Food Allergy

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# Faculty disclosure

## FINANCIAL INTERESTS

I have disclosed below information about all organizations and commercial interests, other than my employer, from which I or a member of my immediate family or household receive remuneration in any amount (including consulting fees, grants, honoraria, investments, etc.) or invest money which may create or be perceived as a conflict of interest.

<table>
<thead>
<tr>
<th>Name of Organization</th>
<th>Nature of Relationship</th>
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<td>Allertein</td>
<td>Minority Stockholder</td>
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<td>Dannon Co. Probiotics</td>
<td>Advisory Board</td>
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<tr>
<td>ExploraMed</td>
<td>Consultant</td>
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<td>Intelliject</td>
<td>Consultant</td>
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<tr>
<td>Mast Cell, Inc.</td>
<td>Minority Stockholder</td>
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<td>McNeil Nutritionals</td>
<td>Consultant</td>
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<tr>
<td>Merck &amp; Co.</td>
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<td>Novartis</td>
<td>Consultant</td>
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<td>Pfizer</td>
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<td>Portola Pharmaceuticals, Inc.</td>
<td>Consultant</td>
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<td>Schering-Plough</td>
<td>Consultant</td>
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## RESEARCH INTERESTS

I have disclosed below information about all organizations which support research projects for which I or a member of my immediate family or household serve as an investigator.

<table>
<thead>
<tr>
<th>Name of Organization</th>
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<tbody>
<tr>
<td>National Institutes of Health</td>
<td>Grantee</td>
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<tr>
<td>Food Allergy Initiative</td>
<td>Grantee</td>
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<tr>
<td>National Peanut Board</td>
<td>Grantee</td>
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<tr>
<td>Wallace Foundation</td>
<td>Grantee</td>
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Guidelines for the Diagnosis and Management of Food Allergy in the United States

NIAID-Sponsored Expert Panel Report

Primary Authors
Joshua A. Boyce, MD; Amal Assa’ad, MD; A. Wesley Burks, MD; Stacie M. Jones, MD; Hugh A. Sampson, MD; Robert A. Wood, MD; Marshall Plaut, MD; Susan F. Cooper, MSc; Matthew J. Fenton, PhD

Journal of Allergy and Clinical Immunology – Volume 126, Issue 6, Supplement, Pages S1-S58, December 2010
Seventh-grader dies of food allergy at Chicago school

December 20, 2010 | By Noreen S. Ahmed-Ullah, Tribune reporter

Chicago Public Schools sent grief counselors to Edison Regional Gifted Center on Monday after the death of a seventh-grader who had an allergic reaction to food she ate at school.

Katalyn Carlson, 13, of the Sauganash neighborhood, was rushed from the Albany Park school at 4929 N. Sawyer Ave. to Swedish Covenant Hospital on Friday afternoon and transferred to Children’s Memorial Hospital, where she died of anaphylaxis, a severe reaction to a food allergy, according to Fire Department officials and the Cook County medical examiner’s office.

CPS officials said they were conducting an investigation and could not provide details. Two parents of other students said they had been told by school officials that Katalyn had a severe allergic reaction to peanut oil from Chinese food ordered from a restaurant for a class party.
Definition of adverse food reactions

- **Adverse food reaction** - generic term referring to any reaction following the ingestion of a food

- **Food allergy** - reaction presumed to be the result of an abnormal immunologic response following the ingestion of a food
  
  - Spectrum of IgE-, non-IgE, and mixed mechanisms

- **Food intolerance** - result of non-immunologic mechanism
  
  - Ex: Lactose Intolerance
Adverse reactions to food
Immunologic spectrum

**IgE-Mediated**
- Oral Allergy Syndrome
- Anaphylaxis
- Urticaria

**Non-IgE Mediated**
- Eosinophilic esophagitis
- Eosinophilic gastritis
- Eosinophilic gastroenteritis
- Atopic dermatitis
- Protein-induced enterocolitis
- Protein-induced enteropathy
- Eosinophilic proctitis
- Dermatitis herpetiformis

Sampson H. J Allergy Clin Immunol 2004;113:805-9,
What is the mechanism for the development of allergic disease and food allergy?

Vitamin D?
Microbiome?
Complementary feeding?
Diesel particle exhaust?
Food processing?
Genetics/Epigenetics?

Sensitization

Dendritic cells → Peanut-specific T cells → Th2 → B cells → Peanut-specific IgE → Mast cells

IL-4, IL-5, IL-13

Burks AW. Lancet 2008
What is the mechanism for the development of allergic disease and food allergy?

When – in utero?, epicutaneous?, oral?

Burks AW. Lancet 2008
What is the mechanism for the development of allergic disease and food allergy?

**Sensitization**
- Dendritic cells
- Peanut-specific T cells
- Th2
  - IL-4
  - IL-5
  - IL-13
- B cells
  - Peanut-specific IgE
- Mast cells
  - FcεRI

**Allergic reaction**
- **Systemic symptoms**
  - Airway obstruction
  - Hives
  - Low blood pressure
  - Arrhythmia
- **Local symptoms**
  - Itching
  - Swelling
  - Nausea
  - Vomiting
  - Cramping
  - Diarrhoea

- Peanut allergens
  - Histamines
  - Leukotrienes
  - Cytokines
  - Prostaglandins

*Burks AW. Lancet 2008*
Mast cell mediators

Lipid mediators
- Platelet-activating factor
- Leukotriene C4
- Prostaglandin D2

Cytokines
- Interleukin-4, -5, -6, -8, and -13
- TNF-α, GM-CSF, fibroblast growth factor, stem-cell factor

Other enzymes
- β-glucuronidase
- Arylsulfatase
- β-hexosaminidase

Histamine

Proteases
- Tryptase, carboxypeptidase, chymase, elastase, plasminogen activator, matrix metalloproteinase 9

Proteoglycans
- Heparin, chondroitin sulfate

IgE receptor
IgE

Mast cell
Most common foods to cause allergic reactions in children and adults

• Proteins are responsible for the allergy
  • Not the oil or fat or other substance in the food

• Industrialized countries
  • Children
    • Milk, egg, peanuts, tree nuts, fish, shellfish, wheat, soy
  • Adults
    • Peanuts, tree nuts, fish, shellfish
Patient approach with possible food allergy

- Food allergy - immune mediated
  - IgE versus non-IgE – important distinction
    - IgE - symptoms - skin, gastrointestinal, respiratory
    - Non-IgE – symptoms – generally GI only
  - Directed diagnostic testing

Burks 2008 Lancet 371:1538-1546
Laboratory tests for food allergy

• Diagnostic testing
  • **Skin prick tests**
    • Useful in IgE-mediated allergy
    • Highly reproducible
    • Positive predictive accuracy (overall)
      • ~ 50%
        • Peanut – 50%
        • Milk and egg - 40%
        • Soy – 20%
    • Negative predictive accuracy > 95%
    • Larger skin tests correlated with likelihood of reaction **NOT** severity of future reaction

Laboratory tests for food allergy

- **In vitro IgE (serum)**
  - CAP-FEIA (IgE to specific food)
  - Useful in IgE-mediated food allergy

- Represents sensitization, must correlate with clinical symptoms

- Panels/broad screening should NOT be done without supporting history because of high rate of clinically irrelevant ones

- Level of IgE does NOT correlate with severity of allergic reactions

- Component testing – Ara h 2 – interesting?
General principles
treatment of allergic disease

• General principles - treatment of allergic disease
  • Avoidance
  • Medical therapy
  • Immunotherapy - if first 2 are not effective


• Diagnosis, management plan and follow up
  • History and directed diagnosis tests

• Food Allergy Research and Education – FARE
  • FAAN and FAI – merged - foodallergy.org
Can we produce long-term tolerance in allergic diseases?

- What is the ultimate goal for therapy?
- Desensitization
  - In the context of food allergy –
    - tolerate more food on a food challenge while on treatment
    - would this provide protection from accidental food ingestion?
- Tolerance
  - Discontinuation of the therapy –
    - sustained long-lasting therapeutic benefits
- Current paradigm
  - Peripheral T cell tolerance - crucial for such benefits
Can we produce long-term tolerance in allergic diseases?

• **Clinical desensitization**
  • Tolerate the ingestion of more food while on treatment
    • greater than pre treatment
  • Oral immunotherapy - OIT
  • Sublingual immunotherapy – SLIT
Can we produce long-term tolerance in allergic diseases?

- **Clinical desensitization**
  - Tolerate the ingestion of more food while on treatment
    - greater than pre treatment

- **Clinical findings in 3 studies of food allergy**
  
  - CoFAR egg OIT - Jones, Burks, Sampson et al. NEJM July 2012
  
  - Peanut OIT — Varshney, Jones, Burks et al. JACI March 2011
  
  - CoFAR peanut SLIT — Fleischer, Burks, Sampson et al. JACI Jan 2013
Paradigm of food immunotherapy – OIT/SLIT

Allergy → Tolerance

Desensitization food challenge

- Build-up phase
- Maintenance phase
- Initial modified dose escalation
- Weekly/bi-weekly dose escalation

Nowak-Wegrzyn JACI March 2011
Can we produce long-term tolerance in allergic diseases?

- Clinical desensitization
  - Tolerate the ingestion of more food while on treatment
    - greater than pre treatment

- Clinical findings in 3 studies of food allergy
  - CoFAR egg OIT - Jones, Burks, Sampson et al NEJM July 2012
    - 55 subjects (> 5 yrs) – 40-egg OIT, 15-placebo
      - multicenter, blinded treatment, thru 48 weeks
  
  - Peanut OIT – Varshney, Jones, Burks et al. JACI March 2011
  
  - CoFAR Peanut SLIT – Fleischer, Burks, Sampson et al. JACI Jan 2013
Can we produce long-term tolerance in allergic diseases?
CoFAR3 - egg OIT trial - Objectives and study design

<table>
<thead>
<tr>
<th>Clinical desensitization</th>
<th>Placebo</th>
<th>Egg OIT</th>
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<tbody>
<tr>
<td>5 gm desensitization OFC (10 Month)*</td>
<td>0/15 (0%)</td>
<td>22/40 (55%)</td>
</tr>
<tr>
<td>Continue OIT 12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 gm desensitization OFC (22 Month)*</td>
<td>0/15 (0%)(n=1)</td>
<td>30/40 (75%)(n=34)</td>
</tr>
</tbody>
</table>

* P < .001

Jones, Burks, Sampson et al. NEJM July 2012
Can we produce long-term tolerance in allergic diseases?

- **Clinical desensitization**
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- **Clinical findings in 3 studies of food allergy**
  - **CoFAR egg OIT** - Jones, Burks, Sampson et al. NEJM July 2012
  - **Peanut OIT** - Varshney, Jones, Burks et al. JACI March 2011
    - 25 subjects – 16 - active treatment; 9 – placebo (3 withdrew)
  - **CoFAR peanut SLIT** - Fleischer, Burks, Sampson et al. JACI January 2013
Can we produce long-term tolerance in allergic diseases?

Peanut OIT – UNC/Arkansas studies

Peanut OFC – 12 months of treatment

Peanut OIT  Placebo

*P<.001

Varshney et al. JACI March 2011
Can we produce long-term tolerance in allergic diseases?

- **Clinical desensitization**
  - Tolerate the ingestion of more food while on treatment
    - greater than pre treatment

- **Clinical findings in 3 studies of food allergy**
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  - Peanut OIT – Varshney, Jones, Burks et al. JACI March 2011
  - CoFAR peanut SLIT – Fleischer, Burks, Sampson et al. JACI Jan 2013
    - 40 subjects – adolescents and young adults, peanut SLIT or placebo
Can we produce long-term tolerance in allergic diseases?

**CoFAR – Peanut SLIT**

40 subjects – adolescents and young adults, peanut SLIT or placebo

---

**OFC**

Successfully Consumed Dose

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Week 68 - compared to Week 44 (P = .05)
Week 68 – compared to Baseline (P = .009)

Fleischer et al. JACI January 2013
Paradigm of food immunotherapy – OIT/SLIT

Allergy → Tolerance

Desensitization food challenge

Dosing

Build-up phase → Maintenance phase → Discontinuation Tx.

Initial modified dose escalation → Weekly/bi-weekly dose escalation

Elimination diet
Paradigm of food immunotherapy – OIT/SLIT

Allergy → Tolerance

Build-up phase
- Initial modified dose escalation
- Weekly/bi-weekly dose escalation

Maintenance phase

Discontinuation Tx.
- elimination diet

Desensitization food challenge

Tolerance food challenge

How long?

Nowak-Wegrzyn JACI March 2011
Can we produce long-term tolerance in allergic diseases?

- **Clinical tolerance (sustained unresponsiveness)**
  - Tolerate the ingestion of food off treatment
  - how long is enough though? – 1 month, 4 months, 12 months?
Can we produce long-term tolerance in allergic diseases?

• Clinical tolerance (sustained unresponsiveness)
  • Tolerate the ingestion of food off treatment
    • how long is enough though? – 1 month, 4 months, 12 months?

• Clinical findings in 2 studies of food allergy

  – CoFAR egg OIT - Jones, Burks, Sampson et al NEJM July 2012

  – Peanut OIT – Varshney, Jones, Burks et al. JACI March 2011
Can we produce long-term tolerance in allergic diseases?

CoFAR3 egg OIT – sustained unresponsiveness (permanent tolerance?)

** Placebo vs. Egg OIT**

<table>
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<th>Treatment</th>
<th>Placebo</th>
<th>Egg OIT</th>
</tr>
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<tbody>
<tr>
<td>5 gm desensitization OFC (10 Month)*</td>
<td>0/15 (0%)</td>
<td>22/40 (55%)</td>
</tr>
<tr>
<td>10 gm desensitization OFC (22 Month)*</td>
<td>0/15 (0%)(n=1)</td>
<td>30/40 (75%)(n=34)</td>
</tr>
<tr>
<td>Off OIT 4 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 gm tolerance OFC (23 Month)**</td>
<td>0/15 (0%)(n=0)</td>
<td>11/40 (27.5%)(n=29)</td>
</tr>
<tr>
<td>Continue OIT 12 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 gm tolerance OFC (~36 Month)</td>
<td>N/A</td>
<td>18/40 (45%)(n=13)</td>
</tr>
</tbody>
</table>

* p<.001
** p=.025

Jones, Burks, Sampson et al. NEJM July 2012
Can we produce long-term tolerance in allergic diseases?

- **Clinical tolerance (sustained unresponsiveness)**
  - Tolerate the ingestion of food off treatment
  - how long is enough though? – 1 month, 4 months, 12 months?

- **Clinical findings in 2 studies of food allergy**

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  - Peanut OIT – Varshney, Jones, Burks et al. JACI March 2011
Can we produce long-term tolerance in allergic diseases?

Clinical results - UNC and Arkansas studies

• 19 subjects with peanut allergy completed an OIT protocol
  • Oral food challenge (OFC) 4 weeks after stopping OIT
    • evaluate clinical tolerance (sustained unresponsiveness)
  • Peanut OIT - range of 33-70 months
    • Rates of successful tolerance induction?
  • 11 subjects now eat peanut *ad lib* without symptoms
    • Intention-to-Treat Analysis: 11/27 (41%)
    • Per Protocol Analysis: 11/19 (58%)

Vickery, Jones, Burks et al
Can we produce long-term tolerance in allergic diseases?

Peanut IgE results

Baseline – PN-IgE

<table>
<thead>
<tr>
<th>Peanut IgE (kU/L)</th>
<th>Tolerant</th>
<th>Not–tolerant</th>
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<tbody>
<tr>
<td>500</td>
<td></td>
<td></td>
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<tr>
<td>400</td>
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<td>300</td>
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<tr>
<td>200</td>
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<tr>
<td>100</td>
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</table>

p=0.0057

PN-IgE

<table>
<thead>
<tr>
<th>Peanut-specific IgE (kU/L)</th>
<th>Tolerant</th>
<th>Not – tolerant</th>
</tr>
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<tbody>
<tr>
<td>600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>500</td>
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Mechanistic results - UNC and Arkansas peanut OIT studies

Vickery, Jones, Kulis, Burks et al 2013
Peanut OIT changes antigen-specific T regs and suppresses the $T_H2$ response to peanut

Mechanistic results - UNC and Arkansas peanut OIT studies

Kulis, Jones, Burks et al. AAAAAI 2012
Critical knowledge gaps in food OIT/SLIT research

Summary - consistent results

1. **Desensitization** - begins within a few days/months of treatment
   – threshold goes up

2. **Allergic side effects** - primarily GI at the beginning
   - viral infections, exercise

3. **Mechanistic studies** - mast cell, basophil, B-cell and T-cell changes

4. **Tolerance** - not shown in long-term blinded studies
Can we produce long-term tolerance in allergic diseases?

Food allergy immunotherapy: The future?

Life-long?

Transient?
Pregnant mother seeking advice

• Wants to know what to do to prevent food allergy
  • Pregnancy
  • During nursing
  • When to start solid foods

• Recent American Academy of Pediatrics recommendations – for at risk family
  • Breast feeding >4 months (no allergy benefit thereafter)
  • No solids until >4 months

Greer, Sicherer, Burks 2008 Pediatrics 121:183-191
Sicherer, Burks 2008 J Allergy Clin Immunol. 122:29-33
Food allergy summary

• Food allergy is an increasing health problem in “westernized” countries
  – children go on to have other allergic diseases
    • “atopic marathon”
    • children moving to new country have disease at rate of where they move

• Few foods account for ~90% of food allergic reactions
  – milk, egg, peanuts, nuts, fish & shellfish

• New therapies are on the horizon