

Update on Food Allergy: Is an ounce of prevention worth a pound of cure?

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 - clinical trial

Food Allergy Background

- Precise prevalence is unknown, but estimates are:
 - Adults: 1.4% - 2.4%
 - Children < 3 years: ~ 6%
 - Atopic dermatitis (mild/severe): ~35%
 - Asthmatic children: 6 - 8%
- Prevalence depends on: Genetic factors, age, dietary habits, geography and diagnostic procedures
- Prevalence has increased >50% between 1997 and 2011
 - Peanut allergy prevalence has quadrupled!

CDC: NCHS Data Brief 2013:121.
Sampson HA. Adverse Reactions to Foods. In *Allergy Principles and Practice*. Mosby, 2014.

Frequently allergenic foods

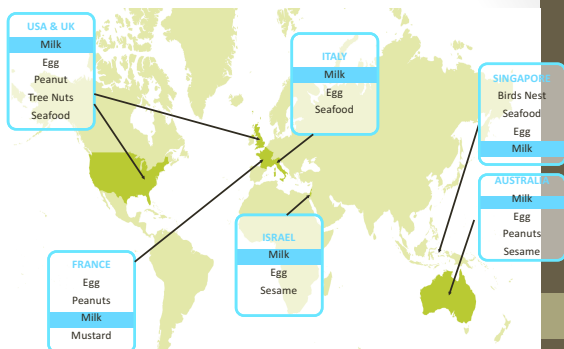
- Most common food allergies in young children:
 - Milk
 - Eggs
 - Peanuts
 - Soy
 - Wheat
- Most common food allergies in older children & adults
 - Fish
 - Shellfish
 - Peanuts
 - Tree nuts

Food	Children (%)	Adults (%)
Cow's milk	2.5	0.3
Egg	1.3	0.2
Soy	0.3-0.4	0.04
Peanut	2.0	0.8
Tree nut	0.2	0.5
Crustaceans	0.5	2.5
Fish	0.2	0.5

Guidelines for the Diagnosis and Management of Food Allergy in the United States. NIAID 2010.



Food allergy in children: International



Updates in Food Allergy 2017

1. Diagnosis



2. Treatment



3. Prevention



FOOD ALLERGY DIAGNOSIS



Diagnosing IgE-mediated Food Allergy

- Skin prick test (SPT)
 - Allergens eliciting a wheal of ≥ 3 mm greater than the negative control are considered positive
 - Overall positive predictive accuracy is $<50\%$
 - Negative predictive accuracy $>95\%$ (negative skin test results essentially confirm the absence of IgE-mediated reactions)

Food	SPT Wheal Size for 95% PPV
Egg	≥ 7 mm
Milk	≥ 8 mm
Peanut	≥ 8 mm

- Specific IgE testing in serum
 - Sensitivity similar to skin prick tests
 - Indicated if SPT are contraindicated (eg, skin disease, medications) and if discrepancy exists between history and SPT

Interpreting Specific IgE's

INTERPRETATION MESSAGE:

Specific IgE Class	ku/L	Level of Allergen Specific Antibody
0	<0.35	Not detectable
1	0.35-0.7	Low Level
2	0.7-1.5	Moderate Level
3	1.5-3.5	High Level
4	3.5-10	Very High Level
5	10-100	Very High Level
6	>100	Very High Level

Food	50% react (mean age 5yo)	95% react (mean age 5yo)	Age <2yo 95% react
Egg	2	7	2
Milk	2	15	5
Peanut	2 (hx of reaction) 5 (no hx)	14	

Component Resolved Diagnostics

- Milk
 - Casein (heat-stable) vs whey (heat labile) as allergenic protein
 - Increased casein-specific IgE predicts baked milk reactivity
- Egg
 - Ovamucoid (heat-stable) vs ovalbumin (heat labile) as allergenic protein
 - Ovamucoid may predict baked egg reactivity, but sensitivity/specificity at various thresholds not established
- Peanut
 - Best studied component testing panel
- Hazelnut
 - Skin prick test/specific IgE testing for hazelnut produce many false-positive due to birch cross-reactive protein
 - \uparrow Cor a 8 or Cor a 9 \rightarrow clinical reactivity; \uparrow Cor a 1 \rightarrow asymptomatic

Caubet JC et al. J Allergy Clin Immunol. 2013;131(1):222-4.
Kattan JD et al. JACI Pract. 2014;2(5):633-4.

Peanut Components

Clinical Allergy

- Ara h 2
- Ara h 1
- Ara h 3

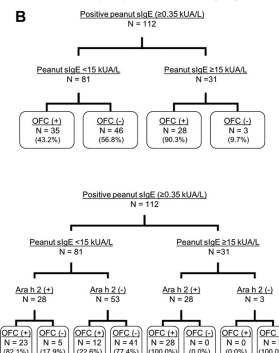
Cross-reactive or OAS

- Ara h 8 (birch allergic pts)
- Ara h 9

Ara h 2-specific IgE is the best discriminant between clinical reactivity and simple sensitivity to peanut (shown in Mt Sinai cohort and HealthNuts cohort)

The Utility of Peanut Components in the Diagnosis of IgE-Mediated Peanut Allergy Among Distinct Populations


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FOOD ALLERGY TREATMENT





Natural History of Food Allergy

- Dependent on specific food
 - Declining/low levels of specific-IgE predictive
 - IgE binding to conformational epitopes predictive
- Cow's milk: 85% remit by 8 yrs
 - *Saarinén et al JACI 2005*
- Egg: 66% remit after 5 yrs
 - *Bovano-Martinez et al JACI 2002*
- Peanut: 20% may remit (8% may recur)
 - *Fleischer et al JACI 2004*
- Allergies to peanuts, tree nuts, seafoods, and seeds typically persist

Oral Immunotherapy to Peanut

- Oral immunotherapy (OIT) to food was first described in 1908.
- Multiple studies since 1998 – most with peanut OIT
- Escalating doses of peanut over months
 - Peanut administered daily
 - Escalations done in office but most doses administered at home
- Benefits of oral immunotherapy
 - Increase the threshold dose of peanut tolerated (between 1-5 grams depending on study)
 - 60-90% of children reach study desensitization goals
- Risks associated with oral immunotherapy
 - >50% of dose escalation steps associated with reaction, though <4% of at-home maintenance doses cause reaction
 - ~10% of reactions require epinephrine.
 - up to 18% of patients undergoing OIT cannot tolerate the associated side effects

Anagnostou K et al. *Lancet*. 2014;383:1297-1304.
Jones SM et al. *J Allergy Clin Immunol* 2009;124:292-300.
Sampson H. *JACI Pract*. 2013;1:1-15.
Varshney P et al. *J Allergy Clin Immunol* 2011;127:654-60.

Transdermal Peanut Patch

- Phase IIb trial of 250µg peanut patch in 221 peanut-allergic subjects, ages 6-55yo
- Daily patch application for 1 year
- Results:
 - **After 1 year, 53.8% of pediatric subjects receiving peanut patch tolerated over 1 gram of peanut protein, vs 19.4% of placebo group (1gm = 4 peanuts; 10x increased threshold dose for reaction)**
 - Low rate of side effects
 - <1% of subjects reported side effects
 - 97% compliance with therapy

Sampson et al. *JACI* 2015; 135(2):AB390

Chinese Herbal Medicine

- Food Allergy Herbal Formula-2 (FAHF-2)
 - 9 herb formula based on Traditional Chinese Medicine –Blocks peanut anaphylaxis in a mouse model
 - In Phase II clinical trials for peanut, tree nut, sesame, fish, shellfish allergy
 - 68 subjects; 12-45yo
 - 30 pills a day for 6 months
 - 44% of subjects had poor adherence for at least one-third of the study period
 - Placebo group had a higher eliciting dose and cumulative dose ($p=0.05$) at the end of treatment food challenge.
 - No difference in the requirement for epinephrine to treat reactions ($p=0.55$).

Wang J et al. *J Allergy Clin Immunol* 2015;135:AB234.



FOOD ALLERGY PREVENTION



Guidelines for the Diagnosis and Management of Food Allergy in the United States Summary of the NIAID-Sponsored Expert Panel Report

5.3. Prevention of Food Allergy

5.3.1. Maternal Diet During Pregnancy and Lactation

Guideline 35: The EP does *not* recommend restricting maternal diet during pregnancy or lactation as a strategy for preventing the development or clinical course of FA.

5.3.2. Breast-Feeding

Guideline 37: The EP recommends that all infants be exclusively breast-fed until 4 to 6 months of age, unless breast-feeding is contraindicated for medical reasons.

5.3.3. Special Diets in Infants and Young Children

5.3.3.1. Soy Infant Formula Versus Cow's Milk Formula

Guideline 38: The EP does *not* recommend using soy infant formula instead of cow's milk infant formula as a strategy for preventing the development of FA or modifying its clinical course in *at-risk* infants ("at risk" is defined in Guideline 32).

5.3.3.2. Hydrolyzed infant formulas versus cow's milk formula or breast-feeding

Guideline 39: The EP suggests that the use of hydrolyzed infant formulas, as opposed to cow's milk formula, may be considered as a strategy for preventing the development of FA in *at-risk* infants who are not exclusively breast-fed ("at risk" is defined in Guideline 32). Cost and availability of extensively hydrolyzed infant formulas may be weighed as prohibitive factors.

5.3.4. Timing of Introduction of Allergenic Foods to Infants

Guideline 40: The EP suggests that the introduction of solid foods should *not* be delayed beyond 4 to 6 months of age. Potentially allergenic foods may be introduced at this time as well.

Baked milk consumption in milk-allergic children

- Majority (75%) of milk-allergic children tolerate baked goods containing milk. However, old recommendations focused on avoiding all forms of milk including baked milk
- Kim et al performed baked-milk challenges on 88 milk-allergic children
 - Those passing baked-milk challenge incorporated baked milk into diet
 - 60% of baked milk-tolerant went on to tolerate unheated milk in next 8-75 months, vs 9% of baked milk-sensitive
 - **baked milk tolerance predicts faster resolution of milk allergy**
 - 47% of all these children tolerated unheated milk at end of study vs 22% of "comparison" group given normal standard of care.
 - **baked milk consumption accelerates resolution of milk allergy (?)**

Nowak-Węgrzyn et al. J Allergy Clin Immunol. 2008; 122(2):342-7.
Kim JS et al. J Allergy Clin Immunol. 2011; 128(1):125-31.

Baked egg consumption in egg-allergic children

- Majority (70%) of egg-allergic children tolerate baked goods containing egg.
- Kim et al performed baked-egg challenges on 79 egg-allergic children
 - Those passing baked-egg challenge incorporated baked egg into diet
 - 64% of baked egg-tolerant went on to tolerate regular egg in next 8-67 months, vs 26% of baked egg-sensitive
 - **baked egg tolerance predicts faster resolution of egg allergy**
 - 53% of all these children tolerated regular egg at end of study vs 28% of retrospective "comparison" group given normal standard of care.
 - **baked egg consumption accelerates resolution of egg allergy (?)**

Lemon-Mule H et al. J Allergy Clin Immunol 2008;122:977-83.
Leonard SA et al. J Allergy Clin Immunol 2012;130:473-80.

Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy

Du Toit et al. JACI. 2008;122(5):984.

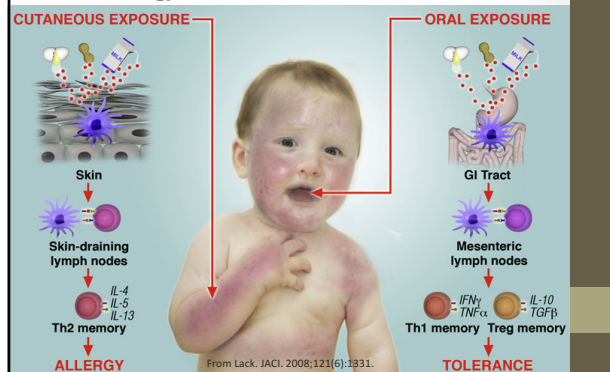
- Background: Peanut allergy prevalence is much higher in Western countries where peanut ingestion is delayed than in African and Asian countries where peanut is in diet very early. Is this due to time of exposure vs genetic differences?
- Questionnaire based study of 8600 Jewish children in the UK and in Israel.

Results:

- Peanut allergy prevalence is 10-fold higher in Jewish children in UK (1.85%) vs in Israel (0.17%)
- Relative risk still 5.8 when adjusted for age and atopy

	Infancy (aged 8-14 mo)		P value
	Israel (%) (n = 86)	UK (%) (n = 50)	
Peanut Grams eaten per month			
0	20.9	80.0	<.0001†
>0-7	27.9	10.0	<.0001*
≥7-14	14.0	2.0	.0001*
≥14-28	18.6	6.0	.0001*
≥28	18.6	2.0	<.0001*
Times eaten per month			
0	20.9	80.0	<.0001†
>0-3	11.6	4.0	.0008*
≥3-6	11.6	6.0	.002*
≥6-9	10.5	4.0	.002*
≥9	45.4	6.0	<.0001*

Environmental Food Exposure Hypothesis of Food Allergy Sensitization



The LEAP Study – “Learning Early About Peanut”

- Randomized open label controlled trial to assess affect of early peanut consumption on development of peanut allergy
- 640 “high risk” infants, ages 4mo-11mo, were assigned to early peanut consumption arm or avoidance arm
 - Consumption = 2 grams of peanut 3 times a week until 60mo.
- Followed to age 5 for evidence of peanut allergy
 - Peanut challenge at age 5
 - 3.2% of consumption arm vs 17.2% of avoidance arm were allergic to peanuts at 60mo.
 - If negative initial SPT: 1.9% of consumption arm vs 13.7% of avoidance arm became allergic
 - If low-positive SPT: 10.6% of consumption arm vs 35.3% of avoidance arm became allergic

Du Toit et al. N Engl J Med 2015;372:803-13.

LEAP-ON Trial

Du Toit et al. N Engl J Med 2016; 374:1435-43.

- Peanut allergy prevention achieved from early peanut consumption persists after a one-year period of avoiding peanut.
- 3.6% of peanut-consumption group were allergic at 60 months and 4.8% were allergic after subsequent 12 months of avoid peanuts

Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants

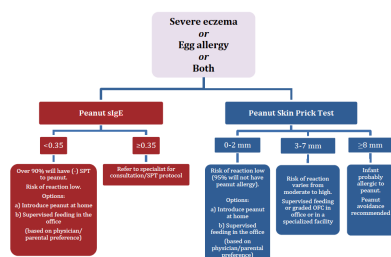
Perkin et al. N Engl J Med 2016; 374:1433-43.

- Randomized open label controlled trial to assess effect of early allergenic food consumption in breast-fed infants
- 1303 breast-fed infants were assigned to early-introduction arm (beginning at 3 months) or standard-introduction arm
 - peanut, cooked egg, cow's milk, sesame, whitefish, wheat
 - Evaluated for food allergies between ages 1-3 years
- **No significant difference between early and standard introduction in intention-to-treat analysis**
- However, only 31.9% of the early-introduction arm were compliant with all early food introductions
- **Per protocol analysis:**
 - **67% risk reduction for any food allergy** (2.4% vs 7.3%, $P=0.01$)
 - **Decreased prevalence of peanut allergy** (0% vs. 2.5%, $P=0.003$)
 - **Decreased prevalence of egg allergy** (1.4% vs. 5.5%, $P=0.009$)
 - No significant effects with respect to milk, sesame, fish, or wheat

New 2017 NIAID food allergy guidelines

(Togias et al. J Allergy Clin Immunol 2017; 139:29-44)

- New guidelines “operationalize” the findings from LEAP trial
- Infants at “high risk” should have introduction of peanut as early as 4-6mo to reduce peanut allergy risk



New NIAID food allergy guidelines (continued)

- “Moderate-risk” infants with mild-to-moderate eczema should have peanut introduction as early as 4-6mo to reduce peanut allergy risk.
 - This introduction may be done at home without IgE evaluation
 - However, if caregiver or HCP prefers evaluation, peanut IgE/SPT algorithm for high risk infants may be followed.
- Infants without eczema or food allergy may have peanut introduced freely in accordance with family preferences.

Gruchalla RS et al. N Engl J Med 2015;372:875-877

Summary of early peanut feeding recommendations

Addendum guideline	Infant criteria	Recommendations	Earliest age of peanut introduction
1	Severe eczema, egg allergy, or both	Strongly consider evaluation by sIgE measurement and/or SPT and, if necessary, an OFC. Based on test results, introduce peanut-containing foods.	4-6 months
2	Mild-to-moderate eczema	Introduce peanut-containing foods	Around 6 months
3	No eczema or any food allergy	Introduce peanut-containing foods	Age appropriate and in accordance with family preferences and cultural practices

Getting 2 grams of peanut into child's diet 3 times a week

	Bamba	Peanut butter	Peanuts	Peanut flour or peanut butter powder	
Amount containing approximately 2 g of peanut protein	17 g or ¼ of a 28-g (1-oz) bag or 21 sticks	9-10 g or 2 teaspoons	8 g or ~10 whole peanuts (2½ teaspoons of ground peanuts)	4 g or 2 teaspoons	
Per approximately 2 g of peanut protein	Bamba* (17 g)	Peanut butter (10 g)	Peanuts (8 g)	Peanut butter powder (4 g)	Peanut flour (4 g)
kcal	93	59	45	15	13
Sugar (g)	0.4	0.65	0.38	0.4	0.33
Salt (mg)	68	48	1	31	7
Fat (g)	6.1	4.95	3.94	0.49	0.02

* The nutritional content of peanut puff products (other than Bamba) can be obtained from their manufacturers.

Conclusions

- While skin testing, specific IgEs and oral challenges are the mainstay for most food allergy diagnosis, “component testing” can clarify the diagnosis of peanut allergy in a subset of patients.
- Oral and transdermal desensitization to peanut can at best allow peanut-allergic patients to tolerate accidental exposure, but not to consume peanut freely.
- The majority of milk and egg allergic children can tolerate baked forms of these foods. Baked food-tolerant children are more likely to outgrow their food allergy. Ingestion of the baked food may hasten allergy resolution.
- Peanut ingestion from infancy to 5yo is associated with a 6-10 fold decrease in peanut allergy in high risk children.
- Updated guidelines recommend early skin testing and peanut introduction in high-risk infants, and consideration of early peanut introduction for all infants.