Introducing highly allergenic foods to infants and children

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INTRODUCTION — Studies support the existence of a critical time early in infancy during which the genetically predisposed atopic infant is at higher risk for developing allergic sensitization [1]. Thus, dietary interventions in the first years of life have been analyzed for their effects on the prevalence of allergic disease including food allergy [2]. Both American and European allergy expert committee guidelines recommend that solid foods be introduced between four to six months of age in all infants [3-6]. Other organizations have also concluded that complementary foods may be safely introduced between four and six months of age [7-9], although many still recommend or prefer exclusive breastfeeding for the first six months of life [8,10-13]. Recommendations regarding when to introduce highly allergenic foods, particularly in high-risk infants, have shifted over time.

Introduction of highly allergenic foods is discussed here. The general approach to introduction of solid foods during infancy is reviewed in greater detail separately, as is use of formula in high-risk infants. (See "Introducing solid foods and vitamin and mineral supplementation during infancy" and "Introducing formula to infants at risk for allergic disease".)

Other aspects of the primary prevention of allergic disease are also discussed in greater detail separately. (See "Primary prevention of allergic disease: Maternal diet in pregnancy and lactation" and "The impact of breastfeeding on the development of allergic disease".)

HIGHLY ALLERGENIC FOODS — While any food has the potential to cause allergy, certain foods are more common triggers of significant acute allergic reactions due to various factors. The most common food allergens in children in the United States and many other countries include cow's milk (CM), hen's egg, soy, wheat, peanut, tree nuts, and seafood (shellfish and fish). (See "Pathogenesis of food allergy", section on 'Factors influencing sensitization or tolerance' and "History and physical examination in the patient with possible food allergy", section on 'Common culprit foods' and "Food allergy in children: Prevalence, natural history, and monitoring for resolution", section on 'Prevalence of childhood food allergy' and "Food allergens: Overview of clinical features and cross-reactivity".)

INTRODUCTION IN A HIGH-RISK POPULATION — Infants and young children with a family history of atopy are at high risk for developing allergic disease, and those with a personal history of atopy, particularly those with moderate-to-severe eczema, are also at increased risk of developing other atopic diseases including food allergies. The American Academy of Pediatrics (AAP) had previously suggested in 2000 that the introduction of certain highly allergenic foods be delayed further in high-risk children: cow's milk (CM) until age one year; eggs until age two years; and peanuts, tree nuts, and fish until age three years [14]. This recommendation was based upon early studies that suggested that delayed introduction of solid foods might help prevent some allergic diseases, particularly atopic dermatitis (AD) [15-17]. (See "Introducing formula to infants at risk for allergic disease", section on 'Infants at high risk for developing allergy'.)

However, this advice was modified in 2008 with consensus that there was insufficient evidence to recommend any specific practices concerning the introduction of these foods after four to six months for the prevention of allergic disease in high-risk infants [3,6,7,18,19]. To the contrary, delayed introduction of solid foods may increase the risk of allergy [20,21], and early introduction of certain foods (eg, egg, peanut) between four to six months of age may decrease the risk of allergy to that specific food [22]. Thus, we recommend **not** delaying the introduction of complementary foods into the diet of high-risk infants beyond what is generally recommended for all infants. The approach for specific highly allergenic foods is reviewed in greater detail below. (See 'Suggested approach' below

and "Introducing solid foods and vitamin and mineral supplementation during infancy", section on 'When to initiate complementary foods'.)

In the first randomized trial examining early introduction of a highly allergenic food, 86 high-risk infants with moderate-to-severe eczema were randomly assigned to daily consumption of 1 teaspoon of pasteurized raw whole-egg powder (n = 49) or rice powder (n = 37) from four to eight months of age [23]. A medically supervised feeding of 2 teaspoons of whole cooked egg was performed at eight months of age, with egg introduced into the diet after that if the feeding was successful. An oral food challenge (OFC) with one-half of a whole pasteurized raw egg was performed at 12 months of age. Although these infants had no known prior direct ingestion of egg, 31 percent (15 of 49) in the egg group reacted to the egg powder, most on initial exposure, and did not continue ingestion. Of the infants who were still participating in the study at 12 months, 33 percent (14 of 42) in the egg group were diagnosed with immunoglobulin E (IgE)-mediated egg allergy (elevated egg-specific IgE and a positive raw egg challenge or history of an allergic reaction to egg) compared with 51 percent (18 of 35) in the control group, a nonsignificant difference. However, the trial was terminated early for safety reasons due to the large percentage of infants allergic at four months and significant allergic reactions at the entry OFC.

The Learning Early about Peanut Allergy (LEAP) trial was the first randomized trial to show benefit of early introduction of a major food allergen, with earlier introduction of peanut at 4 to 11 months of age associated with a decreased risk of developing peanut allergy [20]. In this study, 640 children aged 4 to <11 months (median 7.8 months) with severe eczema and/or egg allergy and a skin prick test (SPT) wheal of ≤4 mm to peanut were randomly assigned to either consumption or avoidance of peanut until 60 months of age. Randomization occurred after participants were stratified into one of two groups: sensitized (SPT wheal 1 to 4 mm; n = 98) or not sensitized (no wheal on SPT; n = 542) to peanut. Infants assigned to the consumption group first underwent an OFC to peanut to confirm lack of peanut allergy. Those with a positive OFC (one in the nonsensitized group and six in the sensitized group) were told to avoid peanut. Those children in the consumption group who had a negative OFC were fed at least 6 grams of peanut protein per week (consumed in three or more meals per week). Adherence to consumption or avoidance was assessed using a validated food frequency questionnaire and measurements of peanut protein in home dust samples. The presence of peanut allergy was then determined at 60 months of age by OFC.

Among the 530 children evaluated for the primary outcome in the nonsensitized group at 60 months of age, 13.7 percent of the avoidance group and 1.9 percent of the consumption group were allergic to peanut (absolute risk difference 11.8, 95% CI 3.4-20.3), which is an 86 percent relative risk reduction. All 98 children in the sensitized group were evaluated at 60 months; 35.3 percent of the avoidance group and 10.6 percent of the consumption group were allergic to peanuts (absolute risk difference 24.7, 95% CI 4.9-43.3), which is a 70 percent relative risk reduction. The retention rate of the study was 98.4 percent, and adherence to the assigned treatment was also high.

In the follow-up (LEAP-On) study that included 550 of the participants from the primary trial, both groups were asked to avoid peanut for 12 months until 72 months of age [21]. Compliance with avoidance was 90.4 percent in the original avoidance group and 69.3 percent in the original consumption group. Peanut allergy continued to be significantly more common in the peanut avoidance group (18.6 percent, 52 of 280 children) than the early peanut consumption group (4.8 percent, 13 of 270 children). Three children in the consumption group who were previously tolerant developed peanut allergy during the 12-month avoidance period. In the group that continued avoidance, three children developed peanut allergy, and four had resolution of the allergy during the follow-up period. Development of peanut allergy in previously tolerant children who cease consumption is consistent with data on peanut allergy recurrence in patients who had outgrown their peanut allergy but did not go on to eat it regularly after a successful OFC. (See "Food allergy in children: Prevalence, natural history, and monitoring for resolution", section on 'Recurrence'.)

In the Prevention of Egg Allergy with Tiny Amount Intake (PETIT) trial, 147 infants with eczema and no prior direct ingestion of egg or history of an allergic reaction to egg were randomly assigned to daily consumption of heated egg powder (50 mg daily from 6 to 9 months of age and 250 mg daily thereafter until 12 months of age) or placebo along with aggressive treatment of eczema [24]. Participants underwent an OFC to 7 grams of heated whole-egg powder equivalent to 32 grams of boiled, whole hen's egg at 12 months of age. The trial was stopped early due to benefit. The 121 infants who performed the egg OFC at 12 months were included in the intent-to-treat analysis. Five of 60 infants (8 percent) in the treatment group had egg allergy confirmed by OFC compared with 23 of 61 (38 percent) in the placebo group (risk ratio 0.22, 95% CI 0.09-0.54). Limitations of this study include stopping early for benefit, which tends to overestimate treatment effect, especially if the event rate is low, as in this case. In addition, baseline eczema was more severe in the placebo group compared with the treatment group based upon the mean SCORAD score (42.0 versus 27.5, respectively), and the mean egg-specific IgE was higher in the placebo group as well (4.46 versus 0.73, respectively).

Two other trials of egg introduction beginning at four to six months of age were performed in infants at risk for food allergies based upon family history of atopic disease. The first of these, the Starting Time of Egg Protein (STEP) trial, enrolled 820 infants of atopic mothers with allergic disease and a positive environmental skin prick test (SPT) who were aged four to six months and did not have a history of eczema or known prior direct ingestion of egg [25]. Testing for egg sensitization was not performed prior to starting the treatment phase of the study. Infants were randomly assigned at four to six months of age to daily ingestion of 900 mg of pasteurized, raw whole-egg protein or placebo daily until 10 months of age. Cooked egg was introduced into the diet in both groups at 10 months of age, and a raw egg OFC was performed at 12 months of age. There was no difference in the percent of infants who reacted to the egg OFC at 12 months of age (7 percent in the treatment group compared with 10.3 percent in the placebo group). However, a higher percentage of infants stopped taking the study powder due to confirmed allergic reactions compared with the placebo group (6.1 versus 1.5 percent, respectively), suggesting that some of these infants were already allergic to egg.

The second trial, the Beating Egg Allergy Trial (BEAT), enrolled 319 infants who were SPT negative to egg but had a first-degree relative with atopic disease [26]. These infants were randomly assigned at four months of age to 350 mg pasteurized, raw whole-egg protein or placebo daily and were treated until eight months of age, at which time egg was introduced into the diet. At 12 months of age, egg sensitization was significantly lower in the treatment group (13 of 122, 10.7 percent) compared with placebo (25 of 122, 20.5 percent). However, there was a significant loss to follow-up, with only 254 infants having at least partial assessment at 12 months of age. In addition, 14 of the infants in the treatment group were lost to follow-up because they reacted to the egg powder at introduction. Presumably, there would have been no difference in the rates of sensitization had those children been evaluated at 12 months. Furthermore, there was no difference in the number of infants with probable egg allergy, a more clinically relevant outcome than sensitization, at 12 months of age.

INTRODUCTION IN THE GENERAL POPULATION — A number of studies, most of which were performed in population-based, prospective birth cohorts, have not supported delaying the introduction of solid foods beyond four to six months for the prevention of allergic disease [27-38]. Similar to the high-risk population, delayed introduction of solid foods may increase the risk of allergy [28], as may restricting the diversity of complementary foods introduced in the first year of life [39], and early introduction between four to six months of age may decrease the risk of allergy [22]. Thus, complementary foods, including highly allergenic foods, may be introduced into the diet of "standard or low" risk children any time after four to six months of age. However, it is still possible that some children in this lower risk stratum will have allergic reactions with introduction since some infants are already allergic to foods such as egg by four to six months of age [40]. Introduction of solids during infancy in the general population is reviewed in detail separately. (See "Introducing solid foods and vitamin and mineral supplementation during infancy".)

One prospective study examined the feeding history of 13,019 infants and evaluated probable adverse reactions to cow's milk (CM) by history and physical exam, milk skin prick testing (SPT), and oral food challenge (OFC) [34]. The cumulative incidence for immunoglobulin E (IgE)-mediated CM allergy was 0.5 percent. CM protein was introduced into the diet significantly later in the allergic group than the tolerant group (mean age at introduction 116 versus 62 days of life, respectively). Early exposure to CM formula (introduction within the first 14 days of life) was associated with a lower rate of CM allergy than those started between 105 to 194 days of age (0.05 versus 1.75 percent, respectively).

A population-based, cross-sectional study examined the prevalence of egg allergy at 12 months of age (based upon positive egg-specific IgE testing followed by confirmation of allergy with an OFC to egg or a prior history of a reaction) in 2589 infants [33]. Later introduction of egg was associated with an increased risk of egg allergy (5.6, 7.8, 10.1, and 27.6 percent of infants at 12 months of age had egg allergy with introduction at 4 to 6, 7 to 9, 10 to 12, and <12 months of age, respectively), with significant differences seen with introduction at 10 to 12 and >12 months compared with 4 to 6 months (adjusted odds ratio [OR] 1.6, 95% CI 1.0-2.6 and OR 3.4, 95% CI 1.8-6.5, respectively). A lower risk of egg allergy was seen in infants who were given lightly cooked egg first rather than egg in baked goods first (OR 0.2, 95% CI 0.06-0.71).

The Enquiring about Tolerance (EAT) trial examined whether early introduction of six highly allergenic foods (hen's egg, CM, sesame, whitefish, peanut, and wheat) beginning at three months of age versus more standard introduction at six months in breastfed infants protected against the development of food allergy [41]. Infants were recruited from the general population and as such were technically not at increased risk for food allergy. However, the group was self-enriched for atopy. The 1303 exclusively breastfed infants were randomly assigned to introduction of highly allergenic foods between three and six months of age or continued exclusive breastfeeding

until six months of age. Milk in the form of yogurt was always the first food introduced, and wheat was always the last, with the other foods introduced in random order.

There was no difference in the prevalence of food allergy at one and three years of age between the two groups in the intention-to-treat (ITT) analysis. However, the prevalence of any food allergy, and peanut and egg allergy in particular, was lower in the early-introduction group compared with the standard-introduction group in the per-protocol analysis (2.4 versus 7.3 percent, respectively for any food allergy). Earlier feeding did not seem to reduce rates of breastfeeding. Adherence to the food regimen was problematic, with 43 percent of the participants in the early-introduction group adhering to the protocol (ie, able to consume all six allergenic foods in the required amount and by the required time). Although the most conservative interpretation of the data from the ITT analysis did not show that this regimen reduces the risk of food allergies. This study does support the recommendation to not withhold allergenic foods, but rather to introduce them as early as four to six months of age. The data also suggest that earlier introduction may be beneficial and may not be harmful nor effect rates of concomitant breastfeeding.

The Hen's Egg Allergy Prevention (HEAP) trial randomly assigned 383 infants four to six months of age who were recruited from the general population and had hen's egg-specific IgE <0.35 kU_A/L to increasing doses of raw, pasteurized egg white three times per week (0.83 g/dose during week 1, 1.67 g/dose during week 2, and 2.5 g/dose week three until 12 months of age) or placebo [40]. There was no difference between the two groups with regard to egg sensitization or egg allergy confirmed by OFC. The adjusted prevalence of egg allergy in the 406 infants screened for the study was 5.3 percent. The authors noted a high rate of anaphylaxis at entry egg introduction, which may be partially attributed to the raw pasteurized form and the relatively larger amounts of egg protein consumed compared with other early egg introduction randomized controlled trials.

A meta-analysis that combined data on trials in both normal- and high-risk infants found that early introduction of egg or peanut at four to six months of age was associated with a decreased risk of allergy to that food specifically (egg allergy risk ratio 0.56, 95% CI 0.36-0.87 and peanut allergy risk ratio 0.29, 95% CI 0.11-0.74) [22]. Although this meta-analysis found "moderate certainty" evidence for a protective association for early introduction of peanut and egg, there are notable limitations. The results for peanut were based on two randomized controlled trials: Learning Early about Peanut Allergy (LEAP), which again was performed in a narrowly selected, high-risk group defined by severe eczema and/or egg allergy, and EAT, which recruited subjects from the general population. While LEAP showed significant risk reduction for preventing peanut allergy in ITT analysis, EAT did not, only showing risk reduction for prevention of peanut allergy in the weaker per protocol analysis. The data for egg included five trials, four of which failed to show a protective effect for early egg introduction that used a raw pasteurized egg product, while the remaining one trial (PETIT, published only in abstract form at the time of the meta-analysis) that showed benefit of early egg introduction used heated egg, which is less allergenic than raw egg. Inclusion of the data from this abstract was strong enough to influence the overall protective effect for early egg introduction. However, more research is needed to better understand the different forms of egg and their effects on egg allergy prevention.

SUGGESTED APPROACH — There are few studies examining the safest way to introduce highly allergenic foods in high-risk children. For some foods, such as peanut, the majority of reactions occur in response to what is often believed to be the initial ingestion [42]. The Learning Early about Peanut Allergy (LEAP) and follow-up LEAP-On trials reviewed above focused on a specific high-risk group and a specific allergen, with skin prick tests (SPTs) and oral food challenges (OFCs) to peanut performed prior to introduction [20,21]. While the results from this trial may not be broadly generalizable to other foods, to infants at high risk for allergy for other reasons, or to infants at low risk for allergy, the findings do suggest that past recommendations to substantially delay introduction of highly allergenic foods were appropriately rescinded. Formal guidelines with respect to introduction of highly allergenic complementary foods are under development. An interim guideline addressing introduction of peanut based upon the LEAP trial and other studies was published in 2017 [43]. Our suggested approach outlined below is consistent with these guidelines.

We counsel parents to introduce highly allergenic foods (eg, cow's milk [CM], hen's egg, peanut, tree nuts, fish, and shellfish) in the following manner in infants who are at risk based upon family history, but who have not had any significant prior allergic reactions to a food or difficult-to-control moderate-to-severe atopic dermatitis (AD) [6]:

- First, the child should be at least four months of age and have shown developmental readiness to consume complementary foods. (See "Introducing solid foods and vitamin and mineral supplementation during infancy", section on 'Developmental skills'.)
- In addition, the child should have tolerated a few of the more typical, initial complementary foods (such as cereals, fruits, and vegetables).

- If these two criteria are met, then the child can be given an initial taste of one of these foods at home (rather than at daycare or at a restaurant), with an oral antihistamine available.
- If there is no apparent reaction, the food can be introduced in gradually increasing amounts.

However, we suggest an allergy evaluation, including a detailed history and possible testing, before introduction of highly allergenic foods in patients with the following histories (see "History and physical examination in the patient with possible food allergy" and "Diagnostic evaluation of food allergy"):

- Recalcitrant, moderate-to-severe AD despite optimal management.
- Signs or symptoms of an immediate allergic reaction while breastfeeding or with the introduction of any food, especially one of the highly allergenic foods.

For children with the above features, evaluation for introducing peanut may follow the consensus recommendations based upon the LEAP study [43]. A suggested approach is shown in the algorithm (algorithm 1).

The general guidelines for introducing solid foods to an infant's diet are discussed in detail elsewhere. (See "Introducing solid foods and vitamin and mineral supplementation during infancy", section on 'Optimal timing'.)

SOCIETY GUIDELINE LINKS — Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Food allergy".)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topic (see "Patient education: Starting solid foods during infancy (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Human milk is the optimal source of nutrition for all term infants during the first four to six months of life, regardless of their risk for allergic disease. (See "Infant benefits of breastfeeding".)
- The most common highly allergenic foods include cow's milk (CM), hen's egg, soy, wheat, peanut, tree nuts, shellfish, and fish. (See 'Highly allergenic foods' above.)
- Previous guidelines recommended delayed introduction of highly allergenic solid foods for the purpose of preventing allergic disease in high-risk infants. However, evidence suggests that this practice may increase rather than decrease the incidence of food allergies. We recommend early introduction of highly allergenic solid foods in high-risk infants (**Grade 1B**). These infants should be at least four months of age, be developmentally ready, and have tolerated a few less-allergenic complementary foods, such as rice cereal and pureed fruits or vegetables. (See 'Introduction in a high-risk population' above and 'Suggested approach' above.)
- Highly allergenic foods can be gradually and carefully introduced to asymptomatic high-risk infants without prior testing. The one exception is liquid, whole CM, which should be avoided in all infants less than one year of age for reasons unrelated to allergy (CM formula and other CM products such as those in baked goods, cheese, and yogurt are not restricted prior to age one year).
- However, an allergy evaluation, including a detailed history and possible testing, is advised before introduction of highly allergenic foods if a patient has had an immediate allergic reaction to a food or breast milk or has difficult-to-control moderate-to-severe atopic dermatitis (AD) despite optimal management. (See 'Suggested approach' above.)
- Complementary foods, including highly allergenic foods, may be introduced into the diet of low-risk children at any time after four to six months of age. All solid food should be introduced in a form that does not present a

choking hazard. (See 'Introduction in the general population' above.)

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