Food Allergen Avoidance in the Prevention of Food Allergy in Infants and Children

Robert S. Zeiger, MD, PhD

ABSTRACT. Food allergy afflicts an increasing number of infants and children and is associated with both clinical and familial burdens. To help lessen this burden, the Nutritional Committees from the American Academy of Pediatrics and jointly the European Society for Pediatric Allergology and Clinical Immunology and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition published recommendations to prevent and treat food allergy. Although there is much in common with these recommendations, differences exist. This review compares, contrasts, and reconciles them, presenting the evidence that has led to their statements. *Pediatrics* 2003;111:1662–1671; cow’s milk allergy, double-blind placebo-controlled food challenge; PH, protein hydrolysate, partial protein hydrolysate, hygiene hypothesis, prevalence.

**ABBREVIATIONS.** CM, cow milk; Ig, immunoglobulin; AAP, American Academy of Pediatrics; CMA, cow milk allergy; OR, odds ratio; CI, confidence interval; DBPCFC, double-blind placebo-controlled food challenge; PH, protein hydrolysate.

Four percent to 6% of children have documented food allergy. Its prevalence and food sensitization have increased during the past decade, presenting a burden to our young. Chicken egg, cow milk (CM; including all dairy products), peanut, fish, nuts, wheat, and soy are foods in the United States that are most likely to induce food-specific immunoglobulin (Ig) E sensitization in infancy and childhood. Studies document that the natural history of food allergy to CM, egg, and soy is usually characterized by remissions early in childhood. In contrast, allergy to peanut, nuts, and fish typically persist to adulthood, although if acquired early and with lower levels of specific IgE and less severe symptoms, it may remit in a minority. After the development of food sensitization and food allergy, avoidance of the allergenic proteins hastens tolerance.

Although immunologic engineering will hopefully deliver the most promising and enduring strategies for food allergy prevention in the near future, food allergen avoidance affords an avenue for prevention at the present time. Avoidance can be instituted at any of the 3 stages of allergy prevention: 1) primary prevention blocks immunologic sensitization to foods, particularly IgE; 2) secondary prevention suppresses disease expression after sensitization; and 3) tertiary prevention averts symptoms after disease expression. Limitations in knowledge, societal compliance, and resources have been obstacles to prevention at all 3 stages. Primary prevention of allergy would be ideal, but secondary prevention may be the option followed by families interested in food allergy prevention only after atopy risk is documented in their offspring. Tertiary prevention is the stage in which clinicians treat patients to avoid recurrence of symptoms. Food allergy prevention strategies must consider its ability to 1) predict the high-risk infant and child, 2) demonstrate effectiveness of the intervention strategy, 3) use acceptable interventions, 4) minimize adverse effects, and 5) generate cost-effective outcomes.

Challenges exist in all of the above criteria; however, nutritional committees from the American Academy of Pediatrics (AAP) and jointly the European Society for Pediatric Allergology and Clinical Immunology and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition have published recommendations for the primary (prophylaxis) and tertiary (treatment) prevention of food allergy. These recommendations are works in progress based on best interpretations of existing data, and as noted in a footnote to the AAP recommendations, “This statement does not indicate an exclusive course of treatment or serve as a standard of medical care.” The recommendations of these American and European committees on nutrition, although generally similar, do have some differences. Tables 1 and 2 summarize and contrast the recommendations and comment on the differences in the prophylaxis of food allergy (primary prevention) and treatment of food allergy (tertiary prevention), respectively.

**PRIMARY PREVENTION OF FOOD ALLERGY**

Convincing studies support the existence of a critical time early in infancy, possibly also prenatally, in which the genetically programmed atopic infant is at higher risk to become sensitized to ingested/encountered food allergens. Intervention efforts, therefore, must be instituted early in the perinatal period to have a chance of success. Important atopic risk factors that are susceptible to modulation include 1) bottle feeding, 2) early introduction of allergenic foods, 3) exposure to environmental tobacco smoke, and 4) ignorance about allergic disease. Although

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and are reviewed in detail elsewhere. However, with the subsequent development of food allergy, eosinophils and basophils, etc. are significantly associated such as elevated peripheral blood and nasal eosinophils and basophils, etc. are significantly associated with the subsequent development of food allergy and are reviewed in detail elsewhere. However, none of these tests possesses adequate sensitivity or predictive power to be practical for population screening for food allergy prevention. None of these tests is superior to determination of family history for population screening. In addition, convincing studies note that allergy prevention interventions are specifically, if not predominantly, beneficial only in infants with an atopic family history. At the present time, the family history, if carefully assessed through questions to both parents, is adequate for large-scale screening. Both the AAP and European committees recommend using atopic family history to identify infants for allergy prevention, with the AAP suggesting using a stronger degree of family atopy than the European group (2 members [biparental or parent and sibling] versus 1 member [parent or sibling]). Scandinavian studies report approximately a 40% prevalence of atopic disease by 7 years for an infant with a history of biparental atopy. An even higher risk (70%) exists for developing the same disorder as one’s parents, given that both parents have the identical disorder. Documented food allergy in a sibling or a parent also increases the likelihood for the development of food allergy in an offspring. In a prospective study of infants with documented atopic parents (approximately half with 1 and half with 2 atopic parents) confirmed that atopic disease develop-

### Selection of High-Risk Infants

A strategy that identifies high-risk newborns and infants and directs preventive measures or advice to them should be adopted. Many genetic linkage markers and immunologic factors (elevated cord blood and infancy IgE levels, egg-specific IgE, lower γ-interferon/interleukin-4 ratio, inflammatory cells such as elevated peripheral blood and nasal eosinophils and basophils, etc.) are significantly associated with the subsequent development of food allergy and are reviewed in detail elsewhere. However, none of these tests possesses adequate sensitivity or predictive power to be practical for population screening for food allergy prevention. None of these tests is superior to determination of family history for population screening. In addition, convincing studies fail to show benefit from prenatal CM and egg avoidance (potential for affecting maternal and infant weights adversely). Peanut is not an essential food, avoidance will not lead to nutritional deficits, and its avoidance may better prepare for postpartum avoidance. Studies confirm at least 4-6 mo may be adequate for beneficial preventive effect. Contradictory because conflicting studies exist and issue not resolved: some believe that such a diet should be investigational at this time; others believe that efforts should be limited to peanut.

### TABLE 1. Summary of Recommendations for Prophylaxis (Primary Prevention) of Food Allergy by the Committees on Nutrition of the AAP and ESPACI/ESPGHAN

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AAP, 2005</th>
<th>ESPACI/ESPGHAN, 1999</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk infants</td>
<td>Yes: biparental; parent and sibling</td>
<td>Yes: affected parent or sibling</td>
<td>Prevention seems limited to high-risk infants</td>
</tr>
<tr>
<td>Maternal pregnancy diet</td>
<td>Not recommended with possible exception of peanut</td>
<td>Not recommended</td>
<td>Studies fail to show benefit from prenatal CM and egg avoidance (potential for affecting maternal and infant weights adversely). Peanut is not an essential food, avoidance will not lead to nutritional deficits, and its avoidance may better prepare for postpartum avoidance. Studies confirm at least 4-6 mo may be adequate for beneficial preventive effect. Contradictory because conflicting studies exist and issue not resolved: some believe that such a diet should be investigational at this time; others believe that efforts should be limited to peanut.</td>
</tr>
<tr>
<td>Exclusive breastfeeding</td>
<td>6 mo</td>
<td>4-6 mo</td>
<td>Studies confirm at least 4-6 mo may be adequate for beneficial preventive effect. Contradictory because conflicting studies exist and issue not resolved: some believe that such a diet should be investigational at this time; others believe that efforts should be limited to peanut.</td>
</tr>
<tr>
<td>Maternal lactation diet</td>
<td>Eliminate peanuts and nuts (consider eliminating eggs, CM, fish)</td>
<td>Not recommended</td>
<td>Studies confirm at least 4-6 mo may be adequate for beneficial preventive effect. Contradictory because conflicting studies exist and issue not resolved: some believe that such a diet should be investigational at this time; others believe that efforts should be limited to peanut.</td>
</tr>
<tr>
<td>Supplemental calcium and vitamins during restricted lactation diets</td>
<td>Yes</td>
<td>Not discussed</td>
<td>Need to prevent nutritional deficiencies with nutritional supplementation.</td>
</tr>
<tr>
<td>Avoid soy formulas</td>
<td>Yes</td>
<td>Yes</td>
<td>Most studies failed to show a benefit with soy formulas in primary prevention. There is greater support for extensively hydrolyzed products at this time, but their greater expense may limit their use and lead to use of partially hydrolyzed products. There is greater support for extensively hydrolyzed products at this time, but their greater expense may limit their use and lead to use of partially hydrolyzed products.</td>
</tr>
<tr>
<td>Hypoallergenic formula for bottle-fed high-risk infants</td>
<td>Yes: use a hypoallergenic (extensive) or possibly PHs when not breastfeeding</td>
<td>Yes: use formula with confirmed reduced allergenicity</td>
<td>There is greater support for extensively hydrolyzed products at this time, but their greater expense may limit their use and lead to use of partially hydrolyzed products.</td>
</tr>
<tr>
<td>Hypoallergenic formula for supplementation</td>
<td>Yes: use extensive or possibly PH</td>
<td>Yes: use formula with confirmed reduced allergenicity</td>
<td>There is greater support for extensively hydrolyzed products at this time, but their greater expense may limit their use and lead to use of partially hydrolyzed products.</td>
</tr>
<tr>
<td>Delayed introduction of solid foods to infant</td>
<td>Start least allergenic at sixth month; CM at 12 mo; eggs at 24 mo; Peanuts, nuts, and fish at 36 mo</td>
<td>Start at fifth month of life</td>
<td>The less restrictive ESPACI recommendations are based on studies in which CMA was prevented even when CM was introduced at 5 mo. The AAP recommendation is based on consensus rather than on direct evidence.</td>
</tr>
</tbody>
</table>

ESPACI indicates European Society for Pediatric Allergology and Clinical Immunology; ESPGHAN, European Society for Pediatric Gastroenterology, Hepatology, and Nutrition.
TABLE 2. Summary of Recommendations for Treatment (Tertiary Prevention) of Food Allergy in Infancy by the Committees on Nutrition of the AAP and ESPACI/ESPGHAN

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AAP, 2000&lt;sup&gt;5&lt;/sup&gt;</th>
<th>ESPACI/ESPGHAN, 1999&lt;sup&gt;6&lt;/sup&gt;</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants with confirmed food allergy</td>
<td>Complete exclusion of causal food</td>
<td>Complete exclusion of causal protein</td>
<td>Avoidance may lead to earlier remission for CM and egg allergy. Avoidance only sure way to avoid symptoms. Definitive studies with DBPCFC demonstrate that infants develop symptoms from food proteins in breast milk and avoidance in lactation diet leads to improvement.</td>
</tr>
<tr>
<td>Exclusive breastfeeding in infant with food allergy</td>
<td>1) Trial of maternal lactation restriction of CM, egg, fish, peanuts, and tree nuts, and then if unsuccessful, 2) use of a hypoallergenic (extensively hydrolyzed protein and if allergic symptoms persist, a free amino acid–based formula) or soy formula (if IgE mediated), either as the initial treatment or after 6 mo of age and the use of a hypoallergenic formula</td>
<td>Trial of maternal lactation avoidance of causal food protein during lactation</td>
<td></td>
</tr>
<tr>
<td>Confirmed CMA in formula-fed infants</td>
<td>Use of a hypoallergenic (extensively hydrolyzed protein or if allergic symptoms persist, a free amino acid–based formula) or soy formula, if IgE mediated. Benefit should be seen within 2-4 wk and the formulas continued until age 1 y.</td>
<td>Use highly reduced hypoallergenic product based on extensively hydrolyzed proteins or, in selected cases, a product based on an amino acid mixture</td>
<td>General agreement, except that the AAP believes that a trial of soy formula in infants with IgE-mediated CMA is warranted if concomitant soy allergy is ruled out. ESPACI does not distinguish treatment for IgE and non-IgE-mediated CMA.</td>
</tr>
<tr>
<td>Avoid partially hydrolyzed protein formulas in CMA</td>
<td>Yes</td>
<td>Yes</td>
<td>Partially hydrolyzed formulas have 1000–100,000 times higher concentrations of intact CM proteins than extensively hydrolyzed products and provoke reactions in a majority of CMA patients and must be avoided.</td>
</tr>
<tr>
<td>Avoid unmodified proteins of goat or sheep milk in CMA</td>
<td>Yes</td>
<td>Yes</td>
<td>A very high degree of homology exists between CM and goat and sheep milk leading to frequent reactions in CMA.</td>
</tr>
<tr>
<td>Infants with food allergy and malabsorptive enteropathy</td>
<td>Use of a hypoallergenic extensively hydrolyzed protein or if allergic symptoms persist, a free amino acid–based formula</td>
<td>Use extensively hydrolyzed formula or amino acid mixture without lactose and with medium chain triglycerides until normal absorptive function returns</td>
<td>Infants with severe gastrointestinal disturbances may benefit from an amino acid–derived formula first to allow gut rest. Switch to an extensively hydrolyzed protein formula, if possible, after gut resolution.</td>
</tr>
</tbody>
</table>

DBPCFC indicates double-blind, placebo-controlled food challenge.

oped in >70% and food allergy in approximately 25% from birth to 7 years of age.<sup>12</sup>

**Should Allergenic Foods Be Restricted in a Mother’s Diet During Pregnancy?**

The fetus can mount an immunologic response to foods and other allergens. Occasionally, specific IgE to foods<sup>13</sup> and frequently T-cell responses to milk and egg proteins and aeroallergens are seen in the fetus and newborn.<sup>14</sup> These responses may be normal immunologic phenomena and not be related to the subsequent development of food allergy. Attempts to prevent CM and egg allergy with maternal CM and egg avoidance during the third trimester failed completely to reduce food allergy or any other atopic disorder or sensitization from birth through 5 years.<sup>15–17</sup> In addition to these negative findings, maternal weight gain during pregnancy was compromised by the restriction of CM and egg. These findings were confirmed by meta-analysis.<sup>18</sup> Both the AAP and European guidelines do not recommend institution of a maternal allergen avoidance diet that excludes essential foods during pregnancy.

On the basis of epidemiologic studies that suggested that the ingestion of peanut during pregnancy may increase the risk of subsequent peanut allergy,<sup>19</sup> the AAP suggested that peanut avoidance during pregnancy be an exception to the above proscription. Peanut is not an essential food, its avoidance will not lead to nutritional problems, and its restriction during pregnancy may help prepare the mother for its avoidance postpartum.

**Breastfeed Exclusively and Prolonged**

Breast milk provides the ideal nutritional, immunologic, and physiologic nourishment for all newborns. Components of breast milk enhance natural defenses and promote immunoregulation.<sup>20,21</sup> These reasons alone justify the AAP and European recom-
recommendations for exclusive and prolonged breastfeeding.

Breast milk also inhibits the increase in food antigen absorption that occurs early postnatally in animals. Differences in study design, outcomes, targeted populations, quality, size, and duration of breastfeeding may be responsible. This subject has been reviewed thoroughly and should be consulted. Although the sheer number of published prospective intervention studies support the beneficial nature of breastfeeding in reducing allergic disease development when compared with CM formula feeding, several prolonged exclusive breastfeeding investigations of atopic-prone infants failed to demonstrate any allergy-protective role of breastfeeding. These investigations may have been compromised by the ethically correct decision not to randomize the study groups, potentially leading to recruitment biases, incomparable groups, and confounding variables. Greater health-promoting activities (not smoking, delaying introduction of solid foods, and avoiding child care) are practiced by mothers who breastfeed compared with those who elect to use formula. Other design weaknesses in these intervention studies include: 1) nonmasked evaluations; 2) unconfirmed diagnoses, either immunologically or by food challenges; 3) no documentation of adherence; 4) inadequate cohort sizes; 5) short-term breastfeeding; and 6) differential environmental control measures.

A 17-year nonrandomized study reported that compared with short or no breastfeeding, 6 months of exclusive breastfeeding is associated with less eczema and food allergy at ages 1 and 3 years and a long-term allergy protective effect on the respiratory allergy during adolescence. The study did not account for possible confounding of group demographics on the lack of randomization.

The only prospective, controlled allergy prevention study to randomize groups to breast milk versus CM formula used banked milks in a preterm infant cohort. In this study, CM formula feedings increased the risk of developing eczema by 18 months (odds ratio [OR]: 3.6; 95% confidence interval [CI]: 1.4–9.1) in the subgroup of neonates with an allergic family history. Food allergy and allergic sensitization were not investigated.

For helping to resolve these differences, a meta-analysis, using recommended standard criteria for trial appraisal, analyzed 18 prospective studies that compared breastfeeding with CM formula feeding on the development of atopic dermatitis in childhood. An overall protective effect of exclusive breastfeeding for 3 months on atopic dermatitis was shown with an overall OR of 0.68 (95% CI: 0.52–0.88). The effect was strongest in children with a family history of atopy (OR: 0.58; 95% CI: 0.4–0.92). No effect was seen in children without at least a first-degree relative with atopy (OR: 1.43; 95% CI: 0.72–2.86). Given the close causal association between food allergy and atopic dermatitis, it would not be too large a stretch to suggest that breastfeeding may be exerting its effect on atopic dermatitis by reducing food allergy.

Childhood asthma, although not typically attributable to food allergies, seems also to benefit from breastfeeding. A meta-analysis of 12 prospective studies that met preestablished criteria found that exclusive breastfeeding for at least 3 months after birth was protective for the development of asthma by 2 to 5 years of age. The effect was mainly seen in studies of children from atopic families (OR; 0.52; 95% CI: 0.35–0.79), because no protective effect was seen in studies involving only children without a family history of atopy (OR: 0.99; 95% CI: 0.48–2.03). Other, more recent nonintervention longitudinal prospective studies confirm the findings from these meta-analyses. In contrast, the Tucson Children’s Respiratory Study, a birth cohort study, noted that the relationship between exclusive breastfeeding and recurrent wheeze varies with the age of the child and the asthma status of the mother. Breastfeeding afforded protection for recurrent wheeze in the first 2 years of life but was associated with increased wheeze or asthma from 6 to 13 years in atopic children with mothers with asthma.

The AAP and European committees both strongly recommend exclusive breastfeeding as the hallmark for food allergy prevention on the basis of the above data, only differing in duration (at least 6 months vs 4–6 months, respectively) as noted in Table 1. The AAP recommends continuing breastfeeding, although not exclusively, to at least 12 months of age. The recommendations of the AAP regarding breastfeeding is the same for all newborns whether at risk for atopy or not. The safety of exclusive breastfeeding for 6 months has been confirmed by a recent meta-analysis. In addition, increasing breastfeeding rates reduces infant illness at the community level and potentially can reduce the increased cost of health services of up to $475 experienced by the never-breastfed infant.

Maternal Avoidance of Allergenic Foods During Lactation

Adding complexity to the benefit of breastfeeding on atopy is the detection of dietary allergens in breast milk and the early sensitization of exclusively breast-
fed infants to egg and CM. In a select group of high-risk infants, up to 6% of exclusively breastfed infants developed food-specific IgE sensitization and food allergy, with symptom onset occurring with the reported initiation of direct food exposure.43 It has also been reported that milk-specific IgE may be found more often in breastfed than formula-fed infants.44 In the general population, however, food allergy in exclusively breastfed infants may range from as low as 0.04%45 to as high as 0.5%.46

In exclusively breastfed infants, rare cases of anaphylaxis to CM proteins57 and CM-induced proctocolitis48 have also been documented. The concentrations of these food allergens in breast milk are sufficient to trigger reactions in allergic infants. CM challenge through breast milk led to positive food challenges in 16 of 17 documented infants with CMA.49

Three bovine milk antigens (β-lactoglobulin, casein, and γ-globulin),50–52 chicken egg ovalbumin,53 gliadin,54 and peanut55 have been detected in nanogram per milliliter concentrations in most samples of breast milk from mothers, irrespective of atopic status, within 1 to 6 hours of consuming these foods. The molecular size of these food antigens in breast milk is similar to their respective allergens (Ara h1 and Ara h2), confirming but not proving their potential for sensitization.55

Studies have evaluated the effect of maternal food allergen avoidance diets during lactation for preventing atopic disease in high-risk infants.56–58 Two prospective controlled studies, 1 of which was truly randomized, evaluated whether maternal avoidance of egg, CM, and fish for the first 3 months of lactation or avoidance of those foods plus soy and peanut avoidance for the entire lactation period compared with unrestricted maternal diets affected atopy in high-risk infants placed on a relatively hypoallergenic diet regimen during infancy. The studies noted significant reductions in eczema in the maternal diet groups by 3, 6, and 18 months. At 10 years, the rates of clinical food allergy, atopic dermatitis, allergic rhinitis, bronchial asthma, and sensitization to the 3 maternally avoided foods (milk, egg, and fish) and aeroallergens were the same between children whose mother did or did not avoid foods during lactation.57 A meta-analysis of these studies concluded that a food allergen avoidance diet of mothers during lactation may substantially reduce the development of eczema in their child in early childhood. However, this meta-analysis concluded also that methodological limitations of the studies suggested caution before implementing the positive findings.59

Two other studies conflict with the above findings. A nonrandomized but well-controlled prospective investigation in high-risk German newborns failed to show any reduction in atopic dermatitis and CM and egg sensitization with maternal avoidance of CM and egg during the third trimester of pregnancy and lactation.60 In addition, a nonrandomized nested case-control investigation from Southampton, United Kingdom, reported that high-risk infants of mothers who avoided food allergens developed significantly more eczema and food sensitization from 6 to 18 months of age.61

The AAP used the studies in the meta-analysis to recommend the elimination of peanuts and nuts and considering eliminating eggs, CM, and fish and other foods during lactation in mothers of high-risk infants. The European group, in contrast, does not recommend a maternal diet during lactation to enhance the protective effect of breastfeeding in preventing atopy as a result of the methodological shortcomings of the positive studies and the 2 nonconfirming reports. Given this difference and the uncertainty of the effect of lactation diets for primary prevention, it might be prudent to implement maternal lactation avoidance diets only after individual evaluation of each family’s atopic risk and circumstances. This suggestion is consistent with the conclusion reached by those who conducted these studies57 and suggested by the European guidelines: that individual rather than general support should be recommended for maternal avoidance diets during lactation for allergy prevention. All mothers must take supplemental calcium (up to 1500 mg daily) and a multivitamin during restricted lactation diets.

However, peanut avoidance poses a special situation. Its prevalence of sensitization and allergy seems to be increasing.62 In addition, an association between a self-reported increase in maternal consumption of peanut products during pregnancy and lactation and a decreasing age of onset of peanut allergy during childhood has been reported in an epidemiologic study of 622 adults and children with suspected peanut allergy.63 Given the seriousness and persistence of peanut allergy, combined with the above findings, the British Medical Council recommends avoidance of peanut products to all high-risk pregnant and lactating women. It might be wise to adopt this recommendation to avoid peanuts to all mothers of high-risk offspring because consumption of peanut will lead to peanut allergens on their body or clothing, providing unknowingly an inadvertent exposure of their newborn to peanut products.

Avoid Soy Formulas for Primary Food Allergy Prevention

Soy protein is immunogenic and allergenic, although less than CM.64,65 The major soybean allergen in children with soy allergy is an IgE-binding epitope on a seed vacuole protein (P34) identified as Gly m Bd 30K.66 An extremely low prevalence of soy allergy has been found by double-blind, placebo-controlled food challenge both in children with food allergy (<5%)67,68 and in infants of atopic parents fed soy formula from birth or early in life (0.5%).69 However, randomized prospective studies of soy versus CM formula feeding in infants, generally from atopic families, have not shown any prevention effect of soy on food allergy or atopic dermatitis.70–73 However, both the AAP74 and the European committees agree that there is insufficient evidence to recommend soy formula feeding for primary food allergy prevention (Table 1).
Use Hypoallergenic Protein Hydrolysates in Bottle-Fed High-Risk Infants and as Supplementation for Breastfeeding

Protein hydrolysates (PHs) are termed partial or extensive depending on the extent of hydrolysis and ultrafiltration to which they are subjected. Allergenicity lessens as hydrolysis and filtration become more extensive.\textsuperscript{75} Significant clinical hypoallergenicity occurs when whey and casein antigenic equivalents are reduced approximately 10\textsuperscript{5}-10\textsuperscript{6.76} Alimentum and Nutramigen, 2 casein hydrolysates, are extensively hydrolyzed formulations\textsuperscript{77,78} and are hypoallergenic as defined by the AAP (95\% confidence that at least 90\% of children with CMA will tolerate the PH formulation). A somewhat less extensively hydrolyzed ultrafiltrated whey PH formula (Profylac) is also hypoallergenic but is unavailable in the United States.\textsuperscript{79} Although hypoallergenic, these extensively hydrolyzed PH are not completely nonallergenic and have occasionally caused allergic reactions or intolerances in children with CMA.\textsuperscript{80,81} These hypoallergenic PHs should be given for the first time to patients with CMA under the direct supervision of physicians who are experienced and equipped to treat anaphylaxis. Elemental amino acid-derived formulas Neocate and EleCare are hypoallergenic, nutritionally adequate, and well-tolerated in subjects who have CMA and are unable to tolerate a hypoallergenic PH or soy formula.\textsuperscript{82}

A partial whey hydrolysate, Good Start (NanHA, outside the US), in contrast to the above hypoallergenic formulas, contains almost 20\% high molecular weight peptides, has 2 to 3 logs higher levels of immunologically identifiable CM proteins than the extensive PH, and induces allergic reactions in approximately 50\% of infants with CMA.\textsuperscript{83} Both committees agree that partially hydrolyzed protein formulas should be avoided in children with CMA (Table 2).

The rationale for the use of extensive PH in primary prevention of CMA is their nutritional adequacy, $\beta$-lactoglobulin levels similar to concentrations found within breast milk (median 4.2 ng/ml),\textsuperscript{84} and hypoimmunogenicity and hypoallergenicity in both normal and high-risk newborns. Randomized controlled studies examining the effectiveness and safety of these PHs in primary allergy prevention have entirely involved high-risk neonates and either evaluated PHs as 1) a single intervention controlling for other hypoallergenic recommendations\textsuperscript{85–89} or 2) part of a multiple hypoallergenic intervention regimen comparing the combined maternal/infant avoidance regimen to established AAP recommendations or no restrictions.\textsuperscript{12,95–98} Amino acid-derived formulas have not been used for primary allergy prevention.

CMA and CM sensitization and atopic dermatitis were reduced significantly by both extensively and partially hydrolyzed PH feedings when used either as the exclusive formula feeding or as supplementation to breastfeeding compared with CM or soy formulas. Outcomes with the PHs were similar to exclusive breastfeeding. The beneficial effect derived by PH feeding seems particularly important when instituted before 6 months of age, as introduction of PH formulas after weaning at 6 months does not add to the allergy-preventive effects of a hypoallergenic regimen including exclusive breastfeeding before 6 months. Two prospective, randomized, controlled studies compared head to head extensive PH versus partial PH feedings for 4\textsuperscript{th} or 9\textsuperscript{th} months as supplements to breastfeeding or in non-breastfed infants in primary allergy prevention. In the Swedish study in which mothers avoided CM, egg, and fish as did their infants, extensive compared with partial PH significantly reduced the cumulative incidence of atopic symptoms and eczema to 9 months of age and positive egg skin tests at 9 months during the time of PH feeding.\textsuperscript{93} A Danish study found that both parental reported and challenged confirmed CMA were significantly reduced from birth to 18 months in high-risk infants fed extensive compared with partial PH as supplements to breastfeeding for up to 4 months.\textsuperscript{94} These reports adhered to the AAP recommendations for conducting primary allergy prevention studies.\textsuperscript{99}

Both the AAP and the European committees recommend, on the basis of the above studies, the use of PH in primary allergy prevention for bottle-fed high-risk infants. The AAP suggests using hypoallergenic (extensively hydrolyzed) or possibly partial PH, whereas the Europeans recommend a formula with confirmed reduced allergenicity. Extensive PHs are more hypoallergenic and hypoimmunogenic but more costly (approximately $3.00 per day more than CM or partial PH formulas) and somewhat less palatable than partial PHs. The palatability issue in practice is not a major drawback because young infants rarely refuse extensive PHs when introduced within the first few months of life.\textsuperscript{96} As such, this can be achieved by using the extensive PHs as a supplement to breastfeeding early in infancy. A recent hypothetical analysis noted that extensive PH feeding as a supplement to breastfeeding is cost-effective for 6 months for the prevention of CMA in a high-risk untreated population with a 10\% incidence of CMA and 50\% prevention efficacy.\textsuperscript{83} Partial PH adds no cost compared with routine CM formula feeding. Given the above findings, if cost is not an obstacle, then an extensive PH should be the PH of choice for primary food allergy prevention.

Delay Introduction of Solid Foods

Early introduction of supplemental feedings seems to increase the risk of atopic disease. A prospective birth cohort study of 1265 New Zealand neonates evaluated by chart review the early introduction of solid foods on eczema by ages 2 and 10 years and asthma by 4 years of age.\textsuperscript{100,101} Solid food feeding patterns were associated with eczema but not asthma.\textsuperscript{102} A significant linear relationship was seen between the number of solid foods introduced from birth to 4 months and the incidence of eczema by 2 years and recurrent/chronic eczema by 10 years. The effect was particularly notable in infants with atopic parents. The diversity of the diet (feeding 4 or more different food groups) rather than a specific food seemed to be responsible for this effect, somewhat
unexpected given the known differences in allergenicity of foods. Supportive of this epidemiologic study, a prospective nonrandomized study of high-risk newborns found that eczema at 1 year (14% vs 35%; \( P < .01 \)) but not at ages 3, 5, 10, or 17 years was reduced in infants exclusively breastfed for 6 months compared with a group of breastfed infants in whom solid foods were introduced at 3 months of age.103,104

Both committees recommend the introduction of solid food after exclusive breastfeeding but differ slightly on the time: at the 5 months (Europeans) and 6 months of age (AAP). The AAP specifies the recommended time of addition of specific allergenic foods: CM at 12 months; egg at 24 months; and peanut, tree nut, and fish at 3 years. Because of incomplete scientific data, the European committees decided on generalities in their recommendation, suggesting adding only a limited number of foods with low allergenicity when starting solid foods.

Promote Primary Food Allergy Prevention

Combined maternal and infant food allergen avoidance generally consistent with the above committees’ recommendations (except that avoidance diets during pregnancy were included) were effective in reducing eczema and CMA in early childhood but not respiratory allergy or asthma by age 7 in prospective, randomized, controlled studies from Canada105 and the United States.12 These studies were initiated before it was reported that maternal food allergy avoidance during pregnancy was ineffective in primary allergy prevention.

These studies suggest that strict prolonged food avoidance postnatally by mother and infant for at least 6 months may reduce eczema and food allergy during early childhood. Evidence for a protective effect on allergic respiratory disorders is less compelling, except for the possible protective effect afforded by breastfeeding, although conflicting data exist. The length of benefit of food allergy prevention may be limited to the first few years of life, although some studies suggest a longer effect.

Cautions, Implications, and Recommendations for Primary Allergy Prevention

Uncertainty still remains with respect to the degree of benefit attainable by food allergen avoidance in primary allergy prevention. Additional well-designed, masked, multicenter trials are welcome. Therefore, at the present time, the AAP and the European recommendations should be considered provisional, should be directed only at high-risk offspring, and should be expected to be updated as new information becomes available. Given the differences in the committees’ recommendations, what should the practicing pediatrician follow? A reconciled compromise might recommend the following:

- Exclusive breastfeeding for at least 4 to 6 months
- No pregnancy allergen avoidance diet except for peanut avoidance
- Maternal lactation avoidance diets determined on an individual basis except for the universal avoidance of peanut

Because primary allergy prevention is not static and is in transition, expect modifications expeditiously presented in the future.

TERTIARY FOOD ALLERGY PREVENTION

(TREATMENT OF FOOD ALLERGY)

The AAP and the European group agree generally on their recommendations for the treatment of the infant and young child confirmed with food allergy (Table 2). The causal food must be avoided. It must not be fed to the child or to the mother if breastfeeding. Exclusive breastfeeding should be continued with the causal food(s) avoided by the mother. The recommendations differ slightly with respect to the maternal lactation avoidance diet. The European committee suggests a trial with avoidance of the causal food, whereas the AAP recommends a trial elimination of the foods most likely to cause food allergy in young children: CM, egg, fish, peanuts, and tree nuts. Both groups agree that extensively hydrolyzed PHs are suitable for supplementation or for bottle-fed infants with CMA, whereas partial PHs must be avoided because of the high frequency of reactions in children with CMA.105 Unlike the European group, the AAP suggests considering soy formula for infants with IgE-mediated CMA and no evidence for concomitant soy allergy or soy IgE, particularly those older than 6 months, because soy allergy is infrequent (14.0%; 95% CI: 7.7%–22.7%) in infants and young children with IgE-mediated CMA.106 In this situation, soy formula can be used either as the initial treatment for CMA or after 6 months of age and extensive PH feeding. Amino acid-derived formulas may be needed in CMA intolerant of PH or soy formulas and in multiple food-allergic infants. Milk from other animals such as goats or sheep must be avoided because a high degree of homology exists with CM allergens, and reactions are frequent in CMA. Introduction of new foods to the infant with food allergy probably should be extremely conservative and would benefit from adhering to the AAP recommendations for primary food allergy prevention (Table 1).

ADDITIONAL RECOMMENDATIONS AND REFLECTIONS

Promote a Pediatrician Allergist Team

Although not specifically discussed in either group’s recommendations, it is essential that pediatricians (primary care providers) and allergists create a collegial team to ensure successful implementation of primary and tertiary food allergy prevention recommendations. Generalists, whether pediatricians or primary care providers, are most often the first to recognize and diagnose atopic risk and atopic disease. Early and accurate diagnosis permits early in-
stitution of preventive strategies. By partnering with an allergy specialist, this team would be better able to deliver preventive allergy advice and care to families. The allergy specialist would provide the necessary expertise to confirm allergy, offer comprehensive guidelines on avoidance measures, and give updates on recent advances in allergy prevention.

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