Evolving Paradigms: Food Allergy Treatment Options

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Disclosures

- Social Media Medical Editor – American Academy of Allergy, Asthma and Immunology
- Consultant –Before Brands, Kaleo, Novartis
- Associate Editor – Annals of Allergy, Asthma and Immunology
- Honoraria – ACAAI, AAP, AAAAI
- Non-financial:
  - Member – Joint Task Force on Practice Parameters for Allergy and Immunology
  - Member – Board of Regents, American College of Allergy, Asthma and Immunology

Objectives

- Prevent misdiagnosis of food allergy through proper use and interpretation of testing
- Discuss risks, benefits and expected outcomes associated with food allergen oral immunotherapy

Initial Thoughts…

- Food allergies are grossly over diagnosed and misdiagnosed
- Many families do not receive proper education to help them navigate risk
- While food allergies CAN be serious and life-threatening, they are also manageable
- A culture of FEAR has been created surrounding food allergies

A Growing Epidemic

PREVALENCE OF FOOD ALLERGY IN THE UNITED STATES*

5-8% of US children have a food allergy

- All races and income groups are affected

*Children <18 years of age; N=3339.

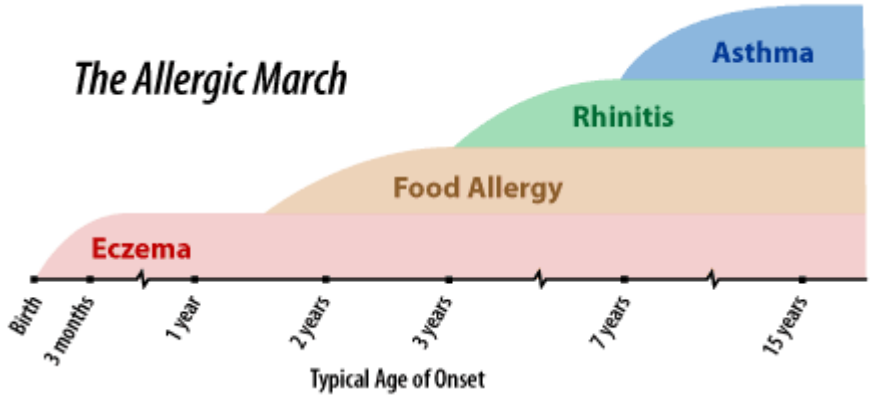
Reference: 1. Gupta RS, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics*. 2011;128(1):e9-e17.

Definitions

- **Allergy:** An immunologic response to an allergen that results in reproducible symptoms with every exposure
- **Intolerance:** A non-immunologic response to a substance (food) that causes gastrointestinal symptoms with exposure
- **Sensitivity:** No agreed upon definition. Not an immune response. Often applied to a variety of symptoms without evidence to support use.

Risk Factors for Development of Food Allergy

- Eczema
- Asthma
- Environmental allergies
- Family history of allergies



Food Allergy Mad Libs

A _____ month/year old boy was eating _____ and within _____ minutes/hours, developed _____

IgE Mediated Food Allergy: The History IS the Test

- Reactions are objective, rapid onset and reproducible with every exposure to the offending food, no matter what form

- Typical symptoms:
  - Hives
  - Swelling
  - Vomiting
  - Runny nose/congestion
  - Wheezing
  - Hypotension
  - Anaphylaxis

What Do You Want to Do Now?

- ❑ Strict avoidance of that food and all similar foods
- ❑ Order a food allergy panel
- ❑ Refer to an allergist

ALLERGEN(S) INTERP...	...	
ALLERGEN: CAT DAND...	<0.10	
ALLERGEN: COCKROAC...	<0.10	
ALLERGEN: DOG DAND...	1.34	!
ALLERGEN: MITE FAR...	<0.10	
ALLERGEN: MITE PTE...	<0.10	
ALLERGEN: ALMONDS IGE	0.22	
ALLERGEN: APPLE IGE		
ALLERGEN: BANANA IGE	2.62	!
ALLERGEN: CASHEWS IGE	0.17	
ALLERGEN: COD IGE	0.48	!
ALLERGEN: CRAB IGE	<0.10	
ALLERGEN: EGG WHIT...	4.97	!
ALLERGEN: LOBSTER IGE	<0.10	
ALLERGEN: MILK (CO...	1.06	!
ALLERGEN: PEANUT IGE	0.48	!
ALLERGEN: PECAN NU...	<0.10	
ALLERGEN: PISTACHI...	0.19	
ALLERGEN: SALMON IGE	0.27	
ALLERGEN: SCALLOP IGE	<0.10	
ALLERGEN: SHRIMP IGE	<0.10	
ALLERGEN: TUNA IGE	0.20	

Sensitization ≠ Allergy

- Sensitization
  - The detection of specific IgE toward an allergen through skin prick, intradermal, or serum specific IgE testing

- IgE mediated hypersensitivity
  - Characteristic clinical symptoms upon exposure to an allergen AND…
  - The detection of specific IgE toward that allergen

Diagnostic Testing

- Skin prick testing
  - Detects presence of specific IgE bound to cutaneous mast cells
  - Introduce small amount of allergen percutaneously – wheal/flare in 15 minutes
    - High negative predictive value
    - Low positive predictive value ~50%

Serum Specific IgE Testing

- Levels of IgE specific for food and/or inhalant allergens can be obtained through routine venipuncture
- Test offers convenience
- Commercial panels widely available and marketed as excellent screening tools

- Results reported in a range from 0.1 kU/L – 100 kU/L
  - Also reported as arbitrary classes (1 through 5)
  - A big "!" will accompany any value reported > 0.10 kU/L

Pearls of Wisdom

- Both skin and blood testing have high FALSE POSITIVE rates
  - Many people without allergy will have positive tests
  - The best test is what happens upon exposure
  - Neither test tells us severity of reaction
  - “Shotgun” testing, or testing of patients without symptoms is not recommended for ANY reason

Specific IgE Cutoff Points

Allergen	Decision Point (kU/L)	PPV	NPV
Egg	7	98	38
Milk	15	95	53
Peanut	14	100	36
Fish	3	56	93
Soybean	30	73	82
Wheat	26	74	87

Boyce JA, et al. Guidelines for the Diagnosis and Management of Food Allergy in the United States: Summary of the NIAID-Sponsored Expert Panel Report.Journal of Allergy Clinical Immunology. 2010;126:S1-58.

Cross-Reactivity: Clinical vs Testing

Foods	Clinical Reactions	Testing
Peanut + Tree nuts	Low/none	Moderate
Tree nuts + Other tree nuts	Pecan + walnut Cashew + pistachio	High
Fish + Shellfish	Low/none	Low/none
Fish + Other fish	High	High
Shellfish + Other shellfish	High	High
Peanut + soy	Low/none	High
Wheat + grains	Low/none	High
Cow's milk + goat/sheep's milk	High	High

Boyce JA, et al. Guidelines for the Diagnosis and Management of Food Allergy in the United States: Summary of the NIAID-Sponsored Expert Panel Report. Journal of Allergy Clinical Immunology. 2010;126:S1-58.

Aeroallergen Cross Reactivity

Aeroallergen	Food
Dust mite Cockroach	Shellfish
Birch tree pollen	Peanut Fruits Soy
Grass pollen	Wheat
Tree pollen	Tree nuts

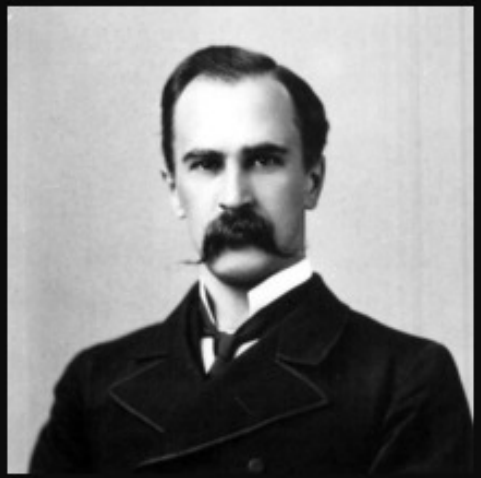
Boyce JA, et al. Guidelines for the Diagnosis and Management of Food Allergy in the United States: Summary of the NIAID-Sponsored Expert Panel Report.Journal of Allergy Clinical Immunology. 2010;126:S1-58.

Peanut/Tree Nut Component Testing

- Predictive capabilities vary according to population background

Nut	Antigens Associated with Clinical Allergy
Peanut	Ara h 1, 2, 3
Hazelnut	Cor a 9, Cor a 14
Cashew	Ana o 3
Walnut	Jug r 1
Pecan	Car I 1, Car I 2
Pistachio	Pis v 1, Pis v 2

BSACI guideline for the diagnosis and management of peanut and tree nut allergy. Clin & Exp Allergy. 2017;47:719-39.



The good physician treats the disease; the great physician treats the patient who has the disease.

~ William Osler

AZ QUOTES

“Treat the patient, not the numbers”

An Ideal Food Allergy Test

Noninvasive
- Readily available
- Easy to use and interpret

Reliable
- High positive predictive value
- Low false positives

Clinically relevant
- Threshold dose
- Severity of reaction

Current Food Allergy Tests

Noninvasive

- Readily available
- Easy to use and interpret

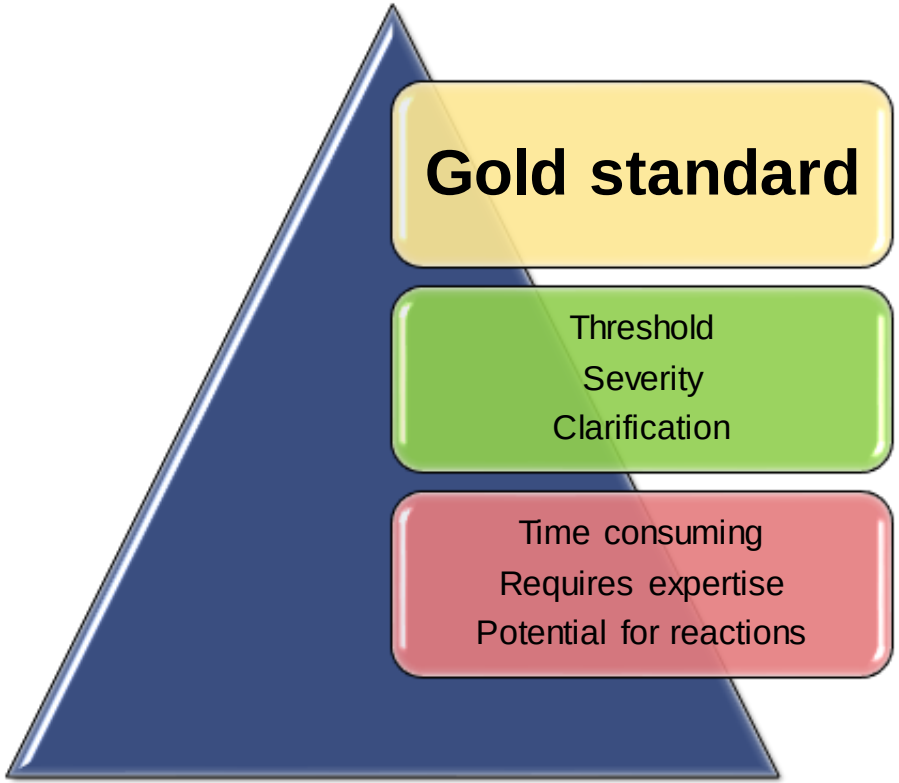
Reliable

- LOW positive predictive value
- HIGH false positives

Clinically relevant

- Threshold dose
- Severity of reaction

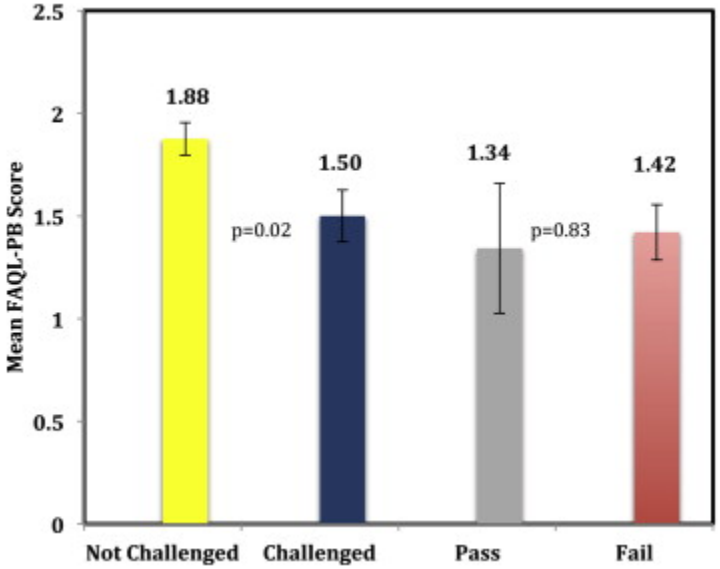
Oral Food Challenges

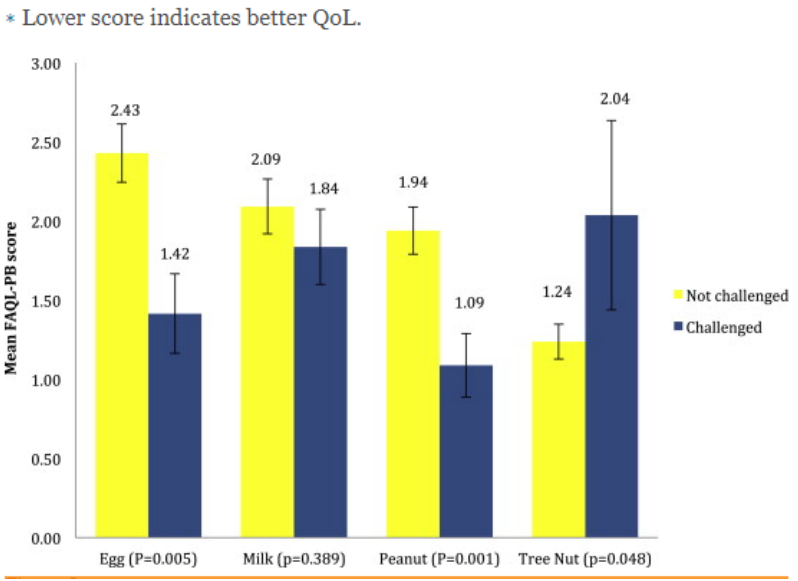


Upton JE, Bird JD. Ann Allergy Asthma Immunol. 2020;124(5):451-458.

Benefits of Unsuccessful Challenge

- Quality of life improves after a challenge





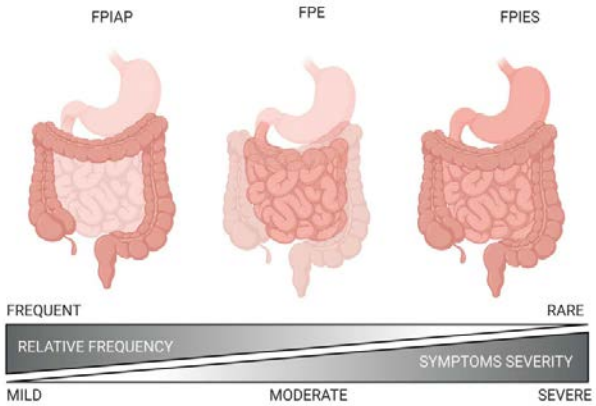
Franxman TJ, et al. J Allergy Clin Immunol Pract. 2015 Jan-Feb;3(1):50-6

Benefits of a Successful Challenge

- Life altering
- Improved quality of life

Non-IgE Mediated Food Allergy: Mostly Gastrointestinal

- Food protein induced enterocolitis syndrome
- Food protein induced allergic proctocolitis
- Food protein induced enteropathy
- Celiac disease
- Eosinophilic esophagitis
- Cow's milk allergy induced iron deficiency anemia



Food Intolerance

- Difficulty with digestion
- Can be temporary or chronic

- Lactose intolerance
- FODMAPs

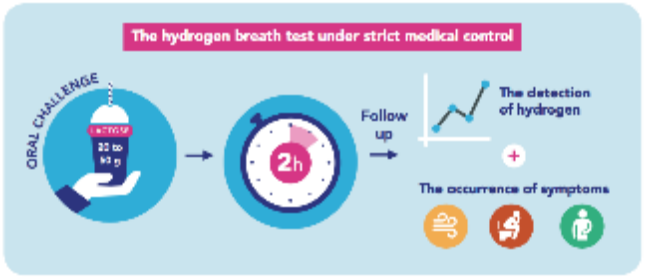


Figure 5. The diagnosis of lactose intolerance.

https://www.yogurtinnutrition.com/lactose-intolerance-diagnostic/

https://www.wellworks.co.nz/author/ray/

Food Sensitivity

- There is no consensus definition of how to diagnose ‘food sensitivity’
- Symptoms of other conditions have been extrapolated (without evidence) to fit under the umbrella of ‘food sensitivity’
- This term has been used in numerous ways to support:
  - Unvalidated testing
  - Marketing
  - Products or services

Clinical Commentary Review

Unproven Diagnostic Tests for Adverse Reactions to Foods

John M. Kelso, MD *San Diego, Calif*

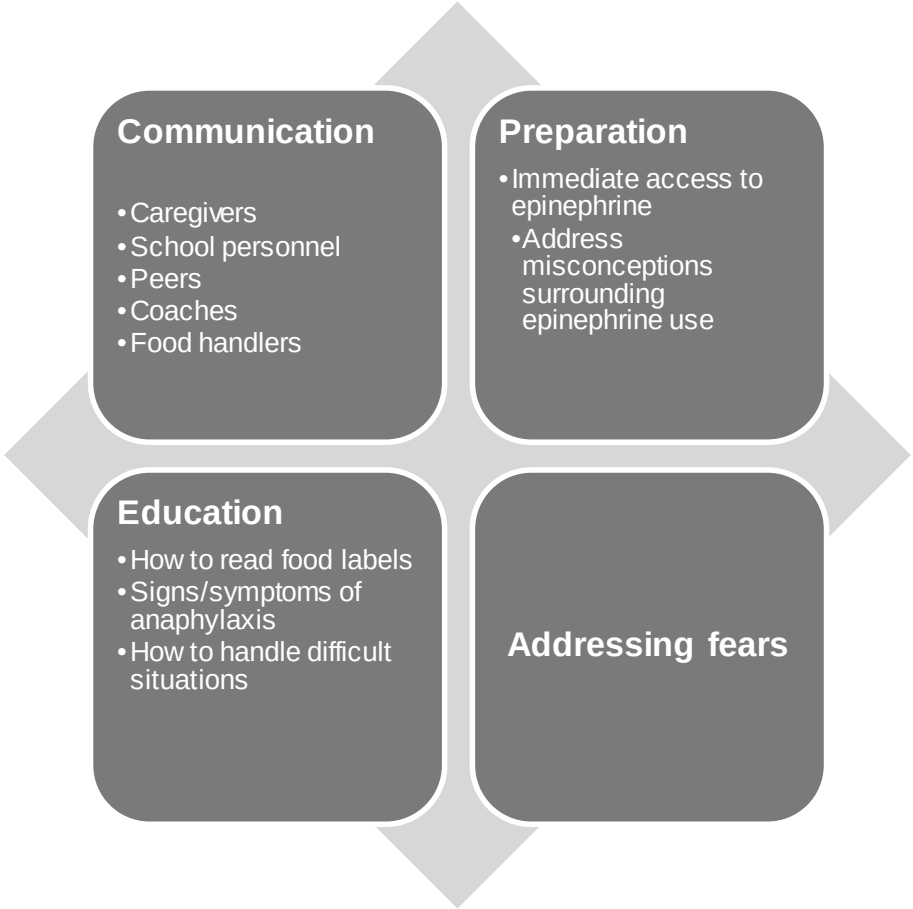
Patients often seek opinions from allergists regarding unconventional testing for adverse reactions to foods. These tests include flow cytometry to measure the change in white blood cell volumes after incubation with foods, measurement of serum IgG or IgG_4 antibodies directed against foods, intradermal provocation-neutralization with food allergens, hair analysis, electrodermal testing, and applied kinesiology. In some cases, although the laboratory methods may be valid, there are no studies showing correlation with disease. In other cases, blinded, controlled studies have shown a lack of reproducibility and a lack of correlation with disease. Most of the tests lack biologic plausibility. By understanding the methodology of these tests and the lack of evidence supporting their utility, allergists can provide knowledgeable, evidence-based information to patients who inquire about them.

Kelso J. JACI:IP. 2018;6(2):362-365

What We Know About Food Allergy

What We ALSO Know About Food Allergy

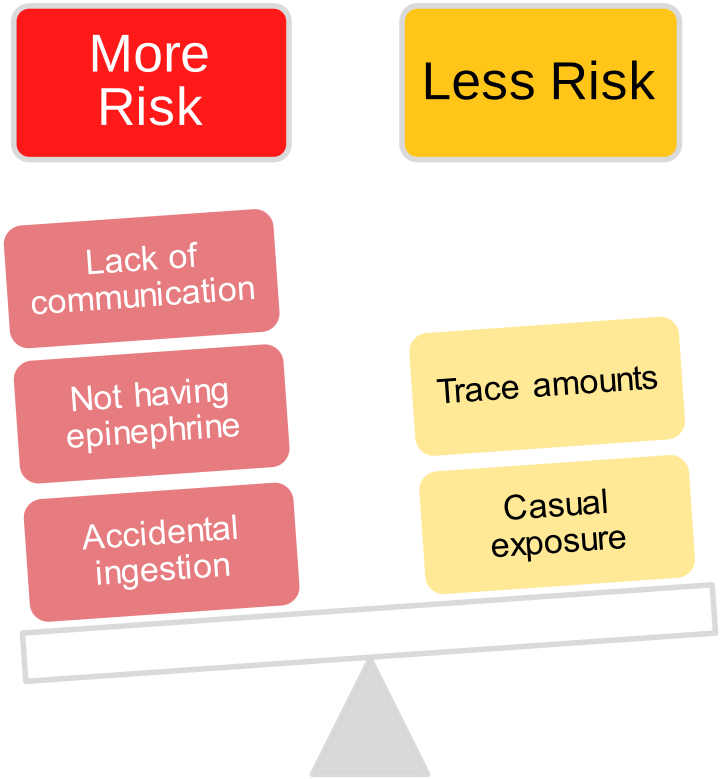
Successful Food Allergy Management



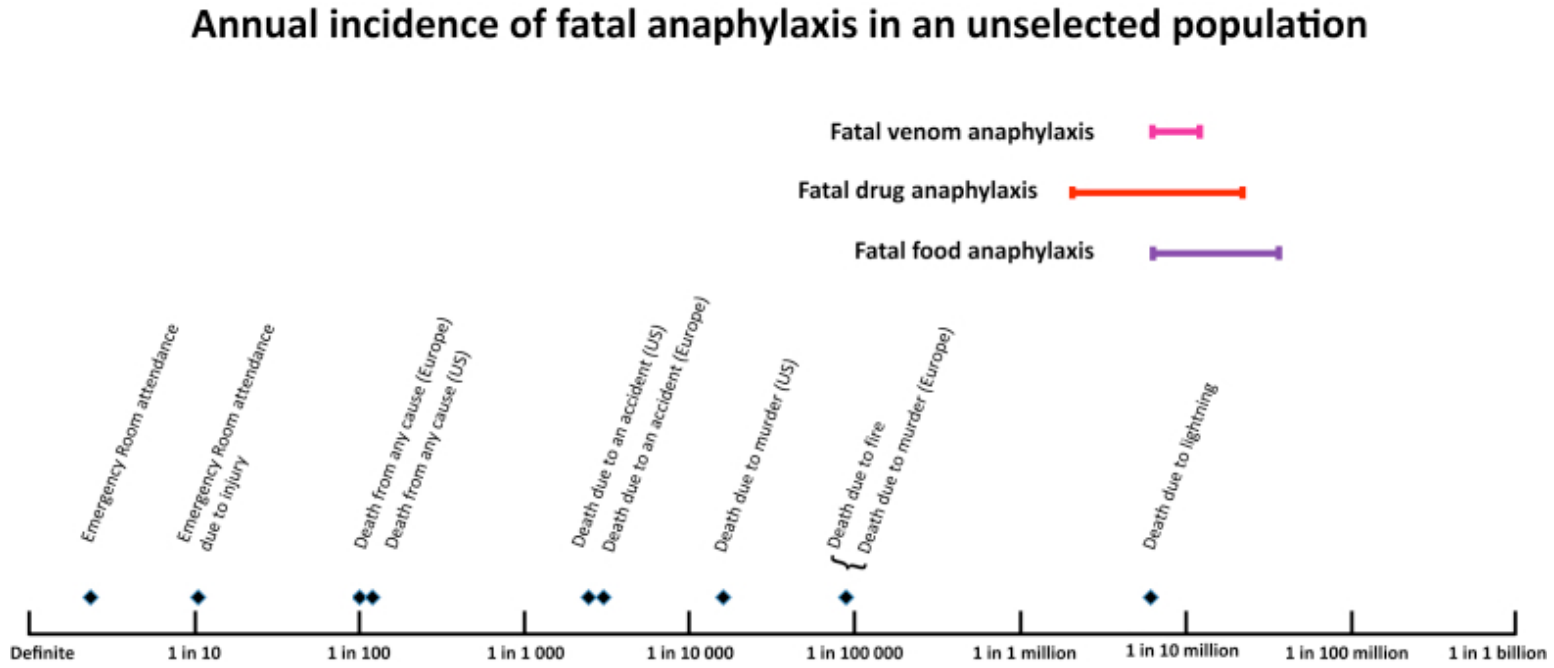
Anyone Who Feels They Are Qualified to Diagnose Food Allergy Needs To:

Shaker M, et al. Current Opinion in Pediatrics. 2017;29(4):497-502.

Risk and Food Allergy



Understanding Risk



Shaker M, et al. Ann Allergy Asthma Immunol. 2020;125(3):252-261.

Important Questions

- Do all foods pose the same risk for causing ANY reaction from ingestion of trace amounts?
- How often does ingestion of trace amounts cause severe allergic reactions?
- Does each individual with a certain food allergy carry the same risk for…
  - ANY reaction?
  - SEVERE reaction?

Controversies in Allergy

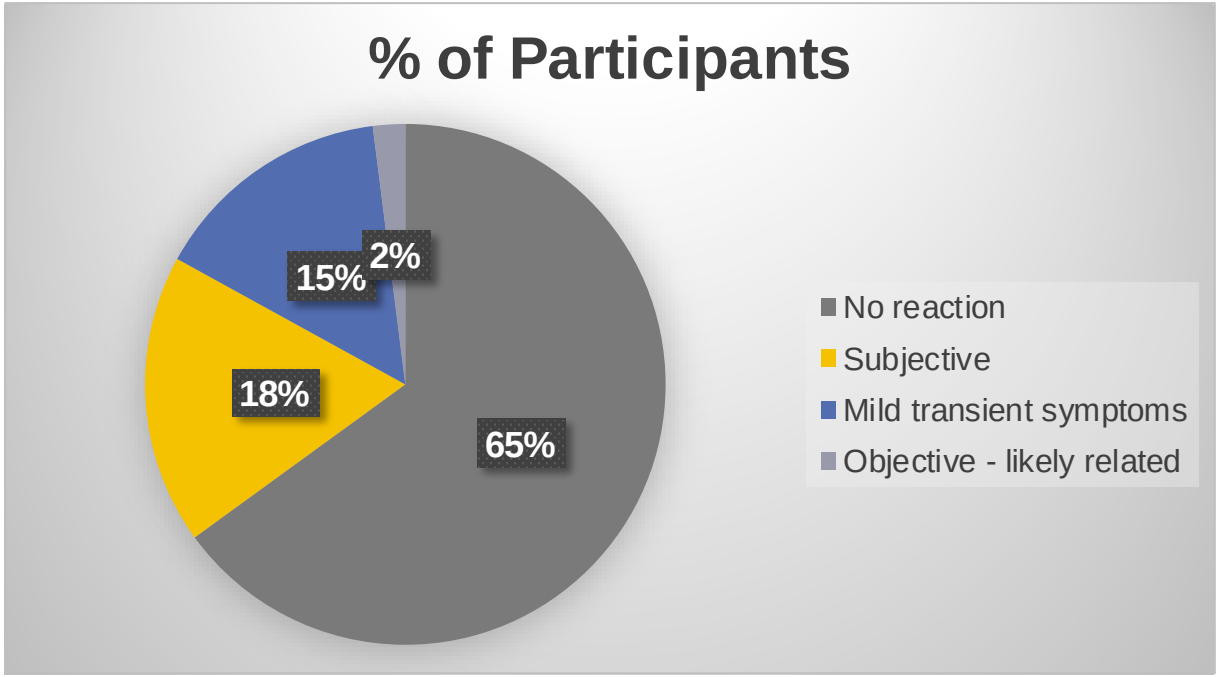
Managing Food Allergy When the Patient Is Not Highly Allergic

Scott H. Sicherer, MD[a], Elissa M. Abrams, MD[b,c], Anna Nowak-Wegrzyn, MD, PhD[d,e], and Jonathan O'B. Hourihane, FRCPI[f,g] *New York, NY; Winnipeg, MB, Canada; Vancouver, BC, Canada; Olsztyn, Poland; and Dublin, Ireland*

J Allergy Clin Immunol Pract 2022;10:46-55

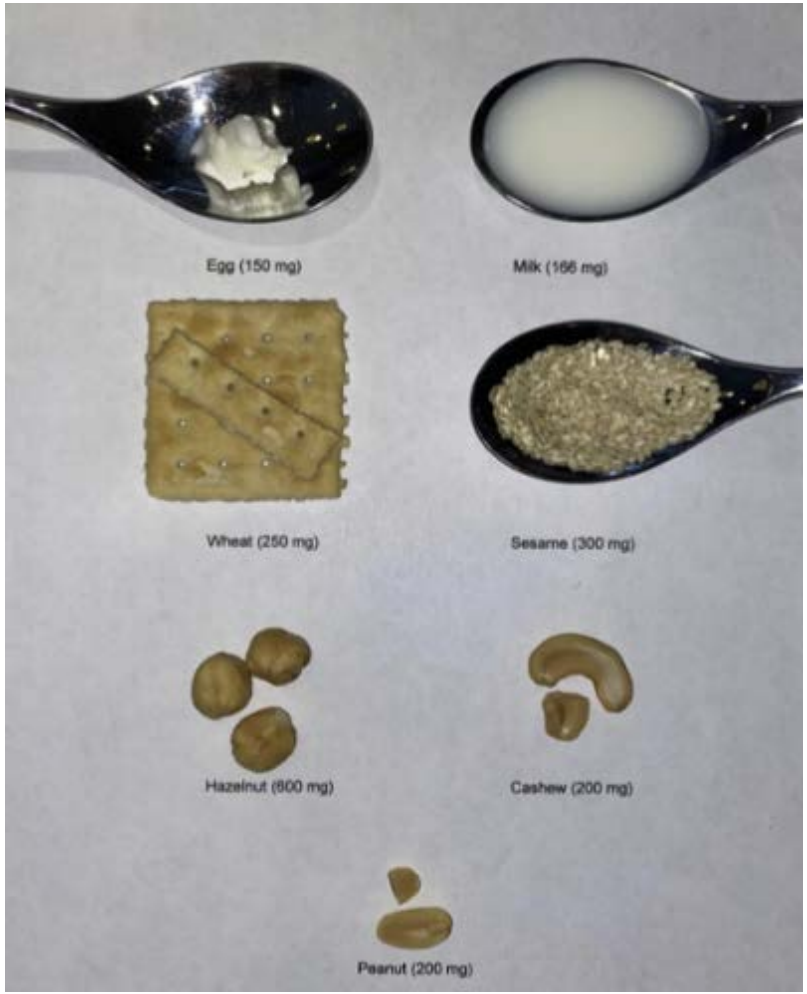
PATS – One 1.5 mg Dose To Find the Outliers

- 378 children with peanut allergy
  - (~50% ignore PAL)
- All in – one dose…what happens?



Hourihane JO, et al. J Allergy Clin Immunol. 2017 May;139(5):1583-1590

Eliciting Dose for 50% of the population with each food allergy



J Allergy Clin Immunol Pract 2022;10:46-55

Shared equipment

May Contain

Processed in the same facility

May contain traces of ___

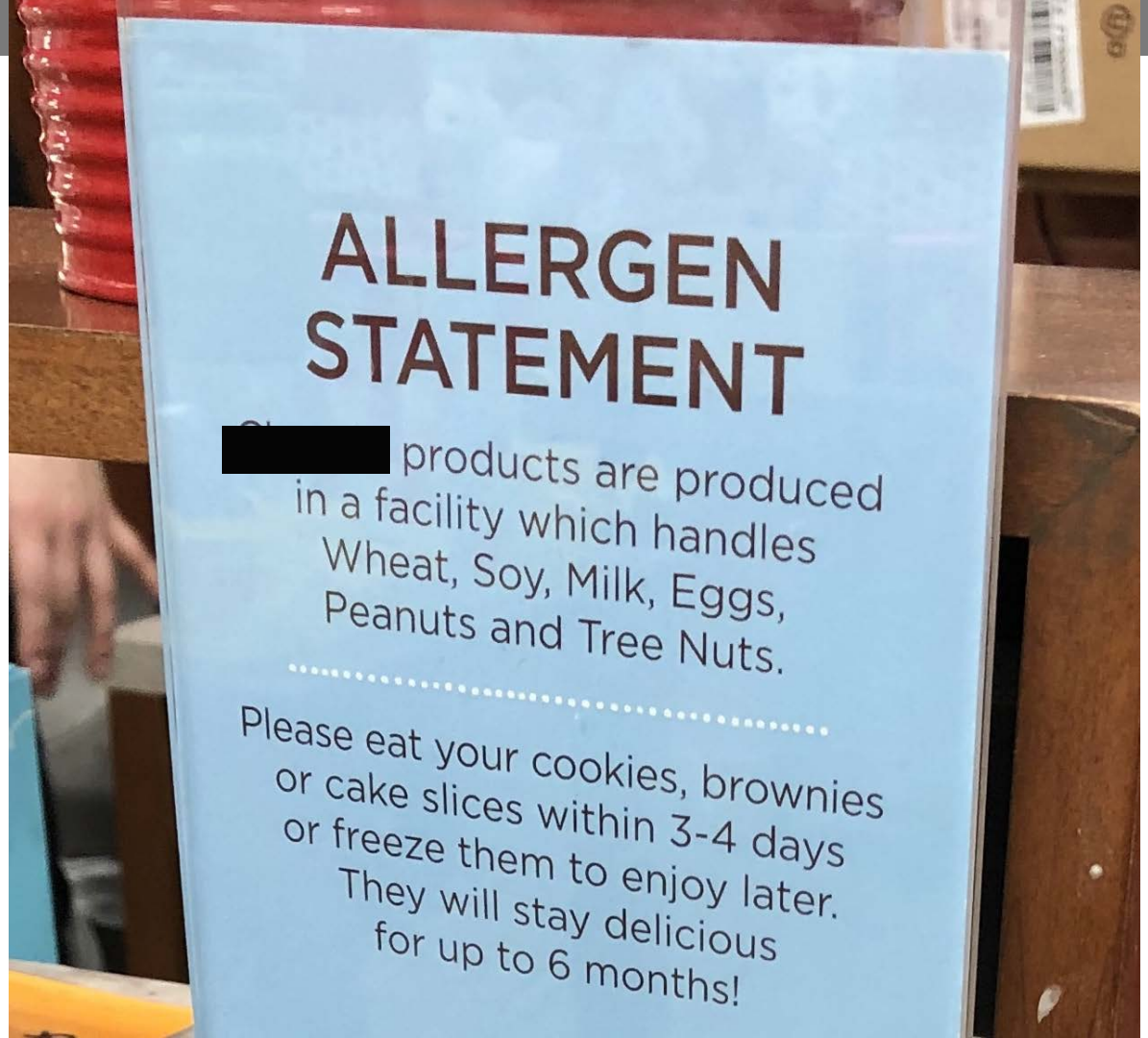
Packed in an environment where __ may be present

Not suitable for ___ allergy sufferers

___ may be present

Due to methods used in manufacturing, this product occasionally contains ___

Good manufacturing practices used to segregate ingredients in a facility that also processes allergens


ALLERGEN
STATEMENT
[redacted] products are produced
in a facility which handles
Wheat, Soy, Milk, Eggs,
Peanuts and Tree Nuts.
Please eat your cookies, brownies
or cake slices within 3-4 days
or freeze them to enjoy later.
They will stay delicious
for up to 6 months!

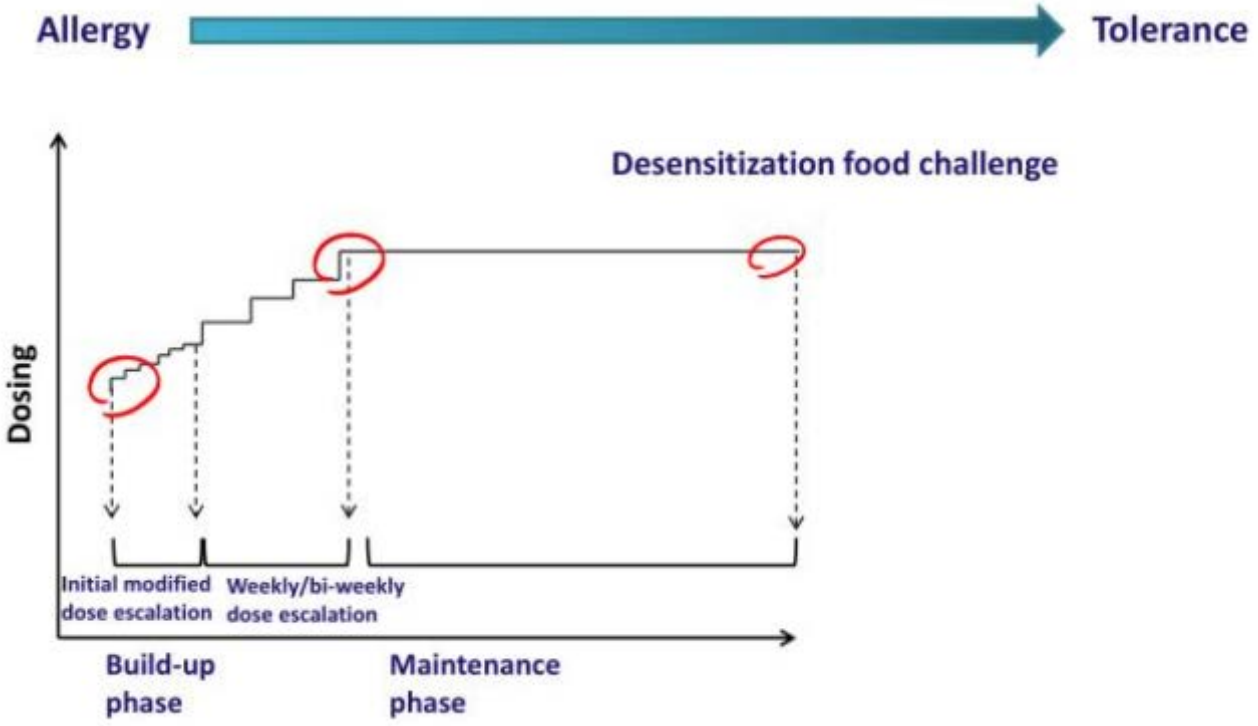
Treatment

- Parents ask about something they read on Facebook…or heard from a neighbor…or saw a news story about
- What do you tell them about food allergy treatment?

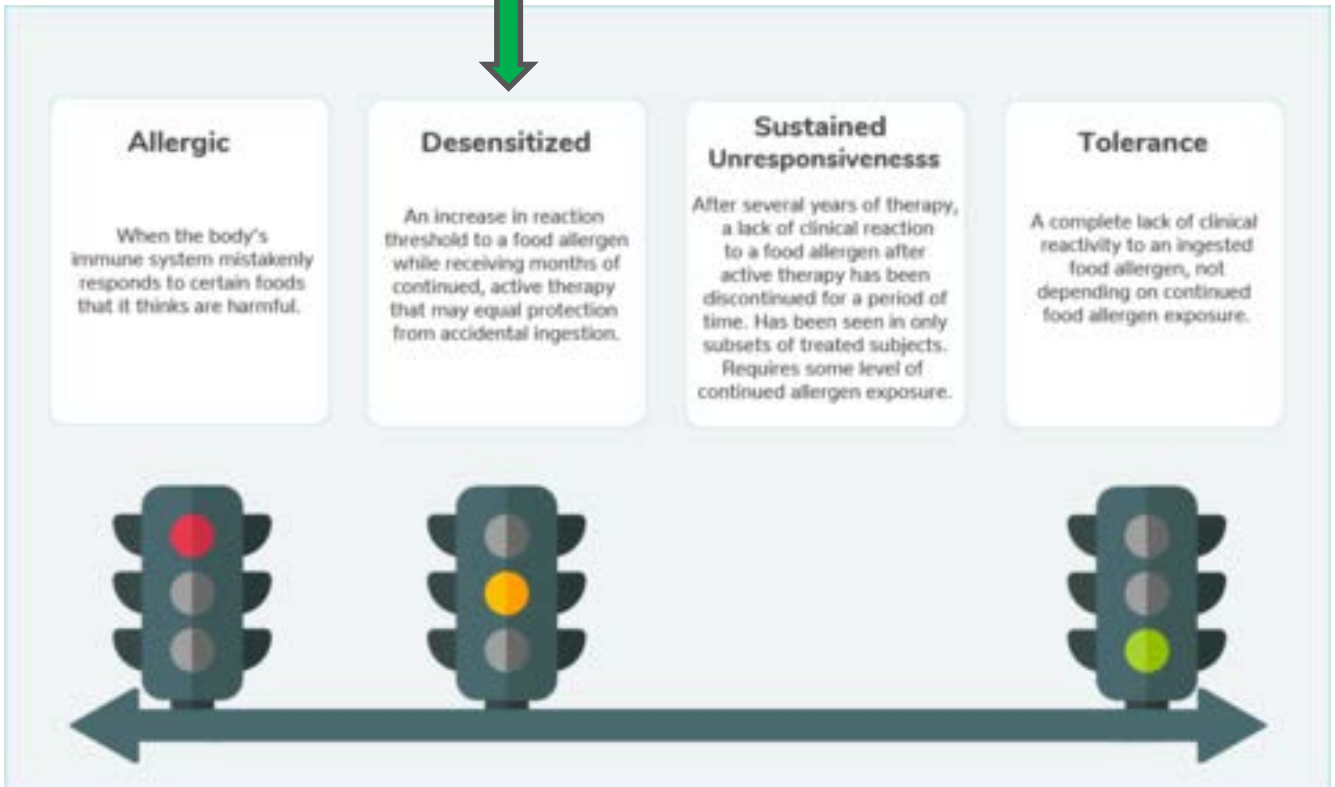
- ❑ There is no treatment available
- ❑ Treatment allows children to eat their allergen
- ❑ Food allergies can be cured if treatment is started early

Evolution of Food Allergy Treatment

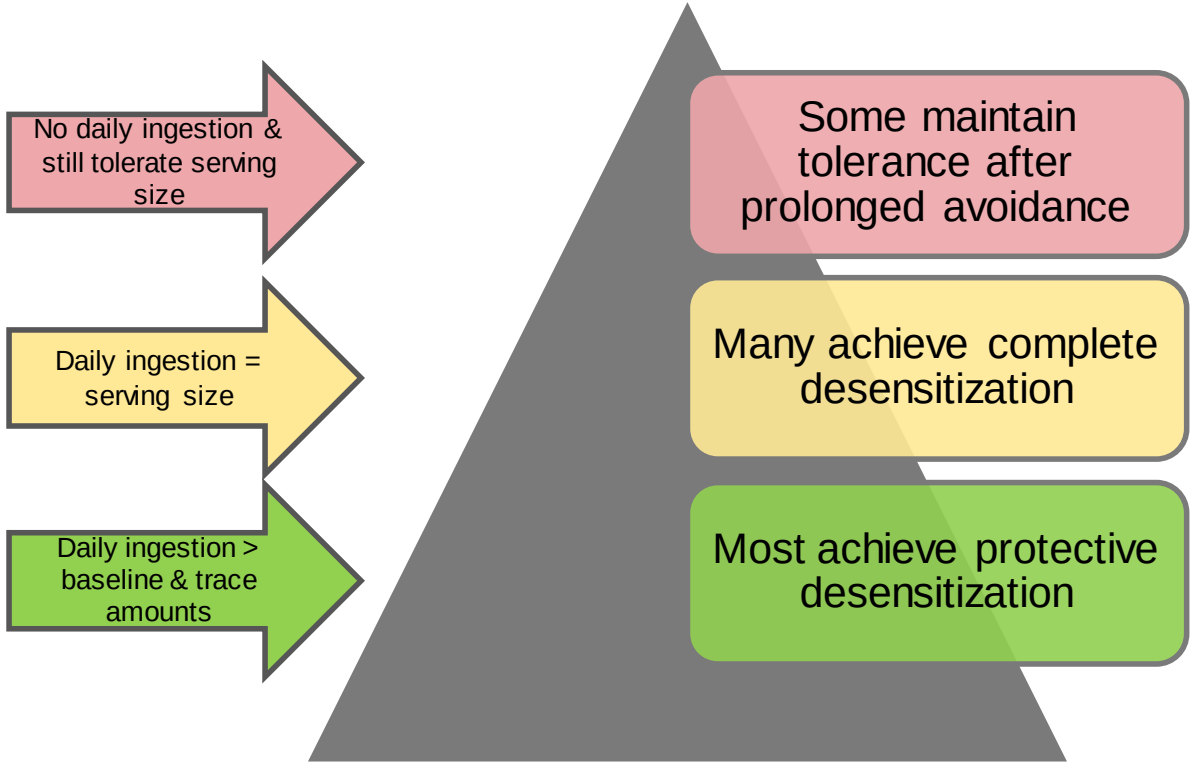
Desensitization Principles



OIT


Allergic
When the body's immune system mistakenly responds to certain foods that it thinks are harmful.
Desensitized
An increase in reaction threshold to a food allergen while receiving months of continued, active therapy that may equal protection from accidental ingestion.
Sustained Unresponsivenesss
After several years of therapy, a lack of clinical reaction to a food allergen after active therapy has been discontinued for a period of time. Has been seen in only subsets of treated subjects. Requires some level of continued allergen exposure.
Tolerance
A complete lack of clinical reactivity to an ingested food allergen, not depending on continued food allergen exposure.

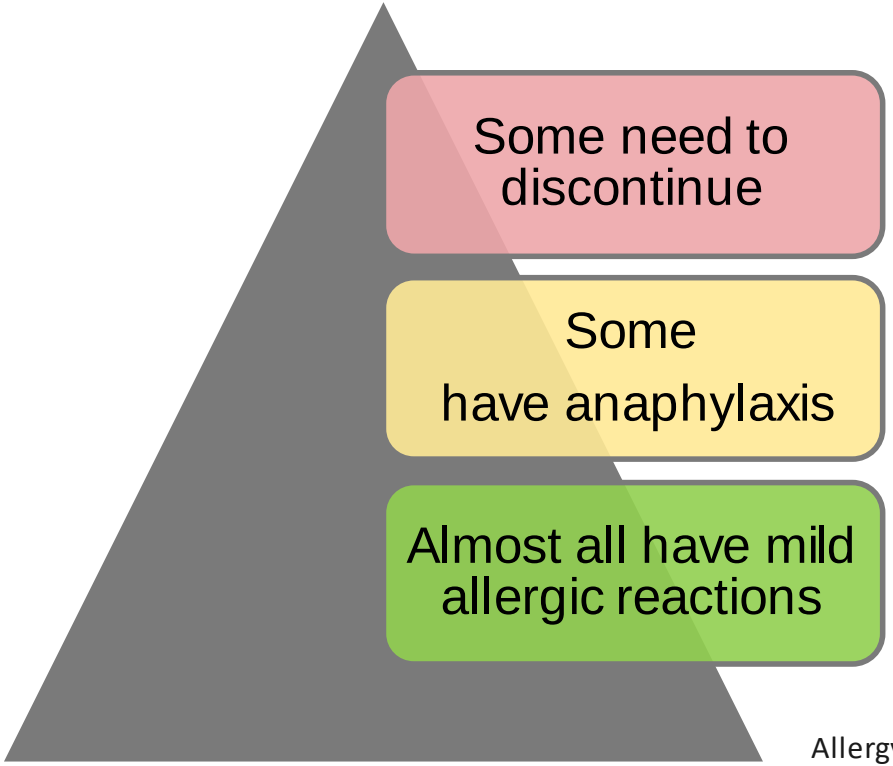
Realistic Expectations



Some maintain tolerance after prolonged avoidance	Peanut: 13-74% Egg: 35-44% Milk: 21% Wheat: 13%
Many achieve complete desensitization	Peanut: 56-78% Egg: 45-84% Milk: 60-71% Wheat: 52-64% Sesame: 88%
Most achieve protective desensitization	Peanut: 73-90% Egg: 82% Milk: 78-89% Hazelnut: 65% Sesame: 100%

Allergy Asthma Clin Immunol. 2020 Mar 18;16:20.

Realistic Risks

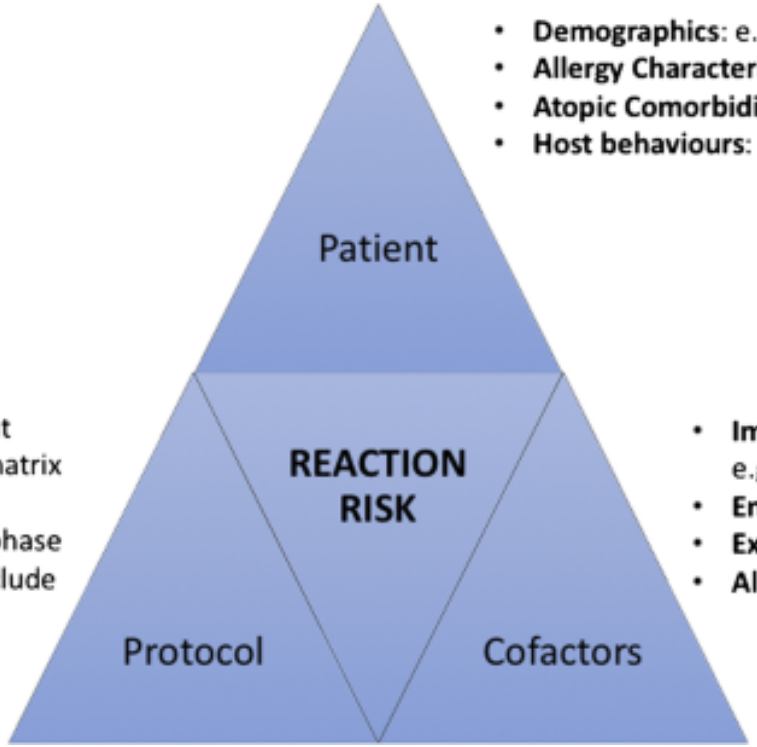


Peanut: 13%
Egg: 18%
Wheat: 43%

16-17% vs 1.6-2.6% controls

Allergy Asthma Clin Immunol. 2020 Mar 18;16:20.

Modifiable and Non-modifiable Risks of OIT



- **Demographics**: e.g. age, gender, pubertal stage
- **Allergy Characteristics**: e.g. IgE profile
- **Atopic Comorbidity**: e.g. allergic rhinitis, asthma
- **Host behaviours**: e.g. patient compliance

- **Product Characteristics**: e.g. heat modified vs raw allergen, food matrix
- **Dosing Characteristics**: e.g. rush protocol vs extended updosing phase
- **Eligibility Criteria** which may exclude higher risk patients

- **Immune stimulation** e.g. intercurrent infection
- **Environmental**: e.g. pollen exposure
- **Exercise**
- **Altered gut absorption**

Curr Treat Options Allergy **6,** 164–174 (2019).

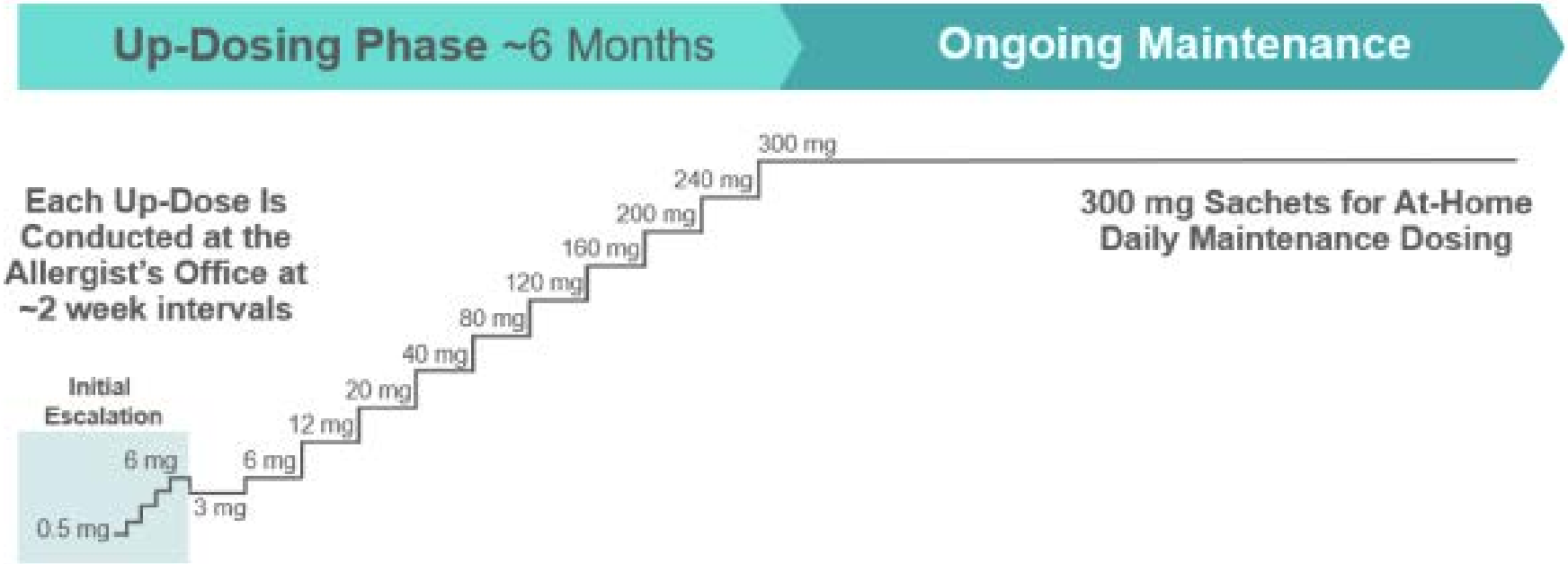
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 22, 2018 VOL. 379 NO. 21

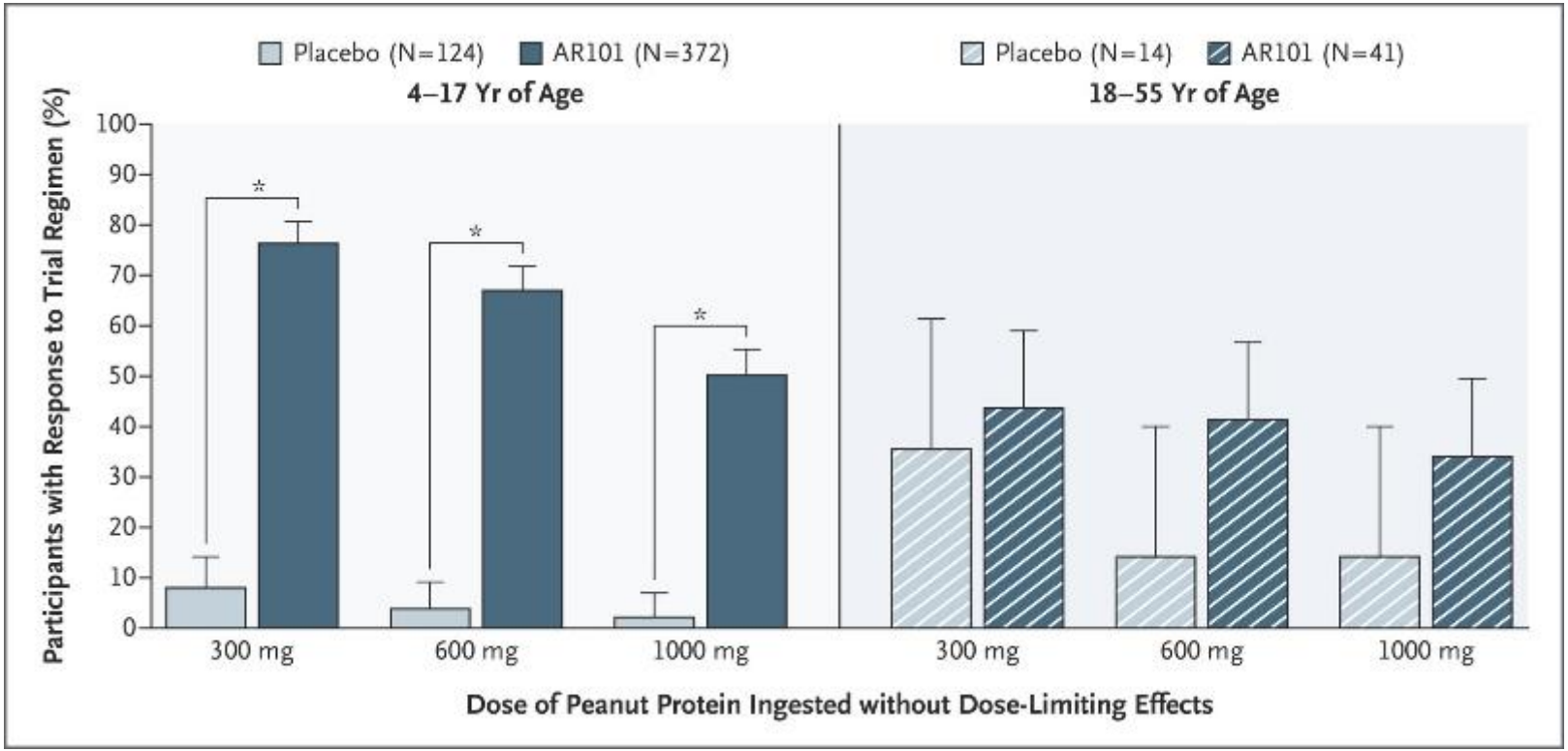
AR101 Oral Immunotherapy for Peanut Allergy

The PALISADE Group of Clinical Investigators*

N Engl J Med. 2018 Nov 22;379(21):1991-2001.



N Engl J Med. 2018 Nov 22;379(21):1991-2001.



N Engl J Med. 2018 Nov 22;379(21):1991-2001.

Bégin et al.
Allergy Asthma Clin Immunol (2020) 16:20
https://doi.org/10.1186/s13223-020-0413-7

Allergy, Asthma & Clinical Immunology

REVIEW Open Access

CSACI guidelines for the ethical, evidence-based and patient-oriented clinical practice of oral immunotherapy in IgE-mediated food allergy

P. Bégin[1,2,3*], E. S. Chan[4], H. Kim[5,6], M. Wagner[7], M. S. Cellier[3], C. Favron-Godbout[8], E. M. Abrams[9], M. Ben-Shoshan[10], S. B. Cameron[4,11], S. Carr[12], D. Fischer[5], A. Haynes[13], S. Kapur[14], M. N. Primeau[15], J. Upton[16], T. K. Vander Leek[12] and M. M. Goetghebeur[7]

Entry Oral Food Challenges

- Misconceptions about safety/risk
- Can demonstrate symptoms with ingestion
- Can establish an idea of threshold dose
- Can remove fear of the unknown
- Can avoid unnecessary OIT in someone not allergic
- Can provide valuable information to influence medical decision making

Shared Decision Making

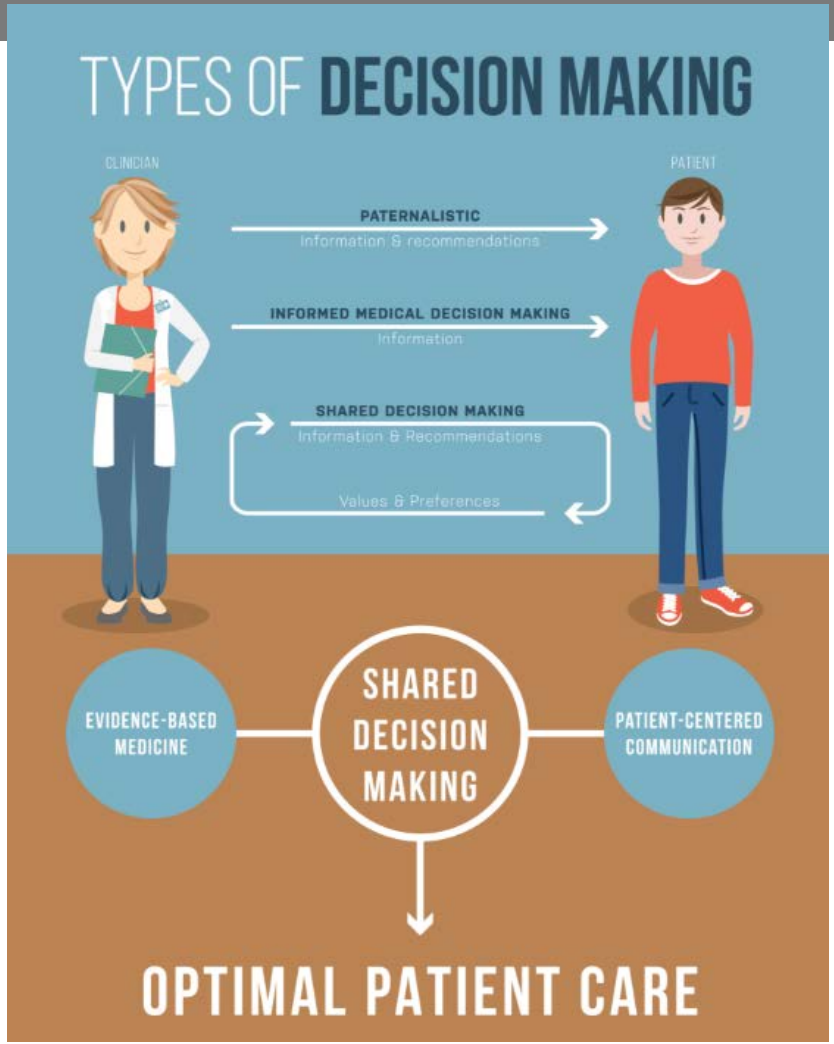
WE discuss evidence, options, risks

+

PATIENTS discuss preferences & values

+

WE help PATIENTS make decisions based upon “what matters most”



Help Families Prepare for Their OIT Journey

- Initial anxiety surrounding purposeful ingestion of known allergen
- Expected reactions and how to manage
  - Distinguish between OIT related symptoms vs anxiety vs comorbid conditions
- Time commitment
  - Up-dosing in office visits
  - Daily regimen at home
  - Scales, measurement of doses

FDA NEWS RELEASE

FDA approves first drug for treatment of peanut allergy for children

For Immediate Release: January 31, 2020

Palforzia®

Peanut (*Arachis hypogaea*)
Allergen Powder-dnfp

Palforzia Protocol

Table 1: Dosing Configuration for Initial Dose Escalation (Single Day Dose Escalation)

Dose Level	Total Dose	Dose Configuration
A	0.5 mg	One 0.5 mg capsule
B	1 mg	One 1 mg capsule
C	1.5 mg	One 0.5 mg capsule; One 1 mg capsule
D	3 mg	Three 1 mg capsules
E	6 mg	Six 1 mg capsules

Initial Dose Escalation supplied as a single card consisting of 5 blisters containing a total of 13 capsules.

Palforzia Protocol

Table 2: Daily Dosing Configuration for Up-Dosing

Dose Level	Total Daily Dose	Daily Dose Configuration	Dose Duration (weeks)
1	3 mg	Three 1 mg capsules	2
2	6 mg	Six 1 mg capsules	2
3	12 mg	Two 1 mg capsules; One 10 mg capsule	2
4	20 mg	One 20 mg capsule	2
5	40 mg	Two 20 mg capsules	2
6	80 mg	Four 20 mg capsules	2
7	120 mg	One 20 mg capsule; One 100 mg capsule	2
8	160 mg	Three 20 mg capsules; One 100 mg capsule	2
9	200 mg	Two 100 mg capsules	2
10	240 mg	Two 20 mg capsules; Two 100 mg capsules	2
11	300 mg	One 300 mg sachet	2

Should We Start OIT in Infants?

- Vickery et al
  - 37 children 9-36 months to peanut maintenance 300 or 3000 mg/day
  - 81% desensitized to 5000 mg
  - 4 weeks sustained unresponsiveness after 29 months: 78% overall; no difference in daily maintenance
- Martorell et al
  - 60 children 24-36 months milk
  - After 12 months: 90% tolerated 200 mL vs 23% controls
- Soller et al
  - 270 children 0.75-5.9 yrs (median 1.9) peanut OIT; 90% reached 300-320 mg daily dose
  - 78% passed 4000 mg OFC at one year

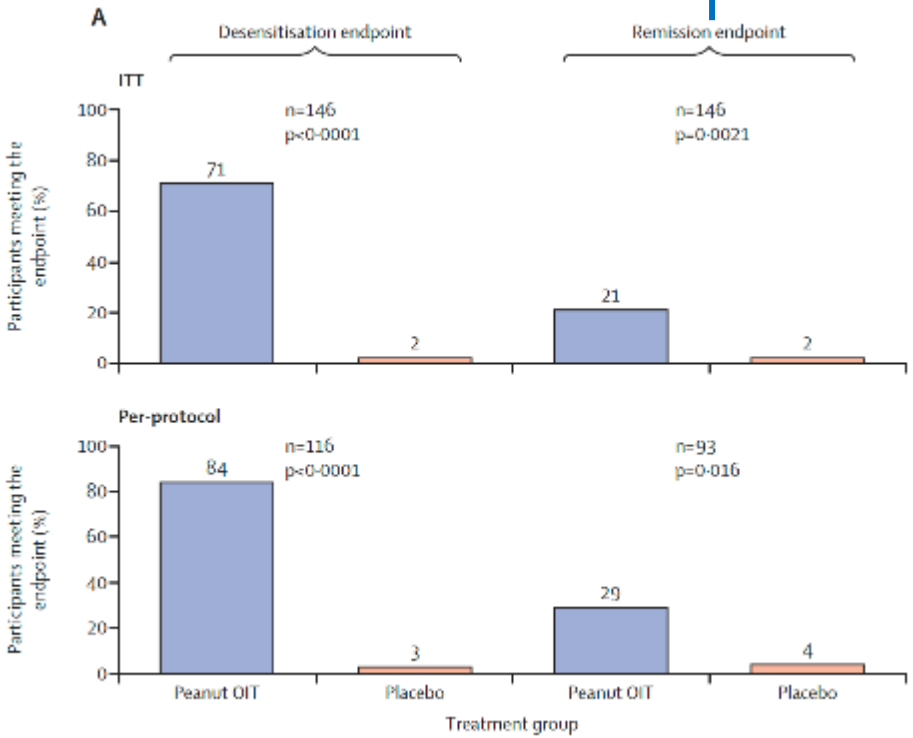
J Allergy Clin Immunol. 2017 Jan;139(1):173-181.e8.
Clin Exp Allergy. 2011 Sep;41(9):1297-304.
J Allergy Clin Immunol Pract. 2021 Mar;9(3):1349-1356.e1.

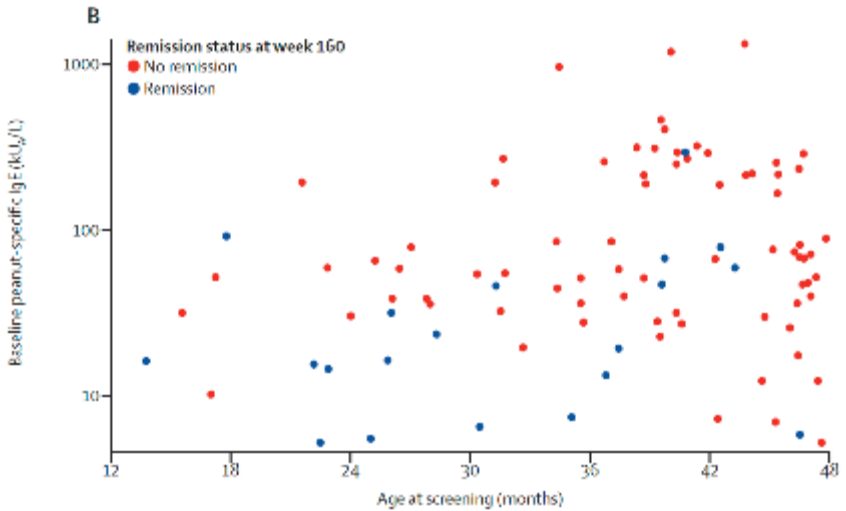
Efficacy and safety of oral immunotherapy in children aged 1–3 years with peanut allergy (the Immune Tolerance Network IMPACT trial): a randomised placebo-controlled study

Stacie M Jones, Edwin H Kim, Kari C Nadeau, Anna Nowak-Wegrzyn, Robert A Wood, Hugh A Sampson, Amy M Scurlock, Sharon Chinthrajah, Julie Wang, Robert D Pesek, Sayantani B Sindher, Mike Kulis, Jacqueline Johnson, Katharine Spain, Denise C Babineau, Hyunsook Chin, Joy Laurienzo-Panza, Rachel Yan, David Larson, Tielin Qin, Don Whitehouse, Michelle L Sever, Srinath Sanda, Marshall Plaut, Lisa M Wheatley, A Wesley Burks, for the Immune Tolerance Network

Lancet 2022; 399: 359–71

12-24 months = 71%
24-36 months = 35%
36-48 months = 19%





Lancet 2022; 399: 359–71

Future (Soon?) Approaches

- Sublingual immunotherapy
- Epicutaneous immunotherapy (patch)
- Biologics

Conclusion

- Accurate diagnosis of food allergy requires careful consideration of the clinical history and knowledge of food allergy reactions
- Food allergy tests are misleading and must be interpreted in the proper context
- We need to help patients understand risk to guide their decisions for self-management