Hydrolyzed formulas: 
For high-risk infants only or are all infants at risk?

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Primary prevention of food allergy

The prevalence of food allergies, such as peanut allergy, is increasing dramatically in both developed and developing countries. In Asia, the reported prevalence of food allergy ranges from 1.1% in Thailand to 10% in Japan. The increasing prevalence of allergy highlights the importance of primary prevention in reducing its burden, particularly in high-risk infants. A high-risk infant has typically been defined in studies as having at least one first-degree relative (parent or sibling) with an allergic condition, such as atopic dermatitis (AD), a food allergy, asthma or allergic rhinitis.

Several studies have reported a possible protective effect of breast-feeding against the onset of allergy in high-risk infants.

In a prospective, case-controlled study, infants with a family history of allergy who were exposed to intact cow’s milk formula (CMF) in the first year of life had more than 3 times the risk of developing atopic manifestations than infants who were breastfed; in infants who received CMF in the first week of life, the risk was 4 times that of breastfed infants.

A systematic review and meta-analysis of prospective studies found that exclusive breastfeeding during the first 3 months of life was associated with a lower incidence of AD during childhood in infants with a family history of atopy.

The role of partially hydrolyzed infant formula in primary prevention

Numerous prospective studies have reported a reduced risk of AD among healthy infants who received 100% whey protein partially hydrolyzed formula (pHF-W) compared with intact protein CMF. A robust meta-analysis of high-quality studies found that giving pHF-W in the first 6 months was significantly more effective at reducing the risk of AD and other atopic manifestations than standard CMF. Furthermore, a subanalysis of 4 studies that reported results specifically for AD, and were considered to be of superior methodological quality, found that the incidence of AD was significantly lower in PHF-W fed infants, by 55% (Figure 1).

Figure 1. Meta-analysis: Relative risk reduction of AD

The landmark independently (government funded, randomized, double-blind, prospective German Infant Nutritional Intervention (GINI) Study is the largest study worldwide to evaluate the allergy-preventive effects of 3 differently hydrolyzed infant formulas, versus a conventional CMF, in infants who had high risk of atopy.
The 10-year follow-up data from GINi found that the use of certain types of pHF in the first 4 months of life was associated with a preventive effect on the cumulative incidence of AD in high-risk infants from birth up to 10 years (Figure 2).13

Figure 2. GINi: Physician-diagnosed eczema 10 years after early intervention with hydrolyzed formulas13

Furthermore, at the 15-year follow-up of GINi, a significant reduction in the cumulative incidence of allergic rhinitis was observed for extensively hydrolyzed casein formula (eHF-C) in the intention-to-treat (ITT) population.14 In this population, the prevalence of allergic rhinitis between 11–15 years was also significantly reduced for partially hydrolyzed whey formula (pHF-W) and eHF-C. In terms of eczema, the cumulative incidence was significantly reduced in the eHF-C and pHF-W groups in the ITT population, and even stronger effects were observed in the per-protocol (PP) population. The prevalence of eczema between 11–15 years was also significantly reduced in the eHF-C group, in the ITT analysis. Notably, the numbers needed to treat to prevent 1 case of eczema up to 15 years of age for the pHF-W, eHF-W, and eHF-C formulas were 7, 11, and 6, respectively, in the PP population, and 14, 30, and 8 in the ITT population.

Most international guidelines endorse the use of hydrolyzed formula in the first 4–6 months of life in place of a standard CMF, in infants who are not exclusively breastfed, for the primary prevention of allergic diseases in childhood.15,16,23-29 However, the role of hydrolyzed formula in the prevention of allergic disease has recently been called to question following the publication of a meta-analysis by Boyle et al.,21 which found no significant difference in the risk of food allergy (including to cow’s milk) with pHF or eHF compared with CMF. However, as Dr Fleischer explained, “In many of the studies included in the different meta-analyses, there were significant bias and conflicts of interest, so the bottom line is that we need more future trials that are perspective-driven and independently funded.”

Food allergy prevention: Current status and future directions

Gene–environment interactions play an important role in the development of food allergy

Evidence suggests that genetics contribute to the development of food allergies; however, to date, conclusive and consistent findings across populations are lacking.52,24 Evidence that the prevalence of peanut allergy is rising rapidly and differs between regions supports the idea that gene–environment interactions are important.25,26 In terms of susceptibility to food allergy, animal models suggest that the microbiome may play a crucial role, particularly in early life.26 Environmental factors that may affect gut microbiota patterns in early life include birth by Caesarean section, farming and animal exposure, antibiotic exposure and diet.27 Further studies are required to confirm the impact of the microbiome on the development of food allergy.

The role of early dietary interventions in the prevention of food allergy

Based on current data, restricting the maternal diet during pregnancy and breastfeeding to avoid highly allergenic foods, as a primary prevention strategy, does not work and may even be detrimental.15,17 Currently, there is also no clearly positive recommendation from the scientific societies to support the use of prebiotics or probiotics for food allergy prevention.15

Previous observational studies suggested that the delayed introduction of complementary foods may increase the risk of food allergy and the early introduction of allergenic foods may prevent the development of food allergy.28,29 The groundbreaking randomized, controlled LEAP trial confirmed that early introduction of peanuts in high-risk infants (4–11 months) significantly decreased the risk of developing peanut allergy, was feasible and did not affect the duration of breastfeeding nor have any detrimental effects on growth or nutrition.28 Another randomized, controlled trial – EAT – demonstrated that early introduction of peanut and egg into the infant diet had the potential to prevent the development of allergy to these foods in infants but only in the per protocol analysis.30 A 2016 meta-analysis on timing of allergenic food introduction determined that the early introduction of egg or peanut to the infant diet was associated with a lower risk of developing egg or peanut allergy (Figure 3).30

Exposure to food antigens, particularly on inflamed skin, may promote the development of food allergy. A strong and dose-dependent association between food allergy and AD was confirmed in a recent systematic review.31 AD of increased severity and chronicity was
Figure 3. Meta-analysis: Pooled data support early introduction of egg or peanut.

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<th>Allergy</th>
<th>Early No. of Events</th>
<th>Early Total No.</th>
<th>Late No. of Events</th>
<th>Late Total No.</th>
<th>Risk Ratio (95% CI)</th>
<th>Decreased Risk of Allergy (%)</th>
<th>Increased Risk of Allergy (%)</th>
<th>Weight (random-effects model) %</th>
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Peanut allergy

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Milk allergy

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<th>Increased Risk of Allergy (%)</th>
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Conclusions

Mothers should be encouraged to eat a healthy, diverse diet during pregnancy and lactation. In addition to providing optimal infant nutrition, breastfeeding provides a variety of long-term health benefits, and mothers should be encouraged to breastfeed. When exclusive breastfeeding is not possible, pHF's are useful alternatives and may be beneficial for the prevention of allergy.

“If you have a family history of allergy, for prevention you could consider using a pHF or eHF. Even if you don’t have a family history, again, consider using a hydrolyzed formula versus standard formula because some of those infants are likely to be at risk of developing allergic disease,” said Dr Fleischer.

A variety of healthy, diverse foods, including all major allergens should be introduced, ideally starting at around 6 months, regardless of babies’ allergy risk, but certainly within the first year of life.

Food allergy: Identifying effective treatment and the role of intestinal microbiota in prevention

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Intestinal microbiota-immune interactions in early life play a critical role in shaping healthy immune programming, supporting the development of tolerance to different types of food. In mouse models, selected bacteria species or signatures were shown to confer protection or risk of food allergy. In humans, intestinal dysbiosis is known to be associated with an increased risk of food sensitization and allergy, but the specific taxa that might protect against or lead to disease remain uncertain. Ultimately, current evidence and opinion suggest that modification of the intestinal microbiota in early life offers an approach to supporting healthy immune homeostasis and prevention of food allergy. However, more studies are needed, for example, into the role of probiotics and prebiotics, and to identify which microbial species actually confer protection, if we are to translate research to clinical practice.
A short interview with Dr Fleischer was conducted following his presentations.

How should physicians act on clinical trial data regarding the early introduction of highly allergenic foods as a strategy for overcoming allergy?

The timing of the introduction to allergenic food is an important aspect of preventing food allergy development. Based on data from randomized, controlled trials and observational studies there appear to be no benefit to delaying the introduction of any major food allergen into an infant’s diet. In certain high-risk infants, certain allergenic foods should be introduced at around 6 months of age (but not before 4 months) and all major food allergens could be introduced before 12 months.

In real-life clinical practice, how should physicians select which children are suitable for this approach?

Those infants with severe eczema and/or egg allergy, which were the high-risk factors defined in LEAP, may benefit from evaluation by an allergist prior to introduction of allergenic foods. However, lower risk infants and those without allergy risk factors may benefit from early introduction of allergenic foods as well, but these groups of infants have not been investigated in randomized controlled trials.

What advice should physicians give parents on how to introduce foods to high-risk children?

There is a danger that we are trying to medicalize something that should be a very natural process. It’s important that doctors make things as simple and stress-free as possible for parents. The introduction of foods to an infant’s diet should be a simple, logical progression. Parents should start by introducing small amounts of typical weaning foods first, like cereals, fruits and vegetables. For peanut, peanut powder or thinned peanut butter (made by heating it) can then be mixed into fruits or cereals (if using heated peanut butter, once it has cooled). For milk and egg, starting with small amounts of milk or egg in baked goods first is reasonable before progressing to other forms such as yogurt, cheese, scrambled or hard-boiled eggs. Small amounts of fish and shellfish should only be introduced when the infant is ready for foods of a denser texture such as having tolerated meats.

Can you summarize what we know about hydrolyzed formulas?

It depends which studies and meta-analyses you look at! Overall, the data suggest there may be some benefit from using a hydrolyzed formula for the prevention of allergy in high risk infants who cannot be exclusively breastfed in the first 4-6 months of life.

Is hydrolyzed formula suitable for all infants if cost is not a concern?

Yes. I think there are enough published data to say hydrolyzed formula is safe to use as a standard formula.

References: