Current Allergy and Asthma Reports (2019) 19: 7
https://doi.org/10.1007/s11882-019-0838-6

PEDIATRIC ALLERGY AND IMMUNOLOGY (WILLIAM DOLEN, SECTION EDITOR)

Primary Prevention of Food Allergy

Ann Marie Kumfer[1] · Scott P. Commins[1,2,3]

Published online: 2 February 2019

Abstract
Purpose of Review The goal of this review is to present an updated summary of the various approaches to prevent childhood food allergies and report recent advances in potential prevention trials for food allergy.
Recent Findings Several approaches related to maternal dietary supplementation as well as infant GI-based supplementation have been tried and are the subject of ongoing clinical investigation.
Summary The prevalence of food allergy appears to be increasing but several, varied approaches to prevention are being actively pursued such that an effective strategy may not be too far in the future.

Keywords Food allergy · Specific IgE · Primary prevention of food allergy · Childhood food allergy

Introduction

The Centers for Disease Control and Prevention (CDC) estimates that food allergies among children increased approximately 50% between 1997 and 2011 [1]. This rise in food allergy was initially noted in the early 1990s with an increase in peanut allergy [2]. Food allergy now affects up to 8% of young children and 5–8% of the entire US population [3–8]. Eight foods account for 90% of all reactions and, among those, peanut allergy is particularly problematic as it is largely a life-long disease and is the leading cause of fatal food anaphylaxis [9–12]. In fact, the prevalence of food allergy is rising in developed nations throughout the world. The increase in atopic diseases has been recognized as a pandemic, thus emphasizing the need for effective allergy prevention [13].

This article is part of the Topical Collection on *Pediatric Allergy and Immunology*

✉ Scott P. Commins
scommins@email.unc.edu

[1] Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC, USA

[2] Department of Pediatrics, University of North Carolina School of Medicine, Chapel Hill, NC, USA

[3] Division of Allergy, Immunology and Rheumatology, University of North Carolina, 3300 Thurston Building, CB 7280, Chapel Hill, NC 27599-7280, USA

Prevention in Allergic Disease

Recently, the Learning Early About Peanut allergy (LEAP) trial provided experimental evidence confirming that allergic sensitization to food begins in the first few months of life and progresses to production of elevated specific lgE and expression of clinical disease in a large proportion of infants [14•, 15–17]. In the LEAP trial, 9% of infants had a positive skin test to peanut prior to any known oral peanut exposure, and yet the same study clearly showed that *oral* exposure to peanut by 12 months of life significantly reduced peanut allergy at age 5 [14•]. Taken together, these observations suggest that an event early in infancy (or in utero) triggers the production of IgE to food and, at least for peanut, this event is not oral exposure. Given the focus on infancy and that the fetus can make immunologic responses to foods and other allergens, dietary interventions instituted during pregnancy, lactation, and the first year of life have been proposed [18]. These include maternal avoidance of allergenic foods and the addition of certain supplements to the maternal diet [18].

There are three types of prevention related to allergic disease [18]:

1) Primary prevention—blocks the initial immunologic sensitization (i.e., the development of allergen-specific IgE)
2) Secondary prevention—reduces the development of further disease post-sensitization
3) Tertiary prevention—reduces symptoms after manifestation of disease

The immune system of a newborn undergoes rapid changes to transition to life ex utero. The most significant immunologic event is the massive antigen exposure at birth, which initiates the development of changes that afford the baby protection from infection. Although stimulation for ex utero immune system development occurs during parturition, it takes time for the immunologic transition to occur. Therefore, medications administered and procedures performed in the immediate post-natal period could be acting upon a fetal immune system. One relevant example may well be immunization of a newborn baby with an alum-absorbed vaccine. In fact, the ability of alum to enhance IgE production is well-known as it is commonly utilized to create the atopic mouse model [19]. Although designed to produce a protective immune response, such an early in life administration may not only be acting upon a fetal immune system but also altering the development of the infant immune system. In sum, transitioning from in utero immunity to ex utero immunity is a process that occurs over a period of time in which the tolerant fetal immune milieu wanes as adult immunity develops and that time of transition may be a critical window for the development of tolerance. This balance of immunity may be altered by immunomodulation, such as changes initiated by immunizations, specifically through the adjuvant properties of aluminum hydroxide or through exposure to live organisms such as OPV or BCG (see vaccination schedule, Fig. 1). Unfortunately, the full potential for aluminum adjuvant to change the developing immune response in humans, specifically during the neonatal and infant periods, has not been thoroughly investigated.

Maternal Avoidance Diets

The best studies and the majority of publications support the conclusion that maternal avoidance diets during pregnancy, lactation, or both are not effective in preventing allergic disease. A 2012 systematic review including five randomized trials and over 900 patients also reached this conclusion [20–25]. Certainly, studies of maternal and newborn diets are difficult to perform and have been attempted without uniform scientific rigor. Variables inherent to such study designs that are difficult to control include length of breastfeeding, use of supplemental formulas, and the introduction of solid foods to infants.

The lack of protective effect in most studies could also be due (in part) to reverse causation. Mothers who thought their infants were at higher risk for atopic disorders might have been more likely to avoid certain foods in their diet, even when requested not to adjust their diet. Equally, mothers could have breastfed and breastfed longer than they had initially planned. For mothers who were going to feed/supplement with formula, they might have been more likely to choose a hypoallergenic formula. In each instance, if such an adjustment was repeated by a sufficient number of participants, this could have led to the observed lack of an effect.

Another issue is one of selection bias, as most of the studies examining the effects of maternal avoidance diets during pregnancy and lactation have been performed in populations at higher atopic risk. An infant's risk for developing allergic disease is based upon the family's atopic history. An infant is defined as "high risk" if there is at least one first-degree relative (parent or sibling) with documented allergic disease [26, 27]. However, this definition is quite broad and could include a parent with allergic rhinitis (relatively benign) or multiple siblings with severe asthma and/or food allergy (relatively significant). Thus, the general nature of this definition can make application of results to specific patients more challenging.

During Pregnancy

The available studies suggest that maternal avoidance of allergenic foods during pregnancy does not reduce the risk of allergic disease in the offspring, regardless of whether the infant is high risk or not. Thus, the American Academy of Pediatrics does not recommend maternal avoidance diets during pregnancy [28].

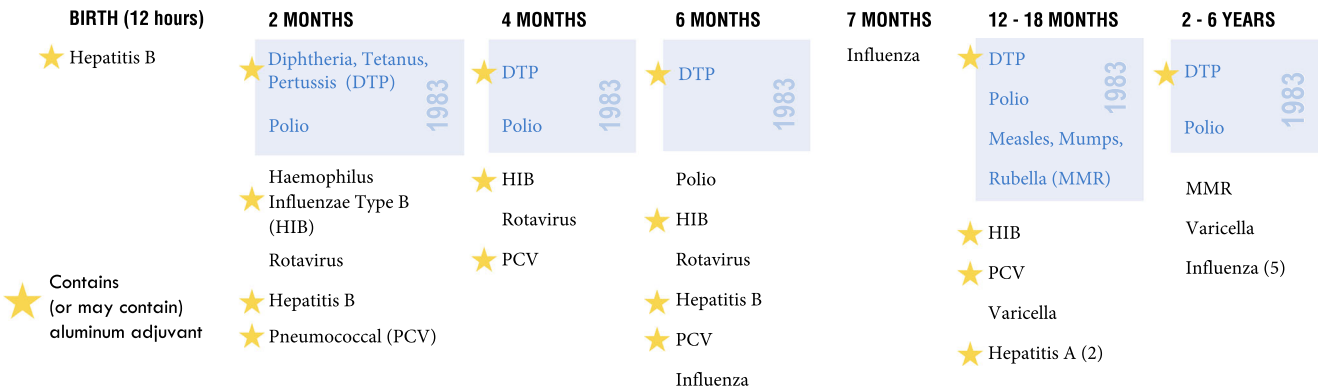

Fig. 1 Vaccines and aluminum-adjuvant: 1983 and 2018

During Lactation

It has been suggested for many years that the presence of food antigens in breast milk might sensitize nursing infants. Results of studies examining this hypothesis have been contradictory, and the cumulative data are not sufficient to support recommending food avoidance to breastfeeding mothers as a means of preventing allergy. Alternatively, maternal elimination diets have become a widely used intervention in breastfed infants with food allergies [29]. Poorly supervised or broad-based maternal elimination diets are not without nutritional risks for both mother and infant [25]. The nutritional adequacy of the maternal diet should be assessed and monitored by a pediatric dietitian [30•]. Calcium supplementation is generally recommended if cow's milk products are eliminated from the maternal diet.

Supplementation of the Maternal Diet

Women may ask if there is any benefit to purposefully ingesting allergenic foods during pregnancy or lactation for the purpose of preventing food allergy or other allergic disorders in the child. If a woman's diet is nutritionally adequate, the decision can be made on an individual basis since the relative importance of maternal diet compared with genetic factors and other risk factors is not fully understood. Supplementation with vitamin D is a common question, and although the evidence is low-quality, a World Allergy Organization (WAO) guideline indicated there is no evidence that vitamin D supplementation in the diets of pregnant women or breastfeeding mothers who had no other indications for vitamin D supplementation reduces the risk of developing allergic diseases in children and suggested against this intervention [31]. Another intervention that has been studied for the prevention of childhood allergic disease is supplementation of the maternal diet with omega-3 (n-3) long-chain polyunsaturated fatty acids. A 2015 Cochrane review of eight trials concluded there was limited evidence to support a beneficial effect [32].

Augmentation of Infant Diet

Modification of early gut colonization and fecal microbial diversity in infancy may provide an avenue for preventive or therapeutic strategies [33]. Probiotic or prebiotic supplementation has been shown to modify the risk of allergies, particularly for atopic dermatitis in infancy [34–36]. The WAO guidelines recommend the use of probiotics and prebiotics for the prevention of eczema and allergies, but caution that the available evidence is of very low certainty [37, 38]. Early introduction of selective, highly allergenic foods can also be considered an augmentation of the infant diet and a strategy for such related to peanut is included (see Fig. 2); however, this review will focus on gut supplementation.

Probiotics

Infants with allergies have been shown to have significantly lower counts of some fecal species, such as Bifidobacteria,

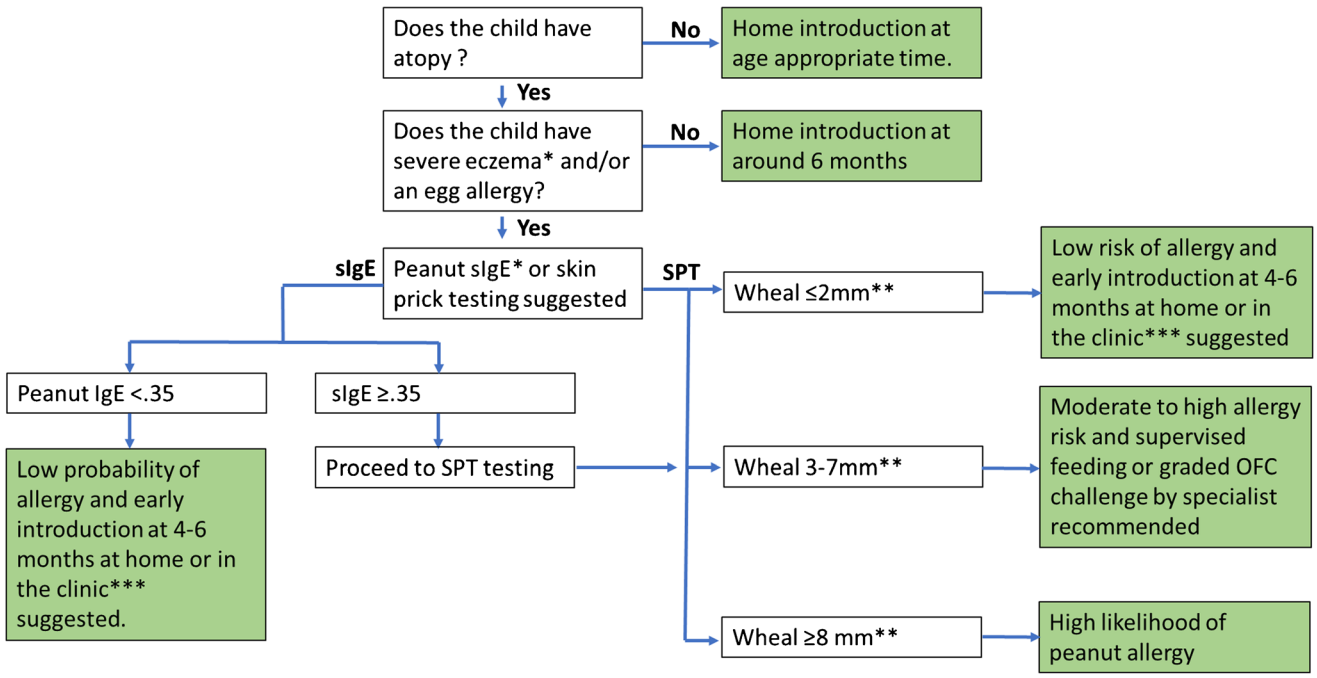

Fig. 2 Sample strategy for possible early introduction of peanut-containing food (Adapted from Greenhawt and Fleisher) [39••]

Table 1 Relevant manner of allergen exposure, prevention, recommendations, and recent studies [60••]

	Important recent research studies	Guideline recommendations	Ongoing research trials
Cutaneous exposure The dual-allergen hypothesis theorizes that eczema leads to cutaneous sensitizations to food allergens and that early oral exposure promotes tolerance [61].	PEBBLES study—non-significant trend toward decreased rates of AD and food sensitization in a study of 80 infants at risk for AD treated with daily lipid barrier replacement at 6 and 12 months LEAP screening study—13% and 19.2% of children with moderate and severe eczema respectively had ≥ 3-mm wheal to peanut on SPT; 76% of infants with severe eczema had ≥ 3 mm to 1 or more of the six food allergens tested.	NIAID 2017 update recommends that in infants with severe eczema, screening with sIgE, or SPT should strongly be considered and early introduction of peanuts at age 4–6 months is encouraged.	The BEEP trial—an ongoing trial of 1400 children in England assessing the effectiveness of daily use of topical emollients in prevention of eczema in high-risk infants with development of food allergies as a secondary outcome.
Dietary exposure Increasing evidence suggests that early oral exposure to foods more commonly associated with allergic responses leads to immunologic tolerance [14•].	LEAP—peanut allergy prevalence at 5 years of age in high-risk children was 13.7% in the avoidance group and 1.9% in the consumption group. CAPPS—secondary analysis of nested cohort from CAPPs study (1995) showed lowest incidence of peanut sensitization (1.7%) among children whose mothers consumed peanuts while breastfeeding and directly introduced peanuts before 12 months. STEP—the effect of early introduction of egg at 4–6 months was studied in infants with hereditary risk of atopy. No significant difference in egg allergy in the early introduction group vs. control group.	Early introduction of peanuts by a strategy such as in Fig. 2 AAAAI/ACAAI 2014 update suggests introducing solid foods including potential allergens at 4–6 months. The 2011 NIAID guidelines recommend against restricting maternal diet in pregnant and lactating women as a method of preventing food allergy.	Early peanut introduction: translation to Clinical Practice (EPI) trial—observational study of 400 high-risk infants aged 4–11 months undergoing peanut introduction according to current guidelines.
Immune exposure The hygiene hypothesis posits that lack of early exposure to infections results in immune dysregulation leading to atopy [62].	PROMPT—cohort of 253 Asian infants supplemented with *Lactobacillus rhamnosus* and *Bifidobacterium longum* probiotics in the first 6 months of life did not prevent eczema or food allergy at 1 year or 5 years of age. Danish Calmette Study—neonatal BCG vaccination had no effect on IgE sensitization to food allergens at 13 months in cohort of 4262 Danish newborns.	EAACI-2014 guidelines and AAAAI/ACAAI and NIAID guidelines do not recommend probiotics to prevent food allergy.	
Vitamin D While vitamin D deficiency and high latitudes are associated with food allergies, there is little data from clinical trials about the efficacy of vitamin D supplementation in the primary prevention of food allergies [31].	Prenatal vitamin D study—vitamin D supplementation in pregnant women was not shown to have a significant difference on offspring development of food allergies at age 3 when studied as a secondary outcome [63].	EAACI-2014 guidelines and AAAAI/ACAAI 2014 and NIAID guidelines have no specific guidelines regarding vitamin D supplementation in prevention of food allergy. WAO 2015 sites no evidence to support supplementation with vitamin D.	VITALITY—the clinical trial examining the efficacy and cost-effectiveness of daily vitamin D supplementation preventing challenge-proven food allergy in 3012 exclusively breastfed Australian infants.

compared to healthy infants [40]. Allergy prevention via supplementation with probiotic bacteria would be a reasonable approach to pursue. The effects of probiotics appear to be primarily mediated via the innate immune system, resulting in the promotion of T-helper 1 differentiation, production of regulatory cytokines (IL-10 and TGF-β), and enhancement of intestinal IgA responses [41]. Several studies have demonstrated that perinatal administration of probiotics to mothers in the last weeks of pregnancy and to infants in the first few months of life was associated with a significant reduction in atopic eczema [42–44]. Nevertheless, results have been varied, depending on the probiotic strain, dose, timing, and food matrix used. In fact, a study using *Lactobacillus acidophilus* even showed a slight increase in allergic sensitization [45]. The discrepant and inconsistent results highlight the complexity of probiotic supplementation and that clinical outcomes depend on the specific probiotic strains used. Clearly, the role of probiotics in allergy prevention requires further study [46].

Prebiotics

Human milk oligosaccharides (HMO) promote colonization of the gut with Bifidobacteria, which—as with probiotics—is thought to promote mucosal tolerance via interaction with regulatory T-lymphocytes and Toll-like receptors. HMO are non-digestible glycans with prebiotic properties in breast milk that provide a specialized substrate for Bifidobacteria. In the past, infant formulas were devoid of prebiotic oligosaccharides [47]. More recently, several manufactured prebiotics have been added to infant formula, including plant-based long-chain fructo-oligosaccharides (FOS) and short-chain galacto-oligosaccharides (GOS). GOS and FOS have been shown to increase numbers of fecal Bifidobacteria in formula-fed infants [48, 49]. A randomized study examined the effects of a FOS/GOS-supplemented hydrolyzed formula on atopic eczema in formula-fed infants during the first 6 months of life [50]. The results showed that FOS/GOS supplementation was associated with significantly lower rates of eczema compared to the placebo group. Notably, eczema severity was similar for both treatment arms. A more recent multi-center, randomized controlled trial in Europe assessed the effect of prebiotics in healthy, low-risk infants from 8 weeks to 12 months [51]. Prebiotics reduced the incidence of atopic dermatitis by 44% at 12 months. Interestingly, eczema severity was again not affected. Further studies are needed to assess the role of oligosaccharide supplementation in prevention of allergic disease [36].

Partially Hydrolyzed Formula

The role of hydrolyzed formula in allergy prevention has been studied for many years. The German Infant Nutritional Intervention (GINI) study is the largest, semi-randomized trial to date that examined the role of hydrolyzed formula in the prevention of allergies [52]. Infants with a family history of allergies were randomized to receive cow's milk-based formula, whey-based PHF, whey-based extensively hydrolyzed formula (EHF), or casein-based EHF at the time of weaning. The results of GINI showed a sustained protective effect against atopic eczema for whey-based PHF and casein-based EHF, even until 10 years of age [52, 53]. A Cochrane review of hydrolyzed formula in allergy prevention found a beneficial effect, albeit limited, in infants at high risk for atopy [54]. Two other meta-analyses also confirmed a preventive effect, mainly for atopic dermatitis [55, 56]. On the contrary, a meta-analysis by Boyle et al. found no support for a preventive effect of PHF against allergic disease [57]. A more recent meta-analysis that did not pool data from various PHF products and only included studies using 100% whey PHF found a preventive effect for all allergies and eczema [58]. The current Allergy Prevention Guidelines by the European Academy of Allergy and Clinical Immunology (EAACI) recommend the use of PHF with a documented preventive effect in infants at high risk of atopy if breastfeeding is insufficient or not possible [59].

Conclusions

Although rates of food allergy continue to rise, novel approaches and research related to prevention and treatment are gaining ground. Further research is needed to inform the most effective food allergy prevention strategies at the population level. As this research yields new strategies for prevention, there is potential to reverse the rising prevalence trends for food allergies. Certainly one consideration is to address the timing and use of vaccine adjuvants that may skew infant immune responses toward atopy. Although not discussed here, the beginnings of approved food allergen immunotherapy interventions may provide better health outcomes and improved quality of life for families affected by food allergies (Table 1).

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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