Role of Early Introduction of Food in Prevention of Food Allergy

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• Importance of food antigen exposure in oral tolerance

• Evidence supporting early introduction of allergenic foods for prevention of food allergy
  – Randomised controlled trials
  – Systematic review

• How can research findings be translated to policy and practice?
  – Expert recommendations arising from the LEAP trial
  – What is the potential impact on allergy services?
Oral Tolerance

• First described by Wells and Osborne\textsuperscript{1} in 1911 ….. Guinea pigs did not develop anaphylaxis to ingested antigen

• Tolerance is an active immune response \textsuperscript{2,3}

Dietary Macromolecules are Required for Development of iTreg in the Small Intestine

Development of iTreg in the small intestine is driven mainly by dietary Ags, whereas iTreg in the colon are induced by the microbiota.

Majority of iTreg cells in the siLP develop in response to Ags derived from proteins in a solid-food diet rather than from maternal milk feeds.

siLP iTreg are continuously replaced in response to dietary Ags, with a half life of 4 to 6 weeks.

Kim et al. Science 2016
Absence of siLP iTreg Results in Exaggerated Symptoms in a Mouse Model of Food Allergy

Depletion of iTreg cells results in an increased susceptibility to intestinal allergy.

- **Protein macromolecules are required for induction of siLP iTreg**
- **siLP iTreg play a key role in oral tolerance induction to foods**
- **Continued intake of solids is necessary for maintenance of siLP iTreg**

Kim et al. Science 2016
Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy


Timing of Introduction of Solids

Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

George Du Toit, M.B., B.Ch., Graham Roberts, D.M., Peter H. Sayre, M.D., Ph.D., Henry T. Bahnson, M.P.H., Suzana Radulovic, M.D., Alexandra F. Santos, M.D., Helen A. Brough, M.B., B.S., Deborah Phippard, Ph.D., Monica Basting, M.A., Mary Feeney, M.Sc., R.D., Victor Turcanu, M.D., Ph.D., Michelle L. Sever, M.S.P.H., Ph.D., Margarita Gomez Lorenzo, M.D., Marshall Plaut, M.D., and Gideon Lack, M.B., B.Ch., for the LEAP Study Team*
Primary Endpoint - proportion of participants with peanut allergy at 72 months of age

**RESULTS:**

- **LEAP Study**
  - 190 of 274 (69.3%) compliant with avoidance
  - No significant increase in peanut allergy prevalence at 60 and 72 months (3.6% vs 4.8%)
  - 3 new cases of PN allergy

- **LEAP-On Study**
  - 255 of 282 (90.4%) compliant with avoidance
  - No significant increase in peanut allergy prevalence at 60 and 72 months (18.8% vs 18.6%)
  - 3 new cases of PN allergy
Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants

Michael R. Perkin, Ph.D., Kirsty Logan, Ph.D., Anna Tseng, R.D., Bunmi Raji, R.D., Salma Ayis, Ph.D., Janet Peacock, Ph.D., Helen Brough, Ph.D., Tom Marrs, B.M., B.S., Suzana Radulovic, M.D., Joanna Craven, M.P.H., Carsten Flohr, Ph.D., and Gideon Lack, M.B., B.Ch., for the EAT Study Team*
Randomized placebo-controlled trial of hen’s egg consumption for primary prevention in infants

Johanna Bellach, a Veronika Schwarz, MD, a Birgit Ahrens, MD, a Valérie Trendelenburg, MSc, a Özlem Aksünger, a Birgit Kalb, MD, a Bodo Niggemann, MD, a Thomas Keil, MD, MPH, b and Kirsten Beyer, MD a, c Berlin, Germany, and New York, NY

A randomized trial of egg introduction from 4 months of age in infants at risk for egg allergy

John Wei-Liang Tan, MD, FRACP, Carolina Valerio, BN, Elizabeth H. Barnes, BAppSc, MStat, Paul J. Turner, MD, PhD, Peter A. Van Asperen, MD, FRACP, PhD, Alyson M. Kakakios, MD, FRACP, Dianne E. Campbell, MD, PhD, Elizabeth H. Barnes, Dianne E. Campbell, Namita Doa, Lara Ford, Maria Gacis, Peter Hsu, Preeti Joshi, Alyson M. Kakakios, Sam Mehr, Reta Nambiar, Claire Nicholls, John Wei-Liang Tan, Paul J. Turner, Carolina Valerio, Peter A. Van Asperen, Karla Villafana Soto, Andrew Williams, Melanie Wong

Randomized controlled trial of early regular egg intake to prevent egg allergy

Debra J. Palmer, PhD, a, b Thomas R. Sullivan, BMa&CompSc(Hons), c Michael S. Gold, MD, d Susan L. Prescott, MD, PhD, a, e and Maria Makrides, PhD b, d, f Perth and Adelaide, Australia
Randomized placebo-controlled trial of hen’s egg consumption for primary prevention in infants

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- RCT in 4 – 6 month old infants with negative egg sIgE comparing egg introduction at 4-6 months vs 12 months
- 406 infants screened; 23 (5.7%) excluded due to +ve egg sIgE ≥0.35 kU/L
- 383 (-ve egg sIgE) randomised to egg powder (n=184) or placebo (n=199)

- **No effect on egg sensitisation at 12 months:**
  - 5.6% egg group vs 2.6% placebo (RR, 2.20; 95% CI, 0.68-7.14; P = .24)
- **No effect on egg allergy at 12 months:**
  - 2.1% egg group vs 0.6% placebo (RR, 3.30; 95% CI, 0.35-31.32; P = .35)

- 17 of 23 with positive egg sIgE had a DBPCFC
  - 16 of 17 confirmed to be allergic
  - 11 had anaphylactic reactions
• RCT in infants with first degree relative with allergic disease comparing egg introduction at 4m vs 8m
  ➢ All infants had egg SPT and those with SPT ≥2mm excluded
  ➢ 319 infants randomized; 165 to egg, 154 to placebo
  ➢ 254 infants (83%) assessed at 12 months

• Early egg introduction was associated with reduced sensitization at 12 months
  ➢ 20% placebo vs 11% egg intake (OR=0.46, 95%CI 0.22-0.95, p=0.03).

• No effect on probable egg allergy at 12 months (placebo 13, egg 8)

• Fourteen with SPT <2mm reacted to egg
Randomized controlled trial of early regular egg intake to prevent egg allergy

Debra J. Palmer, PhD, Thomas R. Sullivan, BMa&CompSc(Hons), Michael S. Gold, MD, Susan L. Prescott, MD, PhD, and Maria Makrides, PhD
Perth and Adelaide, Australia

- RCT comparing egg introduction at 4-6 months vs 10 months
- Excluded infants with allergic disease (eg eczema) or prior egg ingestion
- 820 infants randomised to egg powder (n=407) or placebo (n=413)
- All infants followed an egg-free diet with cooked egg introduced at 10 months
- No difference in the IgE-mediated egg allergy at 12 months
  - Egg 7.0% vs control 10.3%; aRR, 0.75; 95% CI, 0.48-1.17; P = .20
- No difference in egg sensitization at age 12 months
  - Egg 10.8% vs control 15.1%; aRR, 0.77; 95% CI, 0.54-1.10; P = .15
- More infants in egg group stopped study powder because of allergic reaction
  - 25 of 407 [6.1%] vs 6 of 413 [1.5%]
Timing of Allergenic Food Introduction to the Infant Diet and Risk of Allergic or Autoimmune Disease: A Systematic Review and Meta-analysis

Despo Ierodiakonou, MD, PhD; Vanessa Garcia-Larsen, PhD; Andrew Logan, PhD; Annabel Groome, BSc; Sergio Cunha, MD; Jennifer Chivinge, BSc; Zoe Robinson, BSc; Natalie Geoghegan, BSc; Katharine Jarrold, BSc; Tim Reeves, BSc; Nara Tagiyeva-Milne, PhD; Ulugbek Nurmatov, MD, PhD; Marialena Trivella, DPhil; Jo Leonardi-Bee, PhD; Robert J. Boyle, MD, PhD

JAMA. 2016;316(11):1181-1192
Figure 1. Early Allergenic Food Introduction and Risk of Food Allergy or Food Sensitization

A Risk of food allergy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Early</th>
<th>Late</th>
<th>Risk Ratio (95% CI)</th>
<th>Weight (random-effects model), %</th>
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<tbody>
<tr>
<td>Egg allergy</td>
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<tr>
<td>Perkin et al,6 2016</td>
<td>21</td>
<td>32</td>
<td>0.69 (0.40-1.18)</td>
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<td>8</td>
<td>13</td>
<td>0.59 (0.25-1.37)</td>
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<td>Bellach et al,16 2015</td>
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<td>2.20 (0.20-23.97)</td>
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<td>Palmer et al,15 2013</td>
<td>14</td>
<td>18</td>
<td>0.65 (0.38-1.11)</td>
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<td>Random-effects model</td>
<td>943</td>
<td>972</td>
<td>0.56 (0.36-0.87)</td>
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<tr>
<td>Peanut allergy</td>
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<tr>
<td>Perkin et al,6 2016</td>
<td>7</td>
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<td>Du Toit et al,4 2015</td>
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<td>0.29 (0.11-0.74)</td>
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<td>Milk allergy</td>
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<tr>
<td>Perkin et al,6 2016</td>
<td>3</td>
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<td>0.79 (0.18-3.50)</td>
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<td>Lowe et al,19 2011</td>
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Figure 1. Early Allergenic Food Introduction and Risk of Food Allergy or Food Sensitization

B Risk of allergic sensitization

<table>
<thead>
<tr>
<th>Dietary Introduction of Allergenic Food</th>
<th>Early</th>
<th>Late</th>
<th>Risk Ratio (95% CI)</th>
<th>Decreased Risk of Allergic Sensitization</th>
<th>Increased Risk of Allergic Sensitization</th>
<th>Weight (random-effects model), %</th>
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<tr>
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<td>Total No.</td>
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<tr>
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<td>Perkin et al,6 2016</td>
<td>29</td>
<td>568</td>
<td>37</td>
<td>599</td>
<td>0.83 (0.52-1.33)</td>
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<td>Tan et al,18 2016</td>
<td>13</td>
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<td>25</td>
<td>122</td>
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<td>156</td>
<td>2.20 (0.68-7.14)</td>
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<td>22</td>
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<td>Heterogeneity: $I^2 = 37%$; $P = .19$</td>
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<td>12</td>
<td>178</td>
<td>0.75 (0.32-1.74)</td>
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<td>Kjellman and Johansson,20 1979</td>
<td>4</td>
<td>25</td>
<td>4</td>
<td>23</td>
<td>0.92 (0.26-3.26)</td>
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<td>Random-effects model</td>
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<td>0.72 (0.40-1.27)</td>
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<tr>
<td>Heterogeneity: $I^2 = 0%$; $P = .84$</td>
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Ierodiakonou et al. JAMA. 2016;316(11):1181-1192
• Moderate-certainty evidence from 5 trials (1915 participants)
  ➢ Early egg introduction at 4 to 6 months associated with reduced egg allergy (RR 0.56; 95%CI, 0.36-0.87; I² = 36%; P = .009).
  ➢ Absolute risk reduction for a population with 5.4% incidence of egg allergy was 24 cases (95%CI, 7-35 cases) per 1000 population.

• Moderate-certainty evidence from 2 trials (1550 participants) that
  ➢ Early peanut introduction at 4 to 11 months associated with reduced peanut allergy (RR 0.29; 95%CI 0.11-0.74; I² = 66%; P = .009).
  ➢ Absolute risk reduction for a population with 2.5% incidence of peanut allergy was 18 cases (95%CI, 6-22 cases) per 1000 population.

Ierodiakonou et al. JAMA. 2016;316(11):1181-1192
How should these research findings be translated into practice and policy?
Infants with severe eczema or egg allergy by 4-6 months of age may benefit from specialist evaluation and advice regarding introduction of peanut, which might include SPT +/- observed peanut ingestion / challenge.

This guidance is limited to the select group of high risk infants studied in LEAP.... The guidance aims to apply the LEAP findings to “other similar children at high risk in more diverse settings around the world”
Infant feeding and allergy prevention

Introduce solid foods from around 6 months, but not before 4 months, when your infant is developmentally ready whilst continuing to breastfeed.

- When your infant is ready, introduce foods according to what the family usually eats, regardless of whether the food is considered to be a common food allergen. There is some evidence that the introduction of common allergenic foods (including cooked eggs as raw egg is not recommended, peanuts, nuts, wheat, fish) should not be delayed. However further evidence is required to clarify optimal timing for each food.

- There is moderate evidence that introducing cooked egg (raw egg is not recommended) into an infant’s diet before 8 months of age, where there is a family history of allergy, can reduce the risk of developing egg allergy.

- There is good evidence that for infants with severe eczema and/or egg allergy, that regular peanut intake before 12 months of age can reduce the risk of developing peanut allergy. If your child already has an egg allergy or other food allergies or severe eczema, you should discuss how to do this with your doctor.
What advice should be given?

- Current international guidelines all recommend *introducing solid foods (including the allergenic foods) from 4-6 months* without any specific recommendation to seek medical advice or perform prior allergy testing….
  - American Association Pediatrics (AAP)
  - Canadian Pediatric Society
  - Canadian Society of Allergy and Clinical Immunology
  - European Academy of Allergology and Clinical Immunology (EAACI)
  - European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)

- Randomised trials performed SPT/sIgE prior to randomisation and excluded those with likely/probable allergy (except Palmer et al who excluded high risk infants with eczema)

*Should SPT or sIgE testing be performed prior to introducing allergenic foods?*
1. What is the potential impact of the consensus advice on the allergy workforce? i.e. What proportion of infants have severe eczema or egg allergy by 6 months?

2. Are there potential risks associated with implementing this advice? e.g. In regions where there is limited access to allergy services, might these new recommendations have the opposite effect of increasing the risk of peanut allergy because peanut introduction is delayed while awaiting specialist evaluation?

3. Is it safe to introduce peanut without prior testing as currently recommended by international allergy prevention guidelines?
1. What is the expected impact on the allergy workforce?

In the HealthNuts cohort…. 

• **11% of 6 month old infants and 16% of 12 month old infants** have egg allergy or severe eczema → consensus recommendations apply 
  – 10.8% of infants had eczema requiring topical corticosteroid therapy by 6 months 
  – Egg allergy in 0.4% of infants by 6 months and 8.9% at 12 months

• **~84% to ~89% of 6 month old infants are not high risk** → follow current allergy prevention guidelines

• **Can the existing allergy workforce accommodate seeing 11% of infants each year?**
  – In Australia, with a birth rate of 300,000 annually, this equates to 33,000 new referrals to allergists every year and an additional 4,488 challenges (for infants with SPT 1-4mm) 
  – This could not be accommodated by existing allergy services

Koplin et al JACI 2016 In press
2. Are there potential risks associated with implementing the consensus recommendations?

In the LEAP study…

• **75.7% (542/716) of high risk infants had peanut SPT 0mm**
  – Of these, 272 were randomized to peanut consumption and were offered a single dose of 2g peanut protein
  – Only 1 of 272 reacted to peanut at baseline (rash, itch, antihistamine)

• **The majority of high risk infants will be peanut SPT negative and could safely introduce peanut without prior SPT**
  – In regions where there are long wait times to see an allergist, these infants will have unnecessarily delayed peanut introduction while waiting for specialist evaluation / testing
2. Are there potential risks associated with implementing the consensus recommendations?

- **13.7% had SPT 1-4mm.** These infants will have additional delay in introducing peanut while waiting for a challenge (after already having waited for SPT).  
  *This may mean peanut is not introduced until after 12 months.*

- **12.8% of infants with SPT 1-4mm failed the peanut challenge; 87% passed.**  
  *So the majority of infants with peanut SPT 1-4mm can introduce peanut safely but will have additional delay in peanut introduction due to SPT and challenge.*

- **Overall, 12.6% of high risk infants will have likely or proven peanut allergy** (SPT >4mm; and SPT 1-4mm who fail the peanut challenge)

  *If all high risk infants are referred for specialist evaluation, the majority ~87% would delay introducing peanut unnecessarily to identify ~12% who would react to peanut on early introduction.*
An alternative approach to minimize unnecessary delay in peanut introduction, is for GPs or pediatricians to perform initial evaluation of high risk infants using peanut sIgE testing and refer infants with positive peanut sIgE to an allergy specialist for further assessment and advice.

In LEAP, 64% of high risk infants had negative peanut sIgE (Table S3) → these infants could introduce peanut after minimal delay

The remaining 36% of high risk infants with positive peanut sIgE could be referred to a specialist for further evaluation including SPT

This would reduce the number of infants requiring specialist evaluation by more than half and avoid unnecessary delay of peanut introduction for the majority of high risk infants who would have negative tests

- 4% (36% of high risk infants) vs 11% (all high risk infants) require specialist evaluation
- SPT performed by specialist avoids unnecessary food challenges in sIgE +ve SPT -ve
3. Is it safe to introduce peanut without prior testing?

Most reactions to peanut in the first year of life are mild

• In the LEAP study, 7 of 319 (2.2%) high risk infants randomized to peanut ingestion reacted to peanut during the study entry challenge
  – All reactions were mild; no infants required adrenaline, no hospitalisation
  – No challenges in infants with SPT >4mm

• In HealthNuts, 3% of infants who commenced peanut before 12 months reported a possible reaction
  – Reactions were more common in high-risk infants (10.6% vs 1.4%, p<0.001).
  – No cases of anaphylaxis

• ~400 peanut challenges in infants with SPT ≥1mm; 150 were positive
  – Majority of reactions were mild - urticaria
  – 6 cases of anaphylaxis (~0.1% of the cohort)
  – Anaphylaxis was seen in both high and low-risk groups

• Introducing peanut cautiously would further reduce the likelihood of a severe reaction – eg graded daily doses starting with a smear to the inside lip on day 1, 1/8th of a tsp on day 2, ¼ of a tsp on day 3, etc

Koplin et al Manuscript under revision; Du Toit et al. NEJM 2015;372:803
3. Is it safe to introduce peanut without prior testing?

- **An alternative option in settings where allergy services are limited might be to introduce peanut in all infants at ~6 months of age**

- Few infants are expected to react to peanut at 6-12 months
  - Prevalence of peanut allergy at 12 months in HealthNuts is 3%; early introduction would result in a lower rate
  - If early introduction of peanut is effective in high risk infants alone, the rate of peanut allergy at 12 months would be ~1.8%
  - If early introduction is equally effective in low risk infants, the rate of peanut allergy at 12 months would be ~1.2%

- The majority of reactions with peanut introduction in young infants are mild, irrespective of whether peanut is introduced at home or in the hospital, and irrespective of SPT wheal size or clinical risk factors
  - NB: These data are derived from ~150 infants and it is possible that severe reactions may occur when larger numbers of infants are exposed to peanut
Summary

• Oral tolerance to foods requires exposure to food antigens

• There is now level 1 evidence that early introduction of egg (4-6 months) and peanut (4-11 months) into the infant diet can reduce the risk of egg and peanut allergy

• International consensus recommendations arising from the LEAP trial suggest that infants with severe eczema or egg allergy seek specialist assessment prior to introducing peanut (which might include SPT and challenge)…. However the feasibility of implementing this advice is uncertain

• Region-specific factors (such as capacity of the allergy workforce) should be taken into consideration when updating allergy prevention guidelines in response to this evidence

• Recommendations for introducing allergenic foods in infants will likely vary according to the available resources and the family’s need for support