FOOD ALLERGY: UPDATES 2018

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- GSK

OBJECTIVES

- Food Adverse Reactions
- Prevalence and Natural History
- Evaluation
- Management

Case 1

2 week old, breast fed-infant presents with blood in the stool.

- The blood was first noted at 1 week of life and has been progressing.
- Now every stool is streaked with bright red blood.
- The infant is otherwise in no distress.
- He weighs more than his birth weight.
- Physical examination is unremarkable; an anal fissure is not present.

Case 1

What would be your advice to his mother?

A. Stop breast feeding immediately and switch to a soy formula
B. Stop breast feeding immediately and switch to an amino acid formula.
C. Discuss cow's milk elimination diet for the mother and encourage continuation of breast feeding.
D. Refer to a pediatric gastroenterologist for possible colonic biopsies.

Answer C

- Allergic proctocolitis
  - first few weeks to months of life, breast fed infants.
- Elimination of cow's milk from the mother's diet permits the continuation of breast feeding.
- If Bleeding continues:
  - casein hydrolysate formula
  - or in rare instances, an amino acid based formula
  - accomplishes symptom clearance, typically within 48-72 hours.

Non-IgE mediated food allergies

	Enterocolitis (FPIES)	Enteropathy	Proctocolitis
Age Onset:	Infant	Infant/Toddler	Newborn
Duration:	12-24 mo	? 12-24 mo	9 mo-12 mo
Characteristics:	Failure to thrive Shock Lethargy Emesis Diarrhea	Malabsorption Villous atrophy Diarrhea	Bloody stools No systemic sx Well baby

- Typically milk and soy induced
- Spectrum may include colic, constipation and occult GI blood loss
- * More than 50% of proctocolitis cases have been reported in breast-fed infants

Fully reviewed in: Sicherer SH. Pediatrics 2003;111:1609-1616.

AAAAI Resource for Allergists

Case 2

A 6-month old breast-fed baby developed severe, repetitive vomiting on several occasions.

- Admitted twice for dehydration and sepsis work up due to lethargy. His symptoms resolved with intravenous re-hydration and bowel rest.
- No infectious causes were identified for any of the episodes.
- He developed emesis and diarrhea when cow milk formula was supplement in the first week of life
- He has some yellow fruits and vegetables in the past without problems.
- It was recalled that one of his reactions followed a feeding of cow milk formula mixed with rice cereal

Case 2

Please choose one correct statement regarding this child's allergic disorder:

A. Conventional allergy tests (SPT, serum food-specific IgE) are usually positive and food re-introduction may be done at home, based on the results of the allergy tests.

B. Epinephrine is the first line of therapy.

C. Milk, soy, rice, and oat have been reported as a culprits in infants.

D. Symptoms start within minutes following food ingestion.

Answer C

- FPIES:
  - presumed severe intestinal inflammation with third spacing.
- Cow milk and soy are the most common triggers
- Symptoms usually start within 2-3 hours of food ingestion following a period of avoidance.
- Allergy test for IgE are typically negative
- Reintroduction of the food is typically done following about 12-18 months of asymptomatic period
  - under physician supervision, with secure intravenous access.
- RX: intravenous hydration; intravenous methylprednisolone

FPIES manifestations

Acute

- Ingestion following a period of avoidance (at least several days)
- Triggers: milk, soy, cereal (rice, oat)
- Onset of emesis: 2-4 hours
- Lethargy, limpness ("septic appearance")
- 20% go into shock
- 15% may have methemoglobulinemia
- 6-8 hours later: diarrhea

Chronic

- Young infants fed continuously with milk or soy formulas
- Diarrhea
- Blood in stools
- Intermittent emesis
- Low albumin and total protein
- Failure to thrive

Sicherer SH. JACI 2005; 115(1):149-156.
Nowak-Wegrzyn A. JACI 2017; 139(4)

Food protein-induced proctocolitis (allergic proctocolitis)

- Early infancy, 60% breast-fed, 40% milk and soy formula
- Blood-streaked stools in otherwise well infants, occasional anemia
- Rarely mild hypoalbuminemia and peripheral eosinophilia
- Biopsy: distal large bowel, linear erosions, mucosal edema, infiltration of eosinophils in the epithelium and lamina propria
- Resolves promptly with casein hydrolysate formula (e.g. Alimentum, Nutramigen)
- Most tolerate milk and soy after 1st year

Maloney J, Nowak-Wegrzyn A. Pediatric Allergy and Immunology 2007;18 (4):360-7

Mixed IgE and non-IgE mediated food allergy

- Atopic dermatitis
- Eosinophilic gastroenteropathy:
  - Esophagitis
  - Gastritis
  - Gastroenteritis

Sampson HA, Anderson JA. J Pediatr Gastroenterol Nutr 2000; 30:S87-S94.

Atopic dermatitis

- 35% of children with moderate-severe atopic dermatitis have food allergies as a trigger.
- Usually chronic-relapsing course without any clear-cut symptoms to the food ingested on a regular basis
- Removal of culprit foods results in significant improvement in skin symptoms

Sicherer SH, Sampson HA. JACI 1999;104:S114-22.

Sicherer SH, Sampson HA. Annu Rev Med 2009; 60:261-277

Case 3

14-year old boy presents to the ER with sensation of food stuck in his throat.

- An emergency endoscopy removes a piece of chicken lodged in his esophagus.
- He is referred to an allergist for evaluation.
- PMH is significant for frequent complaints of "food gets stuck in my throat" especially with chicken and turkey but also with any hard food.
- He has spring and fall allergic rhinitis and mild intermittent asthma.
- He is on unrestricted diet but has been on Alimentum (extensively hydrolyzed formula) in the first 18 months of life due to symptoms of gastroesophageal reflux.

Case 3

What is the most appropriate next step?

A. Do allergy SPT and blood IgE to chicken and turkey; if positive eliminate from diet.
B. Refer to a gastroenterologist for endoscopy and biopsy.
C. Perform skin tests to all foods in the diet and eliminate those with positive tests for at least 8 weeks.
D. Prescribe a 6 week trial of swallowed inhaled fluticasone.

Answer B

- Esophageal strictures may complicate eosinophilc esophagitis (EoE).
  - Many subjects with emergency food impaction have EoE
- IgE tests are not efficient in identifying offending foods in EoE.
- Elimination of the six common foods
- Endoscopy and biopsy are necessary to confirm EoE diagnosis
  - prior to extensive dietary manipulations or other therapeutic interventions such as swallowed inhaled fluticasone.

Eosinophilic Esophagitis (EoE)

- Symptoms of EoE (chronic, relapsing, no progression to other GI pathology)[1]
  - Post-prandial N/V/D/abdominal pain, weight loss
  - GER, often refractory
  - FTT in infants and young children, irritability, sleep disturbance
  - In teens/adults: dysphagia, food impaction (due to esophageal strictures)
- Symptoms correlate with severity of eosinophilic infiltration in esophagus tissues: mucosa → serosa
- Diagnostic criterion for EoE: eos >15 /high power field[2]

[1]Chehade M, Aceves SS. Curr Opin Allergy Clin Immunol 2010; 10(3):231-237.
[2]DeBrosee CW, et al JACI, 2010;126:112-9.

Eosinophilic Esophagitis (EoE) – endoscopic findings

Ringed appearance of esophagus (trachealization)

Plaques and linear furrowing

[1]Chehade M, Aceves SS. Curr Opin Allergy Clin Immunol 2010; 10(3):231-237.
[2]DeBrosee CW, et al JACI, 2010;126:112-9.

Eosinophilic Esophagitis: Role of Food Allergy

- 50-80% of children with EoE have ≥1 food-sIgE detectable by immunoassay or SPT[1]
- Response to specific food elimination found in a subset of patients[2]
- Can screen for food allergy with prick or *in vitro* IgE; atopy patch testing with food is currently under investigation
- Elemental diet effective in >90% of cases of EoE[3,4]

[1]Spergel J, et al J Pediatric Gastroenterol Nutrition, 2009;48:30-36.
[2]Kagalwalla, AF et al, Clin Gastroenterol Hepatol 2006;4: 1097-1102.
[3]Kelly KJ, et al, Gastroenterology, 1995;109:1503-15.
[4]Assa'ad A, et al; JACI 2007; 731-8.

GI Syndromes of Children and Adults

Celiac Disease (Gluten-sensitive enteropathy)

- In children:
  - FTT or weight loss
  - Malabsorption, diarrhea, abdominal pain
  - Symptoms may be subtle
- In adults, average 10 years of nonspecific symptoms:
  - Diarrhea, abdominal pain
  - GERD
  - Malabsorption
  - May present atypically with osteoporosis, infertility, neurologic sx

Green PH, Cellier C. Celiac disease. N Engl J Med 2007; 357(17):1731-1743.

Wheat Allergy vs. Celiac Disease

- Onset: infancy-adulthood
- Prognosis: mostly outgrown
- Associated with other food allergies and atopic diseases

- Onset: infancy-adulthood
- Life-long
- No other food sensitivities
- Associated with auto-immune phenomena

Non-IgE-Mediated Syndromes of the Skin and Lung

- Dermatitis Herpetiformis
  - Associated with celiac disease
  - Gluten-sensitive, improves on diet
  - Vesicular, pruritic eruption sacrum, extensor knees and elbows
- Heiner's Syndrome
  - Precipitating antibodies to cow's milk
  - Infantile pulmonary hemosiderosis
  - Anemia, failure to thrive

Disorders Not Proven to be Related to Food Allergy

- Migraines
- Behavioral / Developmental disorders
- Arthritis
- Seizures
- Inflammatory bowel disease

Prevalence and Natural History

Prevalence of Food Allergy

- Perception by public: 20-25%
- Confirmed allergy:
  - Adults: 2-3.5%
  - Infants/young children: 6%
- Specific Allergens
  - Geographical and cultural variations
- Prevalence higher in those with:
  - Atopic dermatitis
  - Pollen allergies
  - Latex allergy
- Prevalence increasing – 18% increase between 1997-2007

Branum AM. Lukacs SL. Pediatrics 2009;124;1549-55.

Milk Allergy

- Most common food allergy in children, usually developing in the first year
- Prevalence 2-3% of infants
- Milk proteins: casein (curds) and whey (soluble): lactalbumin, lactoglobulin
- Symptoms: eczema, hives, wheezing, anaphylaxis, colic, GE reflux (10%), bloody diarrhea. NOT nasal congestion and mucous.
- 79% outgrown by age 16 yrs

Skripak JM, et al. JACI 2007;120:1172-7.

Egg Allergy

- Second most common in children; Prevalence 1.3%
- Egg white proteins: ovomucoid, ovalbumin, ovotransferrin, lysozyme C, conalbumin
- Present in influenza, yellow fever vaccines; (MMR **no** problem)
- Symptoms: eczema, hives, asthma, anaphylaxis
- 80% risk of allergic rhinitis and asthma at age 4 yrs for infants with egg allergy and eczema[1]
- Over 70% of children with egg allergy may tolerate extensively heated (baked) foods containing egg[2]
- Positive decision point for reactivity to heated egg: 10.8 kU_A/L; the negative decision point: 1.2 kU_A/L (UniCAP, Phadia)[3]
- 68% outgrown by age 16 yrs[4]

[1] Tariq SM, et al. Pediatr Allergy Immunol 2000;11:162-7.
[2] Lemon-Mule H, et al. JACI 2008;122:977-83.
[3] Ando H, et al, JACI, 2008;122:583-8
[4] Savage JH, et al. JACI 2007;120:1413-7

Wheat Allergy

- Prevalence in children 0.4%[1]
- Wheat proteins: gluten, gliadin, glutein
- Cross-reactivity with other grains (rye, barley, oat, grasses): 20%
- Associated with exercise-induced anaphylaxis[2]
- 65% resolution by age 12 years[1]

[1]Keet CA, et al. Ann Allergy Asthma Immunol 2009;102:410-15.
[2]Morita E, et al. Allergol Int 2009 Dec;58(4):493-8.

Peanut Allergy

- In US, 0.6% population, 1% children
- Prevalence has more than tripled, from 0.4% in 1997 to 1.4% in 2008
- Onset of symptoms by age 2 yrs
- 75% reactions occur with first exposure
- The food allergy most commonly associated with anaphylaxis
- 150 deaths / year, predominantly from peanut and tree nut anaphylaxis
- ~20% peanut allergy resolution. Relapse rate ~ 9%; continued regular ingestion of peanut may promote tolerance.

Skolnick H, et al, JACI 2001; 107:367-74. Skripak JM, Wood RA. Ped All Immunol 2008;19:368-73. Burks AW. Lancet 2008;371:1538-46. Sicherer SH, Sampson HA. JACI 2007;120:491-503. Sicherer SH, et al. JACI 2010;125:1322-6.

Clinical Cross-Reactivity Among Foods

Rates of clinical cross-reactivity:

Allergy to:	Related food	Approximate clinical reaction rate
Peanut	Most legumes	5%
A tree nut	Other tree nut	35% Higher for: walnut-pecan, almond-hazel, cashew-pistachio
A fish	Other fish	50%
Shellfish	Another shellfish	75%
Grain	Another grain	20%
Milk	Goat/sheep milk	>90%
	Mare milk	5%
	Beef	10%

Sicherer et al. Food Allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. JACI 2018; p41-58

Natural History

- ~ 80% of cow milk, soy, egg and wheat allergy remit by teenage years
  - Declining/low levels of specific-IgE predictive
  - Lack of IgE binding to sequential epitopes predictive
  - Milk and egg: tolerance to extensively heated proteins precedes development of tolerance to unheated milk and egg
- Non-IgE-mediated GI allergy
  - Infant forms resolve in 1-3 years
  - Toddler / adult forms more persistent

Natural History (cont'd)

- Allergies to peanuts, tree nuts, seeds, fish and shellfish typically lifelong
- Resolution: ~20% peanut allergy, 9% tree nut allergies[1]
- Favorable prognostic factors[2]:
  - Decreasing sIgE levels over time
  - Resolution of atopic dermatitis
  - Reduction of skin prick test wheal diameter

[1]Fleischer DM. Curr Allergy Asthma Reports 2007;7:175-181. [2]Boyce, JA et al. J Allergy Clin Immunol. 2010 Dec;126(6 Suppl):S1-58

Risk Factors? for Food Allergy

- Male
- Genetics
- Atopy
- Dietary fat
- Vitamin D insufficiency
- Environmental exposures
- Reduced consumption antioxidants
- Increased use of antacids
- Obesity
- Increased hygiene
- Delayed exposure

Sicherer S, Sampson H et al. Food Allergy: Epidemiology, pathogenesis, diagnosis, and treatment. J Allergy Clin Immunogy 2014; 133: 291-307

Case 4

A 3-year-old boy presents with history of generalized hives and wheezing following ingestion of peanut butter and jelly sandwich at age 12 months.

His current test results are:

- peanut IgE = 8 kIU/L
- peanut PST wheal = 3 mm

Case 4

Please select the correct statement about this child.

A. He has about a 50% chance of outgrowing his peanut allergy.
B. His younger brother who has never tried peanut and has not had any allergic reactions has an increased risk of having peanut allergy.
C. He has a 25- 50% chance of reacting to soy.
D. Based on his test results it is 95% likely that he would experience an immediate allergic reaction upon ingestion of peanut.

Answer B

- Peanut allergy may resolve in approximately 20% of young children.
- About 7% of siblings of a child with peanut allergy will also have peanut allergy, compared with a general population risk of about 1%.
- Most (95%) of peanut allergic persons tolerate soy and other legumes.
- This child's test results are below 95% predictive level (15 kIU/L and PST 8 mm).

Evaluation

Evaluation: History & Physical Exam

- History: most important
  - Symptoms, timing, reproducibility, treatment and outcome
  - Concurrent exercise, medications
- Diet details / symptom diary
  - Subject to recall
  - "Hidden" ingredient(s) may be overlooked
- Physical exam: assess for other allergic and alternative disorders
- Identify general mechanism
  - Allergy vs intolerance
  - IgE vs non-IgE mediated

Boyce J, Assa'ad AH, Burks A.W. et al. Guidelines for the Diagnosis and Management of Food Allergy in the United States: Summary of the NIAID Sponsored Expert Panel Report. J Allergy Clin Immunol 2010; 126(6 Suppl):S1-S58.

Evaluation of Food Allergy

- Suspect IgE-mediated:
  - Panels/broad screening should NOT be done without supporting history because of high rate of false positives.
  - Skin prick tests (prick with fresh food if pollen-food syndrome)
  - *In vitro* tests for food-specific IgE
  - Oral food challenge

- Suspect non-IgE-mediated, consider:
  - Biopsy of gut, skin

- Suspect non-immune, consider referral for:
  - Hydrogen breath test
  - Sweat test
  - Endoscopy

Boyce J, Assa'ad AH, Burks A.W. et al. Guidelines for the Diagnosis and Management of Food Allergy in the United States: Summary of the NIAID Sponsored
Expert Panel Report. JACI 2010; 126(6 Suppl):S1-S58.

Evaluation: Interpretation of Laboratory Tests

- Positive skin prick test or specific IgE
  - Indicates presence of IgE antibody NOT clinical reactivity
  - ~90% sensitivity
  - ~50% specificity
  - ~50% asymptomatic sensitization
  - Larger skin tests/higher sIgE correlates with increased likelihood of reaction but not severity
- Negative skin prick test or specific IgE
  - Essentially excludes IgE antibody (>95% specific)

Sampson and Ho. J Allergy Clin Immunol 1997;100:444-51. Sampson HA, J Allergy Clin Immunol 2001;107: 891-96. Celik-Bilgili S, et al. Clin Exp Allergy 2005;35:268-73.

Unproven/Experimental Tests

- Intradermal skin test with foods
  - Risk of systemic reactions and death[1]
  - Not predictive (high false positive rate)

- Provocation/neutralization, cytotoxic tests, applied kinesiology (muscle response testing), hair analysis, electrodermal testing, food-specific IgG or IgG_4 (IgG "RAST")[2]

[1]Lockey RF. Allergy Proc 1995;16:293-6

[2]Boyce J, Assa'ad AH, Burks A.W. et al. Guidelines for the Diagnosis and Management of Food Allergy in the United States: Summary of the NIAID Sponsored expert Panel Report. JACI 2010; 126(6 Suppl):S1-S58.

Evaluation:
Elimination Diets & Food Challenges

- Elimination diets (1-6 weeks) most useful for chronic disease (eg. AD, GI syndromes)
  - Eliminate suspected food(s) or
  - Prescribe limited "few food" diet or
  - Elemental (free amino acid) diet

- Oral food challenge[1] – physician supervised, emergency meds available
  - Open
  - Single-blind
  - Double-blind, placebo-controlled (DBPCFC)

[1]Nowak-Wegrzyn A, et al. JACI 2009;123:S365-83.

Diagnostic Approach: Suspicion of IgE-Mediated Allergy

- If test for food-specific IgE is
  - Negative: reintroduce food*
  - Positive: food avoidance recommended
- If elimination diet is associated with
  - No resolution: reintroduce food*
  - Resolution
    - Open / single-blind challenges to "screen"
    - DBPCFC for equivocal open challenges

** Unless convincing history warrants supervised challenge*

Diagnostic Approach: Non-IgE-Mediated Disease or Those with Unclear Mechanism

- Elimination diets (may need elemental diet)
- Oral Challenges
  - Timing/dose/approach individualized for disorder
    - Enterocolitis syndrome can induce shock
    - Eosinophilic gastroenteritis may need prolonged feedings before symptoms develop
  - Blinded challenges may be necessary
  - May require ancillary testing (endoscopy/biopsy)

Sampson HA. JACI 2004;113:805-19.
Sicherer SA. JACI 2005;115:149-56.
Nowak-Wegrzyn A, et al. JACI 2009;S365-S383.

Case 5

7 year old with asthma ordered a shrimp dinner off the adult menu. Within 30 minutes he developed profuse vomiting, nasal congestion, and itchy skin. You tell the patient he had a reaction to shrimp and prescribe self-injectable epinephrine. Three weeks later, he has a similar reaction after eating pasta with pesto.

You would

A. Refer to an allergist for testing.
B. Get a list of the items in the meals
C. Reinstruct on the use of epinephrine
D. All of the above

(turns out it was pine nut allergy, not shrimp)

Clinical Diagnosis

- Urticaria, erythema, angioedema
- Few minutes to hours after ingestion
- Systemic symptoms may occur
- Infants present differently than adults
- Panel testing…not a good idea

Anaphylaxis

- Acute onset skin, mucosal surface, or both
- One of the following:
  - Respiratory, ↓BP/ end-organ dysfunction
- ↓BP post allergen:
  - age-specific ↓BP
  - systolic ↓BP > 30% (compared with baseline)
- Two or more of the following occur rapidly after exposure:
  - Skin/mucosal surface, respiratory compromise, ↓BP, or persistent gastrointestinal symptoms

Williams KW, Sharma HP. Anaphylaxis and Urticaria. Immunol Allergy Clin N Am 35(2015); 199-219.

Table 1. Diagnostic Criteria for Anaphylaxis.*

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled

Criterion 1

Onset of an illness within minutes to several hours after possible exposure to an allergen, with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, or swollen lips, tongue, or uvula) and at least one of the following signs or symptoms:

- Respiratory compromise (e.g., dyspnea, wheeze or bronchospasm, stridor, reduced peak expiratory flow, or hypoxemia)
- Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia or collapse, syncope, or incontinence)

Criterion 2

Two or more of the following signs or symptoms that occur rapidly (within minutes to several hours) after exposure to a likely allergen:

- Involvement of the skin or mucosal tissue (e.g., generalized hives, itching or flushing, or swollen lips, tongue, or uvula)
- Respiratory compromise (e.g., dyspnea, wheeze or bronchospasm, stridor, reduced peak expiratory flow, or hypoxemia)
- Reduced blood pressure or associated symptoms of hypotension (e.g., hypotonia or collapse, syncope, or incontinence)
- Persistent gastrointestinal symptoms (e.g., crampy abdominal pain or vomiting)

Criterion 3

Reduced blood pressure within minutes to several hours after exposure to a known allergen:

- Infants and children: low systolic blood pressure (age-specific) or >30% decrease in systolic blood pressure
- Adults: systolic blood pressure of <90 mm Hg or >30% decrease from the person's baseline blood pressure

Jones and Burks et al. Food Allergy. N Engl J Med 2017: 377; 12

Biphasic anaphylaxis

- Very rare <1%
- Risks include delayed epinephrine, hypotension, asthma
- Defined as reaction that occurs within 72 hours of allergen exposure after already having improved with first reaction
- Typical ED protocol: watch for 6 hours
- European Guidelines recommend 24 hour

Lee S, Bellolio M, Hess E et. al. Time of Onset and Predictors of Biphasic Anaphylaxis Reactions: A Systematic Review and Meta-Analysis. J Allergy Clin Immunology: In Practice 2015; 3: 408-416 e2.

CURRENT AVAILABLE DIAGNOSTICS

- Skin testing
- IgE testing
- Component Resolved Diagnostics
- Oral Food Challenge

Skin testing

- Determined a 95% positive predictive point for peanut SPT wheal to at least 8 mm[1]
- Immediate hypersensitivity skin testing for foods is associated with an estimated sensitivity and specificity of 85% and 74%[2,3]

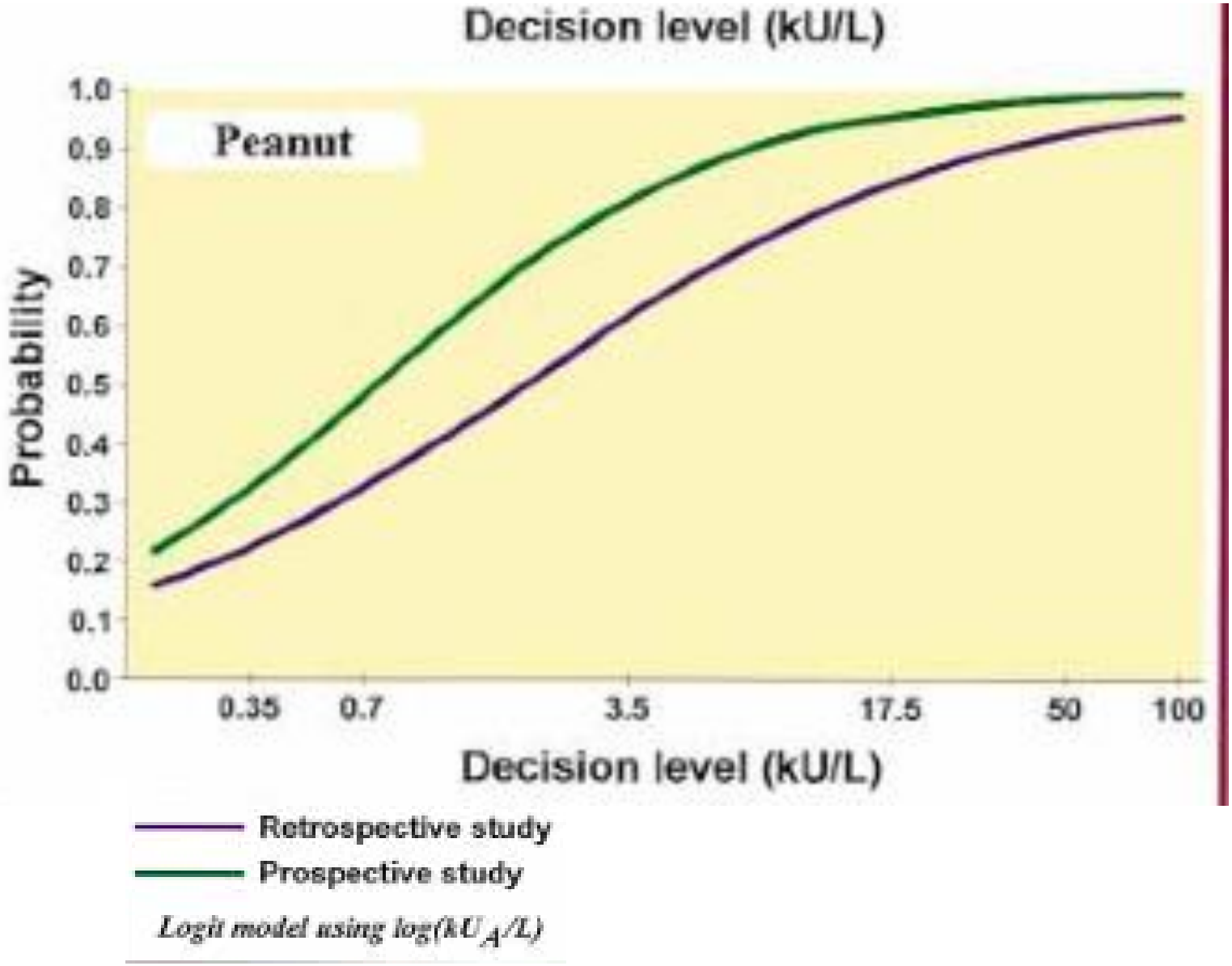
1. Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. Clin Exp Immunol. 2000;30:1540e1546
2. Sampson HA, Albergo R. Comparison of results of skin tests, RAST, and double- blind, placebo-controlled food challenges in children with atopic dermatitis. J Allergy Clin Immunol 1984;74:26-33.
3. Sampson H a, Aceves S, Bock SA, et al. Food allergy: A practice parameter update-2014. *J Allergy Clin Immunol*. 2014. doi:10.1016/j.jaci.2014.05.013.

IgE testing

- IgE levels to predict OFC outcomes
  -95% PPV for peanut IgE=14 kUA/L.

- 50% NPV peanut IgE level ≤2 kUA/L + clinical history or peanut IgE level ≤5 kUA/L –clinical history

1. Sampson H a, Aceves S, Bock SA, et al. Food allergy: A practice parameter update-2014. *J Allergy Clin Immunol*. 2014. doi:10.1016/j.jaci.2014.05.013.
2. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. J Allergy Clin Immunol. 2001;107:891e896.



1. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. J Allergy Clin Immunol. 2001;107:891e896.

CRD

- Ara h 1, 2, and 3= predominant allergens
- Ara h 9 = other geographic regions (ie, the Mediterranean area)
- Diagnostic accuracy, insight regarding the natural history/ severity
- Pediatric investigation CRD did not improve diagnostic accuracy in predicting egg or milk OFC outcome

1. Sampson H a, Aceves S, Bock SA, et al. Food allergy: A practice parameter update-2014. *J Allergy Clin Immunol*. 2014. doi:10.1016/j.jaci.2014.05.013.
2. Bégin P, Vitte J, Paradis L, et al. Long-term prognostic value of component-resolved diagnosis in infants and toddlers with peanut allergy. *Pediatr Allergy Immunol*. 2014;25(5):506-508.

Food	Stable protein(s)
Peanut	Ara h 1, Ara h 2, Ara h 3, Ara h 6, and Ara h 9 (especially southern Europe)
Hazelnut	Cor a 9, Cor a 11, Cor a 14
Walnut	Jug r 1, Jug r 3
Cashew	Ana o 3
Brazil	Ber e 1
Egg	Ovomucoid
Milk	Casein
Soy	Gly m 5, Gly m 6, Gly m 8
Wheat	Tri a 19

Sicherer et al. Food Allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. JACI 2018; p41-58

Management and the Future

CURRENT THERAPY

- Avoidance
- Epi/Auvi-q
- Clinical Trials -desensitization

LET'S LEAP

Randomized Trial of Peanut Consumption

- Prevalence of peanut allergy among children in Western countries has doubled in the past 10 years, reaching rates of 1.4 to 3.0%,
- Becoming apparent in Africa and Asia.
- Leading cause of anaphylaxis and death due to food allergy

Du Toit G., Roberts G., Sayre P.H., et al.
N Engl J Med 2015; 372:803-813

Methods

- early introduction of peanut-based products (before 11 months of age) would lead to the prevention of peanut allergy in high-risk infants?
- N=500 randomly assigned
  - consumption group
  - avoidance group
  - 10% of N with >4mm excluded
- 5 years of age peanut challenge

Prevalence results at age 5

- Overall:
  - peanut-avoidance group was 17.2%
  - consumption group was 3.2%
- Children with negative testing
  - peanut-avoidance group was 13.7%
  - consumption group was 1.9%
- Children with1-4 mm wheals:
  - peanut-avoidance group was 35.3%
  - consumption group was 10.6%

LEAP study take home

- Introduction of peanut between 4 and 11 months in infants with egg allergy and/or severe eczema prevents peanut allergy in most infants.

TABLE IV. Guidelines for introduction of peanut for peanut allergy prevention

Infant criteria	Recommendations	Earliest age of peanut introduction	Rationale/comments
Guideline no. 1: Severe eczema, egg allergy, or both	Strongly consider evaluation by sIgE or SPT and, if necessary, an OFC Based on test results, introduce peanut-containing foods	4-6 mo	Potential advantage to identify infants early (pediatric vaccination visits) and begin peanut before increased sensitization Firm evidence of prevention effect is a rationale for early interruption of exclusive breast-feeding
Guideline no. 2: Mild-to-moderate eczema	Introduce peanut-containing foods	Around 6 mo	Extrapolation of effect to moderate risk from results of a randomized trial on high risk Potential to reduce overall disease burden from a larger group at risk Insufficient proof to broach exclusive breast-feeding
Guideline no. 3: No eczema or any food allergy	Introduce peanut-containing foods	Age appropriate and in accordance with family preferences and cultural practices	Similar rationale to guideline no. 2 above, not introducing before 6 mo but less emphasis on very early introduction for this lowest-risk group

Sicherer et al. Food Allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. JACI 2018; p41-58

Increased food diversity in the first year of life is inversely associated with allergic diseases

Caroline Roduit, MD, MPH,[a] Remo Frei, PhD,[b] Martin Depner, PhD,[c] Bianca Schaub, MD,[c] Georg Loss, PhD,[d] Jon Genuneit, MD,[e] Petra Pfefferle, PhD,[f] Anne Hyvärinen, PhD,[g] Anne M. Karvonen, PhD,[g] Josef Riedler, MD,[h] Jean-Charles Dalphin, MD, PhD,[i] Juha Pekkanen, MD,[g] Erika von Mutius, MD, MSc,[c] Charlotte Braun-Fahrländer, MD,[d,k] Roger Lauener, MD,[j] and the PASTURE study group* *Zurich, Basel, and Davos, Switzerland, Munich, Ulm, and Marburg, Germany, Kuopio, Finland, Schwarzach, Austria, and Besançon, France*

Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy

JACI 2014; 133:468-75

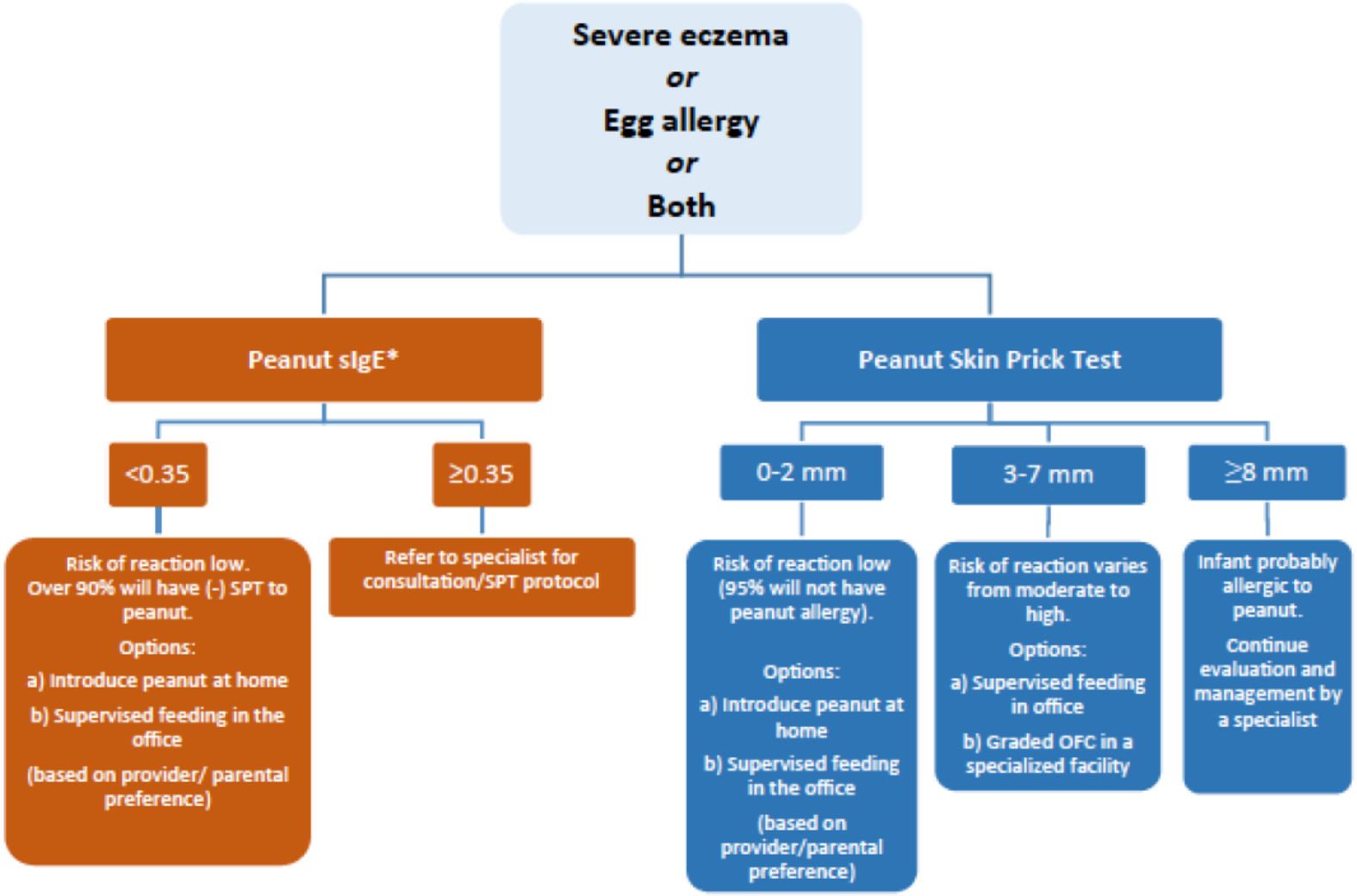
Brian P. Vickery, MD,[a] Amy M. Scurlock, MD,[b] Michael Kulis, PhD,[a] Pamela H. Steele, CPNP,[a] Janet Kamilaris, RN,[a] Jelena P. Berglund, PhD,[c] Caitlin Burk, BA,[a] Anne Hiegel, RN,[b] Suzanna Carlisle, RN,[b] Lynn Christie, RD,[b] Tamara T. Perry, MD,[b] Robbie D. Pesek, MD,[b] Saira Sheikh, MD,[a] Yamini Virkud, MD, MA,[d] P. Brian Smith, MD, MHS, MPH,[d] Mohamed H. Shamji, PhD,[e] Stephen R. Durham, MD,[e] Stacie M. Jones, MD,[b] and A. Wesley Burks, MD[a] *Chapel Hill and Durham, NC, Little Rock, Ark, and London, United Kingdom*

Future of Peanut

- Prevention vs avoidance and desensitization?
- Development of new therapies for anaphylaxis treatment and prevention?

NIH Guidelines 2017

A. Togias et al. / Ann Allergy Asthma Immunol xxx (2016) 1–8



Future therapies

- Oral Immunotherapy
- Peanut Patch
- Chinese herbal therapy
- Modified food protein allergens
- Nanoparticle-encapsulated food antigen
- Lamp-Vax food antigen DNA therapy
- Anti-cytokine therapy

TABLE V. Selected therapeutic strategies with clinical trials

Therapy	Benefits	Limitations	Additional comments
OIT	Robust, possible sustained unresponsiveness	Time-consuming, side effects	Peanut in phase 3
SLIT	Minor side effects, brief exposure	Less robust than OIT	
EPIT	Minor side effects	Less robust than OIT, more effective in younger age group	Peanut in phase 3, milk in phase 2
Subcutaneous immunotherapy with chemically modified, aluminum hydroxide–adsorbed peanut proteins	Convenience	Injection	Safety and efficacy largely unknown, phase 1
Intradermal/intramuscular immunotherapy with lysosome-associated membrane protein DNA vaccine	Convenience, presumed safety	Unexplored	Safety and efficacy largely unknown, phase 1
Omalizumab	Multiple foods	Cost, IgE levels/weight limitations	More studies to characterize efficacy
Dupilumab	Multiple foods (?)		Potential largely unknown; might need OIT in combination
Traditional Chinese medicine	Safe	No effect in phase 2, poor adherence	Trial with OIT underway
Omalizumab plus OIT	Fewer reactions, faster updosing	Cost, convenience, OIT side effects	Trials underway
OIT and probiotics and other adjuvants	Potential to increase efficacy, persistence of effect	As per OIT	Trials underway

Sicherer et al. Food Allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. JACI 2018; p41-58

Table 4. Immunotherapies under Investigation in Clinical Trials for Treatment of Food Allergy.

Feature	Oral Immunotherapy	Sublingual Immunotherapy	Epicutaneous Immunotherapy
Form of study product (protein dose)	Allergen powder (300–4000 mg per day)	Allergen extract drops (2–7 mg per day)	Allergen patch (100–500 μg per day)
Clinical effect			
Desensitization	Large effect	Moderate-to-small effect	Variable effect
Sustained unresponsiveness	Occurs in subgroups of persons	Not known (studies under way)	Not known
Side effects	Oral or gastrointestinal; potential for anaphylaxis in persons with fever, infection, or menses and during exercise after receipt of a dose of oral immunotherapy	Oral or pharyngeal (local effects)	Skin (local effects)
Immune modulation: antibody and cellular changes	Substantial	Small or moderate	Small or moderate

Jones and Burks et al. Food Allergy. N Engl J Med 2017: 377; 12

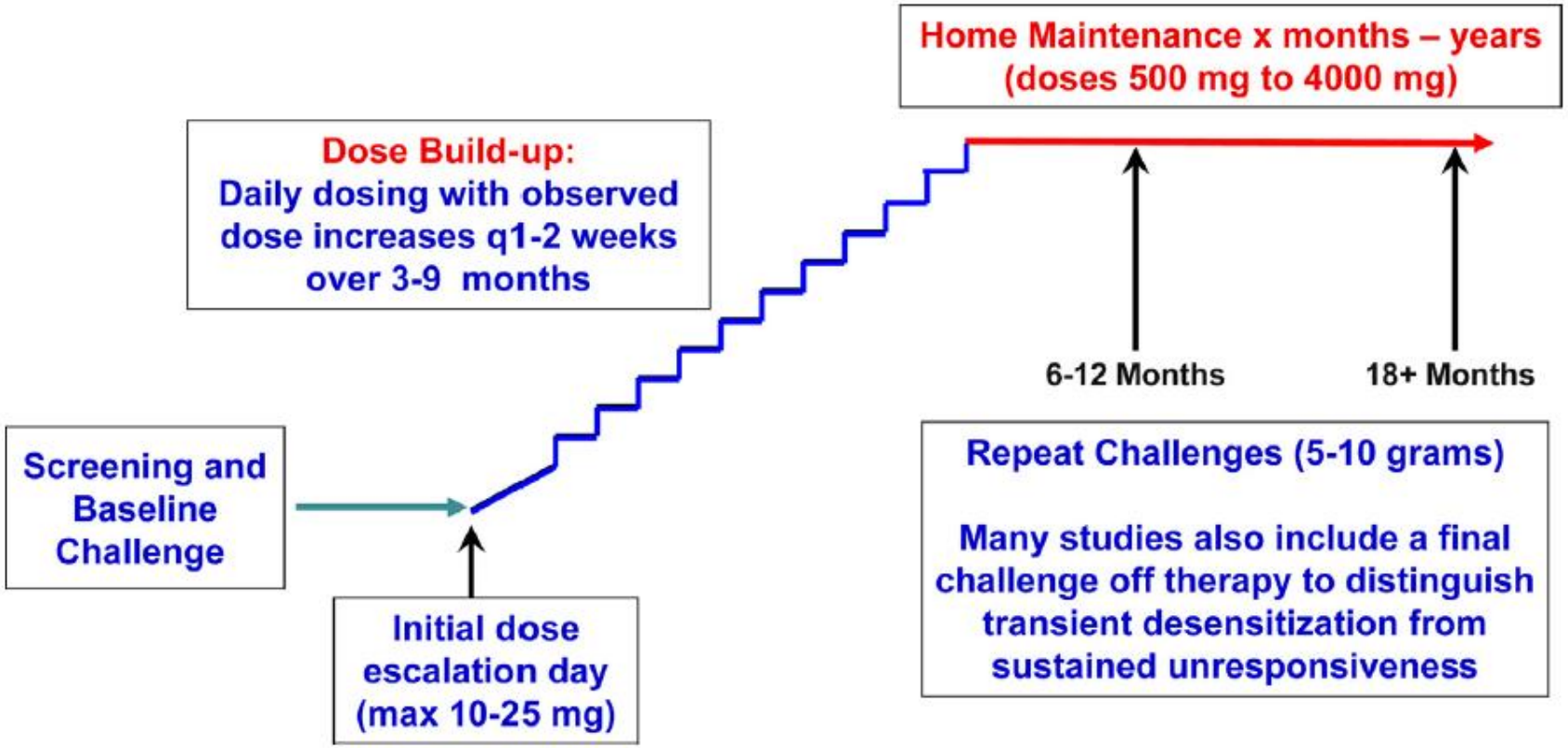


FIG 1. Typical schematic for food immunotherapy, with initial dosing, dose build-up, and maintenance therapy. Adapted from Wood.[18]

Burks et al. Treatment for food allergy. JACI 2018; 141: 1-9

Take Home Points

- Don't Panel Test!!!
- Not all food adverse reactions are food allergies.
- History should guide testing (not the other way around)
- Prevention during early age may be best way to promote tolerance
- Sustained Tolerance on the horizon

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- Haig Tcheurekdjian M.D.
- Ted Sher M.D.

QUESTIONS?

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Peanut Mouse Models:

- Investigation of peanut oral IT using CpG peanut-nanoparticles in a murine model of peanut allergy. *Srivastava KD et al. Journal of Allergy and Clin Immunology 2015; 135: AB759*
- Pioglitazone attenuates peanut induced anaphylaxis in a mouse model of peanut allergy. *Scurlock A et al. Journal of Allergy and Clin Immunology 2015; 135: AB235*

Peanut Mouse Models:

- Maternal allergy increases susceptibility to offspring allergy in association with Th2 biased epigenetic alterations in a mouse model of peanut allergy. *Song et al. J Allergy Clin Immunology 2014; 136: 1339-1334*

CLINICAL ANAPHYLAXIS SCORE: MURINE

*Clinical Assessment score 1-5 per previous protocols in murine models

Score	Symptoms
0	No clinical symptoms
1	Repetitive mouth/ear scratching and ear canal digging with hind legs
2	Decreased activity; self isolation; puffiness around eyes and/or mouth
3	Periods of motionless for more than 1 min; lying prone on stomach
4	No response to whisker stimuli; reduced or no response to prodding
5	Endpoint: tremor; convulsion; death

Sun J. et al. Impact of CD40 ligand, B cells, and mast cells in peanut induced anaphylactic responses. J Immunol. 2007; 179(10):6696-703.

Translation

Mechanisms of allergic diseases

Series editors: Joshua A. Boyce, MD, Fred Finkelman, MD, and William T. Shearer, MD, PhD

Food allergy: Insights into etiology, prevention, and treatment provided by murine models

Michiko K. Oyoshi, PhD, MSc,[a] Hans C. Oettgen, MD, PhD,[a] Talal A. Chatila, MD, MSc,[a] Raif S. Geha, MD,[a] and Paul J. Bryce, PhD[b] *Boston, Mass, and Chicago, Ill*

TABLE I. Key points

- Animal models allow extensive investigation into the mechanisms of allergic sensitization or tolerance to specific allergens under controlled environmental conditions within a defined genetic background, which promotes a better understanding of the etiology of human food allergy.
- Animal models have identified key factors responsible for breakdown in oral tolerance, such as epithelial cytokines that activate DCs to promote a T_H2 milieu, altered microbiota, or antigen exposure through alternative routes, such as the skin.
- Animal models have defined effector mechanisms of food allergy, some of which might also play a role in human subjects: IgE- and IgG-mediated pathways of anaphylaxis, variable genetic susceptibility to food allergy, and T cell– and mast cell–dependent diarrhea.
- Animal models enable experimental investigation to delineate the associative or causal influences of epidemiologic findings in human subjects, which might facilitate prevention strategies.
- Animal models allow validation of the utility of existing therapeutics, as well as development of novel therapies, which can lead to significant improvements in therapy options for food allergy patients.

Translation

REVIEW

Lessons learned from mice and man: Mimicking human allergy through mouse models

Michelle T. Graham*, Kari C. Nadeau

Clinical Immunology (2014) 155, 1–16

Translation

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REVIEW ARTICLES

Oral Immunotherapy for Treatment of Immunoglobulin E-Mediated Food Allergy: The Transition to Clinical Practice

Giovanni B. Pajno, MD,[1] Linda Cox, MD,[2] Lucia Caminiti, MD, PhD,[1]
Vincenzo Ramistella, MD,[1] and Giuseppe Crisafulli, MD[1]