FOOD ALLERGY UPDATES

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Disclosures

- **Speakers Bureau**
  - *AstraZeneca*
  - *Sanofi Genzyme & Regeneron*
- **Advisory Boards**
  - *AstraZeneca*
  - *Genentech*
  - *Whole & Free Foods, Inc.*
  - *Food Allergy & Anaphylaxis Connection Team (FAACT)*

Objectives

1. Recognize how to appropriately diagnose and evaluate patients with food allergies.
2. Distinguish the benefits and limitations of food allergy testing.
3. Determine which patients referred to them for diagnosis of food allergy require an oral challenge to confirm or refute the same.
4. Summarize the various therapies currently available for food immunotherapy.

Impact of food allergy diagnosis

- Risk of anaphylaxis just one of many concerns
- **Financial Burden**
  - *Annual U.S. Direct Medical Costs:* ***$24.8 billion overall; $4,184 per child***
  - *Clinician visits, ER visits, hospitalizations*
  - *Specialty foods and diets*
  - *Lost productivity due to time off work*
- **Nutritional Deficiencies**
  - *Broad panel food testing leads to unnecessary avoidance of multiple foods*
  - *Poor weight gain and/or poor food choices due to limited options*
- **Sibling Effect**
  - *Entire family often practices avoidance even if they don't have a food allergy*

Impact of food allergy diagnosis

- **Quality of life**
- **Social & Psychological Consequences**
  - *Creating a safe environment for food allergic children can be **isolating***
    - avoiding sleep-overs and birthday parties
    - avoiding airplanes and sporting events
  - *Hypervigilance can instill excessive amounts of **anxiety and fear***
    - Often spills over into other areas of life
  - *Validated QOL surveys before & after OFCs show significant change*
    - Irrespective of the outcome (for both child and parents)

- Cummings AJ, Knibb RC, King RM, Lucas JS. The psychosocial impact of food allergy and food hypersensitivity in children, adolescents and their families: a review. Allergy. 2010; 65:933-45.
- Ravid NL, Annunziato RA, Ambrose MA, et al. Mental health and quality-of-life concerns related to the burden of food allergy. Immunol Allergy Clin North Am. 2012; 32:83-95.
- Lieberman JA, Sicherer SH. Quality of life in food allergy. Curr Opin Allergy Clin Immunol. 2011; 11:236-42.
- Kansen HM, Le TM, Meijer Y, Flokstra-de Blok BMJ, et al. The impact of oral food challenges for food allergy on quality of life: A systematic review. Pediatr Allergy Immunol. 2018 Aug;29(5):527-537.

Back to Basics

- Oral immunotherapy (OIT) is the culmination of a comprehensive, thoughtful, and time-intensive evaluation with collaborative input from the patient and/or parents
- Choosing appropriate candidates for OIT is more complicated than it may seem
- First step is performing a proper evaluation with detailed food allergy history and select testing based on clinical reactivity

Evaluation

- History and physical examination
  - *clinical history is **critical** in the diagnosis of food allergy*
  - *used to determine subsequent testing and interpretation of results*
- Prick/puncture skin testing
- In vitro testing
- Elimination diets
- Oral food challenges (OFC)

Testing advantages & pitfalls

- Patient-specific factors can modulate the probability of clinical allergy of a given sIgE result
- Component testing can improve the accuracy of food allergy diagnosis
  - *Particularly for peanut allergy where Ara h2 is a strong predictor of disease*
  - *High IgE levels to Gal d1 (ovomucoid) and Bos d8 (casein)*
    - Associated with more persistent allergy
    - Increased reactivity to both heated and concentrated forms of egg and milk

Important point:
validated cutoffs are reliable when applied to a similar patient population to the one where they were developed

- Klemans RJ, Otte D, Knol M, et al. The diagnostic value of specific IgE to Ara h 2 to predict peanut allergy in children is comparable to a validated and updated diagnostic prediction model. J Allergy Clin Immunol. 2013;131:157.
- Caubet JC, Nowak-Wegrzyn A, Moshier E, Godbold J, Wang J, Sampson HA. Utility of casein-specific IgE levels in predicting reactivity to baked milk. J Allergy Clin Immunol. 2013;131:222e224.
- Ando H, Moverare R, Kondo Y, et al. Utility of ovomucoid-specific IgE concentrations in predicting symptomatic egg allergy. J Allergy Clin Immunol. 2008;122:583e588.

Testing advantages and pitfalls

- SPT to foods has high NPV but overall PPV of only ~50%
- Many patients come to office with positive testing but no h/o reaction
  - *i.e. broad panel food testing in moderate-severe eczema or chronic urticaria*

Laboratory Test	Result	Laboratory Test	Result
Total IgE	3873 IU/mL	Hazelnut	10.2 kU/L
Egg white	45.3 kU/L	Cashew	14.9 kU/L
Cow's milk	35.9 kU/L	Pistachio	12 kU/L
Peanut	14.3 kU/L	Walnut	10.8 kU/L
Almond	6.6 kU/L	Pecan	12.5 kU/L

- Perry TT, Matsui EC, Kay Conover-Walker M, Wood RA. The relationship of allergen-specific IgE levels and oral food challenge outcome. J Allergy Clin Immunol. 2004; 114:144-9.
- Sampson HA. Food Allergy. Part 2: Diagnosis and management. J Allergy Clin Immunol. 1999; 103:981-99.

Testing methods

- Larger SPT wheal size (>8mm) or higher food-sIgE levels are associated with persistent food allergy
  - *SPT and sIgE appear sensitive although not specific for diagnosing FA*
- Rate of change can help predict likelihood that food allergy has resolved
- Testing methods being investigated for diagnosis, monitoring for tolerance:
  - *IgE epitope specificity*
  - *Component-resolved diagnostics*
  - *IgE/IgG4 ratio*
  - *Cellular-based assays*
  - *Basophil activation test*
  - *Specific IgA and IgA2 levels*

- Soares-Weiser K, Takwoingi Y, Panesar SS, et al; EAACI Food Allergy and Anaphylaxis Guidelines Group. The diagnosis of food allergy: a systematic review and meta-analysis. Allergy. 2014 Jan;69(1):76-86.

Identify biomarkers that can predict therapeutic outcomes and monitor treatment responses in OIT

- OFCs are laborious and not without risk: more accurately diagnose food allergies, reduce the need for OFCs
- BAT proved to be superior to other diagnostic tests in discriminating between peanut allergy and tolerance, particularly in difficult cases, and reduced the need for OFCs
  - *Reduced number of required OFCs by 2/3*
  - *Useful in cases in which specialists could not accurately diagnose peanut allergy with SPT and sIgE to peanut and to Arah2*
  - *Using a 2-step diagnostic approach in which BAT was performed only after equivocal SPT or Arah2-sIgE, BAT had a major effect (97% reduction) on the number of OFCs required*

Santos AF, Douiri A, Bécares N, et al. Basophil activation test discriminates between allergy and tolerance in peanut-sensitized children. J Allergy Clin Immunol. 2014 Sep;134(3):645-52.

Sustained successful peanut OIT associated with low basophil activation and peanut-specific IgE

- Clinical tolerance diminishes over time on discontinuation or low-dose maintenance
- OIT significantly decreases basophil activation, peanut sIgE, Ara h 1, Ara h 2, and Ara h 3 IgE levels, and sIgE/total IgE, but increases sIgG4/sIgE.
  - *Participants who became reactive to 4 g of peanut 13 weeks off active OIT exhibited higher peanut-induced basophil activation ex vivo and higher peanut sIgE levels and sIgE/total IgE, but lower sIgG4/sIgE*
  - *Substantial suppression of basophil activation was required to maintain long-term clinical tolerance after peanut OIT*
- These values can help to predict treatment outcomes; differentiate transient desensitization vs sustained unresponsiveness after OIT

Tsai M, Mukai K, Chinthrajah RS, Nadeau KC, Galli SJ. Sustained successful peanut oral immunotherapy associated with low basophil activation and peanut-specific IgE. J Allergy Clin Immunol. 2019 Dec 2. pii: S0091-6749(19)31620-3.

OFCs: gold standard for diagnosing food allergy

- **Underutilized** in clinical practice
- Not prudent or necessary if patient has unequivocal, convincing history of clinical reactivity and positive specific IgE testing (SPT or serum sIgE)
- Patient's history should take priority over laboratory findings

Results of specific IgE testing should not be interpreted as absolute indications or contraindications for conducting an OFC

Reasons to perform OFCs

- Identify food that caused the allergic reaction for the initial diagnosis
- Monitor for resolution of food allergy
- Assessing the status of tolerance to cross-reactive foods
  - *Tree nuts in peanut allergy (35% will react to at least one TN)*
  - *Non-crustacean shellfish (mollusks) in crustacean shellfish allergy*
- Relieve parental or patient anxiety
- Determine if patient is a candidate for oral immunotherapy (OIT)

- Requires ingestion of meal-sized portion of tested food prepared in usual state
- Some rely too heavily on results of SPT/serum sIgE when deciding which patients should undergo OFC
  - *Large proportion of patients have intermediate values*
  - *Limited predictive power for which patients are likely to pass*
- **Food allergy is still an art as much as a science**
  - *Experience and clinical judgement matter!*
- Ultimately current testing modalities are inadequate

- Perry TT, Matsui EC, Kay Conover-Walker M, Wood RA. The relationship of allergen-specific IgE levels and oral food challenge outcome. J Allergy Clin Immunol. 2004; 114:144-9.
- Sampson HA. Food Allergy. Part 2: Diagnosis and management. J Allergy Clin Immunol. 1999; 103:981-99.
- Santos AF, Brough HA. Making the Most of In Vitro Tests to Diagnose Food Allergy. J Allergy Clin Immunol Pract. 2017 Mar - Apr;5(2):237-248.

Guidelines to predict when OFC is unnecessary

- Sampson et al published 2 studies that proposed 90% and 95% PPVs for milk, egg, and peanut IgE levels and 50% to 75% PPVs for soy and wheat IgE levels.
  - *Helps determine when sIgE level is so high that a challenge is unnecessary*

Recommended interpretation of food allergen–specific IgE levels (kUA/L) in the diagnosis of food allergy							
	Egg	Milk	Peanut	Fish	Soy	Wheat	
Reactive if ≥ (no challenge necessary)	7	15	14	20	65	80	 Probability of reaction
Possibly reactive (physician challenge)					30	26	
Unlikely reactive if < (home challenge)	0.35	0.35	0.35	0.35	0.35	0.35	

Need more accurate tests to predict the likelihood of passing an OFC

- Sampson HA, nHo DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. J Allergy Clin Immunol 1997;100:444-51.
- Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. J Allergy Clin Immunol 2001;107:891-6.

When will patients fail OFC…

sIgE levels associated with a 50% and 95% PPV for clinical allergy

TABLE II. Assessment for food allergy resolution*

	50% positive predictive value		95% positive predictive value	
Food allergen	Age, if investigated	Specific IgE level (kUA/L)	Age, if investigated	Specific IgE level (kUA/L)
Milk*	—	2[37]	<1	5[38]
			—	15[39]
Egg*	—	2[37]	1	1.7[40]
			5.2	6[41]
Peanut	—	2[40]	1	34[40]
			4	2.1[33]
Wheat	<1	1	—	—
	>1	20[42]		
Soy	—	20-30[42]	—	—
Tree nuts	—	NA	—	15[43]

NA, Not available/applicable.

Specific IgE levels associated with a 50% positive predictive value and a 95% positive predictive value for clinical allergy. In general, we use the 50% positive predictive value to guide the timing of an oral food challenge to assess for resolution, but caution should always be exercised in considering when to perform a food challenge. See text for additional details.

*These are published values for uncooked milk and lightly cooked egg. Higher levels can be used when considering assessing for resolution to extensively heated milk and egg.

Table I: Examples of diagnostic cutoffs with 95% PPV and 50% NPV for specific IgE to food allergen extracts

Approximate predictive value	Cow's milk	Egg	Peanut	Fish
95% PPV	32 kU/L	7 kU/L	15 kU/L	20 kU/L
50% NPV	2 kU/L	2 kU/L	2 kU/L*	–
			5 kU/L*	

NPV, Negative predictive value; *PPV*, positive predictive value.

* The 50% NPV cutoff is different depending on the previous history of reaction: 2 kU/L if the patient reports a reaction and 5 kU/L if the patient has never had an allergic reaction to peanut in the past.

- Savage J, Sicherer S, Wood R. The Natural History of Food Allergy. J Allergy Clin Immunol Pract. 2016; 4:196-203.
- Santos AF, Brough HA. Making the Most of In Vitro Tests to Diagnose Food Allergy. J Allergy Clin Immunol Pract. 2017 Mar - Apr;5(2):237-248.

Factors affecting accuracy of testing

Peanut challenges by specific IgE cutoff level (n=169)				
	<0.35 kUA/L	0.36 - 2 kUA/L	2 – 4.9 kUA/L	>5 kUA/L
Clear history of previous reaction (n=110)	29/38 (76%) passed	17/38 (44%) passed	11/27 (40%) passed	0/7 (0%) passed
Unclear history or positive test response only (n=59)	15/17 (88%) passed	15/21 (71%) passed	4/12 (33%) passed	7/9 (77%) passed
Out of 173 peanut challenges, 59% passed Median for those who passed 0.5 kUA/L Median for those who failed 1.9 kUA/L				

- Perry TT, Matsui EC, Kay Conover-Walker M, Wood RA. The relationship of allergen-specific IgE levels and oral food challenge outcome. J Allergy Clin Immunol. 2004; 114:144-9.

Guidelines to predict the likelihood of passing an OFC

- Perry et al. performed a retrospective chart review of 604 food challenges in 391 children

Food	Cutoff sIgE level at which a 50% pass rate could be expected	
Milk	2 kUA/L	
Egg	2 kUA/L	
Peanut	2 kUA/L	5 kUA/L without a clear history of reaction
Data was less clear for wheat and soy		

- Suggests 50% pass rate as the ideal circumstance for performing an OFC
  - *Data should be used to make individual decisions for each patient based on personal preferences and clinical history*

- Perry TT, Matsui EC, Kay Conover-Walker M, Wood RA. The relationship of allergen-specific IgE levels and oral food challenge outcome. J Allergy Clin Immunol. 2004 Jul;114(1):144-9.

Standardized Clinical Assessment and Management Plan (SCAMP) for Food Challenges

TABLE IV. Iteration 3 criteria for recommended challenge location

	Best clinical judgment (consider for home)	Home	Clinic	Infusion center	Best clinical judgment (consider for CAT/CR)	Not recommended
Egg		sIgE ≤ 0.35 kU/L SPT ≤ 5 mm	sIgE > 0.35 and ≤ 2 kU/L SPT > 5 and ≤ 7 mm	sIgE > 2 and ≤ 6 kU/L SPT > 7 and ≤ 8 mm	sIgE > 6 and ≤ 10 kU/L SPT > 8 and ≤ 10 mm	sIgE > 10 kU/L SPT >10 mm
Baked egg		EW sIgE ≤ 1 kU/L OVM sIgE ≤ 1 kU/L SPT ≤ 10 mm	EW sIgE > 1 and ≤ 10 kU/L OVM sIgE > 1 and ≤ 10 kU/L SPT > 10 and ≤ 25 mm	EW sIgE >10 and ≤ 20 kU/L OVM sIgE >10 and ≤ 15 kU/L SPT > 25 and ≤ 35 mm	EW sIgE > 20 and ≤ 40 kU/L OVM sIgE >15 and ≤ 35 kU/L SPT > 35 mm	EW sIgE > 40 kU/L OVM sIgE > 35 kU/L
Milk		sIgE ≤ 0.5 kU/L SPT neg (0)	sIgE > 0.5 and ≤ 2 kU/L SPT > 0 and ≤ 8 mm	sIgE > 2 and ≤ 5 kU/L SPT > 8 and ≤ 10 mm	sIgE > 5 and < 15 kU/L SPT > 10 and ≤ 12 mm	sIgE ≥ 15 kU/L SPT > 12 mm
Baked milk		sIgE ≤ 1 kU/L SPT ≤ 10 mm	sIgE > 1 and ≤ 15 kU/L SPT > 10 and ≤ 15 mm	sIgE >15 kU/L and ≤ 20 kU/L SPT > 15 mm and ≤ 20 mm	sIgE > 20 and ≤ 40 kU/L SPT > 20 and ≤ 35 mm	sIgE > 40 kU/L SPT > 35 mm
Peanut	sIgE ≤ 0.35 kU/L SPT neg (0) Ara h2 ≤ 0.35 kU/L		sIgE > 0.35 and ≤ 0.7 kU/L SPT > 0 and ≤ 5 mm Ara h2 ≤ 0.35 kU/L	sIgE > 0.7 and ≤ 1 kU/L SPT > 5 and < 8 mm Ara h2 > 0.35 and ≤ 1 kU/L	sIgE > 1 and < 15 kU/L SPT ≥ 8 and < 10 mm Ara h2 > 1 and < 2 kU/L	sIgE ≥15 kU/L SPT ≥ 10 mm Ara h2 ≥ 2 kU/L
Tree nut	sIgE ≤ 0.35 kU/L SPT neg (0) mm		sIgE > 0.35 and ≤ 0.5 kU/L SPT > 0 and ≤ 5 mm	sIgE > 0.5 and ≤ 3 kU/L SPT > 5 and ≤ 6 mm	sIgE > 3 and <18 kU/L SPT > 6 and < 8 mm	sIgE ≥ 18 kU/L SPT ≥ 8 mm
Fish	sIgE ≤ 0.35 kU/L SPT neg (0) mm		sIgE > 0.35 and ≤ 0.9 kU/L SPT > 0 and ≤ 5 mm	sIgE > 0.9 and ≤ 5 kU/L SPT ≤ 5 mm	sIgE > 5 and < 10 kU/L SPT > 5 and < 20 mm	sIgE ≥ 10 kU/L SPT ≥ 20 mm
Shell fish	sIgE ≤ 0.35 kU/L SPT neg (0) mm		sIgE > 0.35 and ≤ 1 kU/L SPT > 0 and ≤ 5 mm	sIgE > 1 and ≤ 5 kU/L SPT ≤ 5 mm	sIgE > 5 and < 20 kU/L SPT > 5 and < 40 mm	sIgE ≥ 20 kU/L SPT ≥ 40 mm
Soy	sIgE ≤ 0.35 kU/L SPT neg (0) mm		sIgE > 0.35 and ≤ 2 kU/L SPT > 0 and ≤ 5 mm	sIgE > 2 and ≤ 5 kU/L SPT > 5 and ≤ 10 mm	sIgE > 5 and < 65 kU/L SPT > 10 and < 20 mm	sIgE ≥ 65 kU/L SPT ≥ 20 mm
Wheat	sIgE ≤ 0.35 kU/L SPT neg (0) mm		sIgE > 0.35 and ≤ 2 kU/L SPT > 0 and ≤ 5 mm	sIgE > 2 and ≤ 10 kU/L SPT > 5 and ≤ 10 mm	sIgE > 10 and < 80 kU/L SPT > 10 and < 20 mm	sIgE ≥ 80 kU/L SPT ≥ 20 mm
Sesame seed	sIgE ≤ 0.35 kU/L SPT neg (0) mm		sIgE > 0.35 and ≤ 1 kU/L SPT > 0 and ≤ 3 mm	sIgE > 1 and ≤ 7 kU/L SPT > 3 and ≤ 6 mm	sIgE > 7 and < 10 kU/L SPT > 6 and < 8 mm	sIgE ≥ 10 kU/L SPT ≥ 8 mm
Sunflower seed	sIgE ≤ 0.35 kU/L SPT neg (0) mm		sIgE > 0.35 and ≤ 5 kU/L SPT > 0 and ≤ 5 mm	sIgE > 5 and ≤ 7 kU/L SPT > 5 and ≤ 6 mm	sIgE > 7 and < 10 kU/L SPT > 6 and < 8 mm	sIgE ≥ 10 kU/L SPT ≥ 8 mm
Fruits/v						
Meats						
Grains						
Other						

SCAMP is an attempt to improve sIgE and SPT thresholds
Triage safely into either a low- or high-intensity care setting for OFC

- Simberloff T, Parambi R, Bartnikas LM, et al. Implementation of a Standardized Clinical Assessment and Management Plan (SCAMP) for Food Challenges. J Allergy Clin Immunol Pract. 2017 Mar - Apr;5(2):335-344.e3.

Factors modulating the interpretation of allergy test results

Factors identified in the clinical history		Effect on the probability of clinical allergy for a given specific IgE level
Reported immediate allergic reaction to the specific food		A history of reacting to the tested food supports the clinical relevance of detected IgE.
(Younger) Age		Lower levels of allergen-specific IgE have increased clinical relevance in young children.
(Black) Ethnicity		Black race is associated with higher levels of allergen-specific IgE with decreased clinical relevance.
Atopic eczema		Polyclonal IgE response can be non-allergen-specific and thus decrease clinical relevance of a given specific IgE level.
Concomitant inhalant allergies		Pollen sensitization can cause false-positive results of specific IgE to plant food extracts.
Atopic population		Positive predictive value of a given specific IgE level increases with the increase in the prevalence of the disease in the population.
Geographical Location	Variable	Clinical relevance of IgE to extracts and patterns of sensitization to allergen components can vary with inhalant allergen exposure typical of certain geographical locations.

These factors affect the pretest probability and therefore influence the resulting post-test probability

Factors influencing the decision to perform an oral food challenge

Factors		Effect on the decision to perform an OFC
History of an allergic reaction	↓	A previous history of a reaction to the specific food increases the chance of reacting during the OFC.
Recent exposure to the food	↓	A recent allergic reaction or the consumption of age-appropriate amount of the food precludes the OFC.
(Low) specific IgE levels	↑	Current low level of food-specific IgE and >50% decline within the last year indicate lower likelihood of a positive OFC.
Importance of the food	↑	The importance of the food to the child's diet and social life and her or his willingness to eat the food regularly in the case of a negative challenge favor performing an OFC.
Resources available	↓	The resources available may limit the number of OFCs offered to patients.
Patient preferences	Variable	Patient may wish to undergo an OFC or not and her or his preferences need to be taken into account.

The decision to perform an OFC is made when the probability of a systemic reaction is sufficient for there to be concern and low enough that the OFC is likely to be passed. The arrows indicate the effect on the decision to perform an OFC: the arrow pointing up means weighing pro and the arrow pointing down means weighing con performing an OFC.

- Santos AF, Brough HA. Making the Most of In Vitro Tests to Diagnose Food Allergy. J Allergy Clin Immunol Pract. 2017 Mar - Apr;5(2):237-248.

AAAAI AFRC Workgroup Report: Oral food challenge practices among allergists in the United States

Justin Greiwe, John Oppenheimer, David Fleischer, J. Andrew Bird, Jacqueline Pongracic, & Matthew Greenhawt

- Distributed to both ACAAI and AAAAI members (~10% response rate)
- Based on food allergy survey published by Pongracic et al in 2012
- Updated to reflect recent advances in food allergy and knowledge gaps that were not addressed in previous survey, such as OFCs in infants

Highlights from Survey

- 92% feel there's a need to perform OFC in clinical practice
- Open (non-blinded) challenges method of choice

Top 3 perceived barriers to performing OFCs	
2009	2019
1. Lack of time 2. Reimbursement 3. Risk of adverse events	1. Lack of time 2. Lack of staff 3. Lack of office space

- 58% generally perform 1 to 5 OFCs per month
- 82% obtain written informed consent

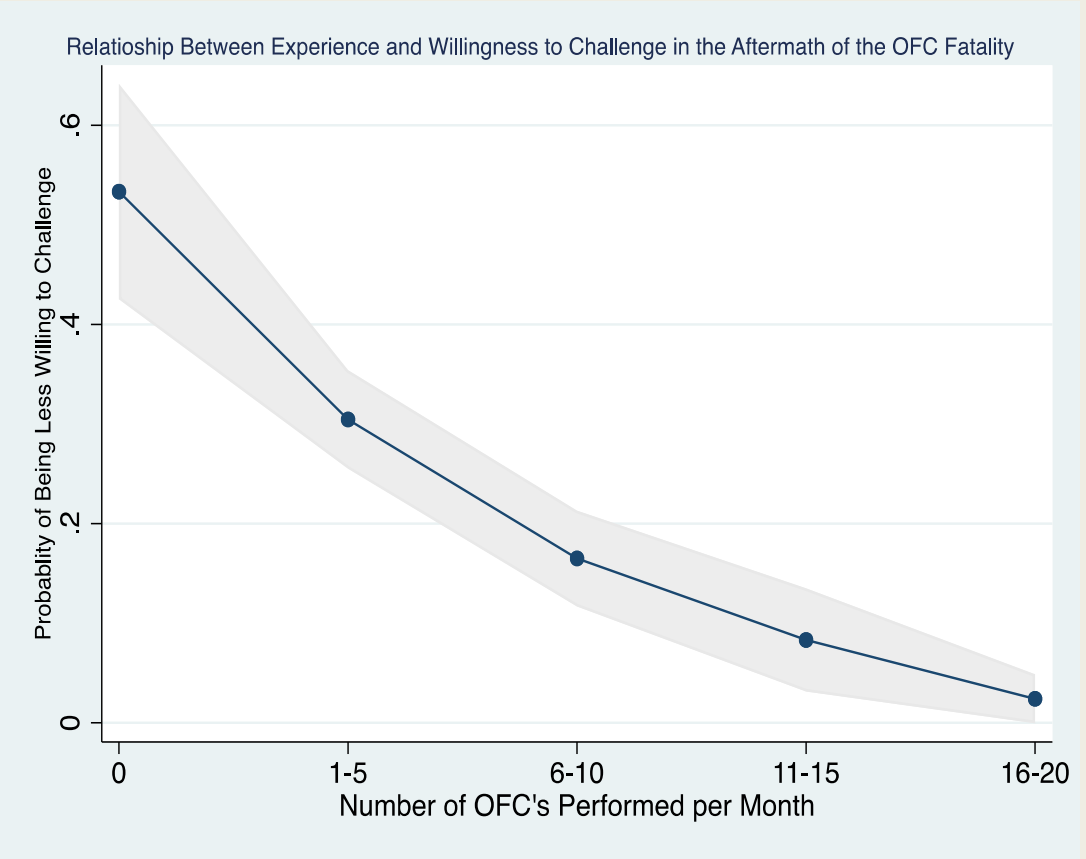
Highlights from Survey: Training & Safety

- Poor Fellowship Training:
  - *56% of respondents performed <10 OFCs in their entire fellowship*
  - ***29% performed no OFC***
    - ACGME requirements: recent fellowship graduates expected to participate in minimum of 5 OFCs
- Safety
  - *One known OFC related fatality in U.S. since description of modern OFC procedure was published in 1976*
    - One fatality outside U.S. as part of an OIT entry challenge
  - *Top priority among allergists offering OFCs however…*
    - Only 60% reported having a standardized protocol for stopping challenges and treating reactions
    - Only 56% had emergency medicine ready and available

- Clopton, J. (2017, August 8). Alabama Boy's Death Worries Food Allergy Parents. WebMD Health News. Retrieved from https://www.webmd.com/allergies/news/20170807/alabama-boys-death-worries-food-allergy-parents.
- Nowak-Wegrzyn A, Assa'ad AH, Bahna SL, Bock SA, Sicherer SH, Teuber SS; Adverse Reactions to Food Committee of American Academy of Allergy, Asthma & Immunology. Work Group report: oral food challenge testing. J Allergy Clin Immunol. 2009 Jun;123(6 Suppl):S365-83.

Highlights from Survey: Infant OFCs

- 79% encourage caregivers of infants to incorporate peanut into diet
- 50% followed recommendations for skin testing high-risk infants
- 38% routinely perform in-office open feeding for high-risk infants for the purposes of early peanut introduction
  - *36% did not provide this resource at all*
- 25% less willing to provide OFCs in the office after recent food challenge fatality
  - *willingness inversely proportional to number of OFCs provided per month*



As defined in the National Institutes of Allergy and Infectious Diseases addendum guidelines

- Togias A, Cooper SF, Acebal ML, et al. Addendum guidelines for the prevention of peanut allergy in the United States: Report of the National Institute of Allergy and Infectious Diseases–sponsored expert panel. World Allergy Organ J. 2017;10(1):1.

Insights from Survey

- Since initial workgroup report 10 years ago some improvements in OFCs have been made
- Lack of training and experience continues to be a major issue
- **Hesitancy in challenging infants**
- Concern that obtaining written consent prior to OFC is not universal, especially with recent fatality
- More targeted efforts recommended
  - *Expanding OFC fellowship training opportunities observing higher risk challenges*
  - *Increase comfort among allergists performing challenges, especially in infants*

Coaching parents and children after failed challenge

- Use failed challenge as teaching point both during and after reaction
- Our responsibility as allergists to reduce anxiety and fear
- Instill healthy respect for foods without crippling parents and children
- Food allergy does not have to define the patient

Confidence not Fear

Empowerment not Despair

Coaching parents and children after passed challenge

- Advised to incorporate tested food into diet on a regular basis to maintain tolerance
  - *failure to incorporate challenged food into diet regularly linked to recurrence of food allergy*
- ~25%-30% of previously allergic patients continue a food avoidance diet despite negative challenge
  - *peanut and TNs most common*
- Reasons for not consuming food regularly
  - *child disliking the food*
  - *fear of a reaction*
  - *food not being a routine part of the family's diet*
- Importance of post-challenge counseling and dietary guidance
  - *address potential barriers to food introduction*
  - *should patients continue to carry their autoinjector at least a year after a negative OFC?*

- Gau J, Wang J. Rate of food introduction after a negative oral food challenge in the pediatric population. J Allergy Clin Immunol Pract. 2017 Mar-Apr;5(2):475-476.
- Busse PJ, Nowak-Wegrzyn AH, Noone SA, Sampson HA, Sicherer SH.Recurrent peanut allergy. N Engl J Med 2002;347:1535-6.
- Fleischer DM, Conover-Walker MK, Christie L, Burks AW, Wood RA. The natural progression of peanut allergy: resolution and the possibility of recurrence. J Allergy Clin Immunol 2003;112:183-9.

Classic Case Examples

5-year-old coming in for OIT evaluation	12-month-old with a history of moderate/severe atopic dermatitis here for interpretation of recent serum sIgE testing	3-year-old referred for multiple food allergies on a restricted diet

Patient: OIT evaluation

- Noone et al. performed retrospective review of challenges performed in higher risk group (highly atopic)
  - *1/3 had h/o anaphylaxis requiring epinephrine*
- Reactions for screening OFCs tend to be more severe and require more aggressive treatment
  - *Reactions that required epinephrine:* ***39.2%***
- Screening OFCs did NOT have higher rates of requiring multiple epinephrine doses or biphasic reactions
- Clinics should NOT offer OIT if hesitant to provide OFCs at any age

- Noone S, Ross J, Sampson HA, Wang J. Epinephrine use in positive oral food challenges performed as a screening test for food allergy therapy trials. J Allergy Clin Immunol Pract. 2015 May-Jun;3(3):424-8.

Patient: Food allergy & atopic dermatitis

Serum sIgE and SPT may not be reliable in predicting food allergy in AD populations

- Specific cutoffs in food-triggered AD are not known
- Exacerbations of skin disease do in fact occur in relation to food ingestions
  - *Occurrence not as prevalent as is often perceived by the community*
  - *Dietary elimination may put children at risk for developing an IgE-mediated food allergy*
- Be more aggressive about offering OFCs in patients with moderate to severe AD and elevated total IgE levels

Robison RG, Singh AM. Controversies in Allergy: Food Testing and Dietary Avoidance in Atopic Dermatitis. J Allergy Clin Immunol Pract. 2019

Patient: Rare food allergy

- Occurrence of any reaction or anaphylaxis after OFCs to less commonly challenged foods is 18.8%
  - *Much lower than reactions observed during OFCs to peanut, egg, milk, and wheat at CHOP: 45%*
- Pass rate for rare foods in these studies is around **80% overall**
  - 73% for grains
  - 94% for fruits and veg
- Strict/unproven food elimination diets lead to poor weight gain, malnutrition, picky eating
- Most common FAs have not changed in the last 3 decades

- Cianferoni A, Garrett JP, Naimi DR, Khullar K, Spergel JM. Predictive values for food challenge-induced severe reactions: development of a simple food challenge score. Isr Med Assoc J 2012;14:24-8.
- Lieberman JA, Cox AL, Vitale M, Sampson HA. Outcome of office-based open challenges in the management of food allergy. J Allergy Clin Immunol 2011;128:1120-2.
- Fleischer DM, Bock SA, Spears GC, Wilson CG, Miyazawa NK, Gleason MC, et al. Oral food challenges in children with a diagnosis of food allergy. J Pediatr 2011;158:578-83.e1.

FOOD ALLERGY THERAPIES

Therapies Currently Being Studied

As food allergy rates and awareness increase, demand for disease-modifying therapies has intensified

- Oral immunotherapy (OIT)
  - *Private practice OIT*
  - *Palforzia (formally known as AR101)*
  - *OIT with anti-IgE (omalizumab)*
- Subcutaneous immunotherapy
- Patch (epicutaneous) immunotherapy
- Sublingual immunotherapy
- Peanut vaccine
- Anti-IgE (omalizumab) solo treatment for multiple food allergies
- Food allergy herbal formula-2 (FAHF-2)
- Etokimab (anti–IL-33 biologic)

Subcutaneous Peanut Immunotherapy

- Initially attempted years ago in two separate studies, showed good efficacy (Oppenheimer et al. 1992, Nelson et al. 1997)
- Study terminated early due to **fatal reaction** following formulation error in pharmacy
  - *accidental administration of maintenance dose of peanut to placebo-treated*
  - *lead to fatal anaphylaxis*
- High rate of systemic reactions (13.3–39%) made this form of treatment unacceptable for routine use

- Oppenheimer JJ, Nelson HS, Bock SA, Christensen F, Leung DY. Treatment of peanut allergy with rush immunotherapy. J Allergy Clin Immunol. 1992;90(2):256–262.
- Nelson HS, Lahr J, Rule R, Bock A, Leung D. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. J Allergy Clin Immunol. 1997;99(6, Part 1):744–751.

Epicutaneous Peanut IT (Viaskin® Peanut)

- Based on epicutaneous immunotherapy, or EPIT®
  - *DBV's method of delivering biologically active compounds to the immune system through intact skin*
  - *Ongoing clinical trials of Viaskin Peanut and Viaskin Milk*
    - preclinical development of Viaskin Egg
    - human proof-of-concept clinical study of Viaskin Milk for the treatment of EoE
- After 3 years, **83.3%** were able to tolerate more peanut protein
  - *compared to 53.6% after 1st year of trial*

Epicutaneous Peanut IT (Viaskin® Peanut)

- At study entry, median cumulative reactive dose was 44mg of peanut protein. After 3 years reactive dose increased to 1,440mg (~6 peanuts)
- Compliance was >95%, no serious adverse events reported (dropout rate 2.3%)
- Resubmitted a BLA for their Viaskin Peanut therapy in August 2019
  - *submission addresses additional data needed on manufacturing procedures and quality controls*
  - *DBV voluntarily withdrew its prior BLA submission in Dec 2018*

Peanut Sublingual IT

- Kim et al. evaluated 37/48 subjects who completed 3 to 5 years of peanut SLIT
- 67% (32/48) successfully consuming 750 mg or more during DBPCFCs
- 25% (12/48) passed the 5000-mg DBPCFC without clinical symptoms
  - *10 of these 12 demonstrating sustained unresponsiveness after 2 to 4 weeks*
- Side effects reported with 4.8% of doses
  - *transient oropharyngeal itch most common*
- Extended-therapy peanut SLIT provided clinically meaningful desensitization in the majority of children
  - *balanced with ease of administration and a favorable safety profile*

Kim EH, Yang L, Ye P, Guo R, Li Q, Kulis MD, Burks AW. Long-term sublingual immunotherapy for peanut allergy in children: Clinical and immunologic evidence of desensitization. J Allergy Clin Immunol. 2019 Aug 29.

Peanut Vaccine

- **Phase 1 trial of EMP-123**
  - *rectally administered vaccine containing modified Ara h1, Ara h2 and Ara h3 (heat/phenol-killed, Escherichia coli-encapsulated, recombinant modified peanut proteins)*
  - *vaccine failed to induce tolerance to dominant peanut proteins, 50% unable to complete*
  - *no significant changes were detected in peanut-specific IgE and IgG4*
  - *overall vaccine not efficacious or safe, frequent adverse reactions including severe allergic reactions in 20%*
- **Aravax's PVX108**
- **HAL Allergy's HAL-MPE1**

Wood R., Sicherer S., Burks A., Grishin A., Henning A., Lindblad R., et al. (2013) A phase 1 study of heat/phenol-killed, E. coli-encapsulated, recombinant modified peanut proteins Ara h 1, Ara h 2, and Ara h 3 (EMP-123) for the treatment of peanut allergy. Allergy 68: 803–808.

Intradermal & Subcutaneous Immunotherapy Vaccines

- **Aravax's PVX108:** Australian biotechnology company
- Positive Phase I data evaluating the safety and tolerability of PVX108 (peptide IT)
  - *peptides don't activate the kinds of cells responsible for extreme reactions*
- May be a more specifically targeted form of therapy that moves beyond desensitization
  - *more convenient (does not have to be taken daily) and with potentially less risk*
- **HAL Allergy's HAL-MPE1:** natural peanut allergen extract that has been chemically modified to limit allergenicity
  - *adsorbed to aluminium hydroxide to enhance the tolerogenic immune response*

Bindslev-Jensen, Carsten et al. SCIT-treatment With a Chemically Modified, Aluminum Hydroxide Adsorbed Peanut Extract (HAL-MPE1) Was Generally Safe And Well Tolerated And Showed Immunological Changes In Peanut Allergic Patients. Journal of Allergy and Clinical Immunology, Volume 139, Issue 2, AB191

Dampen the Immune Response

- Food immunotherapy can cause significant side effects leading to drop out
- One possible way to get patients to stay with program is to dampen immune system before getting dose of allergen
- Two options:
  - ***Anti-IgE monoclonal antibody: Omalizumab***
    - approved for asthma and chronic urticaria
    - inhibits IgE which is typically elevated in people who have severe allergic reactions
  - ***Food Allergy Herbal Formula-2 (FAHF-2)***
    - combines medicinal herbs: reduces allergies, inflammation, and GI problems
    - in clinical trials: thought to work on a similar principle as monoclonal antibody drugs

1. Omalizumab monotherapy
2. Omalizumab + OIT

- Given during up-dosing phase of single and multi-allergen OIT has been studied for milk and peanut
  - *intended to reduce side effects and/or go faster*
- Data from 7 studies evaluating safety and efficacy generally indicate improved safety and time to maintenance
  - *no increase in efficacy compared with OIT alone*
- Some preliminary evidence of efficacy using omalizumab as monotherapy
- Recently granted breakthrough therapy designation by FDA
  - *with and without multi-food OIT in upcoming multicenter study*

- Nadeau KC, Schneider LC, Hoyte L, Borras I, Umetsu DT. Rapid oral desensitization in combination with omalizumab therapy in patients with cow's milk allergy. J Allergy Clin Immunol 2011;127:1622-4.30.
- Wood RA, Kim JS, Lindblad R, et al. A randomized, double-blind, placebo-controlled study of omalizumab combined with oral immunotherapy for the treatment of cow's milk allergy. J Allergy Clin Immunol. 2016; 137:1103-10.
- Bégin P, Dominguez T, Wilson SP, et al. Phase 1 results of safety and tolerability in a rush oral immunotherapy protocol to multiple foods using Omalizumab. Allergy Asthma Clin Immunol. 2014; 10:7.
- MacGinnitie AJ, Rachid R, Gragg H, Little SV, Lakin P, Cianferoni A, et al. Omalizumab facilitates rapid oral desensitization for peanut allergy. J Allergy Clin Immunol. 2017 Mar;139(3):873-881.

Food Allergy Herbal Formula-2 (FAHF-2)

- Traditional Chinese medicine (TCM) has been used to treat various diseases for thousands of years
- FAHF-2 is a 9-herb formula developed using TCM principles
- Efficacy for improving tolerance to food allergens has not been demonstrated
- Poor adherence given large number of capsules required
- Major advantage: therapy is nonspecific, could theoretically be used to treat individuals with multiple food allergies if efficacy can be demonstrated

Wang J, Jones SM, Pongracic JA, et al. Safety, clinical and immunologic efficacy of a Chinese herbal medicine (Food Allergy Herbal Formula-2) for food allergy. J Allergy Clin Immunol. 2015;135:AB234.

Etokimab (anti–IL-33 biologic)

- 6-week placebo-controlled phase 2a study evaluated safety and the ability of a single dose of etokimab to desensitize peanut-allergic adults
- Participants received either etokimab (n = 15) or blinded placebo (n = 5)
  - *Clinical tests included oral food challenges (cumulative 275mg protein) and skin prick tests at days 15 and 45*
- 73% and 57% increases in the tolerated threshold allergen dose of the active treatment group (day 15 and 45, respectively), but saw 0% in the placebo group on either of the 2 days.
- IL-4, IL-5, IL-9, IL-13, and ST2 levels in CD4+ T cells were reduced in the active vs. placebo arm upon peanut-induced T cell activation
- Peanut-specific IgE was reduced in active vs. placebo (P = 0.014 at day 15)
  - *With OIT IgE decreases are seen typically after 12 months of treatment. Intriguing to see this level of change after 15 days*
- Single dose of etokimab could have the potential to desensitize peanut-allergic participants and possibly reduce atopy-related adverse events

Chinthrajah S, Cao S, Liu C, Lyu SC, Sindher SB, Long A, Sampath V, Petroni D, Londei M, Nadeau KC. Phase 2a randomized, placebo-controlled study of anti–IL-33 in peanut allergy. JCI Insight. 2019 Nov 14;4(22).

Oral Immunotherapy

- OIT has generated the most interest, press, and research attention over the last decade
- A lot has changed over this time period

Timeline of OIT Trials

Modern OIT in clinical practice is only recently gaining traction, but concept of oral desensitization is not new

- **1908:** Schofield desensitized 13yr old boy with h/o egg anaphylaxis by starting at a 1/10,000 dose followed by gradual increases over 6 months, eventually leading to negative challenge
- **1990s:** desensitization to peanut via subcutaneous route reported unacceptably high rates of anaphylaxis (one fatality)
- **2006:** two case reports of successful desensitization to peanut using OIT
- **2009:** first clinical trial of peanut OIT. Induced clinical desensitization to peanut safely and with minimal side effects
- **2011:** Food Allergy Research & Education (FARE) helped found a company that would become known as Aimmune

Protocol for OIT Administration

Protocols vary considerably but follow a similar pattern

solution → *→ natural form*

(capsule →)

- *Initial Rapid Dose Escalation (~6 hours)*
- *Build-up Phase (6-12 months)*
- *Maintenance Phase*

Palforzia

- Will be the first FDA-approved treatment for peanut allergy
- Comes in the form of a powder that parents mix into foods like apple sauce, yogurt, and pudding once per day
  - *after dose escalation period (~6 months), patient continues daily therapeutic dose to maintain desensitization*

Standardized, pharmaceutical-grade

- Employs Good Manufacturing Processes (GMP)
  - *Ensures product is consistently produced and controlled according to industry-recognized quality standards*
  - *All allergists will be using the identical formulation*
- Phase 3 PALISADE trial of the drug in 554 patients aged 4-17
  - *Of the 79.6% of those that completed the trial:*
    - 96.3% tolerated a 300-mg dose of peanut protein in the exit food challenge
    - 84.5% tolerated a 600-mg dose
    - 63.2% tolerated a 1000-mg dose

PALISADE Group of Clinical Investigators, Vickery BP, Vereda A, Casale TB, et al. AR101 Oral Immunotherapy for Peanut Allergy. N Engl J Med. 2018 Nov 22;379(21):1991-2001.

Selecting Appropriate OIT Candidates

- Confirm IgE-mediated food allergy before starting OIT
- Good Candidates:
  - *Failed an OFC*
  - *Recent history of severe reaction*
  - *High and unchanged sIgE levels/skin prick wheals over time*
  - *Poor QoL due to avoidance*
  - *Safety concerns from parents and/or child*
- If there is any doubt regarding clinical reactivity, OFC is indicated

Majority Experience Significant QOL Improvement with OIT

OIT patients may experience

- ***reduced anxiety***
- *increased social engagement*
- *reduced fear of accidental exposure*
- *reduced psychosocial burden associated with food allergy diagnosis*

- Opposite is true when patients experience frequent adverse reactions
- 2019 systematic review and meta-analysis of 12 trials (n=1041; median age across trials 8-7 years)
  - ***available peanut OIT regimens considerably increase allergic and anaphylactic reactions over avoidance or placebo***

- Chu DK et al. Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety. Lancet. 2019 Jun 1;393(10187):2222-2232.
- Anagnostou K, Islam S, King Y, et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. Lancet. 2014; 383:1297-1304.
- Otani IM, Bégin P, Kearney C, et al. Multiple-allergen oral immunotherapy improves quality of life in caregivers of food-allergic pediatric subjects. Allergy, Asthma Clin Immunol. 2014; 10:25.
- Epstein Rigbi N, Katz Y, Goldberg MR, Levy MB, Nachshon L, Elizur A. Patient quality of life following induction of oral immunotherapy for food allergy. Pediatr Allergy Immunol. 2015; 27:263-268.

Safety Concerns and OIT

- **Pre-screen** patients before starting OIT to mitigate risks:
  - *Evaluate atopic status*
  - *Maximize control of allergic rhinitis and atopic dermatitis*
  - ***Asthma screening:*** *PFT pre/post bronchodilator and FeNO if available*
  - *Exclude patients with uncontrolled asthma or h/o eosinophilic esophagitis (EoE)*
    - relationship between OIT and EoE continues to be examined

Reactions to OIT

Most participants experience adverse events during OIT, most are benign

- oropharynx itching
- mild GI discomfort

Almost every trial to date has documented **one or more severe reactions** requiring epinephrine

Severe reactions most often reported in office with **up-dose**

some reactions at home with maintenance doses for various reasons

OIT and EoE

- Repetitive oral administration of allergens to atopic individuals mimics exposures thought to trigger EoE
- Typical rates of “new-onset” EoE diagnosed during OIT range from 2-5% but are likely higher
  - *Many patients drop out of OIT with GI symptoms before being referred for endoscopy*
  - *Study patients not routinely scoped prior to treatment, and rarely during treatment*
- Remains unknown whether OIT-associated EoE is specifically caused by the OIT allergen, becomes unmasked during OIT, or develops concurrently

- Lucendo AJ, Arias A, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis. Ann Allergy Asthma Immunol 2014;113:624-9.
- Semancik E, Sayej W. Oral immunotherapy for peanut allergy induces eosinophilic esophagitis: three pediatric case reports. Pediatr Allergy Immunol 2016;27:539-41.

Eosinophilic Esophagitis Like Oral Immunotherapy Related Syndrome (ELORS)

- Comprises a recognizable syndrome affecting some OIT patients
- Characteristic presentation of vomiting with or without epigastric abdominal pain or nausea occurring 2-6 hours after OIT doses
  - *accompanied by increased peripheral blood eosinophilia*
- In many patients, ELORS resolves after 2-3 months of OIT dose reduction and successful desensitization can ultimately be achieved
- ELORS substantially limits OIT for some patients

Silvers, Stacy K. et al. Eosinophilic Esophagitis Like Oral Immunotherapy Related Syndrome (ELORS). Journal of Allergy and Clinical Immunology, Volume 139, Issue 2, AB134

Screening, Education, & Close Monitoring

- The relationship between food OIT, GI side effects, and EoE deserves future study
- More invasive surveillance may be necessary
- Long term follow up is critical, especially in those who withdraw
- Importance of educating potential OIT subjects about the risk of developing EoE
- Proactively screen for concerning symptoms prior to starting OIT and follow closely:
  - *dysphagia, chest tightness, abdominal pain, heartburn, vomiting, regurgitation, weight loss/poor growth; “reflux”; ask about family history*
- Low threshold for starting an EoE evaluation

Increased likelihood of reactions to OIT

- Concurrent viral illness
- Undiagnosed or sub-optimally controlled asthma
- Administering dose on an empty stomach
- Physical exertion after dosing
- Dosing during menses
- NSAIDs
- Sleep deprivation/stress
- Likely others – e.g. still have ”unexplained” cases

Varshney P, Steele PH, Vickery BP, et al. Adverse reactions during peanut oral immunotherapy home dosing. J Allergy Clin Immunol. 2009; 124:1351-1352.

OIT Failure: causes of dropout from OIT both during and after completion (10-20% of cases)

- Persistence of chronic symptoms, especially **chronic abdominal pain** and/or vomiting
  - *Prophylactic probiotics, H2 blockers, spacing out dosing, altering dosing protocol*
- **Taste aversion**
- Epinephrine-treated reactions
- Severe anxiety
  - *Psychiatry/psychology consultation*
- Poor adherence and/or inconvenience
- Development of EoE

- Wasserman RL, Factor JM, Baker JW, et al. Oral immunotherapy for peanut allergy: multipractice experience with epinephrine-treated reactions. J Allergy Clin Immunol Pract. 2014; 2:91-96.
- Tang ML, Ponsonby AL, Orsini F, Tey D, Robinson M, Su EL, Licciardi P, Burks W, Donath S. Administration of a probiotic with peanut oral immunotherapy: A randomized trial. J Allergy Clin Immunol. 2015 Mar;135(3):737-44.

The OIT Debate Continues

TO USE

Utilization in private practice has dramatically increased and demand for treatment continues to grow

- Growing number of board-certified allergists around the country currently offering food OIT
- Drastic improvement in QOL has been demonstrated for both parents and patients
- OIT efficacy is higher compared with SLIT and EPIT

NOT TO USE

Some experts believe that OIT is still not ready for routine clinical practice despite all the progress made

- Risks of adverse reactions
- Lack of long-term safety data
- Lack of standardization in private practice
- Higher rate of systemic adverse events compared with SLIT and EPIT
- Billing codes are not standardized or currently available

More Questions than Answers

1. How long must a patient avoid a food for a sustained unresponsiveness challenge to be truly predictive?
2. How does sustained unresponsiveness compare to naturally acquired tolerance to a food at the cellular and molecular immunological level?
3. How long do I have to continue maintenance?
4. Do I have to take my dose every day?

- After more than 100 years of experience, we know SCIT often must be individualized
  - *there are some clearly wrong ways to do SCIT but there are many acceptable variations of the right way*