



Pro/Con Debates

Solid foods should be introduced into susceptible infants' diets early in life-CON

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The Con Position

Food allergy (FA) is a relevant clinical problem, in particular in childhood, potentially resulting in life-threatening reactions and having a huge negative impact on the quality of life of the entire family. Moreover, FA incidence has been increasing over time; it is currently estimated at approximately 3% to 4% of children overall in westernized countries. In the past, the general recommendations to prevent FA development focused on the avoidance of allergenic foods in infancy. Many recommendations were published worldwide suggesting avoidance of milk, egg, and peanut until 1, 2, or even 3 years of age to prevent FA. However, since 2004 recommendations from The European Academy of Allergy and Clinical Immunology—updated in 2008 and in 2014—found no evidence to support delayed introduction of solid food after 4 months of age for prevention purposes, recommending starting weaning for healthy children at high allergic risk between 4 and 6 months of life.¹ The failure of the avoidance strategy promoted the investigation of the so-called dual-barrier hypothesis. According to this, the avoidance of a specific food (such as egg or peanut) does not provide the child with the usual gastrointestinal exposure for achieving oral tolerance and thus may increase the risk of FA, regardless of whether the infant is still exposed to food allergen(s) in the environment and is sensitized via the skin.

In the last 10 years, more and more efforts have been devoted to evaluating new interventional approaches modulate the infant's immune system, focusing on the assessment of the potential preventive role of the early introduction of allergenic foods into the diet, with a main focus on egg and peanut.^{2,3} A recent meta-analysis concluded with moderate certainty that early egg (and peanut)

introduction at 4 to 6 months was associated with reduced egg (and peanut) allergy.² However, the results from each trial need to be read with caution. First, the method and duration of cooking may influence differently food allergenicity. This effect is well known for hen's egg proteins: raw egg proteins are more allergenic than heated egg. Therefore, this has to be considered in the review and interpretation of egg prevention literature.

Hen's Egg

Among randomized controlled trials using raw egg as an intervention, the Solids Timing for Allergy Research (STAR) study randomly allocated high-risk infants to 6 g raw egg protein per week (approximately 1 large egg) or placebo from 4 months of age.² The authors found a trend of reduced development of FA to egg; however, one third of study participants reacted to the intervention, including 1 case of anaphylaxis at the first dose. At least 3 other prospective placebo-controlled randomized controlled trials used raw egg proteins: the Solids Timing for Allergy Research (STAR) trial,² Starting Time of Egg Protein (STEP) trial,³ and Beating Egg Allergy Trial (BEAT).² They were all conducted in Australia and intervened in what were considered to be higher-risk populations based on either the presence of atopic eczema (STAR trial), maternal atopy (STEP trial), or atopy in a first-degree relative (BEAT). Among them, BEAT was the only trial showing a significant reduction in sensitization to egg white at 12 months, but oral food challenges were not performed. In the STAR study, a lower proportion of infants developed an IgE-mediated egg allergy compared with the control cohort, but the difference was not significant; however, the trial was not sufficiently powered to rule out a significant difference. Data from the STEP trial were not available and therefore were not included in the previously mentioned meta-analysis.² In another prospective randomized controlled trial that was conducted in Germany, the Hen's Egg Allergy Prevention (HEAP) study, high-risk infants were randomly allocated to raw eggs (initially 2.5 g per week) or placebo from 4 to 6 months of age. No difference was noted

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between the groups at follow-up, but many infants were already egg allergic at enrollment.² Despite the negative results, these studies provided a glimmer of hope that very early introduction of egg into the diet might prevent the development of egg allergy. However, safety issues should be considered together with the aforementioned limitations. In this perspective, less allergenic forms of egg have been investigated (eg, heated eggs).

With regard to discussion of the studies using heated egg powder or cooked egg, in the Enquiring About Tolerance (EAT) study, infants were randomly allocated to early introduction of various foods, including 1 small hard-boiled egg per week from 3 to 4 months of age. The use of hard-boiled egg may be directly connected to the poor adherence to the diet in the intervention arm (and hence the per-protocol benefit but lack of benefit in intention-to-treat analysis), illustrating the difficulty in finding an appropriate option for feeding egg in a form that is both safe and accepted by infants. In the PETIT study, authors describe another approach to prevent development of egg allergy.² They randomly allocated high-risk infants (affected by atopic eczema) aged 4 to 5 months to very small quantities (0.2–1.1 g per week) of cooked egg or placebo. The Independent Data and Safety Monitoring Committee terminated the study when a scheduled interim analysis found a highly significant reduction in egg allergy in the egg group, halfway through recruitment. Challenge-proven egg allergy was found in 5 (8%) of 60 participants in the egg group and 23 (38%) of 61 in the placebo group ($P = .0001$). This finding gives a number needed to treat to prevent egg allergy of 3.40 (95% CI, 2.30–6.52). Although this preventive strategy could be effective, caution is particularly required when the results of a study that has been prematurely stopped are interpreted: such trials may overestimate the effect size by 50%. Furthermore, few participants were randomized to treatment, meaning that important adverse events might not have been seen. Stopping a trial early for benefit is not generally recommended. The different results in these egg allergy prevention studies suggest that differences in study populations or the specific interventions might predict various levels of efficacy. Furthermore, the egg powder used in the PETIT study is not readily available commercially, and those subjects were not challenged to other forms of egg (eg, boiled, scrambled, omelette) that are more likely to be offered in “real-life” scenarios. This is a major limitation in trying to apply the findings of PETIT more generally. The other limitation of the PETIT trial is the use of a gradual up-dosing, somewhat akin to immunotherapy. Assuming that ad libitum introduction of egg in commonly fed forms (eg, scrambled eggs) will have the same efficacy and safety as gradual up-dosing of a less allergenic heated egg powder that families do not have access to use is problematic.

The question is raised of whether the excluded sensitized children prone to develop a clinical relevant egg allergy might have been those who could have received the true benefit. Egg allergy also seems to be preventable even when allergic sensitization has already developed. Infants who are already sensitized to eggs are more likely to have an allergic reaction with ingestion of eggs, as seen in the STAR study.² The STAR and HEAP studies both used products allergenically equivalent to raw egg.² A potential way to reduce the likelihood of reactions is to use a heat-treated egg protein with lower allergenicity rather than raw egg. Fewer reactions to the egg were seen in the EAT study and PETIT study,² probably because the egg was cooked. Findings from the EAT study suggested that ingestion of at least 2 g egg protein per week is effective in prevention of development of egg allergy in infants. However, the PETIT study suggests that 10-fold less egg protein may be equally effective²; this finding is relevant because a smaller dose also may be much less likely to cause an allergic reaction in infants who are already sensitized to eggs. Although caution is needed because of the early termination of the PETIT study and the

previous negative studies, there is the expectation that small quantities of cooked egg introduced very early into the infant diet might be an effective preventive strategy. Further studies are needed in larger populations with different diets and environmental exposures to better evaluate the relevance and safety of this preventive approach at the general population level.

Peanut

The dual-barrier hypothesis has been tested with the aim of preventing peanut allergy in atopic children suffering from eczema. The prevalence of peanut allergy among children doubled in the United States between 1997 and 2003 and is now considered a huge socioeconomic burden. Peanut allergy appears to be usually persistent over time, differently from other foods (such as milk and egg), and it is usually related to a high risk of severe, even fatal or near-fatal, reactions. In the LEAP study, 640 infants (4–10 months old) with severe eczema, egg allergy, or both were assigned to consume or avoid peanuts until 60 months of age.⁴ The intention-to-treat analyses show that among the 530 participants who initially had negative results on the skin prick test, the prevalence of peanut allergy at 60 months of age was 13.7% in the avoidance group and 1.9% in the consumption group ($P < .001$); and among the 98 infants who initially had positive test results, the prevalence of peanut allergy was 35.3% in the avoidance group and 10.6% in the consumption group ($P = .004$). Longer-term effects were confirmed by the LEAP-ON study.⁵ Among children at high risk for allergy in whom peanuts had been introduced in the first year of life and continued until 5 years of age, a 12-month period of peanut avoidance was not associated with an increase in the prevalence of peanut allergy.

Foods Other Than Egg and Peanut

Currently, data on early introduction of other foods are lacking. The EAT study evaluated early introduction of 6 allergenic foods into the diets of breastfed infants from an unselected population, commencing with yogurt at age 3 months. Sesame, fish, wheat, peanut, and egg were subsequently introduced by 5 months. No benefit was assessed for milk, sesame, fish, or wheat. Similarly, a meta-analysis found no effect on the prevention of milk, fish, or wheat allergy with early introduction. In a prospective cohort, Katz et al⁶ showed possible benefit of milk introduction in the first 2 weeks of life. Overall data on milk are limited. No data exist on prevention of tree nut allergies. Results from ongoing trials are highly awaited.

Conclusion

The “optimal” window for introduction of complementary foods for allergy prevention remains highly debated (Table 1). However, to start complementary foods before 3 to 4 months of age may increase the risk of allergic disease.⁷ At that age, the gut is more permeable, and gastrointestinal colonization is not yet well established.⁸ Consequently, many international infant feeding guidelines for allergy prevention recommend introduction of any solid food after 4 months of age.⁹ In addition, the current recommendation should take into account other pivotal aspects such as the infant's developmental readiness, nutritional needs, parental opinion/needs, and the risk for developing very selective eating habits. In

Table 1
Potential Pitfalls in Early Weaning

Potential pitfalls in early weaning
> Safety issues
> Lack of infant readiness
> Difficulty in adhering to regular feedings
> Foods not present in the family's diet

summary, there are still many open issues to be clarified (eg, age of introduction, type of population, type of food, raw or heated allergen, and amount of allergen) before recommendations for FA prevention based on introduction earlier than 4 months become applicable for a public health strategy. Based on the current available evidence, we recommend introducing complementary foods from 4 to 6 months of age according to standard local practices and the needs of the infant, irrespective of atopic heredity, until more data on safety and preventive efficacy in introducing before the age of 4 months of age are available.¹ This is the bottom-line common-sense approach suggested by the Australasian Society of Clinical Immunology and Allergy (ASCIA) (“When your infant is ready, introduce foods according to what the family eats, regardless of whether the food is considered to be a common food allergen”),¹⁰ in line with the European Academy of Allergy and Clinical Immunology guidelines.¹

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