Current Allergy and Asthma Reports (2019) 19:60
https://doi.org/10.1007/s11882-019-0891-1

FOOD ALLERGY (E KIM, SECTION EDITOR)

Prevention of Non-peanut Food Allergies

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Abstract

Purpose of Review The purpose of this review article is to discuss the recent literature around methods of prevention of food allergies other than peanut allergy.

Recent Findings While the most robust data to date exists for peanut, there are emerging studies suggesting a beneficial effect to early introduction of cooked egg, and cow's milk as well. While the literature is sparse for other allergens such as tree nuts, finned fish, and shellfish, the mechanism of sensitization is thought to be the same and no study to date has demonstrated a harm with allergenic introduction in the 4–6 months of age window (nor has there been level 1 evidence of benefit to delay of such allergens). This strategy is safe, and pre-emptive testing is not required prior to allergenic solid introduction.

Summary All allergenic solids should be introduced at around 6, but not before 4, months of age in infants at high risk.

Keywords Food allergy · Allergy prevention · Food introduction · Complementary feeding · Eczema · Primary prevention · Pediatric allergic disease

Prevention of Non-peanut Food Allergies

Food allergy is estimated to affect 2–10% of the population, and there has been an increase in food allergy prevalence over time [1]. The US Centers for Disease Control and Prevention documented an almost doubling of food allergy prevalence in the USA between 1997 and 2011 (3.4% to 5.1%) [2]. There has been significant focus on the prevention of peanut allergy since the publication of the Learning Early About Peanut (LEAP) study, the first randomized controlled trial to demonstrate up to an 80% reduction in peanut allergy with early peanut ingestion in a high-risk group of infants [3••]. This study was largely the impetus for the subsequent release of the National Institute of Allergy and infectious Diseases (NIAID) guideline on the prevention of peanut allergy in the USA, which recommends that infants with the same risk factors as the LEAP study (severe eczema and/or egg allergy) be introduced to peanut at 4–6 months of age [4••]. However, less is known about prevention of allergies other than peanut, and less definitive guidance is available. The goal of this review is to discuss prevention of non-peanut food allergies and to review what gaps in the literature yet remain. The first section of this review will focus on the studies that have examined early introduction of allergenic solids other than peanut (such as egg, cow's milk, and wheat). Subsequently, the review will examine implementation of this research into policy, and therein what questions remain.

This article is part of the Topical Collection on *Food Allergy*

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Early Introduction of Allergenic Solids Other than Peanut

There are 8 common allergens that account for over 90% of all food reactions in children—milk, egg, peanut, tree nuts (almond, hazelnut, pistachio, cashew, walnut, pecan, Brazil nut), wheat, soy, finned fish, and shellfish [5]. In general, while the preponderance of the literature has been focused on peanut, it is thought that the mechanism of sensitization to allergenic foods is similar, no matter the allergenic solid. This mechanism is termed the dual-allergen exposure hypothesis and notes that cutaneous exposure to allergens in the absence of ingestion increases the risk of food sensitization [6•]. This

Published online: 28 November 2019

theory is supported by studies noting, for example, that mutations in the filaggrin (FLG) gene (involved in skin hydration and water retention) have been strongly linked with eczema, and independently with food allergy as well [7–9]. A cohort study of 13,971 preschool children noted that the use of peanut oil in infancy was significantly associated with the development of peanut allergy among children with eczema (odds ratio [OR] 6.8; 95%CI, 1.4–32.9) [10].

Multiple Allergenic Solids

There has been one study, Enquiring About Tolerance (EAT), that randomized 1303 general population infants to early introduction of 6 common allergens (peanut, cow's milk, finned fish, wheat, egg, sesame) at 3 versus 6 months of age in previously exclusively breast-fed infants [23••]. In the intention to treat analysis, there was no significant difference in the rate of food allergy between the early and standard introduction groups (5.6% vs 7.1% respectively; $P = 0.32$) although in the per-protocol analysis, there was a significant reduction in food allergy overall with early introduction (2.4% vs 7.3%; $P = 0.01$). In the per-protocol analysis, there was a 75% reduction in egg allergy (1.4% vs 5.5%; $P = 0.009$) and 100% reduction in peanut allergy (0% vs 2.5%; $P = 0.003$) with early introduction. Adherence was a significant issue in this study (42.8% overall). Rates of adherence to early ingestion varied, with higher rates for milk (85.2%), peanut (61.9%), and fish (60.0%) than for sesame (50.7%), or egg (43.1%).

Egg

There has been one observational study and five randomized controlled trials examining early egg introduction as a means of allergy prevention. The results of these studies are less consistent than for peanut, although it is hypothesized that part of this discrepancy between studies is related to the form (i.e., cooked vs baked vs raw) in which egg is introduced.

The most successful studies to date have been the HealthNuts population-based observational study and PETIT, a randomized study in Japan [11, 12••]. The HealthNuts, a population-based study of 2589 general risk infants in Melbourne, Australia, noted that introduction of egg at 4–6 months of age was associated with a lower prevalence of egg allergy compared with later introduction in both high risk, which was defined as having a family history of food allergy or a personal history of eczema or reactions to other foods (aOR 1.6 for introduction at 10–12 months and 3.4 for introduction after 12 months) and lower risk infants (OR 3.3; 95%CI, 1.1–1.9 at 10–12 months) [11]. In addition, the PETIT study randomized 147 infants with eczema (of any severity as long as it met diagnostic criteria) to introduction of heated (cooked) egg powder at 6 months of age or avoidance until a year and noted a significantly lower rate of cooked egg allergy with earlier introduction (risk ratio 0.222; 95%CI, 0.081–0.607; $P = 0.0012$) [12••]. In fact, the study was so successful that it was halted prematurely.

In contrast, four randomized controlled trials examining early pasteurized raw egg introduction have either not shown a significant benefit or have noted high rates of adverse events with early ingestion of raw egg in infancy. The Beating Egg Allergy Trial (BEAT) randomized 319 infants with a family history of atopy to freeze-dried whole raw pasteurized egg powder ingestion at 4 months of age or placebo until 8 months of age, with outcome of sensitization to egg white at 1 year of age. There was a significant reduction in egg white sensitization with early egg introduction (OR 0.46; 95%CI, 0.22–0.95) although there was a non-significant trend in the reduction of egg allergy and a high rate of reactions with early introduction [13]. The Hen's Egg Allergy Prevention (HEAP) study randomized 406 infants to pasteurized egg white equal in its allergenicity to raw hen's egg or placebo from age 4–6 until 12 months of age and found no significant difference in rate of egg sensitization (5.6% vs 2.6% respectively, $P = 0.24$) or allergy (2.1% vs 0.6% respectively, $P = 0.35$) at a year of age and a high rate of reactions on initial exposure to egg [14]. The study was terminated early due to high rates of reactivity noted on initial egg ingestion and this recruitment termination is a limitation of the study. The Solids Timing for Allergy Research (STAR) trial randomized 86 infants with moderate-to-severe eczema to pasteurized raw whole egg powder introduction at either 4 months or avoidance until 8 months, with an outcome of egg allergy at a year of age. There was a non-significant trend towards lower rates of egg allergy in the early introduction group compared with those in the control group (51% relative risk; 95%CI, 0.38–1.11; $P = 0.11$) although a high rate of allergic reactions (31%) was noted with early introduction [15]. The Starting Time of Egg Protein (STEP) study randomized 820 infants with a family history of atopy to pasteurized raw whole egg powder introduction at 4 to 6 months of age or avoidance until 10 months of age and found a non-significant reduction in egg allergy with early introduction (7.0% vs 10.3%; adjusted relative risk 0.75; 95%CI, 0.48–1.17) [16].

Despite the discrepancy in the literature to date, a recent meta-analysis and systematic review of timing of allergenic food introduction and risk of allergic disease found that there was moderate-certainty evidence (5 trials, 1915 participants) that early egg introduction at 4–6 months of age was associated with reduced egg allergy (risk ratio 0.56; 95%CI, 0.36–0.87) [17••]. The means by which egg is introduced (cooked versus raw) can influence its allergenicity and likely explain the discrepancy in results. The HealthNuts study noted that first ingestion of cooked egg compared with that of baked egg reduced the risk of egg allergy (OR 0.2; 95%CI, 0.06–0.71) [11].

Cow's Milk

The studies on early cow's milk introduction are all observational and all have focused on early, regular (often daily) cow's milk ingestion in the first 3 months of life (i.e., cow's milk formula vs breastmilk). The first study of early cow's milk introduction, from 2010, was a prospective study of 13,019 infants from Israel and noted that regular exposure to cow's milk formula starting within the first 14 days of life was associated with a lower risk of cow's milk allergy compared with later exposure (OR 19.3 for introduction after 14 days of age) [18]. This study on cow's milk introduction, in contrast to the early egg introduction literature, also noted irregularity of exposure to increase the risk of cow's milk allergy. A case-control study of 51 children with diagnosed cow's milk allergy compared with 102 controls and 32 egg allergic children (to minimize the effect of confounders) noted early (< 1 month of age) and regular (> 1/day) cow's milk ingestion significantly reduced the risk of cow's milk allergy [19]. Of note, this study also found irregular cow's milk exposure to increase risk. Finally, a recent analysis of the HealthNuts data noted that early exposure to cow's milk within the first 3 months of life was associated with a reduced risk of cow's milk allergy (aOR 0.31; 95%CI, 0.10–0.91) at a year of age [20].

While the literature to date with cow's milk ingestion is observational, there is certainly an association between early cow's milk ingestion and lower rates of cow's milk allergy. A randomized trial of cow's milk formula versus breastmilk sis unlikely due to ethical considerations and any benefit of early cow's milk ingestion in the first few months of life must be balanced against the many known benefits to mother and child from exclusive breastfeeding [21].

Wheat

There is one observational study looking at early wheat introduction. A cohort of 1612 children who were enrolled at birth and followed into toddlerhood noted that children who were first ingesting wheat cereal before 6 months of age had a lower risk of wheat allergy than those who started ingesting wheat cereal after 6 months of age (OR 4.77; 95%CI, 1.33–17.09) [22]. There have been no randomized trials on early grain ingestion to date. However, grains are a commonly introduced early solid especially in higher income countries where infant grain cereals are iron-fortified.

Tree Nuts, Soy, Finned Fish, Shellfish

There are no studies to date specifically examining early introduction of these allergens alone as a means of allergy prevention.

What Should Future Guidelines Recommend for Introduction of Foods Other than Peanut?

While there is now specific North American guidance on early peanut introduction, other guidelines are less clear for allergens other than peanut. For example, the British Society of Allergy and Clinical Immunology (BSACI) counsels that infants who are at higher risk (eczema or food allergy) introduce egg and peanut from 4 months of age, but does not comment about earlier introduction of other allergenic solids [24]. For lower risk infants, it recommends complementary food introduction at "around 6 months of age but not before 4 months of age" and aims to include "foods associated with food allergies" (egg, nuts, cow's milk, finned fish, shellfish, wheat) before 12 months of age. The Australasian Society of Clinical Immunology and Allergy (ASCIA) recommends introducing solids at "around 6 months, but not before 4 months" and focuses on peanut and egg introduction in the first year of life [25]. However, the ASCIA also has advice for parents that other common allergy-causing foods such as cow's milk (dairy), tree nuts, soy, sesame, wheat, fish, and other seafood be introduced by 12 months. The Canadian Pediatric Society (CPS) also focuses on "around 6 months, but not before 4 months" for introduction of allergenic solids in infants at higher risk (eczema, food allergy, or immediate family history of atopy) and, while not limited to egg or peanut, notes the evidence is strongest for early introduction of these two allergens [26].

While many guidelines also emphasize early egg introduction, there is a dilemma about how to counsel families about introduction of other allergens such as cow's milk, tree nuts, wheat, finned fish, and shellfish. There are benefits to focusing on only peanut and egg—the message is simple, there is good evidence of benefit, and for peanut the risk of lifelong allergy is high. However, there are benefits to including all the "common 8" allergens in guidance on early introduction—the mechanism of sensitization (and hence protection) is likely the same, it is unlikely for clinical trials like LEAP and PETIT to be repeated for all allergenic foods, and it removes variability in approach. However, this recommendation would be admittedly less evidence-based, and a take-home lesson from EAT is that adherence to early introduction of multiple allergenic solids is difficult.

In the authors' opinion, a simpler message for future guidelines may be that parents should introduce high-risk infants to all allergenic solids early "at around 6 months but not before 4 months" of age. The issue of pre-emptive screening will be discussed later in this review. This could be based on extrapolating the evidence from peanut and cooked egg to other allergenic foods, as well as the absence of level 1 evidence for benefit to intentionally delaying the introduction of any allergenic food. This simpler message would allow for regional variability in prevalence of food allergy (e.g., in countries where seafood allergy is more prevalent, it would permit consideration of early introduction of seafood). Among the list of allergenic foods, the foods of highest priority (in sequence)

appear to be peanut, cooked egg, cow's milk, and tree nuts in countries like the USA and Canada. For tree nuts, there is for example some evidence that cashew allergy is increasing in frequency [27]. This allergy is commonly severe and is rarely outgrown [28–30]. It has been noted that cashew nut allergen has "high potency" and is a "clearly underestimated important public health problem, especially in children" [27]. It has been noted that identifying how to prevent tree nut allergy is an "urgent priority" for future research [31]. As a result, despite the paucity of literature on early tree nut introduction, the authors also tend to counsel families, especially families at risk, to feed commonly allergenic tree nuts such as cashew and walnut early in life, in an age-appropriate way to prevent choking risk (such as smooth cashew or walnut butter).

Which Infants Will Benefit from Early Introduction?

As highlighted above, the definitions of high risk used in guidance vary. Traditionally, until the LEAP study, the definition used in most guidelines on allergy prevention was a first-degree family history of atopy [32, 33]. This definition is supported by genome-wide association studies and population studies as well [34, 35].

However, in keeping with the dual-allergen exposure hypothesis, eczema, and in particular eczema severity, is increasingly being recognized as likely the most significant risk factor for food allergy development. Results from the HealthNuts study note that infants with eczema are 11.0 times more likely to develop peanut allergy (95%CI, 6.6–18.6) and 5.8 times more likely to develop egg allergy (95%CI, 4.6–7.4) than infants without eczema [36]. A recent systematic review of 66 studies identified a strong and dose-dependent association between eczema, food sensitization, and food allergy [37]. This systematic review also noted evidence that eczema preceded the development of food allergy, in keeping with the dual-allergen exposure hypothesis.

As a result, the CPS guidance includes infants with a history of allergies themselves, such as eczema or other food allergy, and/or an immediate family history of atopy, as the definition of high risk. This broad definition also encompasses the current thinking that, as noted in the NIAID guideline, the "mechanisms of protection" are not likely different, especially among infants with mild eczema compared with those with more severe eczema.

How Frequently Do Allergenic Foods Need to Be Fed Once Introduced?

As noted with the observational studies on early cow's milk introduction, frequency of ingestion of allergenic solids may be as important as age of introduction. This is well illustrated by a case that one of the authors had of a 5-year-old child who since the age of a year had ingested cashew about a dozen times at a frequency of once every 3–4 months. At about age 4 years, he began to have reactions to cashew, which occurred on three separate occasions (abdominal pain, vomiting, and lethargy). Skin prick testing was highly positive (8 mm) to cashew. This case suggests that early introduction is not sufficient for prevention of cashew allergy and that frequency may be equally important, but difficult to implement and quantify.

However, other than peanut, there is very little guidance available about the frequency, or amount, that is required of allergenic solids to maintain tolerance. The EAT study noted that weekly consumption of 4 g of egg protein (2 g of egg white protein) was effective in the prevention of egg allergy [23••], but no guidance exists at all for any of the other non-peanut allergenic solids.

The CPS practice point recommends feeding allergenic solids "a few times a week" in keeping with the LEAP protocol although this recommendation was an expert opinion and not evidence-based [26]. The ASCIA and BSACI guidelines recommend ongoing ingestion but do not specify the amount or frequency [24, 38]. Practically, it may be simplest to counsel a family that, once it is in the diet, keep it in the diet as they would any other food that is well tolerated and integrate it into the family diet as well. However, this remains an area where further research is required to provide a definitive recommendation.

Should Testing Be Done Prior to Introduction of Allergenic Solids Other than Peanut?

The NIAID guideline recommends that infants at high risk (severe eczema and/or egg allergy) have pre-emptive screening prior to peanut introduction [4]. In general, no guideline to date has recommended blanket pre-emptive screening be initiated to allergenic solids other than peanut. In addition, significant concerns about the feasibility (including limited availability of confirmatory infant oral food challenges), implementation, cost-effectiveness, and possibility of a "screening creep" have been raised with pre-emptive peanut testing [39–42]. A Canadian editorial on the NIAID guideline specifically noted concern that "healthcare providers…may order testing to foods other than peanut (during the process of testing peanut)…" [43].

One common previous exception was testing for tree nut in a child with peanut allergy who had not ingested tree nuts, which was recommended as a possible reason for pre-emptive testing as recently as 2010 as co-allergy was thought to be common [44]. It is increasingly recognized that this may be in fact cross-sensitization instead of co-allergy. For example, a

study of 324 patients referred for food allergy noted that while the majority (86%) of patients with peanut allergy were sensitized to tree nuts, only 34% had documented allergy [45]. A recent study of oral food challenge outcomes noted that among children with peanut allergy and tree nut co-sensitization, the tree nut oral food challenge passage rate was 96%, "questioning the clinical relevance of 'co-allergy" [46].

Allergy testing, both skin prick testing (SPT) and specific-IgE (sIgE) testing, has low specificity in the absence of a history of a reaction. A retrospective chart review of 125 children with a history of positive allergy testing noted that 84–93% of the foods being avoided due to positive allergy tests could be reintroduced into the diet after an oral food challenge [47]. The Choosing Wisely campaign has recommended against pre-emptive testing, noting "false or clinically irrelevant positive allergy tests for foods are frequent…IgE testing for specific foods must be driven by a history…." [48]. Pre-emptive screening to any food carries the risk of false-positive testing, which could inadvertently negate the possible benefits of early allergenic solid introduction.

As a result, pre-emptive testing to any allergen other than peanut, including tree nuts in a child with peanut allergy, is not recommended. The one possible exception would be if a family would not feed tree nuts, or other allergens without testing (i.e., hesitancy despite counseling). To use tree nuts as an example, in that situation one could consider either a graded oral challenge to tree nuts in the allergy office, or skin prick testing with consideration of an oral challenge if the results were moderate or less. The goal would be early ingestion in the absence of pre-emptive testing, with testing only used in a circumstance where feeding would not occur without it.

Safety of Early Food Introduction in Infancy

It should be noted that first ingestion of allergenic solids, particularly in infancy, is safe. There has been no fatality on first ingestion of a food in infancy. In the LEAP study, the rate of adverse events was not different based on sensitization. At baseline screening, only 7/319 infants failed the oral food challenge and all 7 had mild reactions that did not require epinephrine [3••]. In the EAT study, there were no cases of anaphylaxis in the early introduction group [23••]. Population-based studies such as the HealthNuts have noted early ingestion to be safe as well [40].

What About Use of Hydrolyzed Formula as a Means of Allergy Prevention?

Previous guidelines recommended the use of hydrolyzed formula in high-risk infants when mothers could not, or chose not to, breastfeed, as a means of cow's milk allergy and eczema prevention [32, 33]. This recommendation was based in part on the results of the prospective German Infant Nutritional Intervention Study (GINI), which found a reduced risk of allergic disease with the use of hydrolyzed formula compared with that of standard cow's milk formula for the first 4 months of life [49]. Despite this, a Cochrane review noted "limited evidence" that hydrolyzed formula compared with regular cow's milk formula reduced the risk of infant and childhood allergy and cows' milk allergy [50].

In addition, a recent meta-analysis of 37 studies (over 19,000 participants) noted no evidence that partially or extensively hydrolyzed formulas reduced the risk of any allergic outcomes including cow's milk allergy and most concerningly noted a high degree of bias in positive outcome published studies to date [51]. It should also be noted that these formulas are cost-prohibitive and poorly tolerated in infancy.

As a result, current evidence does not support the use of hydrolyzed formulas as a means of cow's milk allergy prevention. As noted in the ASCIA guideline, "there is no consistent convincing evidence to support a protective role for partially hydrolysed formulas…or extensively hydrolysed formulas for the prevention of..food allergy" [52].

What Other Measures Can Be Useful in Preventing Food Allergy?

Several other measures—early skin moisturization [7–9], vitamin D supplementation [53, 54], and dietary diversity [55, 56]—have been proposed as other possible measures that may have a role in allergy prevention. However, the literature to date on these measures is conflicting and no firm recommendation can be given at this time for any of these measures.

There were three initial randomized controlled trials on the use of early skin moisturization as a means of allergy prevention in high-risk infants that were promising, noting decreased rates of eczema and in some cases food sensitization with early skin moisturization [57–59]. This practice, which is safe and easy to implement, would also fit with the theory of cutaneous sensitization to foods. However, recent data suggests that this practice is not as effective as initially anticipated. For example, preliminary data from Preventing Atopic Dermatitis and ALLergies in Children (PreventADALL) [60], presented at the 2019 European Academy of Allergy and Clinical Immunology conference, noted no benefit to early and regular moisturization at least 3.5 days/week on the outcome of eczema at a year of age.

While studies have linked vitamin D exposure (or lack thereof) to the development of food allergy [53, 61, 62], the data on vitamin D insufficiency during pregnancy or perinatally and its association with the development of food allergy remains mixed. While the HealthNuts data noted an association between parental vitamin D insufficiency and risk of

peanut and/or egg allergy in childhood [54], a recent study of 1074 infants noted no association between vitamin D insufficiency at birth and the risk of food allergy at a year of age [63].

In addition, while increased diversity of diet has been shown in some observational studies to be associated with reduced risk of food allergy, this approach has limitations including a lack of biologic plausibility, concerns that dietary diversity may be prioritized over allergenic solid introduction, and no randomized studies to date [55, 56].

Putting It All Together: While Waiting for Future Guidelines to Give More Specific Advice for Foods Other than Peanut, What Can We Do for High-Risk Families Who Remain Hesitant and Confused?

A case such as the following highlights how difficult it is for practitioners in 2019 to give clear advice to parents for introducing allergenic foods other than peanut and cooked egg. At 6 months of age, a girl with moderate/severe atopic dermatitis has been referred to you for consideration of allergy testing, given the 2½-year-old brother has anaphylactic wheat allergy and the mother has anaphylactic fish allergy. The brother has been on your waiting list for wheat oral immunotherapy for the past year, due to repeated anaphylaxis from accidental wheat exposures despite the family trying very hard to avoid wheat. The referring physician had already discussed early use of emollients with the family when the infant was born. Although you have a 1 year waiting list, you triage the infant to be seen at 7 months.

When the family arrives for their visit, the history confirms moderate/severe eczema since 3 months, treated with topical corticosteroids and topical antibiotics, for which she has been followed by a pediatric dermatologist. At 4 months, she tried cow's milk formula but they have been hesitant to re-try it because they feel it made her eczema worse. At 5 months, they tried peanut butter on two occasions 2 weeks apart, both tolerated, but since the referral peanut butter was re-tried during a viral cold and she vomited a couple of times, within 2 h of ingestion. When you ask the parents whether they would feel comfortable trying any allergenic foods again, they express extreme hesitancy and demand testing. Skin prick testing is positive for cow's milk (8 × 4 mm) and peanut (7 × 4 mm) and negative to egg, cashew, walnut, wheat, fish, and shrimp. You offer to bring her back for oral challenges to milk and peanut due to the history being not entirely convincing, but the parents prefer re-trying at home to avoid your wait list, now that they have an Epipen Jr. You suggest introducing the foods that tested negative as soon as possible on a regular basis, such as 3 times a week. In the days that follow, re-trying peanut butter results in immediate hives and facial swelling and milk results in milder scattered hives. Over the next month, they give egg once a week with no problems, but have not had a chance to give tree nuts because of several viral colds recently. Due to the colds, 2½ weeks go by before they get a chance to give egg again, but when they do, she has her most severe reaction to date (hives, vomiting several times, face pale) requiring her Epipen Jr. and an emergency visit. Shortly after, sIgE testing returns at 15 kU/L to egg white, 0.74 kU/L to milk, and 2.61 kU/L to peanut, with cashew and walnut still negative. In the next few weeks, they try cashew but immediate hives result, while salmon on third exposure (they had been giving it once a week for 3 weeks) results in vomiting 2 h after ingestion. Unlike her older brother, wheat has been tolerated. You book them for a follow-up to repeat skin prick testing to tree nuts and fish, but also suggest the milk ladder at home, plus put her on your very long waiting list for egg and peanut oral immunotherapy.

This case makes you question the utility of current guidelines which focus solely on early introduction of peanut and cooked egg. In the absence of guidelines in your country clearly and firmly recommending early introduction of allergenic foods other than peanut and cooked egg, you decide that if this family has a third child in the future, you will tell them that they "should" introduce "all" allergenic foods at around 6 months but not before 4 months. You remain very perplexed as to how to convince parents that they should continue to quickly introduce other allergenic foods even if their infant experiences a reaction such as vomiting to peanut at 6 months, recognizing that parents who experience such an early reaction in their infant's life may be hesitant to keep trying other allergenic foods and that your waiting list continues to grow because few colleagues offer infant oral challenges in your city. You also wonder how feasible it is in the real world for families like this to give a relatively long list of allergenic foods more often than once a week.

Conclusion

While the most robust data to date exists for peanut, there are emerging studies suggesting a beneficial effect to early introduction of cooked egg, and cow's milk as well. While the literature is sparse for other allergens such as tree nuts, finned fish, and shellfish, the mechanism of sensitization is thought to be the same and no study to date has demonstrated a harm with allergenic introduction in the 4–6 months of age window (nor has there been level 1 evidence of benefit to delay of such allergens). It is important to note that this strategy is safe, and pre-emptive testing is not required prior to allergenic solid introduction.

It must be emphasized that ongoing ingestion of allergens is important and should be considered and asked about. Moving forward, there remains many unanswered questions including the role of measures such as early skin

moisturization, dietary diversity, and vitamin D supplementation on allergy prevention. Further studies are required to assess the strengths and limitations of these approaches.

A simpler message for future clinical practice guidelines is that parents should introduce high-risk infants to all allergenic solids early "at around 6 months but not before 4 months," as it is unlikely for clinical trials like LEAP and PETIT to be repeated for all allergenic foods. A message with the word "should" conveys something active, whereas keeping messages such as "do not delay" convey something passive. Including active messaging for all allergenic solids across all guidelines would allow greater uniformity between them, and clearer messaging when counseling families on prevention.

Compliance with Ethical Standards

Conflict of Interest EMA received an unrestricted educational grant from Novartis and is a member of the scientific advisory board for Food Allergy Canada. ESC has received research support from DBV Technologies, has been a member of advisory boards for Pfizer, Pediapharm, Leo Pharma, and Kaleo, is a member of the scientific advisory board for Food Allergy Canada, and was an expert panel and coordinating committee member of the National Institute of Allergy and Infectious Diseases (NIAID)-sponsored Guidelines for Peanut Allergy Prevention.

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 importance
- •• Of major importance

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