Baked Milk and Egg OFC
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Effect of Heating on Milk Proteins

Majority of children outgrow milk or egg within first 6 years of life
- children who "outgrow" milk / egg allergy have IgE directed
  primarily at conformational epitopes
Baked studies inclusion/exclusion

- **Inclusion**: IgE-mediated food allergy to milk/egg
- **Exclusion**:
  - H/o anaphylaxis to baked products containing milk/egg in the past 12 months
  - EoE, FPIES
  - Unstable allergic disorders (asthma, AD)
  - Second baked milk study: milk-IgE>35 kUa/L

Baked milk: challenge foods

One day, 2 foods; a muffin and a waffle that each contained 1.3 g of milk protein (equivalent 1/6 cup milk) were ingested.

- **Muffin** was baked at 350°F for 30 minutes in an oven
- **Waffle** (<0.625 inches thick to ensure thorough heating) was cooked in a waffle maker at approximately 500°F for 3 minutes.
- Each food was administered in 4 equal portions over 1 hour. The muffin was served first; if no symptoms were observed, 2 hours later, the waffle was served.
"Baked Milk" Study

Re-challenge

BM-Reactive → Strict avoidance for 12 months

BM OFC
N=100

BM-Tolerant
N=77

Not challenged to UHM due to highly predictive test results;

BM Diet*

UHM OFC
N=43

UHM Reactive
N=34

UHM-Tolerant
N=9

3 mo

48 mo

-Mean age: 6.7 yrs; range: 2.6 – 17.3 yrs; 62% males
-No difference between groups: age, family hx, exclusive breast feeding, age of 1st rxn

*The subjects in the BM Diet group are followed every 6 months for up to 48 months or until become cow's milk-tolerant.

Changes in Milk-specific PST, IgE & IgG₄ in Baked Milk-Tolerant Subjects

Milk PST decreases and casein-specific IgG₄ increases

[Graphs showing changes over time]
Baked Milk Follow Up

- 88 children (median age 6.6 years, range 2.1–17.3 years) followed over a median of 37 months (range 8-75 months), were challenged to progressively less heated forms of milk at varying intervals (range 6-54 months).

- 60 comparison subjects matched for age, sex and baseline CM-IgE

- Analysis:
  - Intention to treat (ITT): all subjects in the active group
  - Per protocol (PP): subjects who added baked milk to the diet

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Active ITT group, n=88
Failed initial BM challenge, n=23
  9% developed UHM tolerance

Passed initial BM challenge, n=65
60% added baked milk

Passed subsequent BM challenge, n=5

Active PP group, n=70

Comparison group, n=60
Natural history
22% developed UHM tolerance
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Kim J et al. JACI 2011
TIME TO UNHEATED MILK TOLERANCE:
ITT - ACTIVE VS. COMPARISON

Log-rank p-value comparing survival among ITT Active vs. Comparison groups is 0.0056.
*There is a significant difference in the time to developing UHM tolerance between ITT active patients and comparison patients.

<table>
<thead>
<tr>
<th>Hazard Ratio (95% CI) Comparing ITT Active – Comparison</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude</td>
<td>2.43 [1.25, 4.57]</td>
</tr>
<tr>
<td>Adjusted for sex, age at initial visit, and IGE</td>
<td>2.92 [1.47, 5.80]</td>
</tr>
</tbody>
</table>

TIME TO UNHEATED MILK TOLERANCE:
ITT - INITIAL BM TOLERANCE VS. INITIAL BM REACTION

<table>
<thead>
<tr>
<th>Hazard Ratio (95% CI) Comparing ITT HM Tolerant – HM Reactive</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude</td>
<td>10.95 [2.63, 45.53]</td>
</tr>
<tr>
<td>Adjusted for sex, age at initial visit, and IGE</td>
<td>7.62 [1.75, 33.14]</td>
</tr>
</tbody>
</table>
### Severity of Reactions During Oral Food Challenges

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Total (n=88)</th>
<th>Initially baked-milk tolerant (n=65)</th>
<th>Initially baked-milk reactive (n=23)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td># Challenges performed</td>
<td>172</td>
<td>154 (90%)</td>
<td>18 (10%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td># Failed (%)</td>
<td>58 (34%)</td>
<td>47 (31%)</td>
<td>11 (61%)</td>
<td>0.009</td>
</tr>
<tr>
<td># Treated with epinephrine (%)</td>
<td>8 (4.7%)</td>
<td>5 (3.2%)</td>
<td>3 (17%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

### Clinical Phenotypes of Milk Allergy

**Persistent / Severe**
- **Baked-milk reactivity ~20%**
- Less likely to "outgrow" milk allergy
- More severe reactions
- Most in need of effective therapy

**Mild / Transient**
- **Baked milk tolerance ~80%**
- Excellent chances of outgrowing milk allergy
- Mild reactions
- Introduction of baked-milk products into the diet changes similar to immunotherapy; ↑PST, ↔IgE & ↑IgG4 ["natural OIT"]
- Strict avoidance may account for delay in tolerance in children who have mild / transient milk allergy

New Baked Milk Diet Study is ongoing:
- start with muffin ➔ pizza ➔ rice pudding ➔ milk
- randomized to advance every 6 or 12 months
- Strict avoidance of all milk for 1 month following 3 months of unrestricted milk diet
BAKED EGG

Challenge foods

- **Baked egg**: 1 day, 2 foods; a muffin and a waffle that each contained one third of an egg (approximately 2.2 g of egg protein) were ingested.
- **Muffin** was baked at 350°F for 30 minutes in an oven
- **Waffle** (<0.625 inches thick to ensure thorough heating) was cooked in a waffle maker at approximately 500°F for 3 minutes.
- Each food was administered in 4 equal portions over 1 hour. The muffin was served first; if no symptoms were observed, 2 hours later, the waffle was served.
- **Lightly cooked egg**: scrambled egg or French toast were administered over 1 hour (total dose, 1 egg or 6.5 g of egg protein), as per routine protocol
Baked egg study design

Mean age of 6.9 yrs
(range, 1.6–18.6 yrs)

Lemon-Mule, et al
JACI 2008

Long-term baked egg follow up

- 79 subjects (71% male) with a median age of 5.8 years (range, 1.6–15.8) and a median initial serum egg white-specific IgE level of 2.5 (range, 0.2-101) were followed for a median of 37.8 months (range, 7.6-69.7).

- Retrospective comparison egg-allergic subjects age-, sex- and IgE-matched with active subjects at the time of enrollment. The same inclusion and exclusions criteria were used, and none of the control subjects had tolerated or were ingesting baked egg at time of enrollment.

- Subjects in the comparison group continued strict egg avoidance (current standard of care). N=47

Leonard S, et al, JACI 2013
Outcomes of intent-to-treat and comparison groups

- Tolerated BE at baseline, n = 56 (71%)
- Per-Protocol Group, n = 70
- Tolerated Subsequent BE challenge, n = 14 (18%)
- Continues BE, n = 28 (36%)

Comparison Group, n = 47

Natural History

Baked egg tolerant vs. reactive at baseline

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Versus</th>
<th>BE tolerant vs. BE reactive</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular egg tolerant</td>
<td>Avoiding all egg or</td>
<td>BE tolerant vs. BE reactive</td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td>baked egg tolerant</td>
<td>intent-to-treat, OR (95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.7 (1.7-19.3)</td>
<td></td>
</tr>
<tr>
<td>Regular egg tolerant</td>
<td></td>
<td>BE tolerant vs. BE reactive per-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>protocol, OR (95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baked egg tolerant</td>
<td>3.1 (0.8-11.2)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

OR adjusted for age, sex at initial visit and baseline sex white-specific IgE