The Natural History of Food Allergy

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## Studies on the Natural History of Milk Allergy

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Age at DX</th>
<th>Duration of FU</th>
<th>IgE-mediated</th>
<th>Non-IgE-mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dannaeus</td>
<td>47</td>
<td>&lt; 20 m</td>
<td>6-48 m</td>
<td>29%</td>
<td>74%</td>
</tr>
<tr>
<td>Host</td>
<td>39</td>
<td>0-12 m</td>
<td>up to 3 yrs</td>
<td>76%</td>
<td>100%</td>
</tr>
<tr>
<td>Hill</td>
<td>47</td>
<td>3-66 m</td>
<td>6-39 m</td>
<td>40%</td>
<td>38%</td>
</tr>
<tr>
<td>Bishop</td>
<td>100</td>
<td>1-98 m</td>
<td>5 yrs</td>
<td>67%</td>
<td>86%</td>
</tr>
<tr>
<td>Hill</td>
<td>98</td>
<td>4-100 m</td>
<td>6-73 m</td>
<td>22%</td>
<td>59%</td>
</tr>
<tr>
<td>James</td>
<td>29</td>
<td>3-14 yrs</td>
<td>3 yrs</td>
<td>38%</td>
<td>NA</td>
</tr>
</tbody>
</table>
Studies on the Natural History of Milk Allergy

Saarinen et al JACI 2005

Fiocchi et al Ann AAI 2008
Development of Oral Tolerance to Cow's Milk

N=807
Med FU 5.5 yrs

Persistent CMA (%)

Age (y)

milk tolerant (MT)  
MT or cm-IgE < 3  
MT or cm-IgE < 15

Trend in CM-IgE Over Time by CMA Resolution Status

Persistent CMA  (n=1,651)

Resolved CMA  (n=847)

Skripak et al.  JACI 2007
Milk Tolerance is Predicted by Baseline and Peak Milk-IgE

Development of Oral Tolerance to CM by Peak CM-IgE

<table>
<thead>
<tr>
<th>milk-IgE (kU/L)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50</td>
<td>229</td>
</tr>
<tr>
<td>20 - 49.9</td>
<td>107</td>
</tr>
<tr>
<td>10 - 19.9</td>
<td>115</td>
</tr>
<tr>
<td>5 - 9.9</td>
<td>85</td>
</tr>
<tr>
<td>2 - 4.9</td>
<td>106</td>
</tr>
<tr>
<td>&lt;2</td>
<td>162</td>
</tr>
</tbody>
</table>

CoFAR Study on the Natural History of Food Allergy

• In 2005 – 2006 enrolled 512 infants with milk and / or egg allergy

• 3 – 15 months of age at enrollment
  • 293 with milk allergy
  • 213 with egg allergy

• Main objective to assess for the development of peanut allergy
The natural history of milk allergy in an observational cohort

Robert A. Wood, MD, a, Scott H. Sicherer, MD, b, Brian P. Vickery, MD, Stacie M. Jones, MD, Andrew H. Liu, MD, David M. Fleischer, MD, Alice K. Henning, MS, Lloyd Mayer, MD, A. Wesley Burks, MD, Alexander Grishin, PhD, Donald Stablein, PhD, and Hugh A. Sampson, MD  Baltimore and Rockville, Md, New York, NY, Chapel Hill, NC, Little Rock, Ark, and Denver, Colo

- N=293
- Milk allergy resolved in 52.6% at a median age of 63 months
CoFAR Natural History of Milk Allergy: Relationship to Baseline IgE
CoFAR Natural History of Milk Allergy: Relationship to Baseline Skin Test

![Graph showing the relationship between age and the probability of milk allergy based on baseline skin test results. The graph includes lines for different skin test (ST) readings: ST <5 mm, ST 5-10 mm, and ST >10 mm.](image)
CoFAR Natural History of Milk Allergy: Relationship to Baseline Atopic Dermatitis

![Graph showing the relationship between age and the probability of milk allergy based on baseline atopic dermatitis severity.

- **None - Mild**
- **Mod - Severe**

**Axes:**
- **Y-axis:** Probability of Milk Allergy (%)
- **X-axis:** Age (Mos)

**Legend:**
- Blue line: None/Mild
- Red line: Moderate/Severe
Composite Index to Predict Milk Natural History
(http://www.cofargroup.org)

IgE = 2, ST = 4 mm, no AD
IgE = 20, ST = 7 mm, no AD
IgE = 20, ST = 7 mm, mod AD
The Natural History of Egg Allergy

N=890
Med FU 5.0 yrs

Egg Tolerance is Predicted by Peak Egg-IgE

CoFAR Natural History of Egg Allergy

- N=213
- Egg allergy resolved in 49.3% at a median age of 72 months
CoFAR Natural History of Egg Allergy: Relationship to Baseline IgE

![Graph showing the relationship between baseline IgE levels and the probability of milk allergy over age.](image)

- **IgE < 2**
- **IgE 2-10**
- **IgE > 10**

(Mos)
CoFAR Natural History of Egg Allergy: Relationship to Baseline Skin Test

![Graph showing the relationship between age (months) and the probability of egg allergy, with different skin test (ST) results (≤5 mm and >10 mm).]
CoFAR Natural History of Egg Allergy: Relationship to Initial Presentation
Composite Index to Predict Egg Natural History

![Graph showing the probability of egg allergy resolution over age (months) for different patient characteristics.

- **Patient Characteristics**
  - **Egg IgE = 0.5, Skin Limited Reaction**
  - **Egg IgE = 10, Atopic Dermatitis Flare**
  - **Egg IgE = 10, Skin Limited Reaction**
  - **Egg IgE = 15, Systemic Reaction**
  - **Egg IgE = 5, Systemic Reaction**

The graph illustrates the likelihood of egg allergy resolution over time, with distinct lines for each patient characteristic.
Development of Tolerance Over Time

**Wheat**

Keet et al. Ann Allergy Asthma Immunol 2009

N = 103
Med FU 2.7 yrs

**Soy**

Savage et al. JACI 2010

N = 114
Med FU 3.9 yrs

- Wheat tolerant (WT)
- WT/wh-IgE <20 kU/L
- WT/wh-IgE <50 kU/L
Wheat Tolerance is Predicted by Peak Wheat-IgE

Keet et al. Annals Allergy Asthma Immunol 2009
Soy Tolerance is Predicted by Peak Soy IgE

Savage JACI 2009
The prognoses for the resolution of milk, egg, wheat, and soy allergy appear worse in recent studies than in earlier studies.

Whether these findings represent a true change in the natural history of these allergies is not clear.

For each food, specific IgE levels are most predictive of clinical outcome.

Other risk factors for persistent allergy are skin test size, atopic dermatitis, and reaction severity.

Patients and families, especially those with very high specific IgE levels, should be counseled accordingly.
The Natural History of Peanut Allergy

Background
• Peanut and tree nut allergies are less often outgrown
• Early studies suggested that they were never outgrown

Study design
• N = 223 patients
• 4 -18 yrs of age
• Clear diagnosis of peanut allergy
• Oral challenges offered if:
  • PN-IgE <20KU/L
  • no reaction in past year

Skolnick JACI 2001
The Natural History of Peanut Allergy

Results (Skolnick JACI 2001)

• 21.5% of children with a clear diagnosis of PN allergy were shown to have outgrown their allergy

• PN-IgE levels at diagnosis and at evaluation were the best predictors of outgrowing a peanut allergy

  • Only 2 patients with a PN RAST >20 kU/L at diagnosis were shown to have outgrown their PN allergy

  • Negative challenges in
    • 61% with a PN-IgE <5 kU/L
    • 67% with a PN-IgE <2 kU/L
    • 73% with a PN-IgE <0.35 kU/L

→ Peanut allergy less often outgrown but more often than previously thought, now shown ~20% in multiple studies
• Patients with peanut-IgE levels <5 or less were offered an OFC
• Those who passed were further evaluated by questionnaire to assess reintroduction of peanut into their diet
• 2 patients with initial peanut-IgE levels greater than 70 passed their challenge.
• Follow-up of those who passed in both studies showed that the majority of patients continued label reading and had infrequent/limited ingestion and aversion to peanut
• Two patients had suspected subsequent reactions to peanut after passing their challenge.
Children who outgrew peanut allergy were evaluated with questionnaires, skin tests, peanut-specific IgE levels, and OFCs.

68 patients were evaluated; 47 continued to tolerate peanut, of whom 34 ingested concentrated peanut products at least once per month and 13 ate peanut infrequently or in limited amounts but passed their OFC. The status of 18 patients was indeterminate because they ate peanut infrequently and declined to have a DBPCFC.

3 of 15 patients who consumed peanut infrequently or in limited amounts had recurrences, compared with no recurrences in the 23 patients who ate peanut frequently (P = .025). The recurrence rate was 7.9%.

Conclusion: Children who outgrow peanut allergy are at risk for recurrence, and this risk is significantly higher for patients who continue largely to avoid peanut after resolution of their allergy. On the basis of these findings, we now recommend that patients eat peanut frequently and carry epinephrine indefinitely until they have demonstrated ongoing peanut tolerance.
The Natural History of Persistent Peanut Allergy
(Newman et al Ann Allergy, Asthma Immunology 2012)

- 793 patients, 532 male, 261 female
- Median age at initial observation 1.5 years
- Median duration of follow-up 5.3 years
- Median initial P-IgE 27.5, median peak P-IgE 68.4
- We saw 714 exposures among 471 patients
  - Overall reaction rate 5.2% / year
  - Severe reactions 1.7% / year
Study of Patients with Persistent Peanut Allergy

N = 792 patients
N = 2491 PN-IgE measurements
Median Age at 1st obs = 1.5 years
Med FU duration = 5.3 yrs

Trend in Peanut IgE Levels Over Time

Newman et al Ann Allergy, Asthma Immunology 2012
Relationship of Peanut IgE to Reaction Severity with Accidental Exposure

Newman et al. *Ann Allergy, Asthma Immunology* 2012

P <0.001 for Trend
Relationship of Peanut IgE to Lower Respiratory Symptoms

Newman et al Ann Allergy, Asthma Immunology 2012

Peak P-IgE
P <0.001 for Trend
The natural history of tree nut allergy

David M. Fleischer, MD, Mary Kay Conover-Walker, MSN, RN, CRNP, Elizabeth C. Matsui, MD, and Robert A. Wood, MD Baltimore, Md  

- 278 patients with TN allergy
- 9% with a clear history of prior reaction outgrew their allergy
- 58% with TN IgE levels <5 and 63% with IgE <2 passed their challenge

JACI 2005
Natural History of Food Allergy Summary

- Assessment of food specific IgE has been the best predictor of the natural history of food allergy.
- The natural history of milk, egg, soy, and wheat allergy is still generally positive, although an important subset do have persistent disease.
- For patients with persistent peanut allergy:
  - The rates of accidental peanut exposures and severe reactions may be lower than 10 – 20 years ago.
  - While peanut IgE levels cannot be used to predict reaction severity in individual patients, higher levels are overall associated with more severe reactions.