EAT (Take 2)
Have LEAP and EAT really changed anything?

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Senior Lecturer in Clinical Epidemiology

Midlands Paediatric Allergy Group
28th April 2017
An opinion poll....

1. Infants should introduce allergenic foods into their diet early?
   A. Yes
   B. No
An opinion poll....

2. When should infants introduce allergenic foods? *(How early is early.....?)*
   
   A. From 4 months
   
   B. From 6 months
   
   C. By one year of age
   
   D. Shouldn’t offer any age by which infants should introduced allergenic foods (i.e. it is entirely up to the individual family)
   
   E. Not before six months of age...
3. What allergenic foods should they introduce early?
A. Peanut
B. Peanut, Egg, Wheat, Sesame, Cow’ milk and Fish
C. Peanut & Egg
D. All nuts...
E. All allergenic foods...
F. Some other permutation of allergenic foods...
An opinion poll....

4. Should infants be screened before introducing allergenic foods?
   A. No
   B. Yes – high risk infants
   C. Yes – all infants
An opinion poll....

5. How do you define a high risk infant?
   A. Egg allergy
   B. Significant egg sensitization and/or egg allergy
   C. Significant eczema
   D. Any eczema
   E. Family history of atopy
   F. Some other definition...
BREASTFEEDING’S WORLD OF BENEFITS

FOR BABY
- Protection against ear infections
- Protection against chest infections and wheezing
- Lower risk of diabetes
- Less eczema
- Protection against diarrhoea, gastro-enteritis and tummy upsets
- Less smelly nappies

FOR MOTHER
- Better mental development
- Better mouth formation and straighter teeth
- Lower risk of ovarian cancer
- Lower risk of pre-menopausal breast cancer
- Stronger bones in later life
- Faster return to pre-pregnancy figure
## Oral Tolerance Induction trials

<table>
<thead>
<tr>
<th>High-risk strategy</th>
<th>Population strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• LEAP (P)</td>
<td>• EAT (E, P, W, S, M, F)</td>
</tr>
<tr>
<td>• STAR (E)</td>
<td>• HEAP (E)</td>
</tr>
<tr>
<td>• PEAAD (P)</td>
<td>• PreventADALL (P, M, E, W)</td>
</tr>
<tr>
<td>• BEAT (E)</td>
<td></td>
</tr>
<tr>
<td>• STEP (E)</td>
<td></td>
</tr>
</tbody>
</table>
LEAP and LEAP-On Studies

**LEAP**
- n=628
- Consumption
- Avoidance
- 4 to < 11 Months

**LEAP-On**
- n=556
- 60 Months
- Avoidance
- 72 Months

**Primary Endpoint:**
Persistent tolerance
Comparison of proportion with peanut allergy in LEAP Consumers vs LEAP Avoiders at 72 Months

**Secondary Endpoint:**
Transient desensitization
Comparison of proportion with peanut allergy in LEAP Consumers at 60 and 72 Months
What about the study that can’t be named.....

81% Relative Reduction


LEAP nagged mothers into perfect compliance...

- Weekly phone calls from 4-11 months of age
- Fortnightly phone calls from 12-30 months of age
- Monthly phone calls from 30 to 60 months of age

A 4 month old LEAP family was phoned 104 times to remind them to eat peanut...

Real world? ...............I think not......
What about the study that can’t be named.....

**Intention-to-Treat Population**

LEAP (60 Months of Age)  
(N=556)  
P<0.001

LEAP-On (72 Months of Age)  
(N=550)  
P<0.001

- **Avoidance Group**: 18.8%  
- **Consumption Group**: 3.6%

- **Avoidance Group**: 20%  
- **Consumption Group**: 4.8%

**Per-Protocol Population**

LEAP-On (72 Months of Age)  
(N=445)  
P<0.001

- **Avoidance Group**: 19.2%  
- **Consumption Group**: 2.1%

81% Relative Reduction  
74% Relative Reduction  
89% Relative Reduction

LEAP- Peanut Allergy Prevalence

• **The good**: After 12 months of peanut avoidance, peanut allergy (PA) was still significantly higher in LEAP Avoidance group (18.6%) than LEAP Consumers (4.8%) at 72 months.
• **The bad**: 3 new cases of PA in LEAP control group
• **The ugly**: a **massive 33% increase** in peanut allergy in the LEAP consumers after 12 months of avoidance from 3.6% at 60 months to 4.8% at 72 months
How long do you need to eat the allergenic food for....?
Table S3. Frequencies and Percent of Peanut Allergy across Per Protocol and Non Per Protocol Consumption of Peanut (Defined by Food Frequency Questionnaires)

<table>
<thead>
<tr>
<th>Category of Peanut Consumption and Per Protocol Status</th>
<th>LEAP Avoiders (N=282)</th>
<th>LEAP Consumers (N=274)</th>
<th>Overall (N=556)</th>
<th>P-value [4]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did Subject Meet All Per Protocol Definitions?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>255 (90.4%)</td>
<td>190 (69.3%)</td>
<td>445 (80.1%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>27 (9.6%)</td>
<td>84 (30.7%)</td>
<td>111 (19.9%)</td>
<td></td>
</tr>
<tr>
<td>Complete avoidance of peanut, Per Protocol</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number (%) with Peanut Allergy</td>
<td>223 (79.1%)</td>
<td>127 (46.4%)</td>
<td>350 (62.9%)</td>
<td></td>
</tr>
<tr>
<td>Consumption of some peanut [1], Per Protocol</td>
<td></td>
<td></td>
<td></td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Number (%) with Peanut Allergy</td>
<td>48 (21.5%)</td>
<td>3 (2.4%)</td>
<td>51 (14.6%)</td>
<td></td>
</tr>
<tr>
<td>Consumption of some Peanut [2], Not Per Protocol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%) with Peanut Allergy</td>
<td>32 (11.3%)</td>
<td>63 (23.0%)</td>
<td>95 (17.1%)</td>
<td></td>
</tr>
<tr>
<td>Other Non-Per Protocol Participants [3]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%) with Peanut Allergy</td>
<td>1 (0.4%)</td>
<td>1 (0.4%)</td>
<td>2 (0.4%)</td>
<td></td>
</tr>
</tbody>
</table>

[1] Per Protocol Consumption is defined as: No more than 2g of peanut protein on 6 occasions over a period of 12 months (or prorated by the duration the participant is on study) with a maximum of one event per month. AND No more than 1g of peanut protein on 12 occasions over a period of 12 months (or prorated by the duration the participant is on study) with a maximum of two events per month.

[2] Peanut consumption exceeding the amounts specified above in [1].

[3] These participants did not meet the LEAP Per Protocol definition (N=56) or had a missing LEAP-On primary outcome (N=2).

[4] P-values come from a Fisher’s Exact test comparing the number of participants with peanut allergy between the two groups within each category of consumption.
Adherence to LEAP-On recommendation to stop eating peanut in consumption arm

- 0.00%
- 0.50%
- 1.00%
- 1.50%
- 2.00%
- 2.50%
- 3.00%

Good as gold and stopped all peanut
Bit naughty and ate some peanut
Completely ignored the daft advice to stop eating peanut and ate loads

Conclusion: Need to eat peanut forever....
**EAT Study Design**

**Recruitment and randomisation**

- Clinic visit 3m

**Key Period of Intervention**

- Monthly questionnaires
  - 3 months
  - Clinic visit 3m

**Monthly questionnaires**

- 6 months
- Clinic visit 12m

**Three monthly questionnaires**

- 12 months
- Clinic visit 36m

**Outcome**

- Ongoing Intervention & Follow Up

**EAT cohort**

- N=1303

**Standard Introduction Group**

- n=651

**Early Introduction Group**

- n=652

**Tolerant**

- Allergic

**Allergic**
IFS 2010 – Allergen avoidance

N= 9416 Stage 3 mothers (infants aged 8-10 months) in the IFS 2010

4463 mothers were avoiding at least one food. 43% of these stated that the reason was a concern about allergies.

Avoidance of specific foods as ingredients was common. For egg (n=627), 24% avoided it because they considered it harmful and 44% because of concerns about allergies.

For dairy products (n=484), 17% were concerned about harm, 50% allergies and 8% concerned with eczema.

For nuts (n=2153) 33% were concerned about harm and 70% allergies (mothers could report more than one concern).
Frequency of allergenic food consumption in UK infants aged 8-10 months

<table>
<thead>
<tr>
<th>Food</th>
<th>Percentage giving food:</th>
<th>1/day or more</th>
<th>1-6 times a week</th>
<th>&lt;1/week or never</th>
<th>3/week or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheese, yoghurt, fromage frais</td>
<td></td>
<td>64</td>
<td>26</td>
<td>9</td>
<td>85</td>
</tr>
<tr>
<td>Breakfast cereals</td>
<td></td>
<td>82</td>
<td>8</td>
<td>9</td>
<td>88</td>
</tr>
<tr>
<td>Bread</td>
<td></td>
<td>36</td>
<td>38</td>
<td>25</td>
<td>58</td>
</tr>
<tr>
<td>Eggs</td>
<td></td>
<td>2</td>
<td>23</td>
<td>76</td>
<td>6</td>
</tr>
<tr>
<td>Fish (incl. Tuna)</td>
<td></td>
<td>3</td>
<td>45</td>
<td>52</td>
<td>18</td>
</tr>
<tr>
<td>Nuts (incl. Ground nuts)</td>
<td></td>
<td>&lt;1</td>
<td>1</td>
<td>99</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>
EAT Study Design

**Standard Introduction Group (SIG)**
UK Infant feeding advice (based on WHO): exclusive breastfeeding for around 6 months with no introduction of wheat/gluten, eggs, fish, shellfish, nuts and seeds before 6 months.

**Early Introduction Group (EIG)**
Continued breastfeeding alongside sequential introduction of 6 allergenic foods: milk, egg, fish, peanut, sesame and wheat (aiming for 4g protein/week in 2 divided doses)
## EIG Food portions

<table>
<thead>
<tr>
<th>Introduced</th>
<th>Allergenic Food Portion (containing 4g Protein)</th>
<th>Median age intro (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>Milk (40-60g yogurt)</td>
<td>17.3</td>
</tr>
<tr>
<td>Randomised</td>
<td>Peanuts (3 rounded tsp peanut butter)</td>
<td>19.6</td>
</tr>
<tr>
<td>Randomised</td>
<td>Fish (25g cod)</td>
<td>19.6</td>
</tr>
<tr>
<td>Randomised</td>
<td>Sesame (3 rounded tsp tahini)</td>
<td>19.6</td>
</tr>
<tr>
<td>Randomised</td>
<td>Egg (1 hard-boiled egg)</td>
<td>19.6</td>
</tr>
<tr>
<td>Last</td>
<td>Wheat (2 weetabix)</td>
<td>20.6</td>
</tr>
</tbody>
</table>
1319 Participants were screened for EAT study

16 ineligible for enrollment: major health concerns identified from blood test results/clinical findings

1303 eligible infants enrolled in study

651 Were assigned to the Standard Introduction Group
- 56 Had missing data on outcomes
- 7 Exceeded visit window at final visit
- 6 Could not be evaluated by means of diagnostic algorithm
- 43 Withdrew voluntarily

652 Were assigned to the Early Introduction Group
- 85 Had missing data on outcomes
- 9 Exceeded visit window at final visit
- 7 Could not be evaluated by means of diagnostic algorithm
- 69 Withdrew voluntarily

595 Were included in the ITT analysis
- 31 Had missing data on SIG adherence criteria
- SIG Adherence non-evaluable

567 Were included in the ITT analysis
- 81 Had missing data on EIG adherence criteria
- EIG Adherence non-evaluable

564 Were evaluable for per-protocol adherence
- SIG Per-Protocol: 524
- SIG Non Per-Protocol: 40

486 Were evaluable for per-protocol adherence
- EIG Per-Protocol: 298
- EIG Non Per-Protocol: 278

80.5% 31.9%
Primary Outcome
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*
Primary Outcome: Prevalence of Allergy to One or More Foods

**ITT** - 20% **Non-significant** reduction in prevalence in EIG

**PP** - 67% **Significant reduction** in prevalence in EIG

Perkin M, Logan K, Tseng A et al. Randomized trial introducing allergenic foods in breastfed infants. March 4th 2016, at NEJM.org
Prevalence of Individual Food Allergy

Per-protocol – 100% Significant reduction in Peanut allergy prevalence in EIG
Per-protocol – 75% Significant reduction in Egg allergy prevalence in EIG

Perkin M, Logan K, Tseng A et al. Randomized trial introducing allergenic foods in breastfed infants. March 4th 2016, at NEJM.org
EAT Results Conclusions
The EAT study failed to show efficacy in an intention-to-treat analysis. Further analysis suggests that the possibility of food allergy prevention through the early introduction of multiple allergenic foods in normal breastfed infants may depend on adherence and dosage.
Negative ITT, Positive PP Effect

1. The early introduction of allergenic foods prevented food allergy developing.

2. Reverse causality.

3. Bias that could lead to increased atopy and food allergy in children outside the per-protocol analysis is an important consideration given that only 31.9% (208/652) of all the enrolled early-introduction-group participants were per-protocol-evaluable versus 80.5% (524/651) in the standard-introduction-group.

4. Selective removal of baseline food allergic participants exclusively from the early-introduction-group.
1. The early introduction of allergenic foods prevented food allergy developing

This has some plausibility...

*Effect is potentially allergen specific*

- 67% reduction in overall food allergy in per-protocol adherent EIG participants
- 100% reduction in peanut allergy in peanut per-protocol adherent EIG participants
- 75% reduction in egg allergy in egg per-protocol adherent EIG participants
- No allergy to sesame or wheat among sesame and wheat per-protocol adherent participants respectively.

*Effect suggests a dose dependent relationship*

- Effectiveness of the intervention increased with the number of weeks the food was eaten and the percentage of the recommended dose that was eaten.
- And for the EAT primary outcome with an increase in the number of foods that were eaten
A Food allergy/skin prick test positive status: by quartiles of weekly allergen consumption

B Food allergy/skin prick test positive status: predicted probability plots by quartiles of weekly allergen consumption
2. Reverse causality

- Individuals in EIG who did not follow the protocol may have done so because of low level symptoms (food aversion or refusal) even in the absence of obvious clinical symptoms.
- These symptoms could have ultimately resulted in food allergy.
- This would produce an artefactual decrease in the EIG per-protocol food allergy rate by shifting food allergic patients early on towards non per-protocol adherence.
Primary outcome - food allergy to one or more foods

- Percentage: 524 for SIG, 208 for EIG

Per-Protocol
Primary outcome - food allergy to one or more foods

<table>
<thead>
<tr>
<th></th>
<th>Per-Protocol</th>
<th>Non Per-Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIG</td>
<td>524</td>
<td>278</td>
</tr>
<tr>
<td>EIG</td>
<td>208</td>
<td></td>
</tr>
</tbody>
</table>

Percentage
Primary outcome - food allergy to one or more foods

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<th>EIG</th>
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<td>208</td>
</tr>
<tr>
<td>Non Per-Protocol</td>
<td>40</td>
<td>278</td>
</tr>
<tr>
<td>Adherence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Evaluable</td>
<td>31</td>
<td>81</td>
</tr>
</tbody>
</table>
3. Bias

Bias leading to increased atopy and food allergy in children outside the per-protocol analysis.
3. Bias

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16 ineligible for enrollment: major health concerns identified from blood test results/clinical findings
1303 eligible infants enrolled in study

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40 SIG Non Per-Protocol
80.5%

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EIG Adherence non-evaluable

486 Were evaluable for per-protocol adherence
208 EIG Per-Protocol
278 EIG Non Per-Protocol
31.9%
4. ARTEFACT OF STUDY DESIGN

The selective removal of baseline food allergic participants exclusively from the EIG

- 7 baseline visit food allergic participants in the EIG
- 5 of whom were primary outcome positive by 3 years of age
- These 5 were unable to be per-protocol adherent, thus artificially reducing the food allergy rate in the per-protocol group

<table>
<thead>
<tr>
<th>ID</th>
<th>Skin-prick test (mm) at 3m</th>
<th>Enrollment challenge outcome</th>
<th>EIG per-protocol status</th>
<th>Peanut consumption at 6 months</th>
<th>Egg consumption at 6 months</th>
<th>Milk consumption at 6 months</th>
<th>Sesame consumption at 6 months</th>
<th>Fish consumption at 6 months</th>
<th>Wheat consumption at 6 months</th>
<th>Study primary outcome status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RE5</td>
<td>E+</td>
<td>Not tried yet</td>
<td>Not tried yet</td>
<td>50%§</td>
<td>Not tried yet</td>
<td>Not tried yet</td>
<td>Not tried yet</td>
<td>Not tried yet</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>2</td>
<td>M5</td>
<td>M+</td>
<td>Non-evaluable</td>
<td>100%§</td>
<td>100%§</td>
<td>Not tried yet</td>
<td>100%§</td>
<td>100%§</td>
<td>100%§</td>
<td>Positive (E)</td>
</tr>
<tr>
<td>3</td>
<td>M6 P2</td>
<td>M+ P+</td>
<td>No</td>
<td>Not tried yet</td>
<td>100%</td>
<td>Not tried yet</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>Negative</td>
</tr>
<tr>
<td>4</td>
<td>M5 RE16</td>
<td>M+ Eind</td>
<td>No</td>
<td>50%</td>
<td>Not tried yet</td>
<td>Not tried yet</td>
<td>50%</td>
<td>50%</td>
<td>75%</td>
<td>Positive (PE)</td>
</tr>
<tr>
<td>5</td>
<td>RE7</td>
<td>E+</td>
<td>Non-evaluable</td>
<td>100%§</td>
<td>Not tried yet</td>
<td>100%§</td>
<td>100%§</td>
<td>75%§</td>
<td>75%§</td>
<td>Positive (E)</td>
</tr>
<tr>
<td>6</td>
<td>M7 P4</td>
<td>M+ P+</td>
<td>No</td>
<td>Not tried yet</td>
<td>50%</td>
<td>Not tried yet</td>
<td>25% or less</td>
<td>100%</td>
<td>100%</td>
<td>Positive (M)</td>
</tr>
<tr>
<td>7</td>
<td>RE3 P3 W2</td>
<td>E- P- W+</td>
<td>No</td>
<td>50%§</td>
<td>100%§</td>
<td>100%§</td>
<td>50%§</td>
<td>100%§</td>
<td>Not tried yet</td>
<td>Positive (EPW)</td>
</tr>
</tbody>
</table>
Prevalence of Allergy to One or More Foods

Adjusted PP - 62% Significant reduction in prevalence in EIG

Perkin M, Logan K, Tseng A et al. Randomized trial introducing allergenic foods in breastfed infants. March 4th 2016, at NEJM.org
Negative ITT, positive PP effect

1. The early introduction of allergenic foods prevented food allergy developing.

2. Reverse causality.

3. Bias that could lead to increased atopy and food allergy in children outside the per-protocol analysis is an important consideration given that only 34.2% (223/652) of all the enrolled early-introduction-group participants were per-protocol-evaluable versus 85.7% (558/651) in the standard-introduction-group.

4. Selective removal of baseline food allergic participants exclusively from the early-introduction-group.

Nevertheless we cannot be certain that unmeasured sources of bias may still exist.
What to tell patients?

• EAT works – if you do it
• It doesn’t increase risk of food allergy if you don’t
• It is safe
Which foods to introduce...?
Egg allergy – outgrown....

Fig 1. Kaplan-Meier analysis of egg allergy resolution over time with pointwise 95% CIs.

Scott H. Sicherer, Robert A. Wood, Brian P. Vickery, Stacie M. Jones, Andrew H. Liu, David M. Fleischer, Peter Dawson, Lloyd Mayer, A. Wesley Burks, Alexander Grishin, Donald Stablein, Hugh A. Sampson

The natural history of egg allergy in an observational cohort

Journal of Allergy and Clinical Immunology, Volume 133, Issue 2, 2014, 492–499.e8
Milk allergy – outgrown....

Fig 1. Kaplan-Meier analysis of milk allergy resolution over time is shown in blue, with pointwise 95% CIs shown in red.

Robert A. Wood, Scott H. Sicherer, Brian P. Vickery, Stacie M. Jones, Andrew H. Liu, David M. Fleischer, Alice K. Henning, Lloyd Mayer, A. Wesley Burks, Alexander Grishin, Donald Stablein, Hugh A. Sampson

The natural history of milk allergy in an observational cohort

Journal of Allergy and Clinical Immunology, Volume 131, Issue 3, 2013, 805–812.e4
Peanut allergy – outgrown... a little bit

Fig 5. The probability of resolved peanut allergy for children with SPT responses (A) and sIgE levels (B) equal to or less than the stated thresholds.

Rachel L. Peters, Katrina J. Allen, Shyamali C. Dharmage, Jennifer J. Koplin, Thanh Dang, Kate P. Tilbrook, Adrian Lowe, Mimi L.K. Tang, Lyle C. Gurrin

Natural history of peanut allergy and predictors of resolution in the first 4 years of life: A population-based assessment

Journal of Allergy and Clinical Immunology, Volume 135, Issue 5, 2015, 1257–1266.e2
Which nut to introduce....?
Nutritional properties of nuts and oily seeds

National Nutrient Database (NDB) for Standard Reference
# Pronuts portion sizes

Typical nut/seeds portions sizes to be eaten

<table>
<thead>
<tr>
<th>Pronut portion sizes</th>
<th>1-4 year old</th>
<th>5-10 year old</th>
<th>11+ year old</th>
</tr>
</thead>
<tbody>
<tr>
<td>X2 handfuls per nut/seed</td>
<td>3 nuts/ 5g</td>
<td>5 nuts/ 8g</td>
<td>8 nuts/13g</td>
</tr>
<tr>
<td>*Nut per week (gms) (each nut consumed twice weekly)</td>
<td>100g 240g</td>
<td>160g</td>
<td>260g</td>
</tr>
<tr>
<td>*Weekly calories</td>
<td>650 kcals</td>
<td>1,040kcals</td>
<td>1,700 kcals</td>
</tr>
<tr>
<td>*Daily calories</td>
<td>92 kcals</td>
<td>150 kcals</td>
<td>240 kcals</td>
</tr>
<tr>
<td>Daily calorie requirement</td>
<td>1000</td>
<td>1300</td>
<td>1700</td>
</tr>
<tr>
<td>% coming from nuts</td>
<td>9.2% 22.0%</td>
<td>11.5%</td>
<td>14.1%</td>
</tr>
</tbody>
</table>

*Assumes participant tolerant to 10 safe nuts/seeds
Have LEAP and EAT really changed anything....?

New infant feeding guidelines
Australian infant feeding guidelines

Infant feeding and allergy prevention

Key recommendations

- When your infant is ready, at around 6 months, but not before 4 months, start to introduce a variety of solid foods, starting with iron rich foods, while continuing breastfeeding.
- All infants should be given allergenic solid foods including peanut butter, cooked egg, dairy and wheat products in the first year of life. This includes infants at high risk of allergy.
- Hydrolysed (partially and extensively) infant formula are not recommended for prevention of allergic disease.
USA infant feeding guidelines

<table>
<thead>
<tr>
<th>Addendum guideline</th>
<th>Infant criteria</th>
<th>Recommendations</th>
<th>Earliest age of peanut introduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Severe eczema, egg allergy, or both</td>
<td>Strongly consider evaluation by sIgE measurement and/or SPT and, if necessary, an OFC. Based on test results, introduce peanut-containing foods</td>
<td>4-6 months</td>
</tr>
<tr>
<td>2</td>
<td>Mild-to-moderate eczema</td>
<td>Introduce peanut-containing foods</td>
<td>Around 6 months</td>
</tr>
<tr>
<td>3</td>
<td>No eczema or any food allergy</td>
<td>Introduce peanut-containing foods</td>
<td>Age appropriate and in accordance with family preferences and cultural practices</td>
</tr>
</tbody>
</table>
Severe eczema
or
Egg allergy
or
Both

Peanut sIgE*

- <0.35
  - Risk of reaction low. Over 90% will have (-) SPT to peanut.
  - Options:
    - a) Introduce peanut at home
    - b) Supervised feeding in the office (based on provider/parental preference)
- ≥0.35
  - Refer to specialist for consultation/SPT protocol

Peanut Skin Prick Test

- 0-2 mm
  - Risk of reaction low (95% will not have peanut allergy).
  - Options:
    - a) Introduce peanut at home
    - b) Supervised feeding in the office (based on provider/parental preference)
- 3-7 mm
  - Risk of reaction varies from moderate to high.
  - Options:
    - a) Supervised feeding in office
    - b) Graded OFC in a specialized facility
- ≥8 mm
  - Infant probably allergic to peanut.
  - Continue evaluation and management by a specialist

* To minimize a delay in peanut introduction for children who may test negative, testing for peanut-specific IgE may be the preferred initial approach in certain healthcare settings. Food allergen panel testing or the addition of sIgE testing for foods other than peanut is not recommended due to poor positive predictive value.
What difference will the new guidelines make...

Low risk

1000 children

High risk

Whole population: n=1000

- Low risk: No early onset eczema and no egg allergy
  - HealthNuts data: 84% (n=840)
  - No intervention
    - HealthNuts data: 0.8% peanut allergic
      - Cases: n=7
    - LEAP data: 10.6% (n=17)
    - SPT >4mm No intervention
    - LEAP data: 17% allergic without intervention*
      - Predicted cases: n=24
    - Total: 7 PA

- High risk: Early onset eczema (≤6mths) treated with topical steroids and/or egg allergy
  - HealthNuts data: 16% (n=160)
  - Skin prick test screening to peanut +/- intervention (introduction of peanut at 4-11 months)
  - SPT 0-4
  - SPT 0-4mm: Intervention
    - LEAP data: 89% (n=142)
    - 17% allergic without intervention*
      - Predicted cases: n=24
    - LEAP data: 3% allergic with intervention*
      - Cases: n=4
      - Cases prevented: n=20
  - Total: 24 PA

- Only 20 prevented
Feasibility of applying LEAP in real life.....

Based on this large epidemiological study, a population program aiming to identify and screen all infants at risk of peanut allergy would pose major cost and logistic challenges that need to be carefully considered.....
Understanding the feasibility and implications of implementing early peanut introduction for prevention of peanut allergy
Jennifer J. Koplin, PhD\textsuperscript{a, b},
Rachel L. Peters, PhD\textsuperscript{a},
Shyamali C. Dharmage, MD, PhD\textsuperscript{b},
Lyle Gurrin, PhD\textsuperscript{b},
Mimi L.K. Tang, MD, PhD\textsuperscript{a},
Anne-Louise Ponsonby, MD, PhD\textsuperscript{a},
Melanie Matheson, PhD\textsuperscript{b},
Alkis Togias, MD\textsuperscript{c},
\textbf{Gideon Lack, MB, BCh\textsuperscript{d}},
Katrina J. Allen, MD, PhD\textsuperscript{a, e, , ,}
for the
\textbf{HealthNuts study investigators}
THE NEW FOOD REVOLUTION
Filaggrin

EAT infants screened for six most common filaggrin mutations

**Environmental allergen**
Dust samples collected at 3 months and 12 months – peanut and egg measured

**PBMCs**
Blood taken at 3, 12 and 36 months – PBMCs obtained and stored

**Early sensitization**
All infants had specific IgE measured at enrolment

**Skin microbiome**
Skin microbiome assessed at 3 and 12 months – 16S PCR

**Gut microbiome**
Stool samples collected at 3, 5 & 12 months – 16S PCR undertaken

**Coeliac disease**
One of six early intervention foods was wheat – effect on coeliac disease

**Atopic dermatitis**
Association between AD and early food sensitization

**EAT methodology**
EAT study design and effect on breastfeeding

**Water hardness**
Water hardness and chlorine content linked to infant’s address

**Infant sleep**
Unique RCT design allows assessment of impact on sleep

**EAT adherence**
EIG per protocol adherence 42% - detailed analysis of why
Introducing solids early and infant sleep....
PreventCD: a European scientific research project to prevent coeliac disease. The project studies the influence of the dietary history in the prevention of coeliac disease: possibilities of induction of tolerance for gluten in genetic predisposed children for coeliac disease.


Based on previous research it was thought that giving small amounts of gluten at a young age would prevent celiac disease, especially if this gluten was given during the period of breastfeeding. In this way the immune system would get used to gluten and therefore not react with a harmful immune response. However, so far this hypothesis had not been thoroughly studied.

In PreventCD, almost 950 children from 8 different countries participated in the research project. All of them had a genetic predisposition for celiac disease. The study was supported by a grant from the European Commission (FP6-2005-FOOD-4B-36383-PREVENTCD). At the age of 4 to 6 months, half of the children received 100 milligram of gluten daily. At the age of 3 years 5.9 percent of these children were diagnosed with celiac disease. The other half received a placebo during the same period, and received gluten for the first time at the age of 6 months. In this group 4.5 percent got celiac disease. "Not a statistically significant difference", says...
Original Article

Randomized Feeding Intervention in Infants at High Risk for Celiac Disease

Sabine L. Vriezinga, M.D., Renata Auricchio, M.D., Enzo Bravi, M.S., Gemma Castillejo, M.D., Anna Chmielewska, M.D., Ph.D., Paula Crespo Escobar, B.Sc., Sanja Kolaček, M.D., Ph.D., Sibylle Koletzko, M.D., Ph.D., Ilma R. Korponay-Szabo, M.D., Ph.D., Eckart Mummert, Ph.D., Isabel Polanco, M.D., Ph.D., Hein Putter, Ph.D., Carmen Ribes-Koninckx, M.D., Ph.D., Raanan Shamir, M.D., Ph.D., Hania Szajewska, M.D., Ph.D., Katharina Werkstetter, M.Sc., M.P.H., Luigi Greco, M.D., Ph.D., Judit Gyimesi, M.D., Corina Hartman, M.D., Caroline Hogen Esch, M.D., Ph.D., Erica Hopman, R.D., Ph.D., Anneli Ivarsson, M.D., Ph.D., Tunde Koltai, Ir., Frits Koning, Ph.D., Eva Martinez-Ojinaga, M.D., Chantal te Marvelde, B.Sc., Ana Pavic, M.D., Jihane Romanos, Ph.D., Els Stoopman, Vincenzo Villanacci, M.D., Ph.D., Ciska Wijmenga, Ph.D., Ricardo Troncone, M.D., Ph.D., and M. Luisa Mearin, M.D., Ph.D.

Cumulative Incidence of Celiac Disease.

A  All Children

No. of Events/No. at Risk
Gluten group 475 0/440 11/416 14/350 13/214 5/92
Placebo group 469 0/444 8/417 11/356 8/222 5/96

B  Girls

No. of Events/No. at Risk
Gluten group 228 0/213 7/199 11/165 9/99 4/32
Placebo group 226 0/209 4/196 7/170 4/109 0/51

C  Boys

No. of Events/No. at Risk
Gluten group 247 0/227 4/217 3/185 4/115 1/60
Placebo group 243 0/235 4/221 4/184 4/133 5/45
Did PreventCD test the wrong hypothesis?....

- 200 mg of vital wheat gluten mixed with 1.8 g of lactose (equivalent to 100 mg of immunologically active gluten)
- given daily for 8 weeks starting at 16 weeks of age
- All families were advised to gradually introduce gluten into the diet of their child after the 8-week intervention period (mg/day: 250, 500, 1000 and 1500 at months 6, 7, 8 and 9, respectively), using regular food products
Did PreventCD test the wrong hypothesis?....

- EAT study – 2 Weetabix per week
- Each Weetabix is ~2g of wheat protein
- Gluten is ~80% of wheat
- EAT infants having 1.6g of gluten
- Almost 10 times the dose that PreventCD used
- And a dose that PreventCD participants were asked to reach no sooner than 9 months of age...
KEEP CALM AND CURE CELIAC DISEASE
Preventing Food Allergy in Infancy — Early Consumption or Avoidance?

Gary W.K. Wong, M.D.

So feed your children and hope that they will eat.
An opinion poll....

1. Infants should introduce allergenic foods into their diet early?
   A. Yes
   B. No
An opinion poll....

2. When should infants introduce allergenic foods? *(How early is early.....?)*

A. From 4 months
B. From 6 months
C. By one year of age
D. Shouldn’t offer any age by which infants should introduced allergenic foods (i.e. it is entirely up to the individual family)
E. Not before six months of age...
An opinion poll....

3. What allergenic foods should they introduce early?
   A. Peanut
   B. Peanut, Egg, Wheat, Sesame, Cow’ milk and Fish
   C. Peanut & Egg
   D. All nuts...
   E. All allergenic foods...
   F. Some other permutation of allergenic foods...
An opinion poll....

4. Should infants be screened before introducing allergenic foods?
   A. No
   B. Yes – high risk infants
   C. Yes – all infants
An opinion poll....

5. How do you define a high risk infant?
A. Egg allergy
B. Significant egg sensitization and/or egg allergy
C. Significant eczema
D. Any eczema
E. Family history of atopy
F. Some other definition...
Research Fellow/Study Manager
Dr Kirsty Logan

Dieticians
Ms Bunmi Raji
Ms Anna Tseng
Ms Sarah Nesbeth
Ms Charlotte Stedman

Clinicians
Dr Michael Perkin (Co-PI)
Professor Lack (PI)
Dr Tom Marrs
Dr Carsten Flohr

Data Manager
Ms Joanna Craven

Research nurses
Ms Louise Young
Ms Mary DeSouza
Mrs Vicky Offord
Mr Jason Cullen
Ms Katherine Taylor

Recruiters/Administrators
Ms Sharon Tonner
Ms Emily Banks
Ms Yasmin Kahnum
Dr Rachel Babic
Dr Ben Stockwell
Ms Erin Thompson
Ms Lorna Wheatley

Laboratory staff
Dr Victor Turcanu
Mr Alick Stephens
Ms Asha Sudra
Ms Ewa Pietraszewicz

House dust project
Dr Helen Brough
Ms Kerry Richards

Phlebotomist
Ms Devi Patkunam

External experts
Ms Kate Grimshaw
Ms Rebecca Knibb

Trial Steering Committee
Professor Graham Roberts (chair)
Professor David Strachan (vice chair)
Dr Mary Fewtrell
Professor Christine Edwards
Mr David Reading
Professor Ian Kimber
Professor Janet Peacock
Dr Salma Ayis

Food Standards Agency
Dr Joelle Buck
Ms Sarah Hardy
Miss Elizabeth Kendall
Ms Shuhana Begum

Coverage support
Ms Gemma Deutsch
Dr George du Toit
Do you want to ask a question after a speaker's presentation?

- Can you think of a question? No
  - Could you write your question on Twitter (in 140 characters)?
    - No
    - NOT A QUESTION
      - It's a speech. Rephrase and retry.
    - Yes
      - NOT A QUESTION
        - You're just showing off
  - Yes
    - NOT A QUESTION
      - You're just showing off
    - Does the question involve you pointing out the results of your own study?
      - Yes
        - NOT A QUESTION
          - You're just showing off
        - Statistically there is a 95% probability that you missed the answer to the question when you were asleep/outside
      - No
        - Are you about to start the question with "In my experience..."?
          - Yes
            - SURPRISINGLY no-one came to hear about your experience. They want to hear from the speaker. If they wanted to hear about your experience you would BE the speaker.
          - No
            - Are you related to the speaker, specifically are you their spouse?
              - Yes
                - This is a highly RISKY strategy. The outcome is uncertain and may be painful.
              - No
                - Did the person next to you suggest the question?
                  - Yes
                    - If they know that it's too SILLY to ask then so should you.
                  - No
                    - Are you just filling an embarrassing silence?
                      - Yes
                        - Count to 30, someone else will choose to sound DAFT.
                      - No
                        - Do you still want to ask that question?
                          - Yes
                            - Please put your hand up, wait for the microphone and share the love.
                          - No
                            - Do NOT speak