Primary Prevention of Food Allergies

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INTRODUCTION OF COMPLEMENTARY FOODS

There is insufficient evidence to make specific recommendations about the timing of the introduction of complementary foods and individual solid foods in regards of food allergy prevention for all children (C). However, a few studies indicate that it might be an advantage not to introduce solids before four months of age (C). In addition, other aspects have to be considered, such as the infant’s developmental readiness, parental opinion/needs, the nutritional needs and the risk for developing very selective eating habits. Therefore, we recommend introducing complementary foods from 4-6 months of age according to standard local practices and the needs of the infant, irrespective of atopic heredity.
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Introduction

- In the past, the widely accepted approach to preventing food allergy was to delay the introduction of dietary allergens into the diet.

- The failure of these avoidance strategies to reduce the incidence of food allergy has led to a reassessment.

- A number of randomised controlled trials have now assessed whether the dietary introduction of allergens at an early stage 4-6 months leads to a reduction in the development of clinical food allergy (see list below).

- The studies designs and results have been heterogeneous leading to questions as to how the results should inform public health advice.
Modifying the infant’s diet to prevent food allergy

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ABSTRACT

Recommendations and guidelines on the prevention of food allergy have changed in recent decades. The aim of this review of the current evidence and ongoing studies is to provide a comprehensive and up to date picture of prevention of food allergy for healthcare professionals. The review was undertaken as part of the European Union funded Integrated Approaches to Food Allergy and Allergen Management (iFAAM) study. This is a wide ranging project bringing together expertise across the breadth of food allergy research. Specifically, the review discusses dietary manipulation in food allergy prevention, and covers the possible preventive strategies of allergen avoidance, early allergen introduction, general nutrition and supplements, as well as other strategies, such as prebiotics and probiotics. The review concludes that despite agreement that allergen avoidance strategies to the allergen following initial allergen priming was first proposed. This led to the concept that exposure to the food allergen early in an infant’s immunological development was important in food allergy initiation. As knowledge in the field of immunology progressed, with the concept of immunological sensitisation and the discovery of IgE, it became clear that the first exposure could be in utero or during breastfeeding. Consequently, allergen avoidance became the primary strategy for allergy prevention, with an idealised strategy for allergy prevention being published in 1983. It aimed to avoid intrauterine and postnatal sensitisation by minimising exposure to sensitising proteins during the third trimester of pregnancy and during lactation by recommending exclusive breastfeeding of the infant (or fed an extensively hydrolysed infant formula) until...
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<table>
<thead>
<tr>
<th>Name of Trial</th>
<th>Country (institution)</th>
<th>Population</th>
<th>Study details</th>
<th>Results</th>
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<tbody>
<tr>
<td><strong>Egg</strong></td>
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| Hens’ Egg Allergy Prevention (HEAP)(21)            | Germany (Charité Universitätsmedizin Berlin, Germany) | General population, non-sensitised        | • RCT, placebo controlled  
• n = 383  
• Enrolled at 4-6 months then consumption of egg powder (“pasteurized egg white equal in its allergenicity to raw hen’s egg) or placebo until 12 months of age; started with 800mg egg protein three times a week, increasing to 1.6g in week 2 and 2.5g in week 3.  
• Outcome: primary: prevalence of egg sensitisation; secondary: placebo controlled challenge proven IgE-mediated egg allergy at 12 months of age | At 12 months there was a non-significant increase in egg sensitisation (2.6 vs 5.6%, p=0.24) and egg allergy 0.6 vs 2.1%, p=0.35) in the intervention group in ITT analyses; many infants reacted to the intervention. |
| Prevention of egg allergy in infants with atopic dermatitis (PETIT)(22) | Japan (National Centre for Child Health and Development, Japan) | High risk (infants with atopic dermatitis) | • RCT, placebo controlled  
• N=147  
• Enrolled at 4–6 months then consumption of “heated egg powder” or placebo; started on a very small amount (25 mg of egg protein daily increasing to 125mg from 9 months)  
• Outcome: prevalence of open challenge proven IgE-mediated egg allergy at 12 months of age | Recruited finished early after an interim analysis; intervention lead to a significant reduction in egg allergy (38 vs 8%, p=0.0001); no major safety issues. |
| Solids Timing for Allergy Research (STAR)(18)      | Australia (University of Western Australia) | High-risk (infants with moderate / severe eczema) | • RCT, placebo controlled  
• n = 86  
• Enrolled at 4-6 months of age then consumption of egg powder (“pasteurized raw whole egg powder”) or placebo until 8 months of age; 900mg egg protein was given daily  
• Outcome: prevalence of open challenge proven IgE-mediated egg allergy at 12 months of age | A third of infants randomized to egg reacted to the intervention; at 12 months, there was a non-significant reduction in egg allergen in the intervention group (33% vs 51%, ITT analysis, p=0.11). |
| Starting Time for Egg Protein (STEP)(19)           | Australia (University of Western Australia) | Moderate-risk (infants without eczema but atopic mothers) | • RCT, placebo controlled  
• N=804  
• Enrolled at 4-6 months of age then consumption of pasteurized raw whole egg powder or placebo until 12 months of age  
• Outcome: prevalence of challenge proven IgE-mediated egg allergy at 12 months of age | No difference in IgE-mediated egg allergy (egg 7.0 vs control 10.3% P=0.20); there were a number of allergic reactions to the intervention. |
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</tbody>
</table>
| Beating Egg Allergy (BEAT)(20)                                               | Australia (Sydney University Children’s Hospital) | Moderate-risk (sibling / parent with allergy) | • RCT, placebo controlled  
• N=319  
• Enrolled at 4 months of age then consumption of pasteurized whole egg powder, or placebo until 8 months of age  
• Outcome: primary egg white sensitisation; secondary: prevalence of IgE mediated egg allergy at 12 months of age | Early introduction of egg was associated with a reduction in sensitization at 12 months (20 vs 11%, \( p=0.03 \)). There was no effect on the 58 proportion of children with probable egg allergy. A number of infants reacted to the intervention. |
| **Peanut**                                                                   |                           |                                         |                                                                               |                                                                                                                                                                                                       |
| Learning Early About Peanut allergy (LEAP)(23,24)                            | UK (Kings College, London) | High-risk (infants with moderate / severe eczema and / or egg allergy) | • Open-label RCT  
• n = 640  
• Enrolled at 4-11 months then peanut consumption or avoidance until age 5; 6g peanut protein per week  
• Outcome: prevalence of DBPCFC confirmed peanut allergy at 5 years of age | Significant reduction at 60 months in ITT analysis (13.7 vs 1.9% overall, \( p<0.001 \)) regardless of presence of initial cutaneous sensitisation; no significant between-group differences in serious adverse events (Du Toit 2015, 2016). Significant reduction still seen after both groups then avoided peanut for a year (18.6 vs 4.8%, ITT analysis, \( p<0.001 \)). |
| **Multiple foods**                                                           |                           |                                         |                                                                               |                                                                                                                                                                                                       |
| Enquiring About Tolerance (EAT)(25)                                           | UK (Kings College, London) | General population                      | • Cows’ milk, hens’ egg, peanut, cod, sesame, wheat  
• Open-label RCT  
• n = 1106  
• Enrolled at 3 months of age then consumption of 6 allergenic foods until 6 months or exclusive breastfeeding until 6 months of age; 2g protein of each food given twice a week  
• Outcome: prevalence of IgE-mediated food allergy to any of the 6 allergenic foods between 1 and 3 years of age | Non-significant reduction in ITT analysis (7.1 vs 5.6%, \( p=0.32 \)). In PP analysis, a significant reduction was seen for any food allergy (2.4 vs 7.3%, \( p=0.01 \)), peanut (0 vs 2.5%, \( p=0.003 \)) and egg allergy (1.4 vs 5.5%, \( p=0.009 \)). |
| Preventing atopic dermatitis and allergies in children (PreventADALL)(26)    | Norway (Oslo University Hospital) | General population                      | • Hen’s egg, milk, wheat, peanut  
• Open label RCT with four arms: observation, early introduction by 4 months, skin care, both early introduction and skin care  
• N=2500  
• Outcome: food allergy, atopic dermatitis | Ongoing                                                                                                                                                                                                 |
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Updated from Ierodiakonou et al (JAMA 2016). Results for egg, milk and peanut allergy presented separately. Error bars represent 95% confidence intervals.

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome = Egg Allergy</th>
<th>Outcome = Milk Allergy</th>
<th>Outcome = Peanut Allergy</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Experimental Events</td>
<td>Control Events</td>
<td>Effect Measure</td>
</tr>
<tr>
<td>Tan 2016</td>
<td>8</td>
<td>130</td>
<td></td>
</tr>
<tr>
<td>Perkin 2016</td>
<td>21</td>
<td>569</td>
<td>0.69 [0.40; 1.18]</td>
</tr>
<tr>
<td>Natsume 2016</td>
<td>5</td>
<td>60</td>
<td>0.22 [0.09; 0.54]</td>
</tr>
<tr>
<td>Palmer 2016</td>
<td>26</td>
<td>371</td>
<td>0.68 [0.42; 1.09]</td>
</tr>
<tr>
<td>Bellach 2015</td>
<td>2</td>
<td>142</td>
<td>2.20 [0.20; 23.97]</td>
</tr>
<tr>
<td>Palmer 2013</td>
<td>14</td>
<td>42</td>
<td>0.65 [0.38; 1.11]</td>
</tr>
<tr>
<td><strong>Random effects model</strong></td>
<td><strong>1314</strong></td>
<td><strong>1349</strong></td>
<td><strong>0.60 [0.44; 0.82]</strong></td>
</tr>
</tbody>
</table>

Lots of heterogeneity between studies

Heterogeneity: I-squared=22.7%, p=0.2631

<table>
<thead>
<tr>
<th>Outcome = Milk Allergy</th>
<th>Experimental Events</th>
<th>Control Events Total</th>
<th>Effect Measure</th>
<th>RR</th>
<th>95%-CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perkin 2016</td>
<td>3</td>
<td>569</td>
<td>0.79 [0.18; 3.49]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowe 2011</td>
<td>6</td>
<td>193</td>
<td>0.74 [0.26; 2.10]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Random effects model</strong></td>
<td><strong>762</strong></td>
<td><strong>787</strong></td>
<td><strong>0.76 [0.32; 1.77]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: I-squared=0%, p=0.9512

<table>
<thead>
<tr>
<th>Outcome = Peanut Allergy</th>
<th>Experimental Events</th>
<th>Control Events Total</th>
<th>Effect Measure</th>
<th>RR</th>
<th>95%-CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perkin 2016</td>
<td>7</td>
<td>570</td>
<td>0.49 [0.20; 1.19]</td>
<td></td>
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</tr>
<tr>
<td>Du Toit 2015</td>
<td>10</td>
<td>312</td>
<td>0.19 [0.10; 0.36]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Random effects model</strong></td>
<td><strong>882</strong></td>
<td><strong>909</strong></td>
<td><strong>0.29 [0.11; 0.74]</strong></td>
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Heterogeneity: I-squared=66.2%, p=0.0856

Decreased risk

Increased risk
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Where are we today?

- Each discussion group has focused on two questions
- Groups have been asked to think more widely than just food allergy, e.g., nutrition, other disease processed, growth, developmental status and acceptance of recommendations by general public and governmental organisations
- Groups asked to try and come to a consensus – if this was not possible they have been asked to list the options with pros and cons
- Groups are now going to present the summary of their discussions
- Then plan to have a more general discussion
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Questions
1. What are the high risk populations for the development of food allergy?
2. When should allergenic foods be introduced into the diet of high risk infants?
3. When should allergenic foods be introduced into the diet of low risk infants?
4. What are the potential adverse consequences of early introduction of allergenic foods?
5. Should different foods be introduced at different ages?
6. In what format should foods be introduced? (e.g. eggs should be cooked, not only pasteurised)