

Primary Prevention of Allergic Disease Through Nutritional Interventions

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With the rising prevalence of atopic disease, primary prevention may play a role in reducing its burden, especially in high-risk infants. With this in mind, the Adverse Reactions to Foods Committee of the American Academy of Allergy, Asthma & Immunology was charged with the task of developing recommendations for primary care physicians and specialists about the primary prevention of allergic disease through nutritional interventions according to current available literature and expert opinion. Recommendations that are supported by data are as follows. Avoidance diets during pregnancy and lactation are not recommended at this time, but more research is necessary for peanut. Exclusive breast-feeding for at least 4 and up to 6 months is endorsed. For high-risk infants who cannot be exclusively breast-fed, hydrolyzed formula appears to offer advantages to prevent allergic disease and cow's milk allergy. Complementary foods can be introduced between 4 and 6 months of age. Because no formal recommendations have been previously provided about how and when to introduce the main allergenic foods (cow's milk, egg, soy, wheat, peanut, tree nuts, fish, shellfish), these are now provided, and reasons to consider allergy consultation for development of a personalized plan for food introduction are also presented. © 2012 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol: In Practice 2013;1:29-36)

Key words: Primary prevention; Breast-feeding; Lactation; Infant formula; Complementary food introduction; Food allergy; Asthma; Atopic dermatitis; Atopy

Primary allergy prevention refers to inhibiting the development of clinical disease before it occurs. Many studies have been performed to investigate primary allergy prevention and involved infants who are at high risk for developing allergic disease. Several committees representing the American Academy of Pediatrics (AAP),¹ the joint guidelines of the European Society for Pediatric Allergology and Clinical Immunology,²⁻⁵ and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition^{6,7} have defined an infant to be at high risk if there is at least 1 first-degree relative (parent or sibling) with a documented allergic condition. A major problem with this definition of high risk is that it is widely inclusive, so that 1 infant may be at high risk if the father has allergic rhinitis, whereas another infant may be at high risk if multiple siblings have severe asthma and food allergies. These 2 infants are not at equivalent risk, yet the inclusive nature of this definition attempts to ensure that the findings of studies can be applied to significant portions of the general population, although it also may combine higher and lower risk infants in whom the effect of these interventions may differ. Although many studies have been performed with such selected high-risk patients, and many of the following conclusions/recommendations have been made in such studies, one might also consider that there are insufficient studies to truly understand the effect of nutritional interventions in unselected populations.

This document was developed as a resource for primary care providers, allergists, and other specialists. The first part of this document summarizes the main findings and recommendations about the role of maternal dietary restrictions, breast-feeding, the use of different infant formulas, and the timing of introduction of complementary foods on the development of allergic disease in children, with up-to-date references as of August 2012. Recommendations are not intended for children who have already developed an allergic condition, such as food allergy or atopic dermatitis, unless otherwise stated.

When the AAP Committee on Nutrition and the AAP Section on Allergy and Immunology reviewed the above findings in 2008,¹ no formal recommendations were made as to when and how the main allergenic foods (cow's milk, egg, soy, wheat, peanut, tree nuts, fish, and shellfish) should be introduced into young children's diets. Therefore, the final section provides general guidelines for primary care physicians and specialists to provide advice to patients for the introduction of these highly allergenic foods into a child's diet. Note that, when available, evidence from peer-reviewed studies are referenced, but, unfortunately, to date only a few studies provide data to suggest when these highly allergenic foods might be introduced to prevent allergy, so some of these suggestions reflect opinion and are not evidence based. Similarly, no studies discuss in what manner these foods should be

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Abbreviations used

AAP- American Academy of Pediatrics

pHF- Partial whey hydrolysate formula

eHF- Extensive casein or extensive whey hydrolysate formula

introduced and which children truly warrant allergy testing before introduction of these foods. Thus, these suggestions may not be applicable to all patients and must be updated when more data become available.

MATERNAL AVOIDANCE OF HIGHLY ALLERGENIC FOODS FOR PRIMARY PREVENTION OF ALLERGIC DISEASE IN THE CHILDREN

Maternal avoidance of highly allergenic foods during pregnancy

- Maternal avoidance of cow's milk and egg during pregnancy does not affect the incidence of allergic disease.⁸⁻¹³
- Earlier studies found no association between maternal peanut avoidance during pregnancy and lactation and the incidence of subsequent peanut allergy in their children.¹⁴⁻¹⁶ A small retrospective study of 25 subjects showed an increased risk of peanut allergy in the children with maternal consumption of peanut more than once per week during pregnancy.¹⁷ A more recent study of approximately 500 atopic infants with milk or egg allergy found that maternal ingestion of peanut more than twice per week during pregnancy was associated with an increased risk in the children of having peanut sensitization (peanut-specific IgE ≥ 5 kU (kilounits) of antibody/L, a level considered possibly indicative of allergy; however, no food challenges in the children were performed).¹⁸
- One study showed an increased risk of childhood asthma outcomes (but not in reported peanut allergy at age 8 years) during the first 8 years of life with maternal daily versus rare consumption of nut products (not specifically peanut) during pregnancy.¹⁹ On the contrary, another study found that, compared with children whose mothers consumed no peanuts during pregnancy, children whose mothers ingested peanut during pregnancy 1 or more times per week were less likely to have asthma.²⁰
- A systematic review of human studies and expert-led review of animal studies did not provide clear evidence that either early maternal exposure to, or avoidance of exposure to, peanuts has an effect on the later development of peanut sensitization or allergy.²¹

Avoidance of highly allergenic foods during lactation

- Data are conflicting, but there is no significant benefit to the children with maternal avoidance of highly allergenic foods during lactation.^{10,12,14,22-24} A possible reduction of atopic dermatitis exists in the children in the first 2 years of life in some studies but no difference after 2 years.⁴

Summary

- Maternal avoidance during pregnancy of essential foods such as milk and egg is not recommended at this time. On the basis of data that are inconclusive for peanut ingestion during

pregnancy and peanut allergy in the children, no recommendation on maternal avoidance of peanut during pregnancy can be made at this time.

- Maternal avoidance of highly allergenic foods during lactation is not recommended at this current time. Note that this recommendation does not apply to infants who manifest signs of allergic disease shortly after birth, because treatment may, in some cases, involve dietary interventions during lactation.

Note

- *Avoidance diets entail potential risks for the mother and fetus/infant who have significant protein and caloric demands. Although not recommended for primary prevention at this time, if mothers choose to avoid foods during pregnancy or lactation, dietary counseling with a nutritionist is recommended to ensure adequate nutrition and health for both the mother and fetus/infant.*

BREAST-FEEDING FOR PRIMARY PREVENTION OF ALLERGIC DISEASE IN THE CHILDREN

Effect of breast-feeding on atopic dermatitis in the children

- In a meta-analysis, exclusive breast-feeding for 3 months appears to reduce the incidence of atopic dermatitis in the children compared with conventional formula feeding.²⁵ However, this effect was lost when a controversial study was removed from a more recent systematic review and meta-analysis.²⁶
- Reports are conflicting about whether exclusive breast-feeding longer than 3 months decreases, increases, or has no effect on the incidence of atopic dermatitis in the children.²⁷⁻³⁶

Effect of breast-feeding on asthma in the children

- Exclusive breast-feeding for 3 to 4 months reduces the number of early, upper respiratory infection-associated wheezing episodes before the age of 4 years.³⁶⁻³⁹
- Wheezing in later childhood (>6 years of age) is more likely to represent atopic asthma, and the associations between breast-feeding and this type of wheezing are currently unclear, because data from various studies have drawn conflicting conclusions.³⁹⁻⁴²
- Some studies suggest that exclusive breast-feeding increases the incidence of asthma after the age of 14 years.⁴³⁻⁴⁵

Effect of breast-feeding on food allergy in the children

- A systematic review found an association in high-risk infants between exclusive breast-feeding for at least 4 months and a lowered risk of cow's milk allergy (but not food allergy in general) in infants, compared with feeding an intact cow's milk protein formula.^{1,4,46,47}
- However, evidence is insufficient on which to draw more general conclusions, with no clear benefit in unselected populations.⁴⁸⁻⁵⁴

Effect of breast-feeding on allergic rhinitis in the children

- A meta-analysis of prospective studies found a protective effect of breast-feeding for 3 months,⁵⁵ but the effect was of borderline statistical significance. More recent studies have

found a reduced risk of allergic rhinitis in the children with breast-feeding,^{33,45} but only one study was a prospective study, and the reduced risk was only found in the African American subpopulation.⁵⁶

- More prospective studies with strict methodology and longer periods of follow-up are necessary to allow firm conclusions on the effect of breast-feeding on the development of allergic rhinitis in the children.

Summary

- Exclusive breast-feeding is recommended for at least 4 months and up to 6 months of age to possibly reduce the incidence of atopic dermatitis for children younger than the age of 2 years, to reduce early onset wheezing before the age of 4 years, and to reduce the incidence of cow's milk allergy but not food allergy in general in the first 2 years of life. The effects of breast-feeding on allergic rhinitis are not clear at this time.

SELECTION OF INFANT FORMULA FOR PRIMARY PREVENTION OF ALLERGIC DISEASE IN THE CHILDREN

Cow's milk formulas versus partial whey hydrolysate formulas

- Studies suggest that partial whey hydrolysate formulas (pHFs) have a preventive effect on atopic disease and cow's milk protein allergy.^{4,57-64}

pHFs versus extensive casein or extensive whey hydrolysate formulas (ehF)

- A meta-analysis of 2 studies found no significant difference between a pHF and an ehF in the development of infant allergic diseases, including asthma and food allergy.^{65,66}
- One large study found that hydrolyzed formulas, especially the extensively hydrolyzed casein formulas, have the potential to reduce the risk of atopic dermatitis up to age 6 years when used as a supplement or substitute to breast milk instead of conventional cow's milk formulas during the first 4 months of life. No effect was observed on asthma and food allergy.⁶⁷⁻⁶⁹
- Additional prospective trials, also in high-risk infants, are needed to confirm the potential benefits of pHFs or ehFs and to determine whether the benefits persist later into childhood, adolescence, or adulthood.

Soy formula versus other formulas; amino acid–based (elemental) formulas

- The evidence does not show an advantage of soy formula.⁷⁰
- Studies of amino acid–based formulas are lacking at this time.

Summary

- Evidence is not conclusive to support the use of a formula over breast-feeding to prevent atopic disease, but for those infants at increased risk of allergic disease who cannot be exclusively breast-fed for the first 4 to 6 months of life, a hydrolyzed formula appears to offer advantages to prevent allergic disease and cow's milk allergy. An ehF may be slightly more beneficial than a pHF, but the data are inconclusive. Evidence is not substantial that soy formula prevents atopic disease, and studies that use amino acid–based formulas are necessary.

INTRODUCTION OF COMPLEMENTARY FOODS FOR PRIMARY PREVENTION OF ALLERGIC DISEASE IN THE CHILDREN

Timing of introduction

- Between 4 and 6 months of age, complementary foods are necessary to support growth and to supplement nutritional needs. The introduction of complementary foods should be delayed, however, until the infant is able to sit with support and has sufficient head and neck control.⁷¹
- The AAP recommends the introduction of complementary foods be delayed until the infant is at least 4 months old, but exclusive breast-feeding is preferred until 6 months of age.⁷² The expert panel from the European Academy of Allergology and Clinical Immunology recommends introduction of complementary foods between 4 and 6 months of age in breast-fed or formula-fed infants.^{1,5} The World Health Organization recommends exclusive breast-feeding for the first 6 months of life.⁷³
- In an unselected population of children, feeding solids before 4 months of age was associated with a higher incidence of atopic dermatitis, with an effect detected 10 years later.⁷⁴⁻⁷⁶
- No current evidence suggests that the delay of introduction of solid foods beyond 4 to 6 months of age will prevent allergic disease.⁷⁷⁻⁸⁰
- Delayed introduction of solid foods, especially the highly allergenic foods, may increase the risk of food allergy or eczema.⁸¹⁻⁸⁷

Previous AAP recommendations published in 2000 advised delayed introduction of the following highly allergenic foods in infants at high risk for allergic disease to prevent the development of future allergy: cow's milk until age 1 year; egg until age 2 years; and peanuts, tree nuts, and fish until age 3 years.⁸⁸ However, over the next decade, the incidence and prevalence of food allergy and allergic diseases in general have increased substantially, leading to the re-evaluation of the 2000 recommendations. After careful review of the current literature, the AAP's Committee on Nutrition and Section on Allergy and Immunology published an updated Clinical Report in January 2008¹ that determined there was no convincing evidence for delaying the introduction of specific highly allergenic foods, a consensus that was shared with other professional societies, including the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Committee and the Section on Pediatrics of the European Academy of Allergology and Clinical Immunology. In the new report, no specific guidelines on how and when to introduce the highly allergenic foods listed above were provided. Therefore, this report provides *general guidelines and suggestions* for practicing primary care physician colleagues and specialists who must address daily the question of what to tell parents and patients when they ask when and exactly how to introduce the same highly allergenic foods to young children. Note that it is not possible to discuss all scenarios in a general guidelines document. There may be situations when it is appropriate to vary this advice, such as for infants with an established diagnosis of food allergy or severe eczema; in such cases, it may be helpful to seek advice from a primary care physician or a specialist.

Data are now emerging in the literature that suggest the delayed introduction of solid foods may increase the risk of food

allergy or eczema, and the early introduction of allergenic foods may prevent food allergy in infants/children.

- A small study that examined the association between cereal grain exposures (wheat, barley, rye, oats) in the infant diet and the development of wheat allergy reported that delaying the introduction of cereal until after 6 months of age did not protect against the development of wheat allergy but that it may have actually increased the child's risk of wheat allergy.⁸¹ Another study found a significantly increased risk of sensitization to wheat at age 5 years according to food-specific serum IgE testing if wheat was introduced after age 6 months.⁸⁷ The limited information from these reports does not support delaying the introduction of wheat for the prevention of wheat allergy.
- Cow's milk added to complementary foods in small amounts, such as in baked goods and other dairy products (eg, cheese and yogurt), is safe to introduce before age 1 year.⁷¹ In addition, one study showed that early exposure in infancy (age ≤ 14 days) to cow's milk protein via formula as a supplement to breast-feeding might protect against IgE-mediated cow's milk allergy. However, the amount of cow's milk protein needed to prevent cow's milk allergy was not determined from the study.⁸⁹
- Recent studies show that it may be beneficial to introduce egg at an early age in smaller amounts in baked goods or in a cooked egg form (scrambled, hard-boiled, fried, or poached). One such study reported increased risk of sensitization to egg at age 5 years according to food-specific serum IgE testing if egg was introduced after age 10.5 months.⁸⁷ In another study, with egg allergy determined by clinical history of reaction and allergy testing or by food challenge, infants introduced to egg at 4 to 6 months of age had a significantly lower risk of egg allergy than infants introduced to egg after that time. First exposure to the cooked egg form at 4 to 6 months reduced the risk of egg allergy even further compared with first exposure to egg in baked goods.⁸⁶
- A recent study found that early feeding (<4 months of age) of any complementary food (solid food and/or cow's milk) was associated with a reduced risk of peanut sensitization at age 2 to 3 years in children with a parental atopic history; however, food challenges were not done to confirm true allergy.⁹⁰ One study of Jewish children in the United Kingdom found a 10-fold higher prevalence of peanut allergy than that of Jewish children in Israel, where Israeli infants consume peanut in higher quantities at an earlier age than infants in the United Kingdom who avoid peanuts.⁸⁵ These studies raise the question of whether earlier complementary feeding and early introduction of peanut during infancy could prevent peanut allergy. On the basis of current available data, however, peanut butter could be introduced between the ages of 6 and 12 months. A possible exception is the child who has a sibling with peanut allergy, who has a 7-fold risk of peanut allergy⁹¹; often because of parental concerns, this child may be referred to an allergist for testing and counseling before introduction of peanut (refer to scenarios below). Peanut kernels, which carry the risk of aspiration at this age, should be avoided until the primary care physician feels it is safe to consume,⁷¹ but peanut butter, peanut butter cups, other candied peanut formulations, and tree nut butters are safe to introduce at a young age.
- One study found that the introduction of fish before the age of 9 months reduced the risk of eczema in infants at 1 year of age.⁸²

- As of this dated report, no studies have reported on the early introduction of soy or shellfish and the effect on allergy. However, we do not feel that the introduction of soy or shellfish into the diet needs to be delayed.

Summary

- Taken collectively, the above-mentioned studies support the general notion that the highly allergenic foods may be introduced earlier into the diet, that is, as complementary foods. Whether the earlier introduction of these highly allergenic foods proves to truly prevent the individual food allergies remains to be seen, because interventional studies need to be performed to support the limited data reported here from these observational studies.

GENERAL ADVICE FOR COMPLEMENTARY FOOD INTRODUCTION FOR ALL CHILDREN REGARDLESS OF PREDISPOSITION TO DEVELOP ALLERGIC DISEASE

- Most pediatric guidelines suggest first introducing single-ingredient foods between 4 and 6 months of age, at a rate not faster than one new food every 3 to 5 days.⁷¹
- Complementary foods in the United States are typically rice or oat cereal, yellow/orange vegetables (eg, sweet potato, squash, and carrots), fruits (eg, apples, pears, and bananas), green vegetables, and then age-appropriate staged foods with meats.⁹²
- It is common for acidic fruits (eg, berries, tomatoes, citrus fruits, and vegetables) to cause, on contact with the skin, localized, perioral reactions that may include an erythematous rash or urticaria due to irritation from the acid in these foods and high levels of histamine-releasing compounds within the foods, respectively. These do not usually result in systemic reactions; therefore, delayed introduction of such foods is not recommended.
- We do not suggest introducing one of the highly allergenic foods as one of the first complementary foods; however, once a few typical complementary foods (see above bullet) are tolerated, highly allergenic foods may be introduced as complementary foods.
- Whole cow's milk as the infant's main drink, as opposed to cow's milk-based formulas and other cow's milk-based products, such as cheese and yogurt, that are safe before age 1 year, should be avoided until age 1 year for reasons unrelated to allergic disease, that is, increased renal solute load, low iron content.^{71,93,94}
- Whole peanuts and tree nuts, but not peanut/tree nut butters or other formulations, carry aspiration risk and should be avoided until the primary care physician feels they are safe.⁷¹

How to introduce the highly allergenic foods

Few studies have examined the safest way to introduce highly allergenic foods. We recommend counseling parents to introduce them in the following manner:

- The child can be given an initial taste of one of these foods *at home*, rather than at day care or at a restaurant.
- Parents should be advised that for some foods, such as peanut, most reactions occur in response to what is believed to be the initial ingestion.⁹⁵

- If there is no apparent reaction, the food can be introduced in gradually increasing amounts.
- Introduction of other new foods should proceed at a rate of one new food every 3 to 5 days if no reactions occur.⁷¹

Scenarios in which we would suggest consultation with an allergist for development of a personalized plan for food introduction include the following:

- When an infant develops persistent moderate-to-severe atopic dermatitis despite optimized management or has a reliable history of an immediate allergic reaction in relation to eating a food,⁹⁶ although many of the less allergenic initial, complementary foods listed above may still be safe, delay of introduction of the highly allergenic foods is recommended until an evaluation by a specialist, to possibly include allergy testing, is done.
- Children with one underlying food allergy are at risk for other food allergies, for example, peanut for tree nut allergy^{97,98} and cow's milk or egg allergy for peanut allergy,⁹⁹ so referral to an allergist is recommended.
- If commercially available serologic food-specific serum IgE testing is positive in the setting of food that has not yet been introduced into the diet, referral to an allergist with experience in interpreting these results and performing food challenges is recommended to determine whether there is clinical food allergy before multiple foods are eliminated from the diet unnecessarily, especially if the food-specific serum IgE levels are below 95% of the level that predicts clinical food allergy, or if such predictive levels are unavailable for those foods.¹⁰⁰ If, however, a child has experienced an immediate reaction to a food and the food-specific IgE testing is positive, this may confirm the clinical diagnosis of food allergy, including if the food-specific IgE level is below the 95% predictive level of food allergy. Referral to an allergist is still recommended for confirmation of the allergy, management in the prevention of future food allergic reactions, evaluation for other possible food allergy, prescription of appropriate medications to treat anaphylaxis, and follow up for possible resolution of food allergy over time.
- If serologic food-specific serum IgE testing results in an undetectable food-specific IgE level despite a convincing history of an allergic reaction, referral to an allergist is recommended for skin prick testing and possibly an oral food challenge, rather than having the family try the suspect food at home again.⁹⁶
- For the child who has a sibling with peanut allergy, which has a 7% risk of peanut allergy among siblings,^{101,102} parents or physicians may request a food allergy evaluation with a possible food challenge before introducing peanut.⁹⁶ However, parents can be counseled that fatal reactions to peanut have not been reported on first exposure, and the risks of introducing peanut at home in infancy are low. Therefore, initial introduction of peanut at home in the manner outlined above is encouraged.

Note

- *We do **not** recommend routine serologic food-specific IgE screening on children without a history of an allergic reaction or other symptoms/signs of food-related allergic disease. Referral to an allergist before any serologic allergy testing may be warranted if*

*there is concern for food allergy, as per the National Institutes of Health Expert Panel Guidelines for the Diagnosis and Management of Food Allergy in the United States.*⁹⁶

Summary

- Complementary foods can be introduced between 4 and 6 months of age.
- The highly allergenic foods can be given as complementary foods once a few complementary foods have been tolerated first and should initially be given at home first rather than at a day care or a restaurant.
- There are certain situations when consultation with an allergist is recommended to discuss food introduction, including, among others, when an infant has poorly controlled severe atopic dermatitis despite treatment or has a reliable history of reacting immediately to a food.

SUMMARY OF RECOMMENDATIONS

Avoidance diets

- Maternal avoidance diets during pregnancy and lactation are not recommended at this time on the basis of current data; more research is necessary to generate a recommendation about maternal avoidance of peanut.

Breast-feeding

Exclusive breast-feeding is recommended for at least 4 months and up to 6 months of age

- To possibly reduce the incidence of atopic dermatitis for those younger than the age of 2 years,
- To reduce early onset wheezing before age 4 years, and
- To reduce the incidence of cow's milk allergy in the first 2 years of life.
- Despite some studies that showed an increased risk of allergic disease with exclusive breast-feeding, the overall benefits of breast-feeding on the general health of the child are likely to outweigh the potential drawbacks, regardless of the allergic status of the mother or child.

Selection of infant formula

- No conclusive evidence supports the use of a formula over breast-feeding to prevent atopic disease.
- For infants at increased risk of allergic disease who cannot be exclusively breast-fed for the first 4 to 6 months of life, hydrolyzed formula appears to offer advantages to prevent allergic disease and cow's milk allergy.
- There may be a slight benefit of an eHF over a pHF, but the data are not conclusive.
- There is no substantial evidence that soy formula prevents atopic disease.
- Studies of amino acid-based formulas for the primary prevention of allergic disease are lacking.

Introduction of complementary foods

- Complementary foods can be introduced between 4 and 6 months of age.
- There are no current data available to suggest that cow's milk protein (except for whole cow's milk), egg, soy, wheat, peanut, tree nuts, fish and shellfish introduction into the diet need to be delayed beyond 4-6 months of age. Therefore,

complementary foods may include the highly allergenic foods once a few other complementary foods are tolerated first.

- New data are emerging that suggest the early introduction of the highly allergenic foods may reduce the risk of food allergy.
- Highly allergenic foods are best first introduced at home, rather than at a day care or at a restaurant.
- If a patient has had an allergic reaction to a food, has difficulty to control moderate-to-severe atopic dermatitis, or has an underlying food allergy, referral to an allergist for testing is recommended before introduction of the highly allergenic foods.

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