When and how should oral immunotherapy for food allergy become daily clinical practice?

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University of Manchester, University of Athens
## Disclosures

<table>
<thead>
<tr>
<th>Category</th>
<th>Companies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Support</td>
<td>Nestle, Nutricia, MSD, Menarini</td>
</tr>
<tr>
<td>Speaker</td>
<td>Novartis, MEDA, Omega, HAL, Nutricia, Menarini</td>
</tr>
<tr>
<td>Advisory Boards</td>
<td>Abbvie, ALK, Novartis, Chiesi, Biomay, HAL, Nutricia, MEDA, Menarini, Wockhardt</td>
</tr>
</tbody>
</table>
Food allergy – Epidemiology & Impact

Allergy to egg in a European cohort - UK leading

Allergy to peanut in the UK - increasing

Xepapadaki et al, Allergy 2016;71:350-7

Impact on Quality of Life and more

• Reduced general health perception, emotional impact, limitation of family activities
• Pronounced effect in severe cases

Sicherer et al Ann All Asthma Immunol 2001;87:461-4

• May lead to nutritional deficiencies


• Frequent adverse reactions
Current food allergy management strategy

• Identification of offending food
• Management plan
  • Avoidance
  • Treatment of reactions
• Education for the above
Less than what patients or physicians hope for!
Need for more!
Allergen Immunotherapy – a >100-year old tool

PROPHYLACTIC INOCULATION AGAINST HAY FEVER.

BY L. NOON, B.C. CANTAB., F.R.C.S. ENG.
(From the Laboratory of the Department for Therapeutic Inoculation, St. Mary’s Hospital.)

Hay fever is a form of recurrent catarrh affecting certain individuals during the months of May, June, and July. It is caused by a soluble toxin found in the pollen of grasses.

Lancet, 1911
Efficacy & safety of immunotherapy

- Used worldwide
- Effectiveness very well established for several allergens
- Safety acceptable, considerably improved

Matricardi et al, JACI 2011;128:791
So, why don’t we use classical immunotherapy for food allergy?
Early injection immunotherapy promising, but with unacceptable level of adverse events

- 11 patients (14-43 years, moderate-severe allergy to peanut)
- Rush injection immunotherapy protocol with defatted peanut flour
- Study terminated when a placebo patient received an active peanut full dose and died
- Improved challenge scores in 3 active patients
- High level of systemic reactions (13%)

Strategies for improving food immunotherapy

**Food allergen modification**
- Denaturation by extensive heating
- Molecular alteration of IgE-binding epitopes

**Alternative antigen delivery methods**
- Allergen incorporation into nanoparticles
- Epicutaneous immunotherapy (EPIT)

**Adjunct treatment with immunomodulatory agents**
- Anti-IgE therapy
- FAHF-2
- T\textsubscript{H}1 adjuvants
- Monoclonal antibody blockade of T\textsubscript{H}2-promoting factors

Moran TP et al. *Curr Opin Immunol* 2013
Which food?
The natural history of food allergy varies
# Home-made oral immunotherapy: the ‘ladders’

## Milk ladder

<table>
<thead>
<tr>
<th>Stage</th>
<th>Products containing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Small crumb of a biscuit containing &lt;1 g of whole cow’s milk protein per biscuit. Build up to 1 biscuit over 5 weeks as tolerated. This will include shop bought biscuits that contain cow’s milk with protein content listed as &lt; 1 g of protein per biscuit.</td>
<td></td>
</tr>
<tr>
<td>2. Stage 2: Other baked products containing cow’s milk protein, for example biscuits, cakes, muffin, waffles, scotch pancakes.</td>
<td></td>
</tr>
<tr>
<td>3. Stage 3: Products containing cooked cheese or whole cow’s milk as a heated ingredient, for example custard, cheese sauce, pizza, rice pudding.</td>
<td></td>
</tr>
<tr>
<td>4. Stage 4: Uncooked cheese or uncooked non-yogurt desserts, for example ice cream or mousse.</td>
<td></td>
</tr>
</tbody>
</table>

**Cow’s milk**
- UHT milk followed by pasteurised milk and then unpasteurised milk (if this form is preferred by the family).

**NOTES:**
1. Affected individuals and their families are advised to proceed with caution as the classification in a ‘milk ladder’ of milk-containing foods from low to high allergenicity is imperfect and may thus result in a bigger than anticipated step up in exposure.
2. At all stages start with a small amount and gradually increase.
3. Each individual product is introduced in Stage 3. It is to be introduced in trace amounts first as they have more milk protein and a lower degree of heat treatment or protein denaturation. There is also variability in milk protein between products.
4. If a reaction occurs, the culprit food should be stopped and reintroduction should be continued with food from a lower stage in smaller amounts.

**DEVELOPMENT OF MILK LADDER** (rationale for classification)
1. The ‘milk ladder’ considered factors that influence the allergenic potential of cow’s milk food stuffs in their stage classification: volume or quantity, effect of heating (including duration and degree of heat), and wheat matrix effect [135].
2. Classification:
   - **Stage 1:** small quantity, baked, and matrix.
   - **Stage 2:** larger quantity, baked and matrix OR traces without matrix or with minimal heating.
   - **Stage 3:** larger quantity, less heating, and less matrix OR all with some degree of protein change with heating or manufacturing.
   - **Stage 4:** fresh milk products.

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## Egg ladder

**Cracked eggshell**
- Utensils with raw case mixture or raw egg

**Processed meat/burger/sausage**
- Teacakes®, Milly’s Way®, Mars®, Snickers®

**Crème Egg®, Chobani®**
- Hollandaise, Holland and Tarter sauces

**Biscuit**
- Scottie & Mince

**Mayonnaise/salt cream**
- Mayonnaise

**Marshmallow**
- Meringue/fresh ice-cream

**Crème caramel & Crème Brûlée**
- Scrambled eggs

**Omelette**
- French Toast

**Quiche**
- Yorkshire pudding

**Fried/hard-boiled egg**
- Coated batter/tempura/breaded

**Dried & fresh egg pasta & egg noodle**
- Pancake

**2. LIGHTLY COOKED**

**Waffle biscuit**
- Bouchier® & Lady’s finger®

**Baked sponge/muffin/scone & biscuits**

**1. WELL COOKED**

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Luyt et al CEA 2014:44:642

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IFAN 2015
Regular feeding with baked egg in children with egg allergy

<table>
<thead>
<tr>
<th>Age (mo)</th>
<th>No. of patients</th>
<th>IgE f1 (IU/mL)</th>
<th>SPTs (mm)</th>
<th>Challenge outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>Allergic</td>
<td>24 (9)</td>
<td>51</td>
<td>3 (13.42)</td>
<td>7 (3.5)</td>
</tr>
<tr>
<td>Sensitized</td>
<td>24 (18)</td>
<td>36</td>
<td>4.62 (8.04)</td>
<td>7 (4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td>Allergic</td>
<td>24 (9)</td>
<td>51</td>
<td>3.28 (3.83)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Sensitized</td>
<td>24 (18)</td>
<td>36</td>
<td>7.19 (9.9)</td>
<td>8 (2)</td>
</tr>
</tbody>
</table>

6 months daily intake. Tolerance 95% (expected 60%-70%)

Konstantinou et al. JACI 2008
Oral immunotherapy for food allergy: The evidence
Effectiveness of Oral Immunotherapy (OIT)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Control</th>
<th>Experimental</th>
<th>Weight (%)</th>
<th>RR</th>
<th>95 % CI</th>
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</thead>
<tbody>
<tr>
<td>Burks 2012</td>
<td>0</td>
<td>22</td>
<td>4.1</td>
<td>0.06</td>
<td>0.00, 0.88</td>
</tr>
<tr>
<td>Caminiti 2009</td>
<td>0</td>
<td>2</td>
<td>4.2</td>
<td>0.20</td>
<td>0.01, 2.98</td>
</tr>
<tr>
<td>Lacono 2013</td>
<td>0</td>
<td>9</td>
<td>4.0</td>
<td>0.05</td>
<td>0.00, 0.80</td>
</tr>
<tr>
<td>Longo 2008</td>
<td>0</td>
<td>11</td>
<td>4.1</td>
<td>0.04</td>
<td>0.00, 0.71</td>
</tr>
<tr>
<td>Mansouri 2007</td>
<td>0</td>
<td>18</td>
<td>4.2</td>
<td>0.04</td>
<td>0.00, 0.62</td>
</tr>
<tr>
<td>Martorell 2011</td>
<td>7</td>
<td>27</td>
<td>11.1</td>
<td>0.26</td>
<td>0.13, 0.50</td>
</tr>
<tr>
<td>Meglio 2013</td>
<td>2</td>
<td>8</td>
<td>8.6</td>
<td>0.25</td>
<td>0.07, 0.90</td>
</tr>
<tr>
<td>Morisset 2007</td>
<td>18</td>
<td>24</td>
<td>12.0</td>
<td>0.66</td>
<td>0.47, 0.92</td>
</tr>
<tr>
<td>Morisset 2007</td>
<td>18</td>
<td>34</td>
<td>11.9</td>
<td>0.69</td>
<td>0.47, 1.02</td>
</tr>
<tr>
<td>Pajno 2010</td>
<td>0</td>
<td>10</td>
<td>4.1</td>
<td>0.05</td>
<td>0.00, 0.75</td>
</tr>
<tr>
<td>Patriarca 1998</td>
<td>0</td>
<td>12</td>
<td>4.2</td>
<td>0.05</td>
<td>0.00, 0.83</td>
</tr>
<tr>
<td>Patriarca 2003</td>
<td>0</td>
<td>15</td>
<td>4.2</td>
<td>0.04</td>
<td>0.00, 0.60</td>
</tr>
<tr>
<td>Patriarca 2007</td>
<td>0</td>
<td>31</td>
<td>4.2</td>
<td>0.05</td>
<td>0.00, 0.80</td>
</tr>
<tr>
<td>Skripak 2008</td>
<td>0</td>
<td>12</td>
<td>4.2</td>
<td>0.07</td>
<td>0.00, 1.03</td>
</tr>
<tr>
<td>Staden 2007</td>
<td>7</td>
<td>9</td>
<td>10.6</td>
<td>0.96</td>
<td>0.43, 2.15</td>
</tr>
<tr>
<td>Varshney 2011</td>
<td>0</td>
<td>19</td>
<td>4.2</td>
<td>0.06</td>
<td>0.00, 0.91</td>
</tr>
</tbody>
</table>

Total (95 % CI) 270  404  100.0  0.19  0.09, 0.37

Total events 52  290

Heterogeneity: $I^2 = 99.3$%

Test for overall effect: $z = 4.80$ (P < 0.00001)

Risk ratios (RR) of persisting food allergy as assessed by double-blind placebo-controlled food challenge in oral immunotherapy vs. controls.
• 23 children (3-14 years), highly sensitised (median 95kU/L)
• Initial rush protocol (7 days) achieved in only 1/23
• Long-term build up achieved in 14/23 after 7 months
  • 0.5g peanut with 20% increases every 2 weeks
• Maintenance 2 months, then evaluate outcome
Significant increase in tolerated dose with not too many adverse reactions
A randomized controlled study of peanut oral immunotherapy: Clinical desensitization and modulation of the allergic response

Pooja Varshney, MD, a Stacie M. Jones, MD, c Amy M. Scurlock, MD, c Tamara T. Perry, MD, c Alex Kemper, MD, MPH, MS, b Pamela Steele, CPNP, a Anne Hiegel, RN, o Janet Kamilaris, RN, a Suzanne Carlisle, RN, o Xiaohong Yue, MS, a Mike Kulis, PhD, a Laurent Pons, PhD, a Brian Vickery, MD, a and A. Wesley Burks, MD a Durham, NC, and Little Rock, Ark

• 28 children (1-16 years), highly sensitised (sIgE 106kU/)
• 3-phase protocol: rush (1 day), build-up (44 weeks), maintenance (4 weeks)
• Partially defatted peanut flour, up to 4 gr (~16 peanut equivalent)
• 3 drop-outs, 16 active, 9 placebo
Efficacy

Safety

• Initial day: 9/19 of active required treatment (2 adrenaline)

• Build-up: symptoms in 1.2% of 407 doses

Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial

Katherine Anagnostou, Sabita Islam, Yvonne King, Loraine Foley, Laura Pasea, Simon Bond, Chris Palmer, John Deighton, Pamela Ewan, Andrew Clark

- 85 children, 7-16 years, sIgE
- 26 weeks of OIT vs avoidance (open label)
- 2-phase with 2 week increments
- Maintenance of 0.8 gr peanut flour
- Subsequent OIT for the avoidance group

62% of OIT could eat 1.4gr of peanut after 6 months

Efficacy of egg OIT

A DBPC randomised trial on 55 children, 5-11 years old, with egg allergy

<table>
<thead>
<tr>
<th>Table 2. Success Rates on Oral Food Challenge.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Challenge</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Desensitization, 5 g at 10 mo</td>
</tr>
<tr>
<td>Desensitization, 10 g at 22 mo</td>
</tr>
<tr>
<td>Sustained unresponsiveness at 24 mo‡</td>
</tr>
</tbody>
</table>

Burks W et al NEJM 2012;367:233
Milk Oral vs. Sublingual IT

Increased efficacy, less safety

### TABLE II. Clinical outcomes

<table>
<thead>
<tr>
<th>Group</th>
<th>SLIT/SLIT</th>
<th>SLIT/OITB</th>
<th>SLIT/OITA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrew</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Failed full desensitization challenge (T5)</td>
<td>9</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Failed challenge 1 wk off therapy (T6)</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Failed challenge 6 wk off therapy (T7)</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td><strong>Considered tolerant</strong></td>
<td><strong>1</strong></td>
<td><strong>3</strong></td>
<td><strong>5</strong></td>
</tr>
<tr>
<td>Total no.</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

### TABLE III. Symptoms with dosing

<table>
<thead>
<tr>
<th>Type of dose (no. of doses)</th>
<th>Total</th>
<th>Oral</th>
<th>GI</th>
<th>Skin</th>
<th>Upper</th>
<th>Lower</th>
<th>Multisystem</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLIT escalation (2021)</td>
<td>30.28%</td>
<td>26.82%</td>
<td>2.97%</td>
<td>2.23%</td>
<td>0.59%</td>
<td>0.45%</td>
<td>0.10%</td>
</tr>
<tr>
<td>SLIT maintenance (4205)</td>
<td>28.25%</td>
<td>27.99%</td>
<td>0.38%</td>
<td>0.10%</td>
<td>0.07%</td>
<td>0.02%</td>
<td>0.02%</td>
</tr>
<tr>
<td>Initial OIT escalation (1842)</td>
<td>36.21%</td>
<td>29.64%</td>
<td>7.17%</td>
<td>1.79%</td>
<td>1.41%</td>
<td>2.17%</td>
<td>0.71%</td>
</tr>
<tr>
<td>OITB escalation and maintenance (1230)</td>
<td>30.41%</td>
<td>24.07%</td>
<td>7.97%</td>
<td>0.73%</td>
<td>1.30%</td>
<td>2.28%</td>
<td>0.08%</td>
</tr>
<tr>
<td>OITA escalation and maintenance (1396)</td>
<td>26.72%</td>
<td>21.99%</td>
<td>3.15%</td>
<td>1.72%</td>
<td>2.79%</td>
<td>1.00%</td>
<td>0.43%</td>
</tr>
<tr>
<td>Post dose-adjustment maintenance (6029)</td>
<td>16.42%</td>
<td>12.71%</td>
<td>2.82%</td>
<td>1.68%</td>
<td>0.53%</td>
<td>1.01%</td>
<td>0.68%</td>
</tr>
</tbody>
</table>

Epinephrine was used for 2 SLIT doses and 4 OIT doses.
GI, Gastrointestinal; Lower, lower respiratory tract; Upper, upper respiratory tract.

How can we optimise for the clinic?

• Choice of patient
• Optimal schedule
• Very well trained patients/parents
• Very close monitoring
Choice of patient

• Severity of reaction
• Sensitisation level/profile
• Comorbidities (mainly asthma)
• Collaboration/compliance
• Other circumstances

• Irony: chances of success inverse to need!
Typical Oral Immunotherapy (OIT) approach

Typical OIT approach includes:
- **Screening and Baseline Challenge**
- **Initial dose escalation day** (max 10-25 mg)
- **Dose Build-up**: Daily dosing with observed dose increases q1-2 weeks over 3-9 months
- **Home Maintenance**: x months – years (doses 500 mg to 4000 mg)
  - 6-12 Months
  - 18+ Months
- **Repeat Challenges** (5-10 grams)
  - Many studies also include a final challenge off therapy to distinguish transient desensitization from sustained unresponsiveness

Wood R. JACI 2016;137:973–982
Milk-OIT population - Athens

All on free CM diet

1 dropped out because of EoE
Oral food desensitization: the BACH proposal for the very gradual reintroduction of a food

<table>
<thead>
<tr>
<th>Number of steps by which we want to double the dose (n)</th>
<th>$\frac{n}{2}$th root of 2</th>
<th>Increment factor between doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\sqrt{2}$</td>
<td>2.000000</td>
</tr>
<tr>
<td>2</td>
<td>$\frac{2}{2}$</td>
<td>1.414214</td>
</tr>
<tr>
<td>3</td>
<td>$\frac{3}{2}$</td>
<td>1.259921</td>
</tr>
<tr>
<td>4</td>
<td>$\frac{4}{2}$</td>
<td>1.189207</td>
</tr>
<tr>
<td>5</td>
<td>$\frac{5}{2}$</td>
<td>1.149696</td>
</tr>
<tr>
<td>6</td>
<td>$\frac{6}{2}$</td>
<td>1.122462</td>
</tr>
<tr>
<td>7</td>
<td>$\frac{7}{2}$</td>
<td>1.104900</td>
</tr>
<tr>
<td>8</td>
<td>$\frac{8}{2}$</td>
<td>1.090508</td>
</tr>
<tr>
<td>9</td>
<td>$\frac{9}{2}$</td>
<td>1.080060</td>
</tr>
<tr>
<td>10</td>
<td>$\frac{10}{2}$</td>
<td>1.071773</td>
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<td>11</td>
<td>$\frac{11}{2}$</td>
<td>1.065041</td>
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<td>12</td>
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<td>1.059463</td>
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<td>13</td>
<td>$\frac{13}{2}$</td>
<td>1.054766</td>
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<td>$\frac{14}{2}$</td>
<td>1.050757</td>
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<td>15</td>
<td>$\frac{15}{2}$</td>
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<td>17</td>
<td>$\frac{17}{2}$</td>
<td>1.041616</td>
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<td>18</td>
<td>$\frac{18}{2}$</td>
<td>1.039259</td>
</tr>
<tr>
<td>19</td>
<td>$\frac{19}{2}$</td>
<td>1.037155</td>
</tr>
<tr>
<td>20</td>
<td>$\frac{20}{2}$</td>
<td>1.035865</td>
</tr>
</tbody>
</table>

(a) MI of cow's milk

Increment between doses (%)

(b) MI of cow's milk

Increment between doses (%)

Training

• Early recognition of signs
• Comfortable with autoinjector use
• Understanding of additional risk factors
Minimise risk of reactions

• Action plan for cases of infection or other important stressors (e.g. strenuous exercise)
  • Reduction of dose

• Timing

• Use of antihistamines?
Close monitoring

• Increases patient’s confidence and safety
• Access to helpline
• Preparedness of clinical services
OIT : Research or Clinical procedure?

• Can be performed as a clinical procedure only in highly specialised centres*

* EAACI Food Allergy Guidelines
Already happening

http://www.peanut.cuh.org.uk
Still, **a lot** of research is needed (and some is happening)
e.g. use modified food that is less allergenic (hypoallergens)

Immune shift, but not significant clinical effect in 6 months
e.g. new injection IT to fish

SPT change

Papadopoulos et al. EAACI 2017
e.g. immunotherapy through the skin

In clinical trials for peanut, milk, egg
Conclusions

• There is a pressing unmet need for better management of food allergy
• We have the solution, in principle
• Careful steps should be taken to bring this into daily practice, with safety
  • Increased personal attention and patient monitoring, for one
    • Resources needed
Conclusions

• Highly specialised centres are taking the lead in the translation
  • A major challenge is logistics/financing
  • Safety is never underestimated!

• The value of these approaches needs to be appreciated by the NHS

• Further research both towards optimisation and improved alternatives is mandatory
First, do not harm

“Ωφελέειν ἢ μη βλάπτειν”
- Ἰπποκράτης