Evolution of peanut allergy
Cause to cure

Roger Friedman M.D. Ohio Ent and Allergy Physicians
Overview

- Prevalence
- Possible causes
- Prevention
- Treatment
Peanut allergy epidemic

- Food allergy: up to 8% of children and 2% of adults
- Prevalence stats for US kids < 18 years old
  - Food allergy increased by 18% from 1997 to 2008
  - Prevalence of peanut allergy tripled (0.4% to 1.4%)
- Recent Australian study on 12 mo old infants:
  - Challenge-proven food allergy in 10%
  - 3% of infants allergic to peanut

Sicherer SH. Epidemiology of Food Allergy. J Allergy Clin Immunol. 2010
Causes/risk factors

- Genetics
  - Familial associations, HLA, specific genes
  - Male > female
  - Ethnicity: Asian or black > white

Sicherer SH. Epidemiology of Food Allergy. J Allergy Clin Immunol. 2010
Genetics

Table 4. Risk of Peanut Allergy in Siblings of a Peanut-Allergic Child

<table>
<thead>
<tr>
<th>Risk of Peanut Allergy in</th>
<th>Unadjusted Odds Ratio</th>
<th>95% CI</th>
<th>Adjusted Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any sibling</td>
<td>7.12</td>
<td>2.18–23.28</td>
<td>6.72*</td>
<td>2.04–22.12</td>
</tr>
<tr>
<td>Younger sibling†</td>
<td>9.08</td>
<td>1.63–50.40</td>
<td>11.76‡</td>
<td>2.46–56.27</td>
</tr>
<tr>
<td>Older sibling§</td>
<td>5.92</td>
<td>1.14–30.69</td>
<td>6.31*</td>
<td>1.20–33.23</td>
</tr>
</tbody>
</table>

CI = confidence interval.
*Adjusted for parental history of asthma.
†If index child had a peanut allergy, risk of peanut allergy in a younger sibling.
‡Adjusted for parental history of asthma and physician diagnosis of asthma in index child.
§If older sibling had a peanut allergy, risk of peanut allergy in the index child.

Causes/risk factors

- Vitamin D insufficiency
- Changes in dietary practices
  - dietary fat (reduced consumption of omega-3 FAs)
  - reduced consumption of antioxidants
  - increased antacid use (reducing allergen digestion)
  - obesity (being in an inflammatory state)

Sicherer SH. Epidemiology of Food Allergy. J Allergy Clin Immunol. 2010
Causes/risk factors

Atopic dermatitis

Causes/risk factors

Food, drug, insect sting allergy, and anaphylaxis

Distribution of peanut protein in the home environment

Peanut protein can be transferred into the environment through hands or saliva

unlikely to become airborne
Causes/risk factors

- Maternal consumption: prenatal & lactation
  - 1999 study → increased prenatal peanut consumption increased risk of pa in infant
  - 2009 → clarifies that maternal prenatal peanut consumption = surrogate marker for home environmental exposure
    - maternal consumption during pregnancy/lactation not to blame

Causes/risk factors

- Hygiene hypothesis (esp. important in 1st year life)
  - Microbiome
  - Pet ownership (dog > cat)

**Conclusions and clinical relevance**—The first year of life is the critical period during childhood when indoor exposure to dogs or cats influences sensitization to these animals.

- Farm living vs city - amish
- Hand- vs machine-washing dishes
  - Traditional cooking, buying food directly from farmers

Wegienka. Lifetime Dog and Cat Exposure and Dog and Cat Specific Sensitization at Age 18 Years. Clin Exp Allergy. 2011 July
Sicherer SH. Epidemiology of Food Allergy. J Allergy Clin Immunol. 2010
Causes/risk factors

- Hygiene hypothesis (esp. important in 1st year life)
  - Breastfeeding vs formula
  - Vaginal vs cesarean delivery
  - Medication use (ex antibiotics)

Sicherer SH. Epidemiology of Food Allergy. J Allergy Clin Immunol. 2010
Causes/risk factors

- Changes in timing of food introduction
  - Pre-2008 AAP guidelines to not introduce solid foods until after 6 mo
  - avoid nuts until age 3y
  - Fear of introducing peanut & other foods due to allergy epidemic

Sicherer SH. Epidemiology of Food Allergy. J Allergy Clin Immunol. 2010
### Causes/risk factors

**Changes in timing of food introduction**

- **Prevalence of Peanut Allergy in Children 4 - 18yrs**
  - United Kingdom: 1.85%
  - Israel: 0.17%
  - \( p < 0.001 \)

- **Peanut Protein Consumption 8 - 14 month**
  - United Kingdom: 0 g/week
  - Israel: 7.1 g/week
  - \( p < 0.001 \)

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Sicherer SH. Epidemiology of Food Allergy. J Allergy Clin Immunol. 2010
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*

Du Toit, et al. NEJM 2015

Video
Learning Early About Peanut (LEAP) Trial

- Enrolled 4 – 10 mo olds w/severe eczema and/or egg allergy
- Peanut SPT > 4mm excluded
- Split into 2 groups: neg SPT or +SPT groups
- Randomized:
  - 6 g Bamba peanut snack/per week (spread over at least 3 meals) until 5 y old
  - Strict peanut avoidance

Du Toit, et al. NEJM 2015
LEAP Trial

- OFC at 5y
- Babies eating peanut early = lower risk PN allergy

Du Toit, et al. NEJM 2015
**Peanut butter infant-feeding**

6 g peanut protein ≈ 1.2 Tbls peanut butter

6 g peanut protein ≈ 2 small 0.7 oz bags Bamba

In LEAP trial, 6 g peanut protein was divided over at least 3 meals during a week.
Expect new guidelines on timing of food introduction and evaluation of infants at high risk of developing peanut allergy
Clinical implications

- For infants at high risk for atopy
  - Ex. mod – severe eczema/pre-existing food allergy
  - PRIOR TO PEANUT EXPOSURE consider early allergy evaluation for peanut skin testing @ 3 – 4 mo olds
Clinical implications

- If peanut test > 4 mm (or set threshold), avoid?
  - 10.6% of screened infants that met other criteria
  - This group not studied; only way to know is by testing early

- If peanut test 1 - 4 mm, in-office food challenge
  - 12% in LEAP reacted to baseline peanut challenge

- If peanut test -, home challenge?
  - Of 272, 1 child reacted to baseline food challenge and was instructed to avoid peanut
Clinical implications

- For non-atopics, continue to introduce foods as early as 4 months or when it feels natural to do so
- Feed a diverse and healthy diet
Current treatment

- Strict avoidance
- Education
- Epinephrine preparedness
History of food allergy tx

THE LANCET
Volume 171, Issue 4410, 7 March 1908, Pages 716
Originally published as Volume 1, Issue 4410

A CASE OF EGG POISONING.
Alfred T. Schofield, M.D. BRUX., M.R.C.S. ENG., L.R.C.P. LOND.
Peanut allergy treatment RESEARCH

‘90s

Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract.

Nelson HS†, Lahr J, Rule R, Bock A, Leung D.

2000s

Immunotherapy
- +/−probiotics; +/−omalizumab
- Chinese herbal medication
Oral immunotherapy: since 2005 many OIT food trials, most robust desensitization for food allergy

Peanut OIT = prescribed peanut product swallowed daily up to 5 years

Dose-related adverse rxns occur

EoE reported 1.7 – 4%
Treatment research: OIT

**Figure 2.**
Estimated Risk of Specific Symptoms During the Build-up Phase. Symptoms were recorded during the buildup phase in four categories: upper respiratory, skin, abdominal, and chest.

Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy

39 participants enrolled for open-label peanut flour in vehicle or peanut-based food/candy daily up to 5y
24 (62%) attained desensitization
12 with sustained unresponsiveness 4 weeks after tx tolerated 5 g peanut protein (~20 pn/pb)
Treatment failures tolerated mean of 12 peanuts before reacting
Treatment research: OIT

12 subjects incorporated peanut into their diets ad lib and are being followed for sustained unresponsiveness

**FIG 2.** Food challenge results. Shown are the cumulative amounts of protein successfully ingested before onset of symptoms in TSs (*blue circles*) and TFs (*red circles*). Each circle represents 1 subject.
Treatment research: OIT

- DEVIL trial update: recently reported OIT in 9 – 36 mo old with peanut allergy (first to target preschoolers)

- 29 of 30 passed 5g challenge, the 1 that didn’t went through more tx and then passed rechallenge. 2 more still pending

- all AEs mild or moderate, none received epi

- Post-OIT recommended to ingest peanut regularly ad lib (at least 1g, 5 out of 7 days per week)
OIT clinical desensitization seems quite successful (4yrs out 15% sustained clinical unresponsiveness)
- most experiencing reactions
- Common reason for study drop-out
Common theme in food OIT = high rate of significant reactions, with 10% to 30% having severe reactions/refractory to oral desensitization

- Omalizumab = anti-IgE mAb (Xolair)

- OIT + omalizumab decreased AE by > 60%

- Possible add-on therapy to help those with high IgE to peanut get through OIT build-up phase

Schneider LC. A pilot study of omalizumab to facilitate rapid oral desensitization in high-risk peanut-allergic patients. The Journal of allergy and clinical immunology. 2013
Treatment research: OIT + probiotics

- Probiotics+OIT
- Idea of using bacterial adjuvant with OIT to enhance effectiveness came from studies of IT for allergic rhinitis

Treatment research: OIT + probiotics

Probiotics+OIT

62 children with peanut allergy

0  18  ≥18.5  21 months

T0  T1  T2  T3
Blood SPT  DBPCFC  Blood SPT  Blood SPT

2-week sustained unresponsiveness 82%

First published SLIT peanut trial 2011

- 1–11 year olds with h/o rxn to pn w/in 60 min of ingestion + pn sIgE > 7 kU/L
- Excluded h/o anaphylaxis to pn
- Randomized to 1 year pn SLIT (11) vs placebo (7)
- Daily dosing x 12 mo
- pn SLIT 2mg maintenance dose
## Sublingual immunotherapy for peanut allergy: Clinical and immunologic evidence of desensitization

<table>
<thead>
<tr>
<th>TABLE II. SLIT dosing safety</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Total doses</td>
</tr>
<tr>
<td>Reactions</td>
</tr>
<tr>
<td>Symptoms</td>
</tr>
<tr>
<td>Oropharyngeal</td>
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<tr>
<td>Skin</td>
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<tr>
<td>Upper respiratory</td>
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<tr>
<td>Treatment</td>
</tr>
<tr>
<td>Antihistamine</td>
</tr>
<tr>
<td>Epinephrine</td>
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<tr>
<td>Albuterol</td>
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</tbody>
</table>
Sublingual immunotherapy for peanut allergy: Clinical and immunologic evidence of desensitization

A

Peanut protein (mg)

0 500 1000 1500 2000 2500

Placebo SLIT

* 6 – 7 peanuts

Sublingual immunotherapy for peanut allergy: Long-term follow-up of a randomized multicenter trial

A. Wesley Burks, MD, a Robert A. Wood, MD, b Stacie M. Jones, MD, c Scott H. Sicherer, MD, d David M. Fleischer, MD, e Amy M. Scurluck, MD, f Brian P. Vickery, MD, g Andrew H. Liu, MD, h Alice K. Henning, MS, g Robert Lindblad, MD, g Peter Dawson, PhD, g Marshall Plaut, MD, h and Hugh A. Sampson, MD, d for the Consortium of Food Allergy Research (CoFAR) Chapel Hill, NC, Baltimore, Rockville, and Bethesda, MD, Little Rock, Ark, New York, NY, and Denver, Colo

- 2015 update of long-term pnSLIT data
- Multicenter cross over design
- Good safety profile (no epinephrine needed)
- Modest levels of desensitization
- 4 subjects (10.8%) had sustained unresponsiveness to pn 8 weeks after stopping therapy
- High rate participant withdrawal (daily dosing x 3 y)
Treatment research: EPIT

- EPIT
  - Sampson: US VIPES trial 221 subjects
  - EPIT (phase II) Viaskin showing promise – good compliance

CoFAR6

Consortium for Food Allergy Research 6

In October 2013, the Consortium for Food Allergy Research, or CoFAR, launched a multi-center, randomized, double-blind, placebo-controlled trial to evaluate Viaskin® Peanut in children and adults allergic to peanuts.

This trial is sponsored and funded by The National Institute of Allergy and Infectious Diseases, or NIAID, an institute of the United States National Institutes of Health and coordinated by Professor Hugh Sampson in New York. The trial is being conducted in five hospitals in the United States and includes 75 patients, both adults and children. The recruitment of CoFAR6 ended in July 2014. Subjects will be randomized to two doses of Viaskin® Peanut (100 µg and 250 µg) or matched placebo and will undergo a peanut protein oral food challenge at week 52. Expected to last four years, this trial will enable analysis of the effects of peanut desensitization with Viaskin® Peanut over an initial period of 12 months.

- Peanut Epicutaneous Immunotherapy - clinicaltrials.gov

AMP2015
Treatment research: EPIT
## Food IT comparisons

<table>
<thead>
<tr>
<th>Dose</th>
<th>Immune response</th>
<th>Adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>OIT</td>
<td>grams</td>
<td>Some eating pn ad lib</td>
</tr>
<tr>
<td>SLIT</td>
<td>mg</td>
<td>Tolerating a few peanuts before AE</td>
</tr>
<tr>
<td>EPIT</td>
<td>mcg</td>
<td>Tolerating a few peanuts before AE</td>
</tr>
</tbody>
</table>
Traditional Chinese Medicine has a long history of use/safety and is commonly used in the US, but had not been described in use for food allergy.

FAHF-2 is a formulation of Chinese herbs developed by doctors at Mount Sinai in NY for treating FA.

IND approved by FDA.

FAHF-2 protected peanut allergic mice from anaphylaxis, human trials ongoing.

Treatment research in planning

- ILIT: NCH & Berlin
- Novel adjuvants and recombinant extracts
  - CpG nano particles
  - TLR agonists
  - LAMP-vax DNA vaccine
  - Peptide based vaccines
Many risk factors driving the current peanut allergy epidemic – increased hygiene, delay of food intro

Early introduction of dietary peanut may decrease risk of peanut allergy in high risk infants (medically-observed)

Active treatment for peanut allergy is being researched, but is not ready for general clinical use