active and placebo groups than if the study had not been closed.

In contrast to the above-mentioned studies that included high-risk infants, the Hen's Egg Allergy Prevention (HEAP) study, randomized infants with normal risk (from the general population) to intake of pasteurized egg white powder or rice powder from 4 to 6 months until 12 months of age [49]. Infants were screened for egg sensitization, and all included infants had specific IgE to egg <0.35 kU/L at baseline. As in the BEAT study [47], the primary outcome was egg sensitization at 12 months. 5.6% in the active group were sensitized to egg versus 2.6% in the placebo group (relative risk 2.20, 95% CI 0.68–7.14, $p = 0.24$). At that age, 2.1% in the active group had egg allergy versus 0.6% in the placebo group (relative risk 3.30, 95% CI 0.35–31.32, $p = 0.35$).

Collectively, 4 out of 5 conducted RCTs designed for egg allergy prevention were negative (Table 1), although 3 of these studies [45–47] had nonsignificant results that might suggest a benefit of early egg introduction.

Multiple Foods Approach

Observational studies have also reported an association between low food diversity in early life and both sensitization [50] and allergic manifestations [51]. In the Enquiring About Tolerance (EAT) study [52] (Table 1), 3-month-old breastfed infants from the general population were randomized to continued breastfeeding with introduction of cow's milk, peanut, hard-boiled egg, sesame, white fish, and wheat in a sequential order from 3 months of age or to continued exclusive breastfeeding for the first 6 months of life [52]. In the intention-to-treat analysis, 5.6% of the children in the early-introduction group had developed food allergy at 3 years of age compared to 7.1% in the group that introduced solid foods from the age of 6 months (relative risk 0.80, 95% CI 0.51–1.25, $p = 0.32$). Of note, only 42% in the early-introduction group were able to adhere to the food introduction regimen, demonstrating that it can be difficult to introduce multiple foods as compared to a single food item. In the per protocol analysis, however, the prevalence of "any" food allergy was 2.4% in the early-introduction group compared with 7.3% in the standard-introduction group ($p = 0.01$). The prevalence of peanut and egg allergy was also reduced in the early-introduction group (0 vs. 2.5%, $p = 0.003$, and 1.4 vs. 5.5%, $p = 0.009$, respectively). There was no difference between the 2 groups in the prevalence of allergy to milk, sesame, fish, or wheat.

Table 2. Practical implications for clinical practice based on interim guidelines from 10 International Pediatric Allergy Associations [54]

"Health care providers should recommend introducing peanut-containing products into the diets of 'high-risk' infants[1] early on in life (between 4 and 11 months of age) in countries where peanut allergy is prevalent, because delaying the introduction of peanut can be associated with an increased risk of peanut allergy"
A clinical assessment by a pediatric allergist or a physician trained in pediatric allergy may be considered in infants that have already developed allergic disease (severe eczema and/or egg allergy) in the first 4–6 months of age; this could be helpful in the diagnosis of any food allergy and in the evaluation of appropriateness of peanut introduction
The clinical evaluation may include peanut skin testing, ingestion of peanut in the clinic, or both, for infants with already established allergic disease (severe eczema and/or egg allergy)
If the skin test to peanut is positive, an observed peanut challenge to examine if the infant is clinically reactive before introducing peanuts at home can be considered

[1] High-risk criteria used in the LEAP trial were egg allergy and severe eczema [42].

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Meta-Analysis of Egg and Peanut Prevention Trials

In a recent comprehensive systematic review and meta-analysis, Ierodiakonou et al. [53] included the trials discussed above that had assessed early versus late egg introduction for egg allergy prevention (5 trials, 1,915 participants) [45–49] (Table 1). They found with moderate certainty evidence that early versus late introduction of egg was associated with a reduced egg allergy risk (risk ratio 0.56, 95% CI 0.36–0.87, $p = 0.009$). They also identified the LEAP [43] and EAT [52] studies (Table 1) (2 trials, 1,550 participants) to be included in a meta-analysis of early versus late introduction of peanuts and reported that early introduction was associated with a reduced peanut allergy risk (risk ratio 0.29, 95% CI 0.11–0.74, $p = 0.009$). The authors underscored that the studies were few and that the certainty of the evidence was reduced due to imprecision, indirectness, and heterogeneity in interventions and study populations [53]. An interesting finding, however, was that there was no distinct difference among infants at "normal" versus high risk of allergy in their analyses.

Allergic Reactions and Safety Issues

A shared feature of the studies that included high-risk infants and used pasteurized raw egg powder is that a varying proportion (4.7–31%) of the participants in the early egg intake groups discontinued egg ingestion due to allergic reactions to the egg powder [45–47]. This has raised the question if screening for sensitization would be necessary before introducing egg to the infant diet. Reassuringly, in the STEP trial that included infants with familial predisposition but no eczema, there were no anaphylactic reactions to the egg powder [46]. The authors underscored that assessment of egg sensitization before the introduction of egg and egg-containing products to the infant diet is not necessary in the community setting [46]. In the PETIT trial [48], which included high-risk infants with eczema, a few participants reported mild to moderate allergic manifestations following ingestion of the study powder, but at a similar frequency in the active and placebo groups. No participant discontinued the intervention because of allergic reactions to the egg powder, and it has been argued that this could be a matter of reduced allergenicity of heated versus pasteurized (raw) egg powder [48]. The risk of adverse reactions to peanut was low in the LEAP study; 5% of infants randomized to early peanut intake reacted at the baseline peanut challenge. However, infants at a presumably higher risk (peanut wheal size ≥5 mm) were excluded.

Current Recommendations

Current international guidelines already state that introduction of allergenic foods, including egg and peanut, does not need to be postponed beyond 4–6 months of age [32–36]. With a few exceptions, these guidelines do not, however, advocate that allergenic foods should be *actively* introduced to the infant diet between 4–6 months of age. Based on level 1 evidence from the LEAP study [42], interim guidelines on peanut introduction for allergy prevention in high-risk infants were launched in 2015 (Table 2) [54]. In an opinion paper, Allen and Koplin [55] identified and discussed the challenges in translating the findings from the LEAP study to the general population level. Safety remains one issue, particularly in very high-risk infants, as the LEAP study excluded infants with an SPT to peanut ≥5 mm, cost-effectiveness another [55]. Very recently, addendum guidelines for penaut allergy prevention in the United States were launched [56]. In brief, the guideline panel suggests introducing peanuts at home to the majority of infants in the first year of life. Infants with severe eczema, egg allergy, or both should undergo medical assessment including assessment of sensitization to peanut before peanut introduction at 4–6 months of age [56]. If other allergenic foods, such as egg, should also be actively introduced to the infant diet from 4 to 6 months of age remains undetermined. Recent allergy prevention guidelines in Australia now suggest introducing cooked (but not raw) egg from 4 to 6 months of age irrespective of allergic heredity [36]. As underlined by Ierodiakonou et al. [53], the findings from their systematic review on early versus late introduction of complementary foods for allergy prevention cannot be directly translated to new guidelines. Collectively, the optimal timing, doses and form of egg, and if these regimens should be stratified according to the infant's allergy risk remain to be determined.

Conclusion

The level 1 evidence form the LEAP study [43] has resulted in interim guidelines recommending early introduction of peanut into the diets of "high-risk" infants [54]. Further studies should aim at optimizing infant feeding regimens. Supporting the most favorable "tolerogenic" microenvironment in the gut during the period of food allergen introduction is also likely to involve "optimal" colonization of the gastrointestinal tract, breastfeeding, and other dietary factors with immunomodulatory capacity [39, 40].

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