

Food Allergy Diagnosis and Management

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(Adapted from Uygungil and Sharma 2016)



Objectives

- Overview of Food Allergy Prevalence and Presentation
- Diagnosis:
 - Importance of the history
 - Different types of FA
 - Diagnostic tests
 - Economic impact of FA
 - Interpretation of results and natural history
- Current Management based on NIAID Food Allergy Guidelines

TABLE I. Estimated food allergy rates in North America

Prevalence	Infant/child	Adult
Milk	2.5%	0.3%
Egg	1.5%	0.2%
Peanut	1%	0.6%
Tree nuts	0.5%	0.6%
Fish	0.1%	0.4%
Shellfish	0.1%	2%
Wheat, soy	0.4%	0.3%
Sesame	0.1%	0.1%
Overall	5%	3% to 4%

Prevalence of Food Allergy (FA)

- **8% Children** (2.4% multiple, 3% severe reactions)
 - Cow's milk 2.2%
 - Peanut 1.8%
 - Tree Nuts 1.7%
- **5% Adults**
 - Shellfish 1.9% (3.1% in Blacks)
 - Fruits 1.6%
 - Vegetables 1.3%
- Overall increase in the rates of FA over time
- IgE sensitization to food (milk, egg, peanut) have remained stable over the decades (80s/90s vs 2005-06)

-Gupta et al. Pediatrics 2011;128:e9-17

-Sicherer JACI 2014;133:291-307

-McGowan J Allergy Clin Immunol Pract 2016; in press

Risk Factors for FA

- Gender (males in children)
- SES (increased with more affluence)
- Race (Asian and Black children)
- Genetics (Fam Hx)
- Atopy
- Vitamin D
- Dietary fat – omega-3s
- Obesity (inflammatory state)
- Antacids
- Hygiene/Infections
- Microbiome, antibiotic use
- Endocrine disruptors/toxins
- Timing and Route of exposure to foods
- Place of birth
 - US born
 - children of immigrants
 - arriving before age 2y

-Sicherer JACI 2014;133:291-307

-Keet et al JACI 2012;129:169-175.

Food Allergy: The Basics

“An adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food.”



Diagnosis of FA

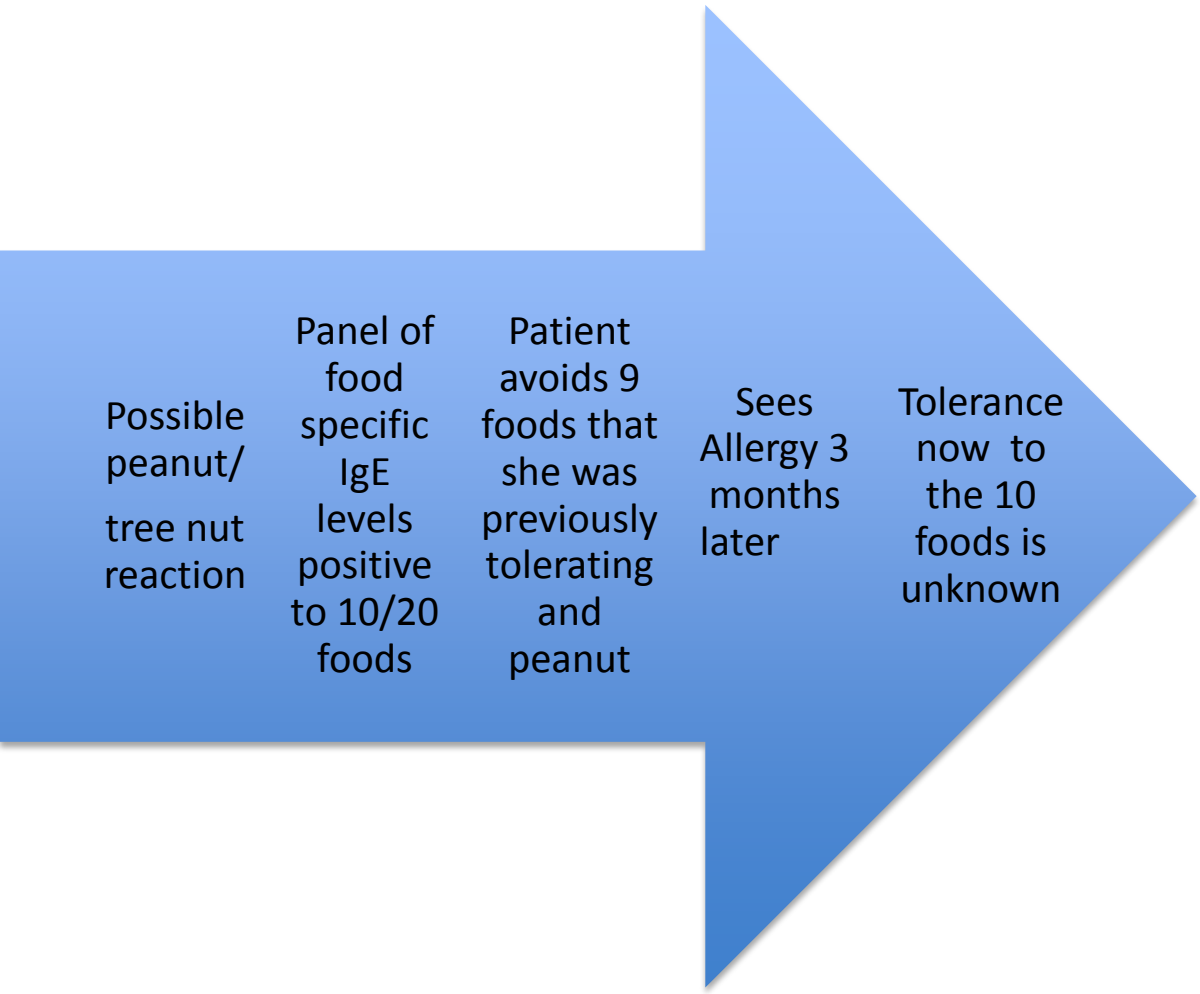
- You are the front line
- You have a major impact on patient outcomes
 - Prevention of FA
 - Diagnosis of FA
 - Economic burden of FA
- We want to help you to be able to do the right thing in the face of pressures from
 - Family requests/demands
 - Provider satisfaction scores
 - Time constraints

Food Allergy Case 1

- A 4 year old girl eats some mixed nuts at her grandmother's house for the first time.
- Never had peanut or tree nuts before
- Within 10 minutes develops facial angioedema, total body hives and coughing
- She is given Benadryl at home and brought to your office with resolved symptoms.
- She otherwise eats a full diet

IgE Mediated

Disorder	Features	Age	Foods	Natural Hx	Tests
Anaphylaxis	Rapid onset, multiorgan	any	PN, TN, F, SF, Milk, Egg, Wheat, Soy	variable	SPT, specific, IgE, Component resolved diagnostics (CRD)
Angioedema/urticaria	20% acute 2% chronic	younger			
GI	Immediate vomiting				
Rhinitis, Asthma	Rarely isolated, inhalation	younger occupational	Wheat, egg, seafood		
Oral Allergy	Oral itching, 1% anaphylaxis	Older children/adults	Fruits, vegetables	persists	Prick-prick or no testing
Delayed Meat Induced	6-8 hour delay rare	α -Gal IgE (CHO moiety)			α -Gal IgE
Food-exercise induced anaphylaxis	Only within 2 hours of exercise rare		Wheat, shellfish, celery	persists	Exercise test SPT, IgE



Patients undergoes repeat testing



Multiple OFC to confirm true FA



Patient now reacts to 2 new foods that she was previously tolerating



Total cost = \$3-4K and new FAs

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graph LR; A[Possible peanut reaction] --> B[You send Peanut and Tree nut IgE only]; B --> C[Patient Avoids Peanut and Tree nuts]; C --> D[Sees Allergy 3 months later]; D --> E[Confirm PN allergy +/- OFC]; E --> F[Follow every year]; F --> G[Normal diet otherwise $300];
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Possible peanut reaction

You send Peanut and Tree nut IgE only

Patient Avoids Peanut and Tree nuts

Sees Allergy 3 months later

Confirm PN allergy +/- OFC

Follow every year

Normal diet otherwise \$300

Case 2

- A 5 month old boy with severe atopic dermatitis covering 80% of his body surfaces.
- His parents think that food allergy is the cause.
- They want to know all the foods that he is allergic to
- They have tried “everything” for his skin and nothing is working

Mixed IgE-Cell Mediated

Disorder	Features	Age	Foods	Natural Hx	Tests
Atopic Dermatitis	Food induced in 35% of moderate-severe	Infants>Children >Adults	Egg, milk	resolves	SPT, IgE
Eosinophilic GI disease	Biopsy proven eosinophils in GI tissue, dysphagia, reflux, weight loss, impaction	any	Many, milk 70%	persistent	Empiric diets, EGD + Bx, SPT, IgE

Natural Hx of AD and FA

- Retrospective chart review 298 patients with possible food triggered AD
- 19% without prior immediate reactions developed new immediate reactions after an initial food elimination diet.
- 30% of these were anaphylaxis
- Cow's milk and egg most commonly
- Avoidance of a food related to development of a new food allergy
- Unrelated to level of specific IgE or the food

Take home for AD and FA

- Strict elimination diets for children with food-triggered atopic dermatitis should be recommended with caution
- These children may develop IgE-mediated food reactions to foods that could be prevented.
- Topical treatment of AD is essential
- Close follow-up of response to diet elimination versus inclusion
- Future studies of the possibility of keeping small amounts of the offending agent in the diet are needed.

Case 3

- A 6 month old girl who is formula fed has persistent spitting up
- Despite changing formulas, adding rice cereal to bottles and antacid use symptoms continue
- She is now falling off of her growth curve.

Mixed IgE-Cell Mediated

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Case 4

- A 3 month old breastfed girl has bloody mucousy stools and persistent crying.
- Mom has taken out milk from her diet but the bloody stools persist.
- She wants to know all the foods that her baby is allergic to.

Non-IgE Mediated

Disorder	Features	Age	Foods	Natural Hx	Tests
FPIES	<p><u>Chronic exposure:</u> Emesis, diarrhea, poor growth, lethargy</p> <p><u>Re-exposure:</u> 1.5-2 h delay in emesis, hypotension, lethargy</p>	Infancy-toddlerhood	Milk and soy, Solids: rice, oat, banana, other solid foods	resolves	IgE helps with persistence
Food protein induced proctocolitis	Mucousy bloody stools in infants	infancy	Milk, soy +/-BF	resolves	Empiric diet, reintro 6-9 months
Celiac Disease	Autoimmune, enteropathy, malabsorption	any	Gliadin (wheat, barley, rye)	lifelong	IgA -TTG, HLA and biopsies
Heiner Syndrome	Rare, pulmonary infiltrates, FTT, anemia	infancy	milk		Milk IgG precipitins

Case 5

- A 7 mo old girl eats banana and oatmeal for breakfast
- After playing for half an hour, she takes a 1 hour nap
- Wakes up projectile vomiting multiple times and appearing listless and pale
- The same reaction happens a week later with oatmeal and raisins

Non-IgE Mediated

Disorder	Features	Age	Foods	Natural Hx	Tests
FPIES (Food Protein Induced Enterocolitis)	<p><u>Chronic exposure:</u> Emesis, diarrhea, poor growth, lethargy</p> <p><u>Re-exposure:</u> 1.5-2 h delay in emesis, hypotension, lethargy</p>	Infancy-toddlerhood	Milk and soy, Solids: rice, oat, banana, sweet potato other solid foods	resolves	IgE helps with persistence
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Economic Impact of Childhood Food Allergy in the United States

- Overall Economic Cost of Food Allergy: **\$24.8 Billion**
- Direct Medical Costs: **\$4.3 Billion**
 - Clinician visits, ED visits, Hospitalizations
- Costs to Family: **\$20.5 Billion**
 - Lost labor productivity, Out-of-pocket, Opportunity costs

Testing and Diagnosis

- *History consistent with IgE-mediated symptoms to a food*

AND

- Positive serum levels of IgE specific to that food protein (“RAST” testing) or positive skin prick testing to food protein

OR

- Positive double blind placebo controlled oral food challenge (**gold standard**)

History

- Symptoms (ever occur without the food?)
- Dose of the triggering food
- Form of the food
 - Does the patient tolerate the food in a different form (heated, baked, cooked, dried)
- Timing of the reaction (minutes, hours, days)
- Other factors: viral illness, exercise, NSAIDs
- Response to medications (Diphenhydramine, Epi)
- **Has the patient tolerated the culprit food SINCE the original reaction**

Pearls and Pitfalls of Diagnosis

- **Pre-test probability is most important**
 - Consider more likely foods for age
 - Consider DDx – lactose intolerance, non-IgE mediated, irritant effects, food poisoning (ie scromboid), gustatory rhinitis, other allergen (ie, medication)
- **Tolerated foods need not be tested:**
 - milk, egg, soy, wheat, peanut, tree nuts, fish, shellfish, fruits, vegetables, meats
- **Do not discount a negative test with a convincing history**

Cross- Reactivity and Co-Reactivity

Table 1. Natural History of Food Allergy and Cross-Reactivity between Common Food Allergies.

Food	Usual Age at Onset	Cross-Reactivity	Usual Age at Resolution
Hen's egg white	6–24 mo	Other avian eggs	7 yr (75% of cases resolve)*
Cow's milk	6–12 mo	Goat's milk, sheep's milk, buffalo milk	5 yr (76% of cases resolve)*
Peanuts	6–24 mo	Other legumes, peas, lentils; coreactivity with tree nuts	Persistent (20% of cases resolve by 5 yr)
Tree nuts	1–7 yr; in adults, onset occurs after cross-reactivity to birch pollen	Other tree nuts; coreactivity with peanuts	Persistent (9% of cases resolve after 5 yr)
Sesame seeds	6–36 mo	None known; coreactivity with peanuts and tree nuts	Persistent (20% of cases resolve by 7 yr)
Fish	Late childhood and adulthood	Other fish (low cross-reactivity with tuna and swordfish)	Persistent†
Shellfish	Adulthood (in 60% of patients with this allergy)	Other shellfish	Persistent
Wheat‡	6–24 mo	Other grains containing gluten	5 yr (80% of cases resolve)
Soybeans‡	6–24 mo	Other legumes	2 yr (67% of cases resolve)
Kiwi	Any age	Banana, avocado, latex	Unknown
Apples, carrots, and peaches§	Late childhood and adulthood	Birch pollen, other fruits, nuts	Unknown

It might be prudent to test for foods with high co-reactivity if not being consumed but generally avoid testing foods that are cross-reactive (exceptions)

Lack N Engl J Med 2008;359:1252-60.

Pearls and Pitfalls of Diagnosis

- Positive SPT or food specific IgE indicates *sensitization not clinical allergy*
 - **Indiscriminate food testing is poorly informative**
 - Leads to unnecessary avoidance
 - Nutritional and growth concerns
 - Cascade of further testing
 - Take care not to “over test”
- Specific IgE levels
 - not correlated to severity
 - trended over time to monitor for persistence/resolution

Food “Panel” Testing

- Serum IGE testing that includes a predetermined list of foods
- May include foods which the child is eating/tolerating
- Risk for false positive results
- Can present confusing results to ordering providers and families
- Potential for increased costs
- Generally not recommended, instead consider single allergens of concern

Unproven/Experimental Tests

- Intradermal skin test with foods
 - Risk of systemic reactions and death; high false positive rate
- Atopy patch testing with foods
 - No standardized reagents; No significant enhancement in diagnostic accuracy compared with skin prick testing
- Provocation/neutralization, cytotoxic tests, applied kinesiology (muscle response testing), hair analysis, electrodermal testing, food-specific IgG or IgG4 (IgG “RAST”)

- Lockey, RF. Allergy Proc. 1995; 16:293-6.
- Boyce J, et al. JACI. 2010; 126(6 Suppl): S1-S58.
- Sampson HA, et al. JACI 2014; 134(5): 1016-25.e43.

Slide adapted from American Academy of Allergy, Asthma, and Immunology.

What About Siblings?

TABLE II. Proportion of siblings who are sensitized to food

	Frequency, % (n)				
	Index child allergic to:				
	Any food (n = 642)	Peanut (n = 324)	Tree nut (n = 132)	Milk (n = 217)	Egg (n = 155)
Sibling sensitized to:					
Any food	53.0 (340)	55.6 (180)	44.7 (59)	51.6 (112)	54.8 (85)
Peanut	24.6 (158)	22.8 (74)	28.0 (37)	23.5 (51)	31.6 (49)
Tree nut	16.7 (107)	16.4 (53)	21.2 (28)	15.2 (33)	21.3 (33)
Milk	35.4 (227)	37.4 (121)	38.6 (51)	27.2 (59)*	31.0 (48)
Egg	35.1 (225)	35.19 (114)	34.9 (46)	31.8 (69)	38.1 (59)
Soy	23.1 (148)	21.6 (70)	28.8 (38)	23.5 (51)	28.4 (44)
Wheat	36.5 (234)	36.7 (119)	43.2 (57)	33.6 (73)	37.4 (58)
Shellfish	14.8 (95)	14.8 (48)	18.2 (24)	11.5 (25)	15.5 (24)
Fish	3.9 (25)	4.3 (14)	6.1 (8)	3.2 (7)	2.6 (4)

The asterisk and dagger symbols indicate statistical significance for association between sensitization and index child allergy.

* $P < .01$.

What About Siblings?

TABLE III. Proportion of siblings who have a clinical food allergy

Sibling allergic to:	Frequency, % (n)				
	Index child allergic to:				
	Any food (n = 642)	Peanut (n = 324)	Tree nut (n = 132)	Milk (n = 217)	Egg (n = 155)
Any food	13.6 (87)	11.7 (38)	22.0 (29)†	12.9 (28)	17.4 (27)
Peanut	3.7 (24)	4.9 (16)	7.6 (10)†	1.8 (4)	3.9 (6)
Tree nut	1.6 (10)	1.5 (5)	2.3 (3)	0.9 (2)	0.7 (1)
Milk	5.9 (38)	4.0 (13)*	6.1 (8)	8.3 (18)	12.3 (19)†
Egg	4.4 (28)	4.9 (16)	8.3 (11)†	4.6 (10)	5.8 (9)
Soy	0.9 (6)	0.3 (1)	0.8 (1)	0.9 (2)	1.3 (2)
Wheat	1.1 (7)	0.9 (3)	0.0 (0)	1.4 (3)	2.6 (4)
Shellfish	0.2 (1)	0.0 (0)	0.8 (1)	0.0 (0)	0.0 (0)
Fish	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)

The asterisk and dagger symbols indicate statistical significance for association between sibling clinical allergy and index child allergy.

* $P < .05$.

† $P < .01$.

Persistence vs Resolution of IgE-mediated FA

- Higher specific IgE levels
- Larger skin prick test
- Reaction on first exposure
- Atopic Dermatitis Severity
- www.cofargroup.org



Risk Factors for More Severe Reactions

- **Concomitant asthma (asthma + PN allergy → most fatal)**
- Amount ingested
- Food form (cooked, raw, or processed)
- Co-ingestion of other foods (fats, alcohol)
- Age of the patient
- Degree of sensitization at the time of ingestion
- Rapidity of absorption, based on whether
 - The food is taken on an empty stomach
 - The ingestion is associated with exercise
- **Lack or delayed administration of epinephrine**
- **Lack of skin symptoms**
- **Denial of symptoms**
- Reliance on oral antihistamines alone to treat symptoms

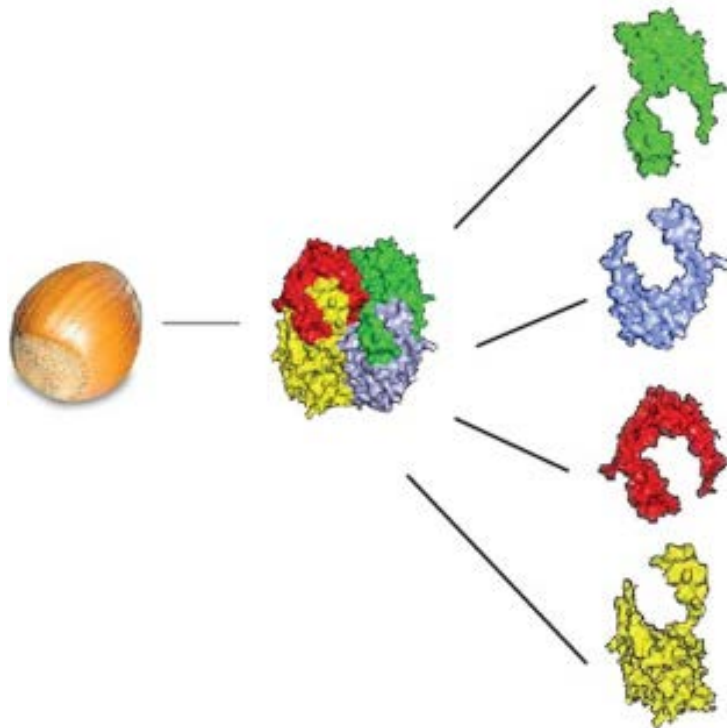
Interpretation of Specific IgE

Food	Age	IgE kU/L		SPT mm	Natural Hx
		50% PPV	95% PPV (high)		
Milk	<1 any	2	5 15		60% by 18y if IgE >50
Egg	1 5	2 2	1.7 6	4mm	Low chance before 18y if IgE >50
Peanut	1 4 5	2 (clear hx) 5 (no clear hx)	34 2.1 14	8mm	-Low chance before 4y if IgE >5 at age 1 -20% by early adulthood
Tree nut			15		9% by early adulthood, if + to 2+ poor prognosis

Variations in these cut-off values are reported depending on the specific food, study center, population

Component Resolved Diagnostics

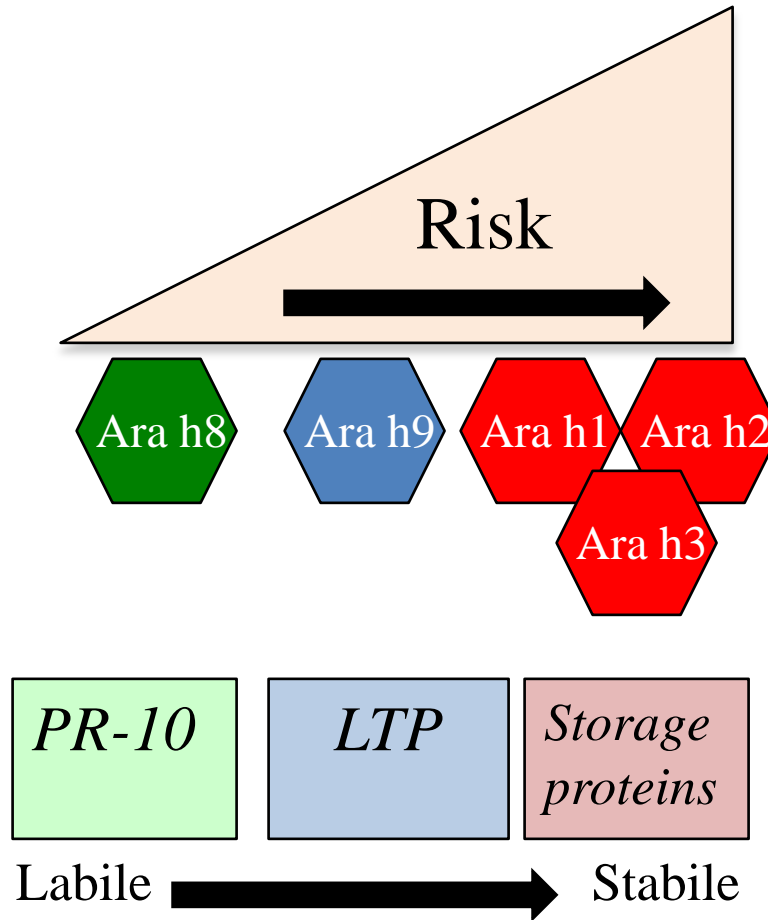
Food Protein Mix Components



Commercially available for a number of foods, but used more frequently for:

- Peanut (“uknow” test)
- Tree nuts
- Milk
- Egg

Component Resolved Diagnostics



NIAID FA Guidelines: Management

- Education families on:
 - Carrying medications at all times
 - 2 epinephrine autoinjectors
 - In purse or bag; not in the car
 - Proper use of medications
 - Preparedness
- Provide a written emergency plan
 - <http://www.foodallergy.org/file/emergency-care-plan.pdf>
- Dosing of epinephrine:
 - 0.15 mg for ≤ 25 Kg*
 - 0.3 mg for > 25 kg
- Benadryl dosing: 1-1.5 mg/kg (max 50 mg)

FA Guidelines: Management

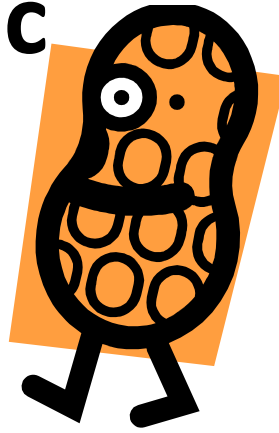
- **Avoidance**

- **Label reading**, labeling laws, advisory warnings
- Restaurant precautions – “chef cards”, cross-contact
- Travel – medication and safe meal preparedness
- **School – written emergency plan**, caution with crafts, field trips, mealtimes
- Home – avoid cross-contact
- **Educate all care givers**
- Vigilance – always have medications ready, medical alert jewelry
- Avoid home trials
- Nutritional counseling and growth monitoring
- Psychological impact – anxiety, bullying, balance in caution

-Sicherer JACI 2014;133:291-307

-J Allergy Clin Immunol 2010;126:S1-S58.

Future Therapies – Allergen Specific



- Allergen Immunotherapy
 - Oral (OIT), Sublingual (SLIT) or percutaneous
 - Food allergen administered slowly, in small but steadily increasing doses, up to a stable daily dose
 - Tolerance desired as opposed to desensitization
- Others?
 - Anti-IgE (omaluzimab)
 - Chinese Herbal Therapy (FAHF-2)
 - Modified allergen protein/peptide vaccines
 - Probiotics

Children's National Food Allergy Program



- Children's National Food Allergy Program

- Inaugural FARE (Food Allergy Research and Education) Clinical Network Center of Excellence
- > 1,100 new and > 2,000 returning food-allergic patients treated annually
 - Immediate appointment availability throughout region
- > 500 oral food challenges performed annually
- One of <5 programs in the US to have a dedicated Food Allergy Psychology Program
- Multidisciplinary clinics: Eosinophilic Esophagitis clinic (Allergy/GI/Nutrition)
- NIAID-CNMC Pediatric Allergy Immunology Fellowship Program
- Clinical trials program for novel food allergy immunotherapies

