Eosinophilic Esophagitis
and other Manifestations of
Food Allergy

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Learning Objectives

Understand Types of Food Allergy

Define Eosinophilic Esophagitis

Understand the epidemiology and diagnostic criteria

Identify the clinical symptoms and endoscopic features

Appreciate the treatment options
Disclosures

Will discuss unlabeled use of medications: methylprednisolone, prednisone, fluticasone, budesonide, omeprazole/PPI’s

Speaker for Mead Johnson Nutritionals
Definition

• **Food allergy**
  - An abnormal immune response to an ingested food antigen (i.e. protein)
  - Requires an initial “sensitizing” event that primes the immune system for future response

• **Sensitivity**
  - The presence of IgE antibodies to a food, often in the absence of clinical symptoms

*Sampson et al. JACI 2014*
Food Allergy Overview

Adverse Food Reaction

Immune Mediated
(Food Allergy and Celiac Disease)

- IgE Mediated (e.g. acute urticaria, anaphylaxis, oral allergy syndrome)
- Non-IgE Mediated (e.g. food protein-induced enterocolitis syndrome)
- Mixed IgE and non-IgE Mediated (e.g. atopic dermatitis, eosinophilic gastroenteritis)
- Cell Mediated (e.g. Allergic Contact Dermatitis)

Non-Immune Mediated
(Primarily Food Intolerances)

- Metabolic (e.g. lactose intolerance)
- Pharmacologic (e.g. caffeine)
- Toxic (e.g. scromboid fish toxin)
- Other / Idiopathic / Undefined (e.g. sulfites)

Food Allergy Overview

Adverse Food Reaction

Immune Mediated
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Impact of Food Allergies

- Direct medical costs to the US health care system of $4.3 billion annually for childhood food allergies\(^1\)
  - Include clinician visits, emergency department visits, and hospitalization

- Costs borne by the family of $20.5 billion annually for childhood food allergies\(^1\)
  - Include lost labor productivity, out-of-pocket, and opportunity costs (caregiver needing to leave or change job)

- Quality of life decreased in UK, North American, European, and Asian studies\(^2\)-\(^5\)

- Risk of compromised nutrition

- Long-term impact on feeding behaviors

- Risk of fatal reaction\(^6\)

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# Food Allergy: Clinical Manifestations

<table>
<thead>
<tr>
<th>IgE (Immediate)</th>
<th>“Mixed” IgE/Non-IgE</th>
<th>Non-IgE (Delayed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate gastrointestinal allergy</td>
<td>Eosinophilic Esophagitis</td>
<td>Food protein-induced enterocolitis</td>
</tr>
<tr>
<td>Urticaria/Angioedema</td>
<td>Eosinophilic Gastroenteritis</td>
<td>Food protein-induced enteropathy</td>
</tr>
<tr>
<td>Oral Allergy Syndrome</td>
<td>Atopic dermatitis</td>
<td>Food protein-induced proctocolitis</td>
</tr>
<tr>
<td>Systemic anaphylaxis</td>
<td></td>
<td>Dermatitis Herpetiformis</td>
</tr>
<tr>
<td>Contact urticaria</td>
<td></td>
<td>Heiner syndrome (Food induced pulmonary hemosiderosis)</td>
</tr>
<tr>
<td>Rhinitis/Bronchospasm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from J Allergy Clin Immunol. 1999;103:717-728
## Food Allergy Prevalence in Specific Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Food Allergy Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylaxis</td>
<td>35-55%</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>37% (children)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>20% (acute cases)</td>
</tr>
<tr>
<td>Asthma</td>
<td>5-6% (children)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>Rare</td>
</tr>
</tbody>
</table>

Food Allergy: Clinical Manifestations

IgE (Immediate)

- Immediate gastrointestinal allergy
- Urticaria/Angioedema
- Oral Allergy Syndrome
- Systemic anaphylaxis
- Contact urticaria
- Rhinitis/Bronchospasm

Adapted from J Allergy Clin Immunol. 1999;103:717-728
Immediate and Late Phase IgE Mediated Reactions

80% are early phase

20% are late phase

Biphasic Response <6%

Ho et al. 2012
Fatal Food Anaphylaxis

Risk factors: 80% Rule

- Underlying asthma
- Delayed epinephrine
- Previous severe reaction with current symptom denial
- Adolescents, young adults (10-29 years old)
- Food obtained outside the home

Key foods

- Peanuts and tree nuts (~90% of fatalities)
- Fish
- Crustaceans

Food Allergy: Clinical Manifestations

Non-IgE (Delayed)

- Food protein-induced enterocolitis
- Food protein-induced enteropathy
- Food protein-induced proctocolitis
- Dermatitis Herpetiformis
- Heiner syndrome (Food induced pulmonary hemosiderosis)

Adapted from J Allergy Clin Immunol. 1999;103:717-728
Food Protein Induced Enterocolitis Syndrome (FPIES)

- Emesis, abdominal pain, diarrhea within **hours** of ingestion
- FTT can happen
- Cow’s milk and soy protein based formulas are the most common
- Rarely may result from food proteins passed in maternal breast milk
- Older infants and children can develop enterocolitis as a result of rice, egg, wheat, oat, peanut, nuts, chicken, turkey and fish.
- Hypotension occurs in about 15% of cases.
- Can be outgrown within 5-10 years of age
- Skin prick tests and serum IgE tests negative

Acquisition of Tolerance in Non-IgE–Mediated CMPA

- **FPIES**
  - Non-IgE–mediated reaction to food
  - Acute gastrointestinal presentation; symptoms include vomiting and diarrhea
  - The most common triggers are cow’s milk and soy

- **Large, prospective, population-based study on CMP-induced FPIES**
  - 13,019 infants with probable adverse reactions to CMP
  - 44 patients (0.34%) fit FPIES criteria
  - 50% of FPIES patients tolerated milk by age 1 year
  - 75% of FPIES patients tolerated milk by age 18 months
  - 90% of FPIES patients tolerated milk by age 3 years

- **No other robust studies on natural history of tolerance development in non-IgE–mediated milk allergy**

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FPIES = food–protein–induced enterocolitis syndrome
Allergic Proctocolitis

- Stool Irregularities: Bloody diarrhea (hematochezia)
  - Most often streaks of bloody mucus mixed with stool
  - Often painless, not life threatening
- Lymphoid hyperplasia in the colon
- Eosinophilic colitis or allergic proctitis
- Skin prick tests and serum IgE tests negative

Allergic Colitis

![Allergic Colitis](image1)

Allergic Proctitis

![Allergic Proctitis](image2)

Food Allergy: Clinical Manifestations

“Mixed” IgE/Non-IgE

- Eosinophilic Esophagitis
- Eosinophilic Gastroenteritis
- Atopic dermatitis

Adapted from J Allergy Clin Immunol. 1999;103:717-728
Background

Diagnostic Criteria

Therapeutic Approach
1995 Distribution of EoE

NE United States

Switzerland
2013 Distribution of EoE

- Switzerland
- Spain
- Belgium
- England
- Netherlands
- Italy
- Germany
- France
- Israel
- Middle East
- Africa
- Canada
- United States
- Mexico
- Brazil
- Japan
- Asia
- Australia
# Prevalence of EoE in the U.S.

<table>
<thead>
<tr>
<th>Source population</th>
<th>EoE cases</th>
<th>Prevalence (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>3,587,571</td>
<td>1,813</td>
</tr>
<tr>
<td>20-64</td>
<td>7,981,646</td>
<td>4,700</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5,544,574</td>
<td>4,257</td>
</tr>
<tr>
<td>Female</td>
<td>6,024,643</td>
<td>2,256</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>East</td>
<td>2,226,470</td>
<td>1,054</td>
</tr>
<tr>
<td>South</td>
<td>4,529,151</td>
<td>2,507</td>
</tr>
<tr>
<td>Midwest</td>
<td>3,569,432</td>
<td>2,567</td>
</tr>
<tr>
<td>West</td>
<td>1,244,164</td>
<td>385</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>11,569,217</td>
<td>6,513</td>
</tr>
</tbody>
</table>

Age of Onset of EoE

Mean age (N=30) | Range
--- | ---
At first diagnosis | 33 | 6-65
At first manifestation | 29 | 6-52

Mean age (N=31) | Range
--- | ---
At first diagnosis | 34 | 14-77
Years “incorrect diagnosis” | 7 | 2-12

Background

Diagnostic Criteria

Therapeutic Approach
2011 Consensus Report

- Panel of 33 physicians (6 months)
- Conceptual Definition
  - “Eosinophilic esophagitis represents a chronic, immune/antigen mediated, esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation”
- Pediatric and adult EoE likely the same disease

Clinical Features

• Male predominance (about 3:1)
• Multiple reports of familial clustering (within and across generations)
• Association with food allergy and atopy
• Chronic condition in adults and children

Furuta et al. Gastroenterology. 2007; 133:1342-1363.
EoE Presentation by Age

- Feeding Disorder: 13%
- Vomiting: 26%
- Abdominal Pain: 26%
- Dysphagia: 27%
- Food Impaction: 7%

Histology of the Esophagus
Endoscopic Features
Background

Diagnostic Criteria

Therapeutic Approach
Proposed Endpoints for Treatment of Eosinophilic Esophagitis

- Symptomatic Remission
- Histological Remission
- Endoscopic Remission

Endoscopic photos from Dr. Ikuo Hirano
EoE as a Progressive Disease

OR = 2.1 (1.7-2.7) per 10 year increase for developing a fibrostenotic EoE phenotype

# Eosinophils Respond to PPI’s Adolescents/Young Adults

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr)/sex</strong></td>
<td>14/M</td>
<td>25/M</td>
<td>13/F</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>Pain</td>
<td>Food impaction</td>
<td>Dysphagia</td>
</tr>
<tr>
<td><strong>Environmental Allergies</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Omeprazole 10 mg BID</td>
<td>Omeprazole 20 mg BID</td>
<td>Omeprazole 20 mg QD</td>
</tr>
<tr>
<td><strong>Eosinophils/hpf</strong></td>
<td>Before treatment</td>
<td>37</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Eosinophils Respond to PPI’s Adults

Oral Steroid Studies

Topical Steroids (Swallowed Fluticasone)

Pre-treatment
Post-treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Eos/hpf</th>
<th>Design</th>
<th>Max Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Konikoff</td>
<td>84.6</td>
<td>RCT</td>
<td>880 mcg/day</td>
</tr>
<tr>
<td>Noel</td>
<td>43.4</td>
<td>Retrosp</td>
<td>1320 mcg/day</td>
</tr>
<tr>
<td>Teitelbaum</td>
<td>23</td>
<td>Prosp</td>
<td>880 mcg/day</td>
</tr>
<tr>
<td>Schaefer</td>
<td>33.3</td>
<td>RCT</td>
<td>1760 mcg/day</td>
</tr>
</tbody>
</table>

*Post treatment data on 16 patients.

Liquid Budesonide

- 20 children with EoE (baseline: 87 eos/hpf)
- Prescribed liquid budesonide (1-2 mg once daily) mixed with a sucralfos (Splenda®) paste
  - 16 responders (< 8 eos/hpf);
  - 3 partial responders (8-23 eos/hpf);
  - 1 non-responder (no change in eos) after 3-4 months of treatment;
  - No significant adverse effects; esophageal Candidiasis in one patient

History of Diet and EoE

• In 1995: “Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula”
  – 10 patients with refractory reflux symptoms
  – 6 had received anti-reflux surgery without resolution
  – All with markedly elevated esophageal eosinophils

• Patients given a trial of an “elemental diet”
  – Amino acid based formula
  – Minimized any risk of food allergy

Diet and Eosinophilic Esophagitis

- After elemental diet:
  - Symptom resolution in 8 patients, improvement in 2
  - Improvement occurred within 3 weeks
  - Biopsies improved as well

- Symptoms returned after food was reintroduced

- Conclusions:
  - EoE is an allergic phenomenon
  - EoE improves with food elimination
Types of Dietary Therapy for EoE

• Total Elimination Diet
  – Amino-Acid based formula

• Selective Diet
  – Empiric Diet
  – Directed (Targeted) Diet
Response of 3 Types of Dietary Restriction

- **Empiric - Kagalwalla**: 74% improvement, 13.6% still present.
- **Directed - Spergel**: 77% improvement, 12.8% still present.
- **Liacouras**: 95% improvement, 1.1% still present.

Advantages of Elemental Diet

• When administered correctly:
  – > 95% demonstrate clinical and histologic response
  – Allows systematic re-introduction of foods

• Can lead to prolonged remission clinically and histologically without the need for medications

• Causative foods may be able to be reintroduced successfully later (tolerance)
Obstacles to Elemental Diet

- Elemental formula is unpalatable
- Commonly needs nasogastric or gastrostomy tube to administer
- Nutritional status must be monitored closely
- Elemental formulas are expensive
  - Variable insurance coverage
  - Usually significant out of pocket expense
- Quality of Life issues
Empiric Diet Elimination

- Easy, do not need testing
- Few studies in the literature
- May not eliminate all foods necessary to induce remission
- May eliminate foods that are not necessary to be eliminated
- May prolong the process of food elimination and re-introduction
Directed Diet Elimination

• Elimination by history/symptoms (or guessing) is challenging
  – Reactions may be delayed several days after exposure
  – Reactions may persist several days after exposure
  – More than one food may be causing reaction
• Elimination based on diagnostic testing is inaccurate
Role of Dietician in EoE

- Assessment of nutritional status
- Determination of dietary adequacy
- Working within dietary restrictions to provide balanced, acceptable diet
- Education of patient & family
- Identification /assessment of barriers to effective nutritional therapy
Conclusions

Food allergy is less common than food “intolerance”

Food allergy has significant economic and quality of life burden

3 mechanisms: IgE, non-IgE, mixed
Conclusions

EoE is a clinico-pathologic disorder diagnosed by clinicians

EoE can occur at any age

Pediatric and Adult EoE are likely the same

Incidence and prevalence increasing

Therapy goal: improve symptoms & prevent complications
Advocacy Groups

• American Partnership for Eosinophilic Disorders
  – www.apfed.org

• Campaign Urging Research for Eosinophilic Disorders
  – www.curedfoundation.org

• Food Allergy Network
  – www.foodallergy.org