FOOD ALLERGY: BY THE GUIDELINES

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Learning Objectives

• Distinguish IgE-mediated food allergy from other forms of food allergy and food intolerance

• List the important aspects of the history required for evaluating patients with adverse reactions to foods, as well as the use and interpretation of skin testing and laboratory testing in the evaluation.

• Review the acute and long term management of a food allergic patient

ADVERSE FOOD REACTION

FOOD AVERSION

IMMUNE MEDIATED (FOOD ALLERGY)
- IgE
- Non-IgE
- Mixed IgE & non IgE
- Cell Mediated
- Other

NON-IMMUNE MEDIATED (FOOD INTOLERANCE)
- Toxic
- Metabolic
- Pharmacologic
- Idiosyncratic

J ALLERGY CLIN IMMUNOL 2010:126:S1-S58
**IMMEDIATE HYPERSENSITIVITY**

**Symptoms**
- Cutaneous
  - Flushing, hives, angioedema, eczema
- GI
  - Oropharyngeal pruritus and edema, abdominal cramping, nausea, vomiting, diarrhea
- Pulmonary
  - Rhinitis, laryngeal edema, wheezing, coughing & shortness of breath
- Cardiovascular
  - Hypotension, tachycardia, arrhythmias
- Neurological
  - Loss of consciousness
- Behavioral
  - Irritability (preceding or in combination with other symptoms)
FOOD ALLERGEN CHARACTERISTICS

CLASS 1 FOOD ALLERGENS
• Water-soluble glycoproteins
• Molecular weights ranging from 10,000-70,000 daltons
• Resistant to
  – Heat
  – Changes in pH
  – Proteases
• Several have been identified, isolated, sequenced and cloned
• Linear and/or conformational epitopes identified

Vicilin Ara h 1
Conglutin Ara h 2
Glycin Ara h 3
Ara h 3 iso. Ara h 4
Profilin Ara h 5
Ara h 2 iso. Ara h 6
Ara h 2 iso Ara h 7

LINEAR VS CONFORMATIONAL EPITOPES

Sampson HA. JACI 113:805-19, 2004

HISTORY OF ALLERGIC DISEASE

Atopic Dermatitis
Food Allergy
Asthma
Allergic Rhinitis
Drug Allergy
Insect Sting Hypersensitivity
**DIAGNOSTIC APPROACH TO THE EVALUATION OF FOOD ALLERGY**

1. **Detailed History & Physical**
2. IgE-mediated → PST or ImmunoCAP
3. Non-IgE-mediated → GI Consultation/Endoscopy
4. Elimination Diet → Food Challenge
5. Specific Allergen Elimination Diet → Reconsider

**SUSPECTED FOODS**

- **Route of exposure**
  - Ingestion
  - Contact
  - Inhalation
  - Injection

- **Amount ingested**
  - Minute
  - Small
  - Medium
  - Large

- **Manner of preparation**
  - Raw
  - Cooked
  - Both
  - Plain
  - Spices
  - Mixed with other foods
  - Preservatives
  - Dyes

- **Simultaneously ingested foods**
  - None
  - Few
  - Multiple

- **Illness in others ingesting the same food**

- **Review of current diet**
  - Which of the simultaneously ingested foods have been eaten again without reaction?
  - Patients are sometimes eating the food to which they think they are allergic as an ingredient in another food.

**SUSPECTED FOODS**

- **Inhalation reactions:**
  - Peanut dust: possible
  - Peanut butter: doubtful

- **Which dye is capable of causing IgE-mediated reactions?**

**YOUNG CHILDREN**

- **PEANUT**
  - INFREQUENTLY OUTGROWN

- **TREE NUTS**
  - INFREQUENTLY OUTGROWN

- **SOY**
  - USUALLY OUTGROWN

- **MILK**
  - USUALLY OUTGROWN

- **EGG**
  - USUALLY OUTGROWN

- **WHEAT**
  - USUALLY OUTGROWN

**Risk of reacting to a tree nut is 35%**

**Risk of reacting to another tree nut is 37%**

**Risk of reacting to another legume is only 5%**

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- Don’t forget to ask about beef!
- Don’t forget to ask about raw egg!
ADOLESCENTS & ADULTS

Risk of reacting to another fish is 50%

Risk of reacting to another shellfish is 75%

Risk of reacting to radiographic contrast dye is 0%!!!!!!

PEANUTS

Risk of reaction to pecan is high if patient is sensitive to walnut

TREE NUTS

Risk of reaction to pistachio is high if patient is sensitive to cashew

FISH

Risk of reacting to another fish is 50%

SHELLFISH

Risk of reacting to another shellfish is 75%

DESCRIPTION OF REACTIONS

- Timing of onset in relation to food ingestion
- Symptoms
- Severity
- Duration of reaction
- Treatment of reaction
- Reproducibility of reaction after ingestion of suspected food
- Most recent reaction

Duration of Reactions
- Dose, emesis, treatment
- Mild to moderate reactions are usually hours long
- Biphasic reactions are rare, but concerning
- Prolonged reactions are extremely rare
  - Hives lasting for days are rarely food-driven without other evidence to suggest food as the cause

Reasons for lack of reproducibility
- Not IgE-mediated food allergy
- Focused on wrong food as cause
- Cross contamination with another food
- Food allergen denatured by cooking
- Added spice rather than the food
- Need another trigger such as exercise

Clinical Relevance of Food Cross-reactivity

Sicherer SH. JACI 2001;108:881
Pollen-Food (Oral Allergy) Syndrome

**Patients**
- Occurs in certain pollen allergic patients

**Mechanism**
- Primary sensitization to pollen with subsequent reaction to cross-reacting allergens in fruits and vegetables

**Symptoms**
- Symptom onset during or soon after food ingestion
- Pruritus & edema of lips, tongue and palate
- Systemic symptoms can occur

**Laboratory**
- Prick to prick skin tests or skin tests with fresh extracts of implicated foods are positive

**Treatment**
- Avoidance with severe symptoms
- Patients usually tolerate same fruit or vegetable when cooked

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**FOOD-DEPENDENT EXERCISE- INDUCED ANAPHYLAXIS**

- Anaphylaxis with exercise following specific food ingestion
  - Ingestion of food without exercise=no reaction
  - Exercise without ingestion of the specific food=no reaction
  - Specific food ingestion followed by exercise=ANAPHYLAXIS
- In rare cases occurs with exercise following the ingestion of any meal
- Variety of foods implicated: shellfish, fish, wheat, celery, fruit, mushroom

**Patients**
- Typical age adolescence through late 30’s
- Females outnumber males

**Mechanism unclear**

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**SOMETIMES IT’ S NOT THE FOOD**

**OTHER CAUSES**
- Viral illness
- Medications
- Contaminant
  - Toxin
  - Other food
  - Spice
  - Preservative
  - Mites
  - Latex
  - Antibiotic
- Other allergen exposure
- Psychological factors
Event factors + Patient factors

• Complicating medical issues
  – Asthmatic
  – On medication that might interfere with response to treatment
  – β-blocker
• Food allergy
  – Peanut or tree nut sensitive
• Level of sensitivity
  – Previous reaction patterns
    • Target organ
    • Life-threatening
• Maturity/psychosocial issues

• Food involved
  – Peanuts, tree nuts
• Route of exposure
  – Contact, inhalation, ingestion, injection
• Dose
• Target organ system
  – Pulmonary, cardiovascular, GI, cutaneous
• Treatment
• Response to treatment

Severity of reaction

FATALITIES DUE TO ANAPHYLACTIC REACTIONS TO FOODS

• Analyzed 32 cases reported to national registry
• Identified food
  – Peanut: 20 cases
  – Tree nuts: 10 cases
  – Milk & fish: 1 case each
• Both sexes equally affected (16 F/16 M)
• Most were adolescents or young adults (r: 2-32 years)
• Previous knowledge of food allergy - all, but one
• Most reactions occurred outside of the home (27/32)
• Asthmatics at higher risk
  – 24 of 25 with complete data had asthma
• Lack of availability of epinephrine at the time of the reaction
  – 4/32 had epinephrine available
  – 4 who received epinephrine in a timely fashion still died

HISTORY: SUMMARY

• Correlates poorly with the outcome of food challenges
  – Certain features of the history can likely significantly improve the correlation (family and personal history of allergic disease, timing of onset, symptoms, reproducibility, etc)

• Unreliable predictor of severity of subsequent reactions
  – Those at high risk of severe reactions
    • Asthmatics
    • Patients with previous history of severe reaction
    • Adolescents and young adults

• May aid in prediction of tolerance, particularly when combined with other information
  – Recent significant exposure without a reaction
# Food Allergy: Diagnostic Toolbox

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<td>Food Challenges: Ingestion Inhalation Contact Elimination diet Impedance/pH probe Endoscopy</td>
<td>Allergist Dietician Gastroenterologist Feeding therapist Psychosocial Clinician</td>
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<td>ImmunoCAP Patch testing Other</td>
<td>Other</td>
<td>Other</td>
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## Sensitization versus Clinical Reactivity

- **Sensitization**
  - Presence of food-specific IgE detected by skin testing or *in vitro* testing (FEIA)
  - Overestimates prevalence
- **Clinical Reactivity**
  - Evidence of symptoms upon exposure to a food
    - History
    - Challenge

## Diagnostic Approach to the Evaluation of Food Allergy

- Detailed History
- IgE-mediated
- PST and/or ImmunoCAP
- Specific Allergen Elimination Diet
- Food Challenge
- Elimination Diet

**Epicutaneous skin testing**
- Glycerinated commercial extracts 1:10 or 1:20 weight/volume
- Consider freshly prepared extracts for fruits and vegetables or if no commercial extract
- Applied by prick or puncture technique
  - Intradermal technique is not recommended
- Positive predictive accuracy
  - Less than 50% (many “false” positives)
- Negative predictive accuracy
  - Greater than 95% (few “false” negatives)

Select skin tests based on history and major foods known to cause symptoms.
RATIONALE FOR PRICK SKIN TESTING WITH FRESHLY PREPARED EXTRACTS

- Instability of selected fruit and vegetable allergens
- Lack of available commercial extract
- Check negative results obtained with a commercial extract in a patient with highly suggestive history
- Detection of unexpected ingredient
- Direction for further evaluation
- Caution: not standardized

PRICK SKIN TESTING

- 487 infants and children (median age 3 yrs) referred to center over 9 yrs (1989-98)
- Prick skin testing to milk, egg, peanut
- 555 open food challenges

• Results
  - Positive challenge was always seen when STP was above a certain size
    • Milk & Peanut > 8 mm
    • Egg > 7 mm
  - In children < 2 yrs SPT sizes were smaller
    • Milk > 6 mm
    • Egg > 5 mm
    • Peanut > 4 mm

Receiver operating characteristic (ROC) curves for skin wheal diameter in predicting a positive food challenge for milk, egg, and peanut. The numbers on the curves represent the corresponding skin wheal diameters in mm.

Sampson JACI 1988; 82: 718-26
3 mm diameter skin test
Sensitivity Specificity
Milk 96% 74% 51% 79%
Egg 98% 84% 53% 70%
Peanut 90% 96% 29% 71

Sporik Study
Skin prick testing (SPT)
- Safe and useful for diagnosis of IgE-mediated food allergy
- Reagents and methods are not standardized
- Intradermal testing not indicated
- Positive SPT correlates with the presence of allergen-specific IgE bound to the surface of cutaneous mast cells.
- Compared with oral food challenges they have low specificity and low positive predictive value for making an initial diagnosis of FA.
- The larger the mean wheal provoked, the more likely that a food allergen will be of clinical relevance

SPT (continued)
- When diagnosing OAS, or in cases where SPT with commercial extracts do not correlate with the clinical histories, the SPT technique with fresh or native foods, especially fruits and vegetables, may prove more sensitive.
- Negative skin test in face of highly suggestive history- consider medically supervised food challenge
- Quality of evidence: Moderate
- Contribution of expert opinion: Significant

Diagnostic Approach to the Evaluation of Food Allergy

Detailed History
- IgE-mediated
  - PST or ImmunoCAP
  - Reconsider Dx
  - Elimination Diet
  - Reconsider Dx
  - Food Challenge
  - Reconsider Dx
  - Specific Allergen Elimination Diet
  - Sampson HA JACI 103:981-8, 1999
Allergen-specific serum IgE

- Useful for diagnosis of IgE-mediated food allergy, but not diagnostic
- "Cutoff" levels, defined at 95% predictive values may be more predictive than SPTs of clinical reactivity in certain populations
- Fluorescence-labeled antibody assays have comparable sensitivity to that of SPT
- Different assays yield variable results
- Absolute levels of sIgE may directly correlate with the likelihood of clinical reactivity when compared with OFC

Guidelines for the Diagnosis and Management of Food Allergy in the United States: Report of the NIAID-Sponsored Expert Panel

Allergen-specific serum IgE

- Predictive values vary among studies
  - Patient selection (patients’ ages)
  - Clinical disorder studied
  - Length of food avoidance
- Negative test in face of highly suggestive history- consider medically supervised food challenge
- Quality of evidence: Moderate
- Contribution of expert opinion: Significant
TYPES OF ELIMINATION DIETS

Basic Concepts
- Remove food
  - Symptoms resolve if food-related
  - Symptoms remain if not food-related
- Monitor diet for nutritional adequacy
- Duration of diet depends upon disease and nutritional adequacy of diet
- Diets

• Limited elimination diet
  - High suspicion foods
  - Skin test or ImmunoCAP positive foods

• Oligoantigenic diets
  - Foods for diet selected on basis of low likelihood of allergenicity
  - Useful when large number of foods are suspected

• Elemental diet
  - Hypoallergenic formula (amino acid based formula)
  - May add few "safe" foods
  - Useful when large number of foods suspected or for infants on no solids
  - Poor compliance outside of infancy

STANDARD FOOD CHALLENGES

• Types
  - Open
  - Single-blind
  - Double-blind placebo-controlled: "gold standard"
• Must be performed in appropriate setting with adequate medical support
• Selection of patients
  - Decide question to be answered
• Selection of initial dose
  - Based on history
  - Final dose (if no reaction) is open ingestion of normal portion of the food
• Time interval between challenge doses
  - Based on history
• Goal
  - Document sensitivity or lack thereof

FOOD CHALLENGES

  - Retrospective chart review of children challenged to milk, egg, wheat, soy and peanut over 7 year period
  - Risk is reasonable when performed by experienced physician in a properly equipped medical setting

  - False negative ~3%
  - False positive < 1%
TREATMENT: PATIENTS AND CARETAKERS

- Recognition of early signs and symptoms
- How and when to give epinephrine (written plan)
- Administration of liquid or chewable antihistamine
- Ambulance to emergency room

TREATMENT: MEDICAL PERSONNEL

- Assess rapidly and provide supportive care
- Medications:
  - Oxygen
  - Antihistamines
  - Epinephrine
  - Bronchodilators
  - IV Fluids
  - Steroids
- Pay attention to factors that might inhibit response to treatment
- Observe for relapse
- Provide prescription for auto-injectable epinephrine device
- Arrange follow-up care

TREATMENT: FOLLOW-UP VISIT AFTER ALLERGIC REACTION

- Monitor response to treatment
- Review circumstances surrounding the reaction
- Review effectiveness of Food Allergy Action Plan
  - Make necessary alterations
- Provide emotional support
LONG TERM MANAGEMENT

• Follow-up visits at appropriate intervals
• History
  • Determine frequency & specifics of reactions
  • Exposure to offending foods without a reaction?
  • Review current diet
  • Development of allergies to other foods?
  • Routinely carrying treatment medications?
  • Impact of food allergy on quality of life?
  • Development of other allergic disease (asthma)?

LONG TERM MANAGEMENT

• Physical examination
  • Appropriate weight gain
  • Findings suggestive of new allergic disease or other disease
• Laboratory data
  • Skin testing?
  • ImmunoCAP?
  • Other testing suggested by history?

LONG TERM MANAGEMENT

• Management
  • Reinforce need to carry medications at all times and review use of medical devices (epinephrine auto-injector, inhaler if asthmatic)
  • Food challenge indicated by history and/or lab results?
  • Aid in interactions with school and community
  • Answer questions
  • Suggestions regarding impact on quality of life
  • Is referral indicated
    • Allergist
    • Gastroenterologist
    • Dietician
    • Psychosocial clinician
FOOD ALLERGY: INDICATIONS FOR REFERRAL TO THE ALLERGIST

- Diagnostic assessment of the patient with:
  - Severe or persistent disease
  - Multiple food sensitivity
  - Complications
  - Coexisting allergic disease (asthma, atopic dermatitis)
- Test interpretation
- Identification of offending foods
- Performance of food challenges
- Development of targeted elimination diets
- Comprehensive patient education