NAVDF 2025

Scientific Track

Food Allergies in Humans Part 1 – Clinical Presentations and Diagnostic Testing

Dr. Amanda Cox

#NAVDF2025

2025 North American Veterinary Dermatology Forum

Food Allergy in Humans – Part 1:
Classification and Diagnosis

Amanda Cox, MD

Associate Professor of Pediatrics

Division of Pediatric Allergy / Jaffe Food Allergy Institute

Mount Sinai

Kravis Children's Hospital

Disclosures

- I have no relevant personal financial or commercial interests to disclose.
- Our division receives research funding from Aimmune, DBV, Siolta, Genentech, Novartis, Alk-Abello, NIH/NIAID and I am a co-investigator on these studies

Objectives

1. Recognize food allergic disorders in humans

2. Understand classification of human food allergy as IgE-mediated and non-IgE-mediated food allergy

3. Review what is new in food allergy diagnostics

Introduction

- Adverse reactions to foods can be divided into immune and non-immune reactions

- Immune reactions to foods can be further classified based on immunopathology or the elements of the immune system that contribute to a food reaction
  - IgE mediated
  - Non IgE- mediated
  - Mixed IgE + non-IgE mediated
  - Cell mediated

- IgE mediated food allergy affects 6-8% of children and has a major impact on quality of life. (*This is the primary focus of my patient care and research.)*

Introduction

- Advances in food allergy diagnostics are helping us to better understand and manage our patients with food allergies

  - Evaluating diagnostic tests against oral food challenge results from large clinical trials is providing better understanding of existing and emerging diagnostic modalities

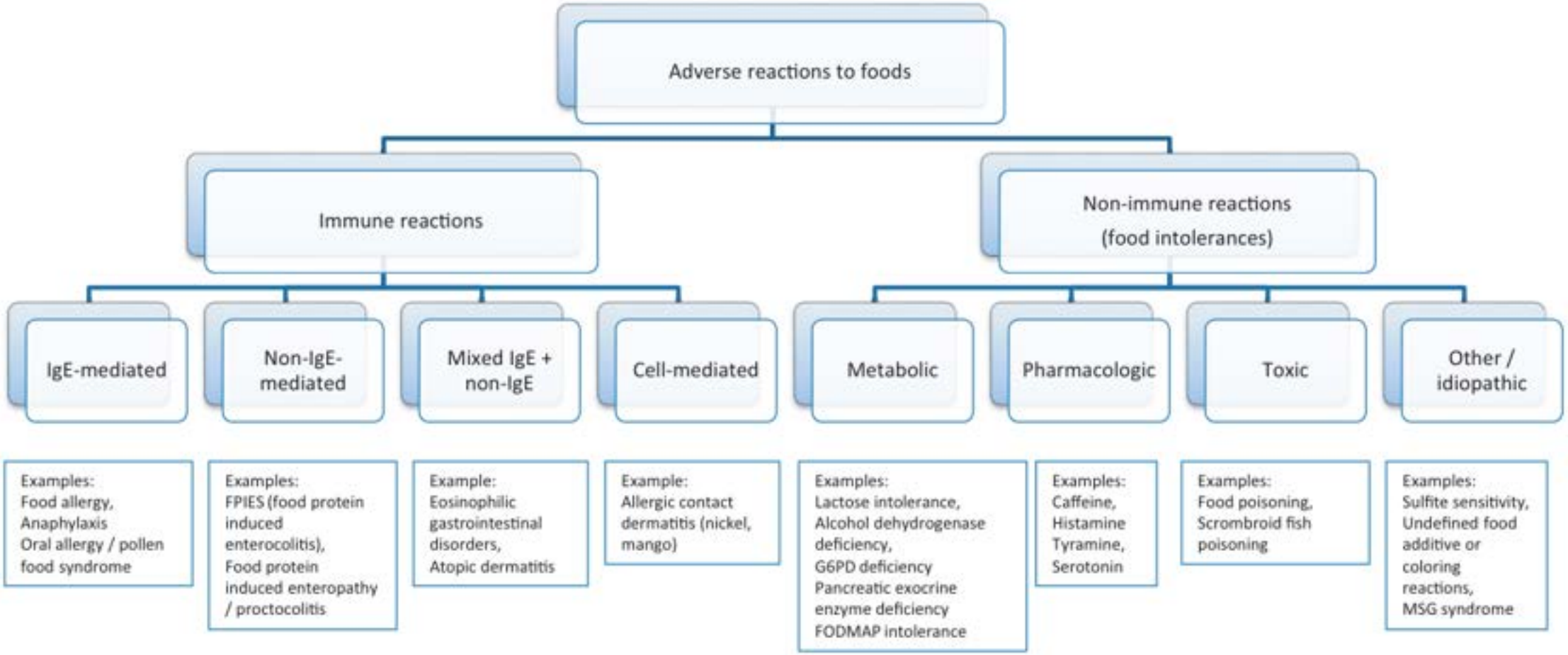
- Improved understanding of the pathophysiology of food allergy as well as global patterns in food allergy development and epidemiology has resulted changes in guidance that may help prevent food allergy development as well as has resulted in novel therapies (Part 2).

Adverse Reactions to foods - classification

- A careful history will aid the clinician in identifying whether the etiology of an adverse food reaction is non-immunologic or allergic.

- Immunologic and non-immunologic adverse reactions to food are associated with characteristic symptoms and chronicity, and differ with regard to severity and impacts on overall health. In contrast to non-immunologic reactions, true IgE-mediated food allergic reactions can be rapid in onset and life-threatening.

- The recognition of typical signs and symptoms of various adverse food reactions guides the clinician in appropriate diagnosis, application of testing, management and patient education.



Cox AL, Sicherer SH. Classification of adverse food reactions. Journal of Food Allergy 2020.

Non-immunologic adverse food reactions

Metabolic

- Inability to metabolize or fully digest a food component due to specific enzyme deficiencies or insufficiencies
- Symptoms typically isolated to GI tract
- Not life-threatening
- Can produce significant discomfort
  - Symptoms of bloating, flatulence, diarrhea, abdominal pain, cramping
  - Degree of symptom severity related to quantity consumed

Non-immunologic adverse food reactions

Metabolic

- **Lactose intolerance (deficiency of small intestinal lactase enzyme)** –
  - Most common type of metabolic food intolerance.
  - Lactose from ingested dairy moves through gut without being digested
  - Hydrogen gas is released due to bacterial fermentation
  - Sugars in the gut draw in fluid, leading to loose stools
  - Affects 70% of world's population
  - Usually develops gradually from childhood into adulthood
  - Is considered a normal variant of human metabolism (not a "disease")
  - Transient form following viral GI infections

Non-immunologic adverse food reactions

Metabolic

- **Lactose intolerance** (continued)
  - Intolerance to very low doses of lactose suggest IBS (irritable bowel syndrome)
  - Diagnosis based on clinical history
  - Can confirm diagnosis with hydrogen breath test or small bowel biopsy lactase enzyme assay, if diagnosis is not clear.
  - Treatment is avoidance of dietary lactose or supplementation with replacement lactase enzymes
  - Is not considered a "food allergy"

Non-immunologic adverse food reactions

Metabolic

- **Alcohol dehydrogyenase deficiency**
  - Flushing and vomiting due to inability to metabolize alcohol
- **FODMAP intolerance**
  - Often occurs in individuals with IBS
  - Poor absorption of short-chain fermentable carbohydrates

    oligosaccharides (wheat, garlic, onion)

    disaccharides (lactose)

    monosaccharides (fructose in fruits, honey, corn syrup)

    polyols (xylitol, mannitol, sorbitol)

Non-immunologic adverse food reactions

Metabolic

Enzyme deficiencies with more serious physiologic effects / reactions

- **Glucose-6-phosphate dehydrogenase (G6PD)**

  X-linked genetic disorder

  Missing enzyme that protects RBCs against oxidative stress

  Can present with acute hemolysis upon intake of certain foods (eg. fava beans) or medications (eg. Chloroquine)

- **Cystic fibrosis related pancreatic enzyme insufficiency**

  Inability to digest fat and protein

  Malabsorption of fat-soluble vitamins A,D,E,K

  Can lead to steatorrhea, growth failure, coagulation defects, bone mineralization

Non-immunologic adverse food reactions

Pharmacologic

- **Components in foods have intrinsic pharmacologic effects that can cause symptoms**, examples include:
  - Caffeine
  - Histamine
  - Tryptamine
  - Tyramine
  - Serotonin
  - MSG symptom complex = headache, myalgia, diaphoresis, flushing due to amino acid neurotransmitter glutamate.
  - Sulfiting agents (preservatives) can cause wheezing in some with asthma

Non-immunologic adverse food reactions

Toxic

Direct toxic effects of foods

- Bacterial food poisoning – GI and neurologic symptoms possible
- Scombroid poisoning – bacterial overgrowth in spoiled dark-meat fish (tuna, mahi-mahi) can cause accumulation of histamine-like chemicals

>> flushing, rash, headache, diarrhea

Idiopathic / other / unproven adverse food reactions

- Ingestion of foods with high levels of natural histamine (fermented foods, aged cheese, processed meats, wine) can mimic IGE-mediated food allergy for some
- Intolerances to flavorings, food colorings, additives often reported, but are actually rare and not well characterized.

Immunologic adverse food reactions = "FOOD ALLERGY"

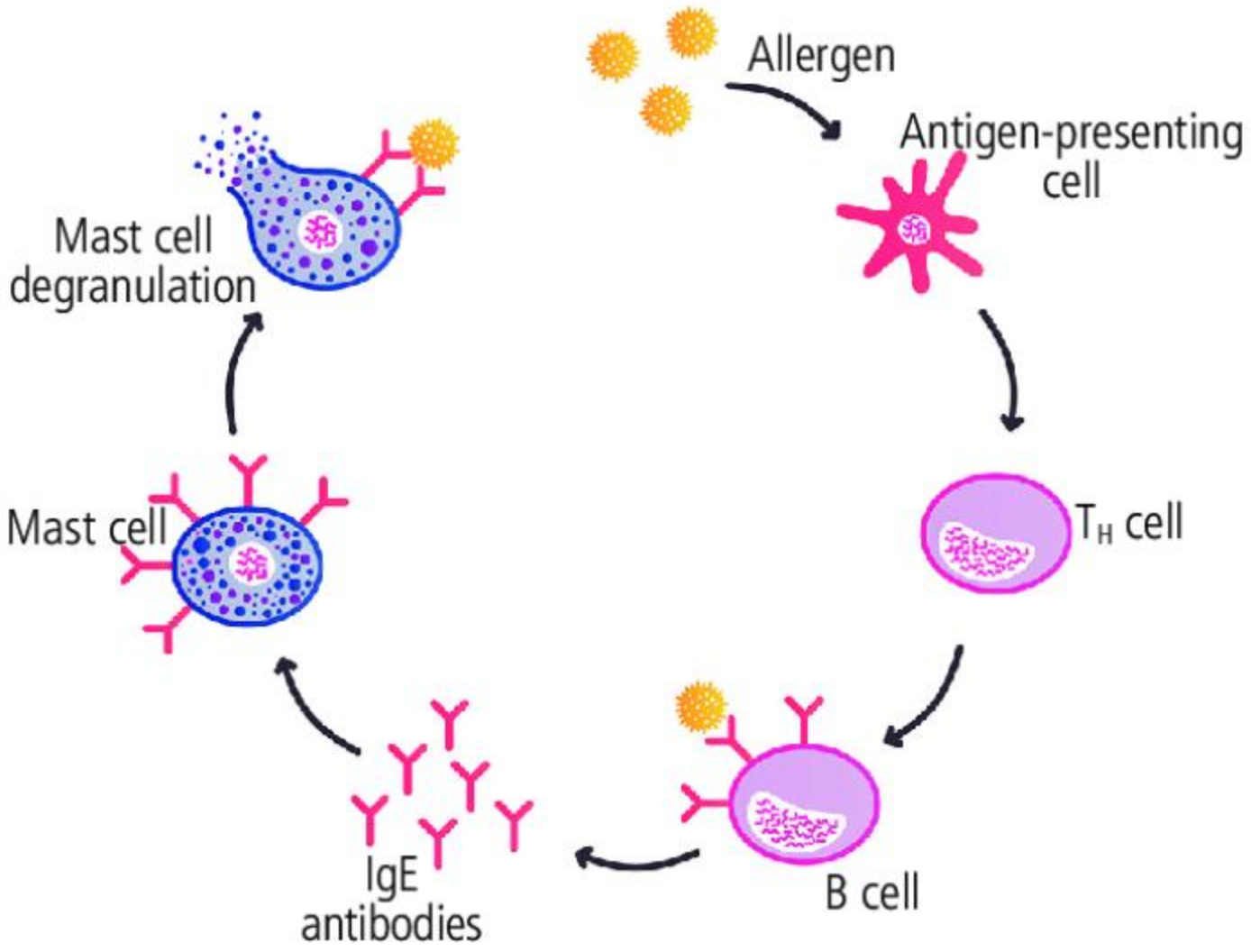
IGE (Immunoglobulin E) mediated

An individual is first SENSITIZED to a particular food component, usually a protein, through GI, skin, or respiratory tract exposure

Then produces allergen-specific IgE that binds to receptors on human mast cells and basophils.

Upon re-exposure to that food, the allergen binds and cross-links mast-cell surface bound IgE, triggering cell degranulation and release of chemical mediators, resulting in the physiologic symptoms of an acute allergic reaction.

IgE mediated reactions are generally rapid in onset (occur within minutes to hours of exposure)



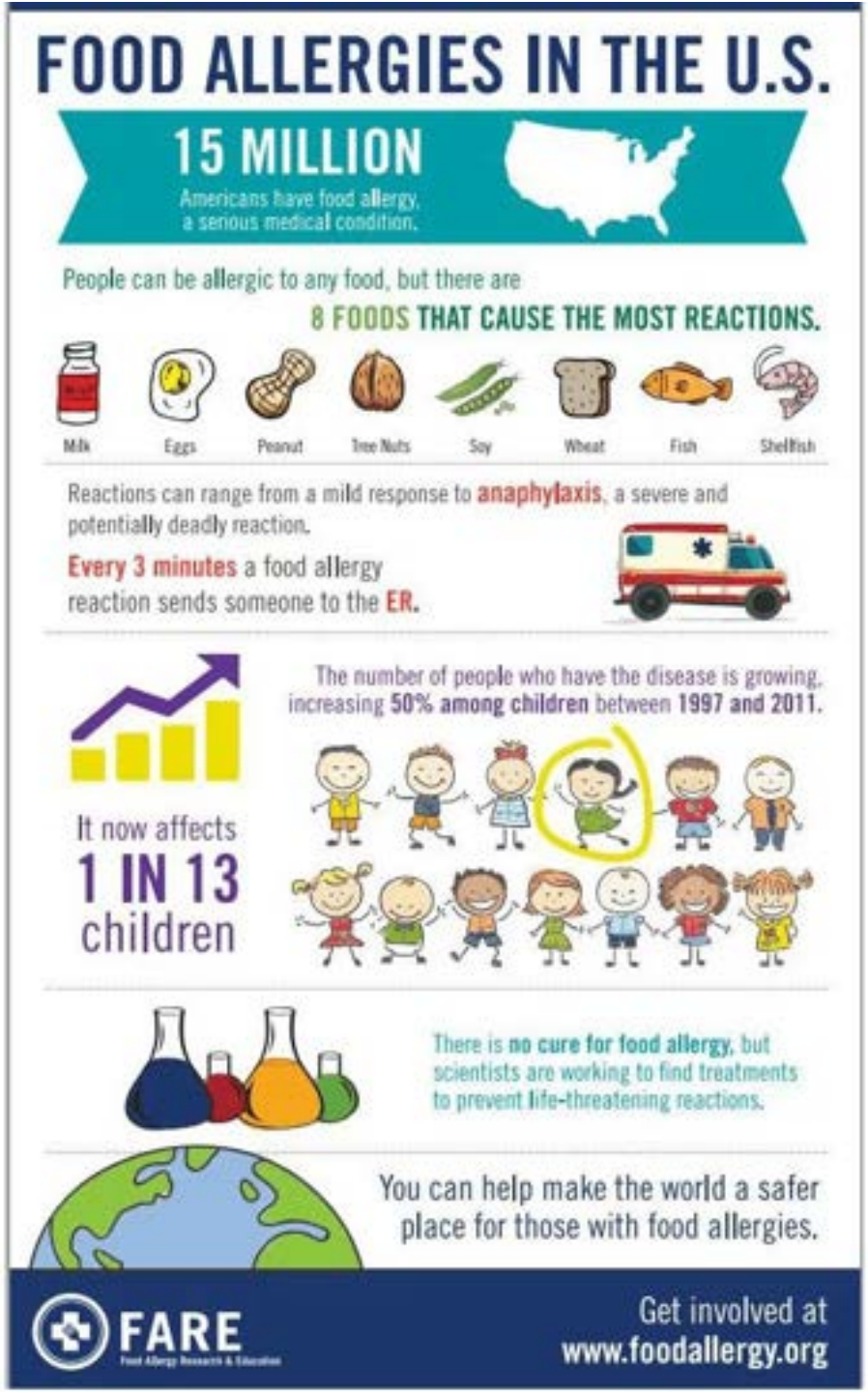
González de Olano, David & Alvarez-Twose, Iván. (2018). Mast Cells as Key Players in Allergy and Inflammation. Journal of Investigational Allergology and Clinical Immunology. 28. 365-378. 10.18176/jiaci.0327.

Immunologic adverse food reactions

IGE (Immunoglobulin E) mediated food allergy

The most common food allergies in humans are milk, egg, wheat, soy, peanut, tree nuts, sesame, finned fish, shellfish

- Anaphylaxis
  - Most severe manifestation of an acute allergic reaction to food
  - May be rapid onset
  - Can be life-threatening
- Oral allergy / pollen food syndrome
- Food-dependent exercise-induced anaphylaxis
- "Alpha-gal" or galactose-alpha-1,3-galactose allergy causing delayed reactions to mammalian meat


FOOD ALLERGIES IN THE U.S.
15 MILLION
Americans have food allergy, a serious medical condition.
People can be allergic to any food, but there are
8 FOODS THAT CAUSE THE MOST REACTIONS.
Milk
Eggs
Peanut
Tree Nuts
Soy
Wheat
Fish
Shellfish
Reactions can range from a mild response to anaphylaxis, a severe and potentially deadly reaction.
Every 3 minutes a food allergy reaction sends someone to the ER.
The number of people who have the disease is growing, increasing 50% among children between 1997 and 2011.
It now affects
1 IN 13
children
There is no cure for food allergy, but scientists are working to find treatments to prevent life-threatening reactions.
You can help make the world a safer place for those with food allergies.
FARE
Get involved at
www.foodallergy.org

AAFA's Recommended Language for Signs and Symptoms of Food Allergy Reactions in Infants and Toddlers

Medical Term	Common Term	What to look for: (Adjusted language for symptoms specific to infants and toddlers)	
 Pruritis	• Itchiness	• Tongue thrusting • Tongue pulling • Repetitive lip licking or licking of hands or objects	• Throat itching • Ear pulling, scratching or putting fingers in the ears • Eye rubbing, eye itching
 Dyspnea	• Shortness of breath • Difficulty breathing	• Belly breathing • Fast breathing	• Nasal flaring (nostrils open wide) • Chest or neck "tugging"
 Stridor	• Noisy breathing • High-pitched sound while breathing (whistling sound)	• Hoarse voice, hoarse cry • Barky/croup-like cough	• Noisy breathing, especially when inhaling
 Reduced blood pressure	• Shock	• Wobbly appearance • Lethargic • Floppy or limp • Poor head control • Difficult to wake up • Crankiness	• Withdrawn or clingy • Inconsolable crying • Subdued or less active • Lace-like appearance of the skin • Blue/grey skin around mouth/lips or hands/feet
 Hypotonia, Syncope	• Poor muscle tone • Fainting ("passing out")	• Wobbly appearance • Lethargic • Floppy or limp • Poor head control • Difficult to wake up	• Crankiness • Withdrawn or clingy • Inconsolable crying • Less active
 Persistent gastrointestinal symptoms	• Gastrointestinal symptoms that are significant	• Abdominal pain • Diarrhea • Hiccups	• Spitting up • Back arching • Vomiting

aafa Asthma and Allergy Foundation of America

KFA Kids with Food Allergies

Adapted from Pistiner, Michael, et al. "Caregiver-Reported Presentation of Severe Food-Induced Allergic Reactions in Infants and Toddlers." *The Journal of Allergy and Clinical Immunology: In Practice*, vol. 9, no. 1, 2021, pp. 311-320.e2.

Immunologic adverse food reactions

Mixed IgE and non-IgE mediated food allergy - Eosinophilic gastrointestinal diseases

EGIDs include eosinophilic esophagitis (EOE), eosinophilic gastritis (EG) and eosinophilic gastroenteritis (EGE)

- Inflammation is characterized by eosinophilic infiltration of esophageal and/or gastric mucosa
- Presents with symptoms of reflux, abdominal pain, dysphagia and food impaction.
- Clinical presentation differs for children versus adults.
- While exact immune mechanisms are not certain, role for foods in the pathogenesis has been shown due to clinical and histologic improvements seen with elemental and elimination diets, and IgE-sensitization is often seen.

Immunologic adverse food reactions

Mixed IgE and non-IgE mediated

Atopic Dermatitis ("eczema")

- Complex inflammatory condition of the skin
- Characterized by impaired skin barrier
- Deffective innate immune responses
- T helper 2 (TH2) skewed adaptive immune responses.
- Can be exacerbated by food and environmental allergens
- Direct role of food allergy in AD is controversial

Immunologic adverse food reactions

Non-IgE mediated food reactions

- **Food Protein Induced Enterocolitis Syndrome ("FPIES")**

  Usually presents in infants with 4th or 5th exposure to food

  Delayed onset (1-4 hours) of protracted repetitive vomiting

  Listless appearance, pallor often seen

  May be associated with diarrhea / loose stools

  In severe cases, hypovolemic shock

- **Food protein induced enteropathy/proctocolitis**

  Commonly seen with milk / soy in infants

- **Celiac Disease**

  Auto-immune disorder causing destruction of small intestine, triggered by ingestion of gluten

Immunologic adverse food reactions

Cell- mediated food reactions

- **Heiner Syndrome**
  - Rare condition affecting infants, food-induced pulmonary hemosiderosis, triggred by cow's milk, and results in symptoms such as pulmonary hemorrhage, iron deficiency anemia, and failure to thrive
- **Allergic contact dermatitis**
  - T-cell mediated inflammation of skin due to hapten (or small molecule) that has repeated and has prolonged contact with skin, resulting in delayed type 4 hypersensitivity reaction, typically a spongiotic rash.
  - Like IgE-mediated food allergy does require sensitization first
  - Poison ivy is classic, but it can be caused by foods like mango, or foods containing nickel.

FOOD ALLERGY DIAGNOSIS

(IGE-MEDIATED FOOD ALLERGY)

Diagnosis

Elements of a **careful (detailed allergy-focused) clinical history** that may guide food allergy testing:

- Description of symptoms
  - Family or patient's report
  - Emergency room or other medical records of descriptions
  - Photos of reaction / rashes
  - Note amount of food ingested, route of exposure, severity of symptoms, treatments
- Foods ingested
  - Amount of food ingested (small amount versus full portion)
  - Food package labels
  - Form of food (raw, cooked, processed)
- Timing of onset of symptoms related to food ingestion
- Presence of augmentation or co-factors
  - Co-ingestion of alcohol, NSAIDs
  - Exercise, menstruation, sleep deprivation, febrile illness / other illness

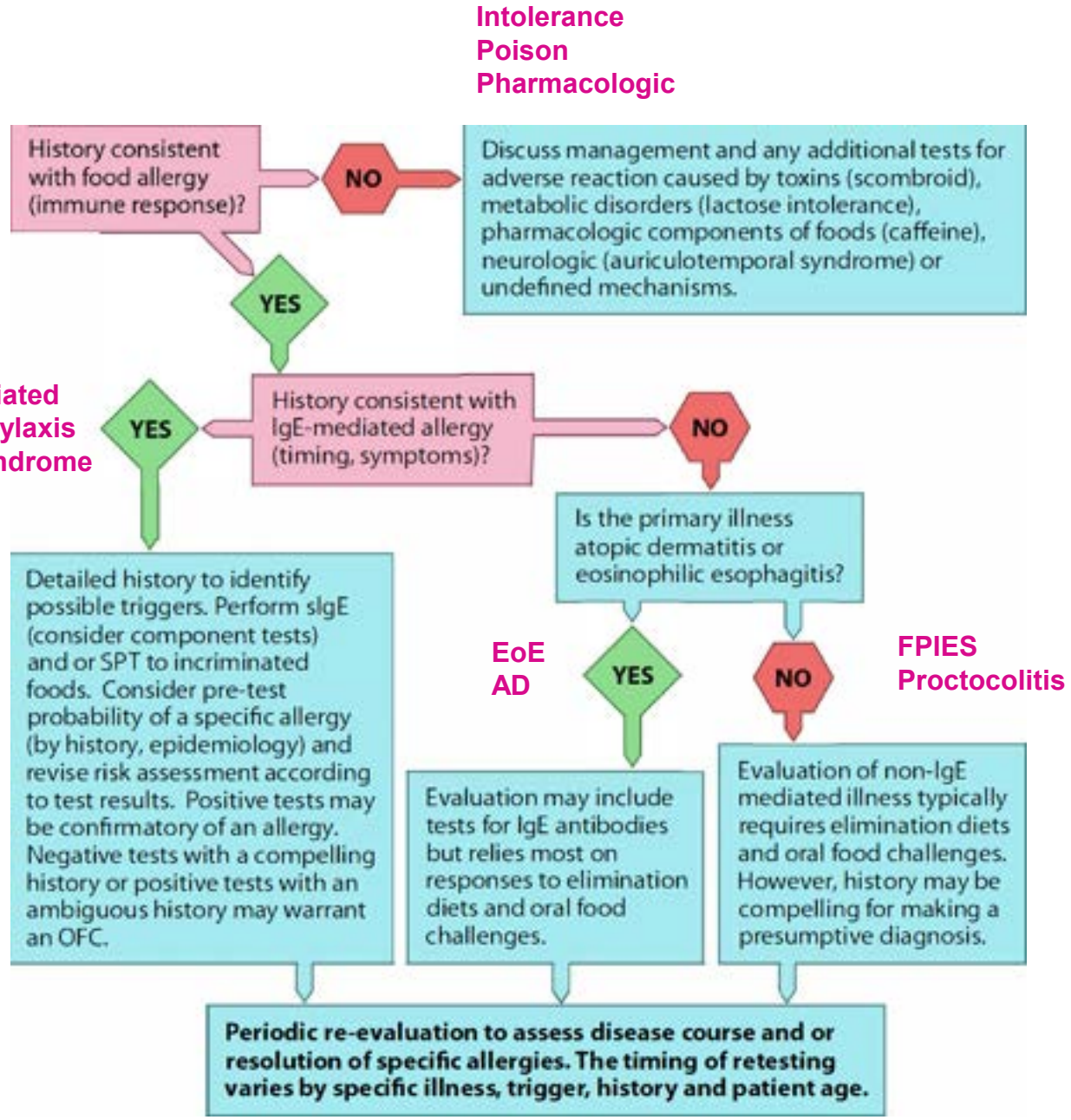
Diagnosis

Using allergy test(s) to aid in diagnosis of food allergy requires knowledge of the clinical history and an understanding of how to interpret the tests.

		Likelihood of allergy from test results		
		Low	Intermediate	High
Likelihood of allergy from clinical history	High	*Possible allergy*	*Probably allergic*	***Likely to be allergic***
	Intermediate	*Possible allergy*	*Possible allergy*	*Probably allergic*
	Low	*Unlikely to be allergic*	*Possible allergy*	*Possible allergy*

Diagnosis

Tests ordered should be based on history and pathophysiology of suspected food allergic disorder



Sicherer SH, Sampson HA. Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. J Allergy Clin Immunol. 2018;141(1):41-58

Diagnosis – EAACI Guidelines

TABLE 6 Recommended tests to support the diagnosis of IgE-mediated allergy.

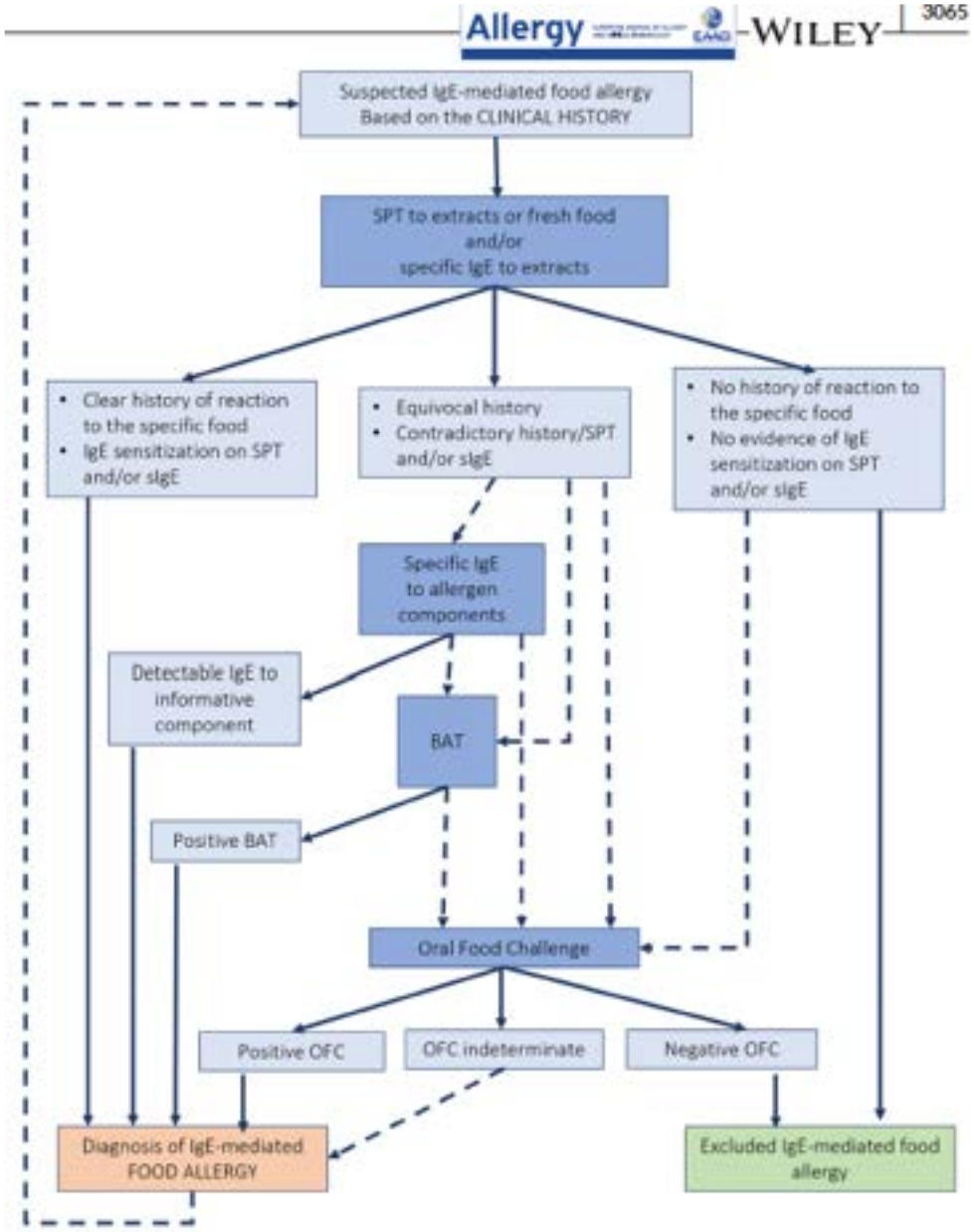
Diagnostic tests	Rationale for using these tests to support the diagnosis of IgE-mediated food allergy
Skin prick test to allergen extracts	Wheal size reflects the amount of mast cell mediators following stimulation with allergen.
Skin prick test to fresh food (prick-to-prick)	Wheal size reflects the amount of mast cell mediators following stimulation with allergen. Use of fresh foods can increase sensitivity of tests as fresh foods contain allergens that may be destroyed or excluded during preparation of allergen extracts (e.g. thermolabile allergens or lipophilic allergens).
Specific IgE to allergen extracts	Concentration of IgE in the serum reflect the amount of circulating IgE antibodies directed to the allergen tested.
Specific IgE to individual allergen components	IgE to specific allergen components shown to be clinically relevant can be more specific than IgE to whole allergen extracts.
Basophil activation test	Proportion of in vitro allergen-activated basophils reflects the amount of mediators released by circulating basophils following stimulation with allergen. This functional test uses patients' own basophils and detects the combined intrinsic cellular response and effect of allergen-IgE binding.

Santos et al Allergy 2023;78:3057

Diagnosis – EAACI Guidelines

Algorithm for recommended sequence of tests to support the diagnosis of IgE-mediated food allergy

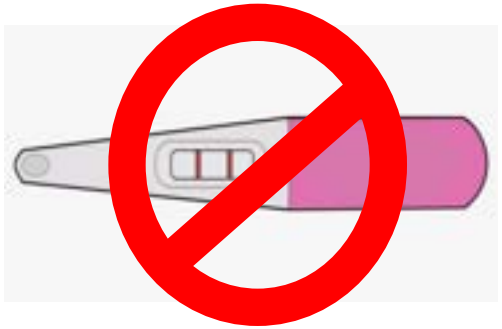
- Not all tests need to be performed for every patient
  - (dashed lines + arrows)
- Long dashed arrow on left represents periodic reassessment for possible resolution in children

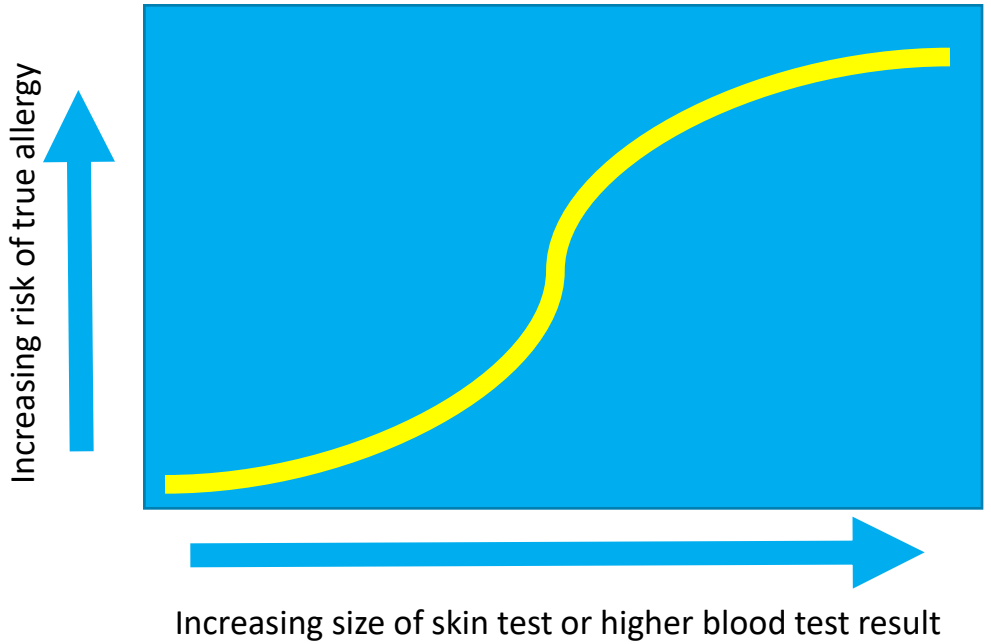


Santos et al Allergy 2023;78:3057

Diagnosis

Food-Specific IgE antibody concentrations (or skin test size) correlate with risk of clinical reactivity





Slide credit SH Sicherer

Diagnosis

Predictive values vary by study : *patient selection, criteria of allergic, age, illness, food, history*

Food	>50% React	>80-95% react	>95% (< age 1-2)
Milk	IgE 2 kU/L	IgE 15 kU/L SPT 8 mm	IgE 5 kU/L SPT 6 mm
Egg	IgE 2 kU/L	IgE 7 kU/L SPT 7 mm	IgE 2 kU/L SPT 5 mm
Peanut	IgE 2 kU/L (history) IgE 5 kU/L (no history)	IgE 14 kU/L SPT 8 mm Infant Aust pop (IgE 34/SPT 8 mm)	SPT 4 mm
Fish		IgE 20 kU/L	
Walnut		IgE 18 kU/L, SPT ≥8 mm	
Sesame		50 kU/L, SPT ≥8 mm	

Reviewed in: Järvinen KM, Sicherer SH. Diagnostic oral food challenges: Procedures and biomarkers. J Immunol Methods. 2012; 383(1-2):30-8.
Peters JACI 2013;132;874.
Foong et al JACI Pract 2020 in press.
Safs et al JACI Pract 2020;8:1681-8.

Slide credit SH Sicherer

Widely commercially available components / molecular diagnostic tests

Tests to specific informative proteins within the food

Food	Potent component	Less potent component
Peanut	Ara h 2, 6 Ara h 1,3,9	Ara h 8
Egg	Ovomucoid	Ovalbumin
Walnut	Jug r 1 (Jug r 3)	
Cashew	Ana o 3	
Brazil	Ber e 1	
Milk	Casein	Alpha lactalbumin, Beta lactoglobulin
Hazelnut	Cor a 14 Cor a 9 (Cor a 8)	Cor a 1

Slide credit SH Sicherer

Diagnosis

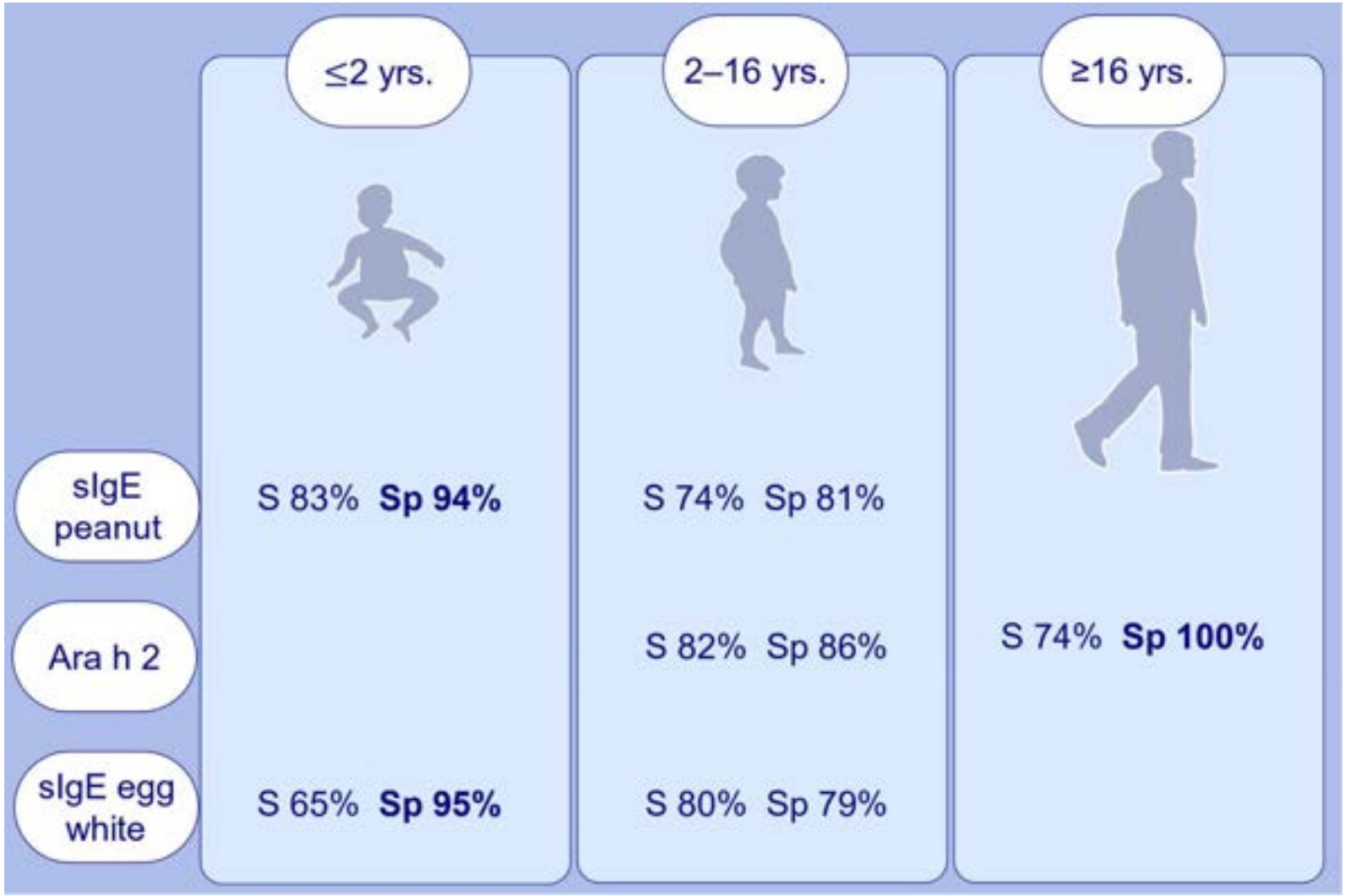
Selected predictive capacity of component tests

Component	IgE (kUA/L)	PPV
Casein (for baked milk)	10 4.95 20.2	95% 54% 69%
Ovomucoid For cooked egg For baked egg	 3.7-27 50	 95% 90%
Ara h 2 (peanut)	0.35-42	90-95%
Cor a 9 (hazelnut)	1-2	79-100% specificity
Cor a 14 (hazelnut)	0.72-47.8	87-90% specificity
Ana o 3 (cashew)	0.16 2	98% specificity 95%
Gly m 8 (soy)	1 3.55	89% 74%

From Foong JACI Pract 2021 (in press) and Santos JACI 2014;134:645. Nicolaou JACI 2010;125:191. Beyer Allergy 2015;70:90-8. Masthoff JACI 2013;132:393. Kattan JACI Pract 2014;2:633. Caubet JACI 2013;131:222. Vazquez-Ortiz Clin Exp Allergy 2014;44:579. Haneda JACI 2012;129:1681. Lemon-Mule JACI 2008;122:977. Eller Allergy 2016;71:556. Savvatianos JACI 2015;136:192. Kattan Jaci Pract 2015;3:970

Slide credit SH Sicherer

Diagnostic test accuracy at different ages

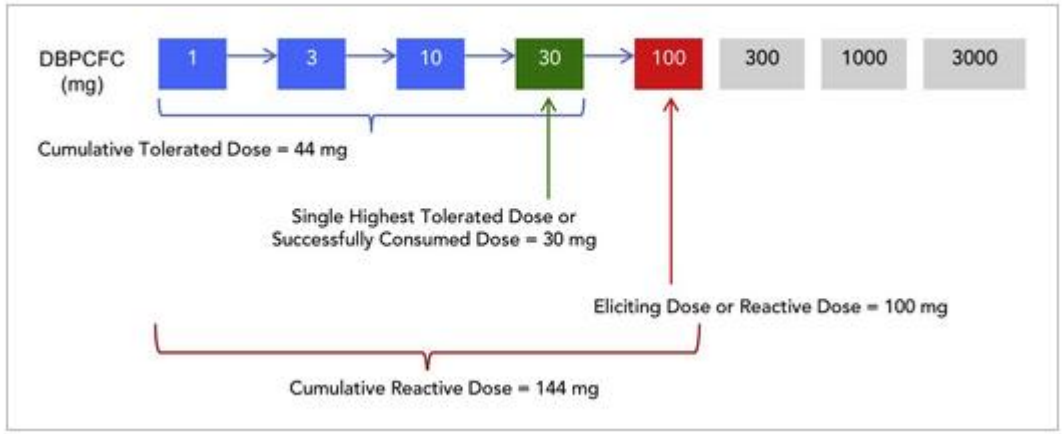


Riggioni C, et al. Systematic review and meta-analyses on the accuracy of diagnostic tests for IgE-mediated food allergy. Allergy. Feb 2024

ORAL FOOD CHALLENGES (OFC)

- An Oral Food Challenge is a highly accurate diagnostic test for food allergies.
- A challenge may be **double-blind placebo-controlled** (the gold standard). This requires two food challenges generally on separate days – one OFC to placebo, one OFC to active food - neither the patient or clinician knows which is which, and this allows for more objective assessment.
- A challenge may also be **single-blind** (only patient is blinded).
- A challenge may be **open and unblinded** (both patient/family and clinician know the allergen is being fed).
- During an OFC, the allergist feeds the patient the suspect food in gradually increasing measured doses.
  - Obtain baseline vital signs and perform a baseline physical examination
  - Start with small amounts, observe for any signs of a reaction
  - Progress to larger doses at 15-30 minute intervals until a full serving has been ingested.
  - The OFC is stopped (and no further doses fed) if there are signs of a reaction (**POSITIVE OFC**)
  - If no symptoms are observed after all doses fed and after a period of 1-2 hours of observation, the food allergy is considered to be "ruled out" (**NEGATIVE OFC**)

ORAL FOOD CHALLENGES (OFC)

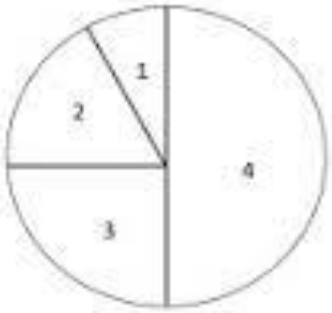


- PRACTALL oral food challenge dosing for double blinded placebo controlled OFCs
- Commonly used in clinical trial settings

Pediatric Allergy Immunology, Volume: 35, Issue: 11, First published: 19 November 2024

- Common protocols for outpatient open (unblinded) OFCs

Four Dose Protocol	Six Dose Protocol
Divide the serving as outlined below. Dose 1 = 1/12th of the total serving Dose 2 = 1/6th of the total serving Dose 3 = 1/4 of the total serving Dose 4 = 1/2 of the total serving	Dose 1 = 1% of total dose Dose 2 = 4% of total dose Dose 3 = 10% of total dose Dose 4 = 20% of total dose Dose 5 = 30% of total dose Dose 6 = 35% of total dose



ORAL FOOD CHALLENGES (OFC)

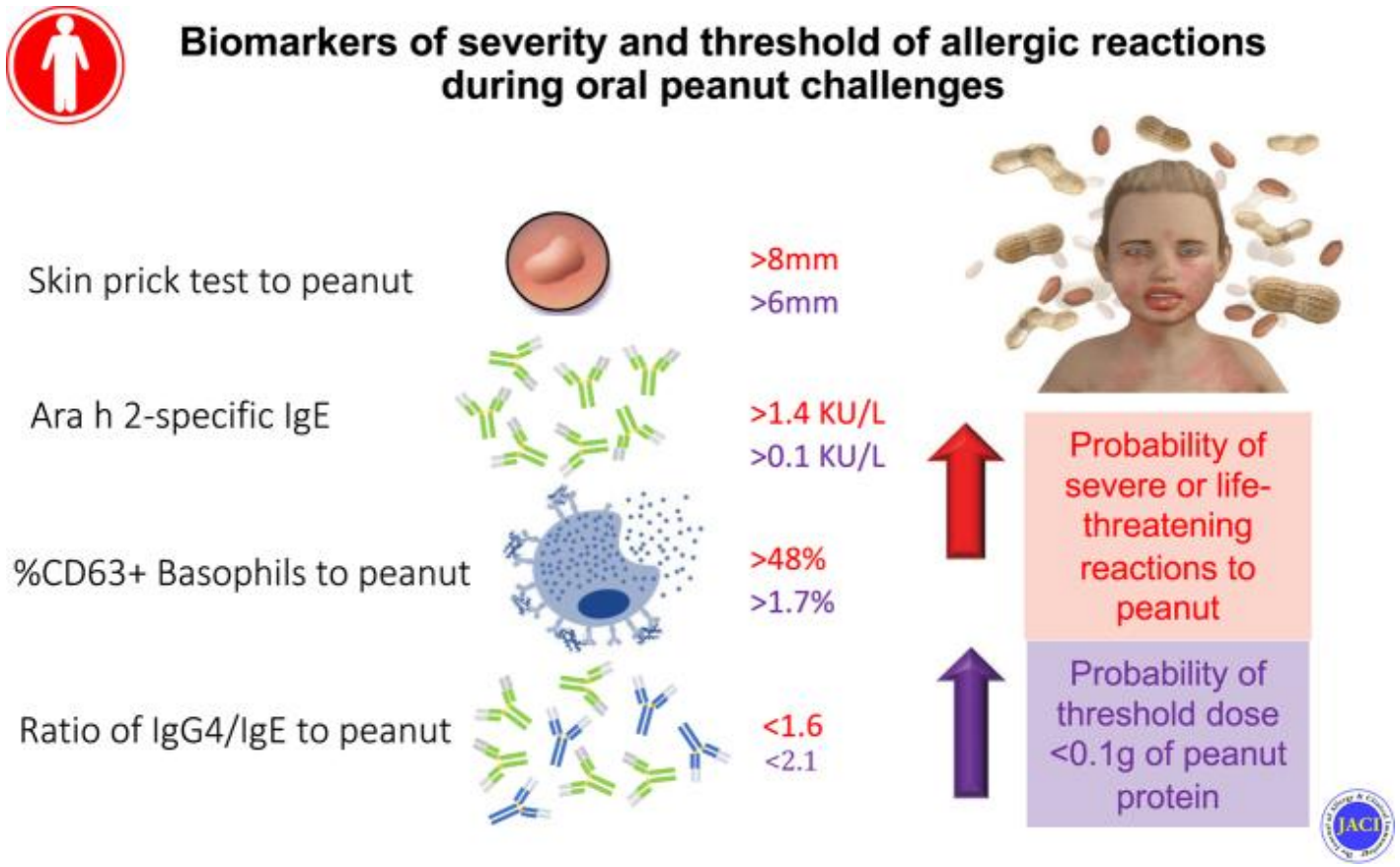
- Anybody performing / supervising an oral food challenge must be trained to recognized and manage any severity of allergic reaction, including anaphylaxis
- The facility must be appropriately staffed and resourced for managing anaphylaxis.
- OFCs carry a risk of allergic reaction, are time consuming, and require significant resources and time to perform
- Benefits include being able to expand the diet if the OFC is negative (food is tolerated) or in the case of a positive OFC (food is not tolerated) learning that a food is truly a problem and needs to be avoided.
- Patients who do have reactions also learn how to manage an allergic reaction and see the efficacy of medications given to treat a reaction (for instance, epinephrine). Can be an excellent learning experience.
- If a food is not tolerated during and OFC, patients may also learn about their threshold for reactions (how sensitive they are and how much of a food it takes to trigger allergic symptoms).

Biomarkers that may predict OFC outcomes

Aim was to identify biomarkers for risk of severe reactions or low dose threshold during peanut OFCs

Applied testing to LEAP, Persistence of Oral Tolerance to Peanut, and Peanut Allergy Sensitization studies

Looked at presence of peanut allergy, severity of reaction, threshold for reacting



BAT diagnosed PA
- 98% specificity
- 75% sensitivity

BAT was the best biomarker for severity

SPT wheal size best at Predicting threshold

Santos AF, Du Toit G, et al. Biomarkers of severity and threshold of allergic reactions during oral peanut challenges. J Allergy Clin Immunol. 2020

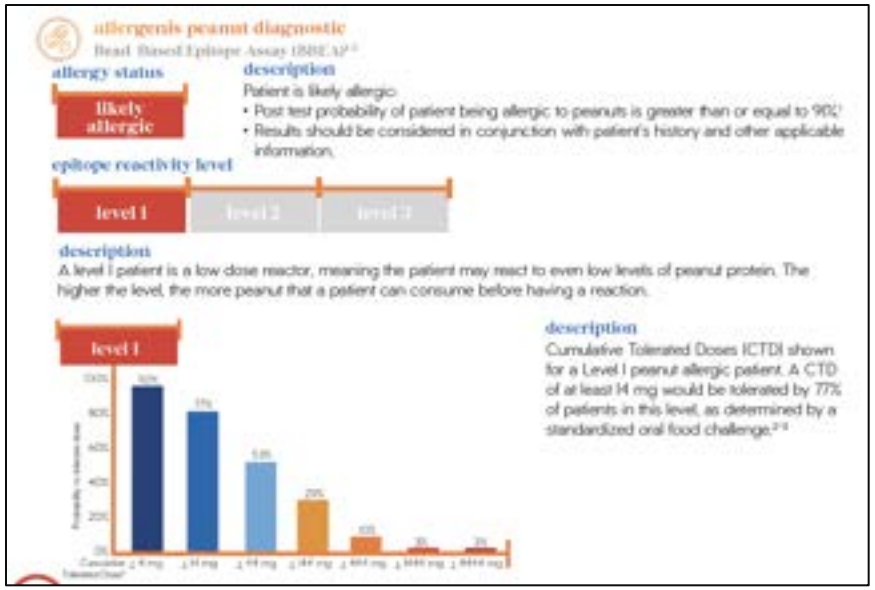
Epitope mapping

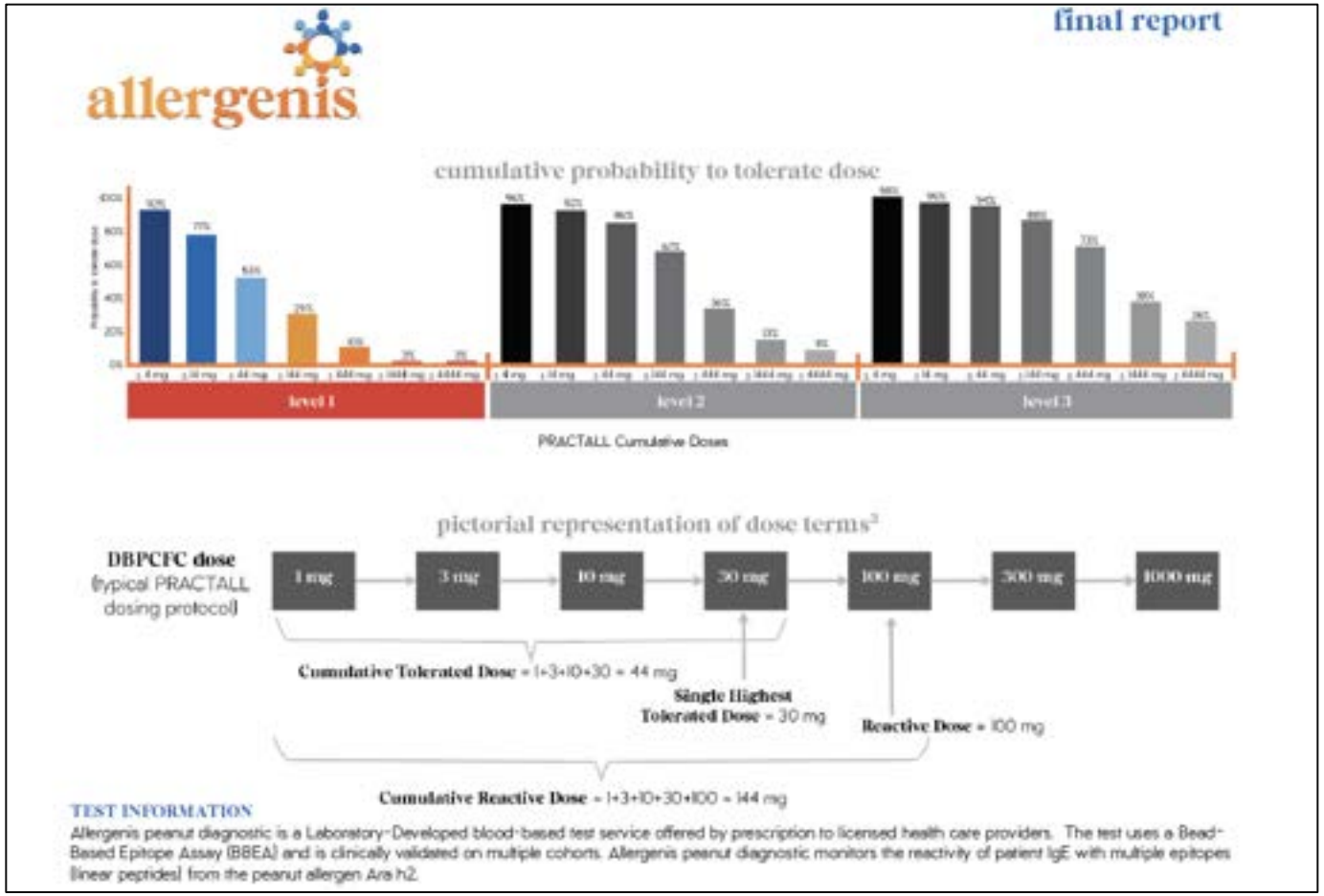
- A sequential (linear) epitope is a sequence of contiguous amino acids in an allergen
- A conformational epitope comprises amino acids that line up due to the tertiary structure (folding) of an allergen
- Sequential (linear) epitopes may be more important in food allergy (they are conserved whereas conformational epitopes break-down with processing and heating) and it has been shown that patients with persistent food allergy or severe FA recognize more sequential epitopes
- The **peanut Bead-Based Epitope Assay (BBEA)** measures IgE binding to linear peanut epitopes
  - Has been validated in clinical cohorts with peanut food challenge outcomes (LEAP, POISED, COFAR-2)
  - Accuracy superior to SPT and whole peanut and peanut component sIgE tests (>90%)
  - Can also be shown to predict amount of peanut tolerated (threshold)

See:

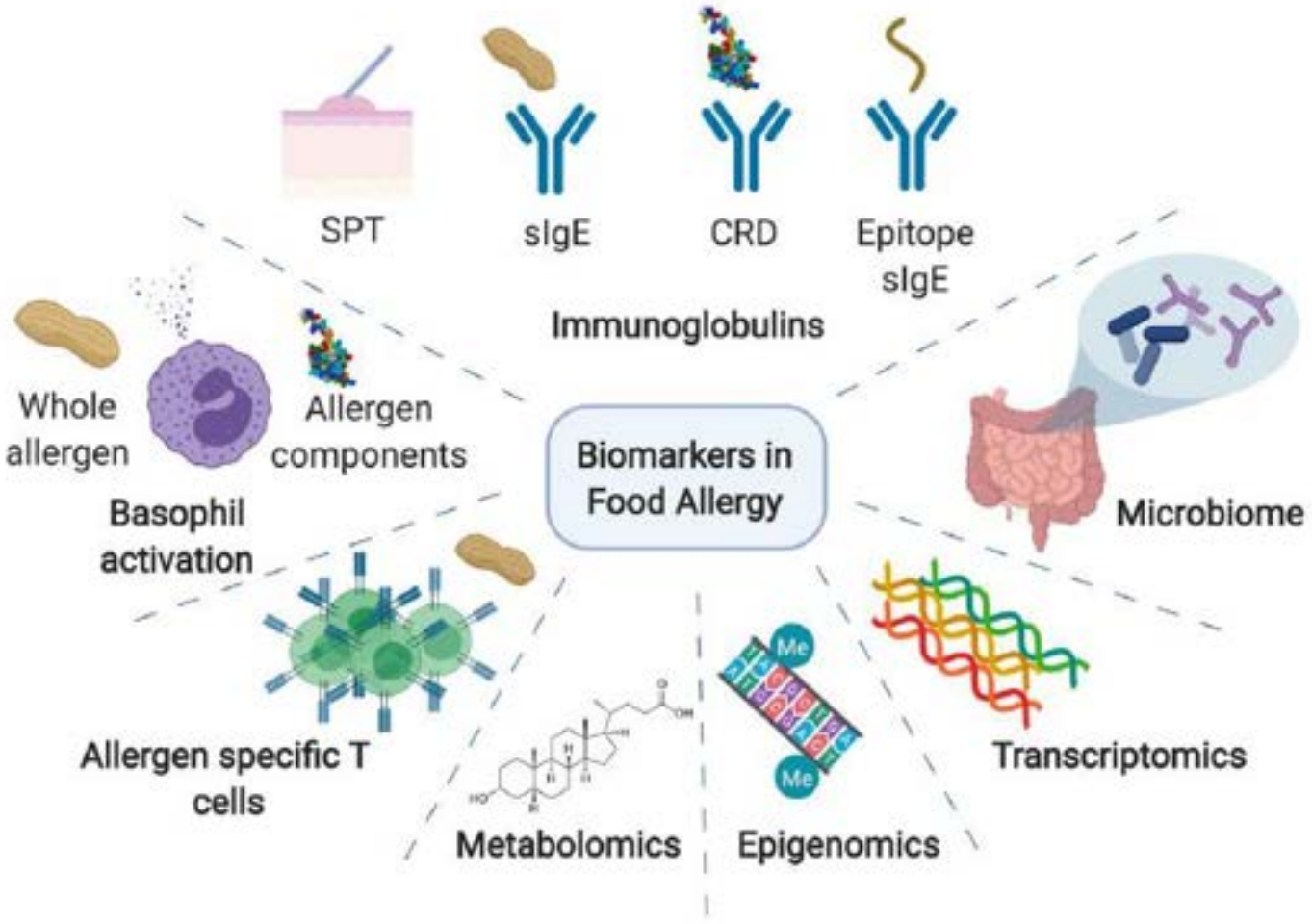
- Suárez-Fariñas M, Suprun M, et al. Accurate and reproducible diagnosis of peanut allergy using epitope mapping. Allergy. 2021 Dec;76(12):3789-3797.
- Suprun M, Sicherer SH, et al. Early epitope-specific IgE antibodies are predictive of childhood peanut allergy. J Allergy Clin Immunol. 2020
- Suprun M, Kearney P, et al. Predicting probability of tolerating discrete amounts of peanut protein in allergic children using epitope-specific IgE antibody profiling. Allergy. 2022

Epitope mapping





Diagnostic tests in development



Improved diagnostics
(Replace need for OFC procedure)
Prognostics
Severity
Threshold
Projected response to treatment
Monitoring response to treatment

Patil, Bunyavanich, Berin J Allergy Clin Immunol Pract 2020;8:2516-24

Food allergy diagnostic pearls

- History! History! History! – a detailed clinical history is key.
  - Pre-test probability is important.
- Testing should be based upon history and epidemiology
- Do not test foods that are clearly tolerated already in the diet
  - Positive results (sensitization) do not indicate clinically relevant allergy
  - Can result in unnecessary food avoidances which carry risks (nutritional and potential development of additional allergies).
- Avoid panel testing!
- Test results have a range and are not simply positive / negative
- We currently have SPT, food specific IgE, component resolved diagnostics, oral food challenges
- Emerging tests: BAT (basophil activation tests), epitope analysis (for peanut only, not in NY)
- Additional test modalities will likely help with determining food allergy severity and threshold

Thank you!

amanda.cox@mssm.edu