GASTROINTESTINAL COMPLAINTS IN FOOD ALLERGY:

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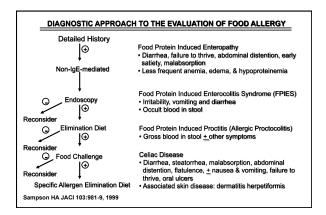
Conflict of Interest Statement

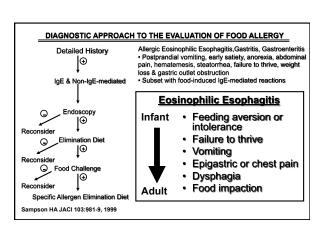
- Consultant for Sunovion
- · Research Support: Astra Zeneca

Learning Objective

 Discuss the symptoms and signs associated with IgEmediated, non-IgE-mediated and mixed IgE- and non-IgEmediated food allergy involving the gastrointestinal tract

ADVERSE FOOD REACTION FOOD AVERSION IMMUNE MEDIATED (FOOD ALLERGY) - IgE - Non-IgE - Non-IgE - Mixed IgE & non IgE - Cell Mediated JALLERGY CLIN IMMUNOL 2010:126:S1-S58





"Normal" numbers of eosinophils in gastrointestinal tract Fundus Antrum Jejunum Term lleum Cecum Asc Colon Trans Colon Desc Colon Sigmoid Rectum 0 10 20 30 40 50 Eosinophils/HPF Figure 1. Mean mucosal eosinophil count/HPF and standard deviation for 11 medical examiner sufferor clean in terms ago 5.5 yrsi according to analysis suffering to the suffering colon for earling colon for earl

Eosinophilic Esophagitis in Children and Adults: A Systematic Review and Consensus Recommendations for Diagnosis and Treatment

GLENN T. FURUTA," CHRIS A. LIACOURAS, MARGARET H. COLLINS, SANDEEP K. GUPTA, CHRIS JUSTINCH, T PHIL E. PUTNAM, PETER BONIS," ERIC HASSALL, "F. ALEX STRAUMANN, MARC E. ROTHENBERG, "I and Membrof the First International Gastrointestinal Eosinophil Research Symposium (FIGERS) Subcommittees

Diagnostic Guidelines

- Clinical symptoms of esophageal dysfunction
- ≥15 Eosinophils in 1 high-power field
- Lack of responsiveness to high-dose proton pump inhibition (up to 2 mg/kg/day)

or

Normal pH monitoring of the distal esophagus

Gastroenterology 2007;133:1342-1363

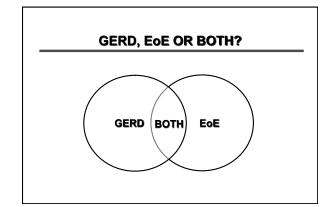
Eosinophilic esophagitis: Updated consensus recommendations for children and adults

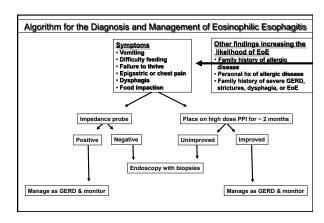
Chris A. Liscouras, M.D. Glenn T. Frunta, MD. Isuo Hirano, MD. Dan Atkins, MD. Stephen E. Attwood, MD. FRCS, FRCSI, MCh. Peter A. Bonis, MD, A. Wesley Burks, MD, Minna Chehade, MD, Margaret H. Collins, MD, Evan S. Deltor, MD, MPH, Rasjan Dold, MD, Gary W. Fals, MD. MS, Primasa Gornsalves, MD, Sandeep K. Quelge, MD, Devid A. Astaka, MD, Alfredo J. Lorendo, MD, Pitol. Jouandan E. Markovitz, MD, MSCE, Richard J. Hoel, MD, Robert D. Odze, MD, PRCP, Philips P. Putham, MD, FAAP, Josel E. Richter, MD, FACP, MACG, Yvorne Romero, MD, Gelaurdo Ruchelli, MD, High A. Sampson, MD, Alain Schoperf, MD, Richter, Schoperr, MD, Status Specieler, MD, Jonathan M. Spergel, MD, PhD-A. Bark Streamann, MD, Barry K. Wershi, MD, Mark E. Rothenberg, MD, PhD- and Seema S. Aceves, MD, PhD-A. Lorend Johnson, MC, Boston, MC, Boston, Mass, Chicago, MI, Shin Diego, Calif, New York, Nr. Indianapolis, Ind. Tomedioss, Spain, Greenslitz, SC, and North Shelds Custed Kingdom.

J Allergy Clin Immunol. 2011 Jul;128(1):3-20.e6; quiz 21-2. Epub 2011 Apr 7. Review

EoE: General Features

- · Can present at any age
- Similar genotypic abnormalities are noted in children and adults
- · Predominantly occurs in males (>70%)
- · More common in Caucasians, but not restricted by race
- · Presentation often more dramatic in children than adults
- · No pathognomonic features have been identified
- · Symptoms may not correlate with histology





Endoscopic Findings in EoE

Linear furrowing, vertical lines of the esophageal mucosa

White exudates, white specks, nodules, granularity

Circular rings, transient or fixed

Fox V et al. Gastrointest Endo 2003;57:30-36 Desai T et al. Gastrointest Endo 2005;61:795 Straumann A et al. Gastrointest Endo 2003; 57:407 Gonsalves N, et al. Gastrointest Endosc 2006;64:313-9

Endoscopic Findings in EoE

Impaction

- Common in untreated adult patients (1/3 require bolus removal)
 - » 30-54% of adults presenting for food impaction had EoE

Desai et al, Gastrointest Endosc 2005

Other concerns

Small caliber esophagus

Linear shearing/crepe paper mucosa with passage of endoscope or dilator

Gonsalves N, et al. Gastrointest Endosc 2006;64:313-9

Histology

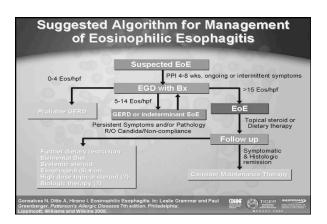
Normal Esophagus

- Stratified squamous epithelium
- · Rete papillae
- Basal zone

EoE

- Basilar hyperplasia
- Rete peg elongation
 Eosinophilic infiltration with degranulation
- Eosinophilic abscesses

Fox VL et al. Gastrointest Endosc 2002; 56: 260



IMMEDIATE HYPERSENSITIVITY

Symptoms • Cutaneous

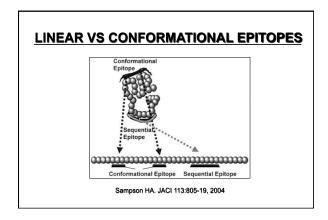
- Flushing, hives, angioedema, eczema
- Oropharyngeal pruritus and edema abdominal cramping, nausea, vomiting, diarrhea
- Pulmonary
 Rhinitis, laryngeal edema, wheezing, coughing & shortness of breath Cardiovascular
- - Hypotension, tachycardia, arrhythmias
- Neurological

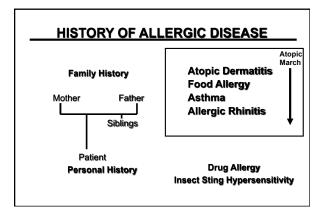
 Loss of consciousness
- Behavioral
 Irritability (preceding or in combination with other symptoms)

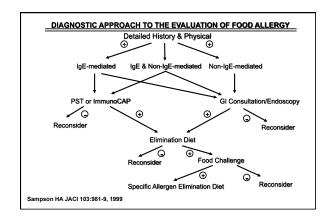
FOOD ALLERGEN CHARACTERISTICS

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







SUSPECTED FOODS Route of exposure - Ingestion Contact Inhalation Injection Amount ingested - Minute Small 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.

COMMON FOOD ALLERGENS

- · Young children to food ingestion
 - Milk
 - Egg
 - Soy
 - Wheat
- Peanut Adolescents/Adults
- Peanut
- Tree nuts
- · Fish/Shellfish

DESCRIPTION OF REACTIONS

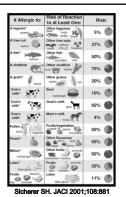
- Timing of onset in relation to food ingestion
- **Symptoms**
- Severity
- **Duration of reaction**
- Treatment of reaction
- Reproducibility of reaction after ingestion of suspected food
- Most recent reaction

- **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
 - 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



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

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

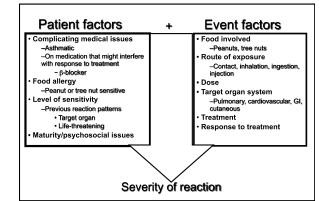
FOOD-DEPENDENT EXERCISE- INDUCED ANAPHYLAXIS

- · Anaphylaxis with exercise following specific food ingestion
 - Ingestion of food without exercise no reac
 Exercise without ingestion of the specific food no reaction
- → ANAPHYLAXIS - Specific food ingestion followed by exercise -
- · In rare cases occurs with exercise following the ingestion of any mea
- Variety of foods implicated: shellfish, fish, wheat, celery, fruit, mushroom
- **Patients**
 - Typical age adolescence through late 30's
 - Females outnumber males
- Mechanism unclear

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



FATALITIES DUE TO ANAPHYLACTIC REACTIONS TO FOODS Bock SA, et al. JACI 2001;107:191-3 (update JACI 2007;119:1016-18)

- 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/16M)
- 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

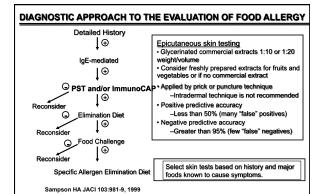


HISTORY: SUMMARY

- 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

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



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

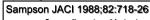
PRICK SKIN TESTING

Sporik R,et al, Clin Exp Allergy 2000; 30: 1540-6

- 467 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

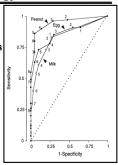
Sporik R,et al, Clin Exp Allergy 2000; 30:1540-6

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.



	3 mm diameter skin test	
	<u>Sensitivity</u>	Specificity
Milk	96% 74	51% 79
Egg	98% 84	53% 70
Peanut	90% 96	29% 71

Sporik Study



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

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-specificlgE 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

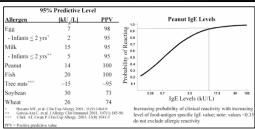
Guidelines for the Diagnosis and Management of Food Allergy in the United States: Report of the NIAID-Sponsored Expert Panel

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

Detailed History | General Hi

IMMUNOCAP PROBABILITY OF REACTING TO A FOOD AT A GIVEN IGE VALUE



Sampson HA. JACI 113:805-19, 2004

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

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

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
- Document sensitivity or lack thereof

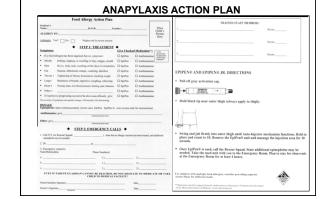
FOOD CHALLENGES

- Perry, TT, et al. Risk of oral food challenges. JACI 2004; 114:1164-8.

 - 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
- Cafarelli C, Petroccione T. Falsenegative food challenges in children with suspected food allergy. Lancet 2001 358:1871
 - 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 - Sternids
- · 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