Adverse Food Reaction

Food Aversion

Immune Mediated (food allergy)
- IgE Mediated
- Non-IgE Mediated
- Mixed IgE and Non-IgE Mediated
- Cell Mediated

Non-Immune Mediated (food intolerance)
- Toxic
- Metabolic
- Pharmacologic
- Idiosyncratic
- Other

Food Aversion
Gastrointestinal Hypersensitivity Disorders
- Pollen-Food Allergy Syndrome
- Immediate GI Hypersensitivity
  - Eosinophilic Esophagitis
  - Eosinophilic Gastritis
  - Eosinophilic Gastroenteritis
  - Dietary Protein Enterocolitis
  - Dietary Protein Proctitis
  - Dietary Protein Enteropathy (Celiac Disease)

Cutaneous Hypersensitivity Disorders
- Acute Urticaria & Angioedema
- Acute Contact Urticaria
- Atopic Dermatitis
- Dermatitis Herpetiformis

Respiratory Hypersensitivity Disorders
- Allergic Rhinitis
- Acute Bronchospasm
- Asthma
- Food-induced Pulmonary Hemosiderosis (Heiner Syndrome)

Systemic Hypersensitivity Disorders
- Generalized Anaphylaxis
- Food-associated Exercise-induced Anaphylaxis
Detailed History & Physical

IgE-mediated

IgE & Non-IgE-mediated

Non-IgE-mediated

SPT or ImmunoCAP

GI Consultation/Endoscopy

Reconsider

Elimination Diet

Reconsider

Food Challenge

Specific Allergen Elimination Diet

Reconsider
IgE-mediated vs non-IgE-mediated Reactions

Important to differentiate clinically between IgE-mediated and non-IgE-mediated characteristics.

<table>
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<th>IgE-mediated</th>
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<td>Time from exposure to reaction</td>
<td>Immediate onset—minutes to 2 hours</td>
<td>Delayed onset; usually ≥2 hours</td>
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<td>Severity</td>
<td>Mild to anaphylaxis</td>
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<td></td>
<td>More severe presentations</td>
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<tr>
<td>Duration</td>
<td>Usually persist beyond 1 year of age</td>
<td>Often persist beyond 1 year of age</td>
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<tr>
<td>Diagnosis</td>
<td>Clinical history</td>
<td>Clinical history</td>
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<td>Specific serum IgE, skin-prick test</td>
<td>Elimination diet</td>
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IgE-mediated vs non-IgE-mediated Reactions

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Cow's milk allergies

- IgE mediated cow's milk allergies
- Non-IgE mediated cow's milk allergies
  - Cow's milk protein-induced enterocolitis/enteropathy/proctocolitis
  - Eosinophilic esophagitis induced by cow's milk
  - Mild to moderate non-IgE mediated cow's milk allergies
## Pathophysiology of Cow’s Milk Allergy

- **Triggers**—Principal cow’s milk allergens
  - Casein fraction of proteins (αs1-, αs2-, β-, and κ-casein)
  - Whey proteins (α-lactalbumin and β-lactoglobulin)
- **Complex interplay**
  - Epithelial barrier
  - Mucosal and systemic immune response
  - Route of exposure
  - Microbiome and other influences resulting in allergy or tolerance
Breast Milk and What it Provides

Tolerance

• Support the infant’s developing immune system
• Tolerance to potential food allergens?

Recommended Treatment of CMA

- Breastfed infants
  - May need to consider avoidance of cow’s milk protein from maternal diet
  - May take up to 72 hrs to clear breast milk antigens

- Infants ≤6 months
  - Formulas extensively hydrolyzed protein or amino acid-based formula

- Infants >6 months
  - Soy formula may be appropriate in IgE-mediated cases
  - Country specific: Not to be used in infants with food allergy <6 months of age
FPIES Clinical Phenotypes

- FPIES phenotype depends on dose and frequency of food allergen ingestion.
- Phenotype provides guidance for diagnosis and management.

<table>
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<tr>
<th>Phenotypes influenced by</th>
<th>early (&lt;9 months)</th>
<th>late (&gt;9 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity</td>
<td>mild-to-moderate</td>
<td>severe</td>
</tr>
<tr>
<td>Timing and duration of symptoms</td>
<td>acute (symptoms resolve in 24 hrs)</td>
<td>chronic (resolution may take days to weeks)</td>
</tr>
<tr>
<td>Associated IgE-mediated food allergy</td>
<td>IgE negative</td>
<td>IgE positive</td>
</tr>
</tbody>
</table>

### FPIES Phenotypes (continued)

<table>
<thead>
<tr>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingestion following a period of avoidance (at least several days)</td>
<td>Young infants fed continuously with milk or soy formulas</td>
</tr>
<tr>
<td>Onset of emesis: 1–4 hours</td>
<td>Watery diarrhea</td>
</tr>
<tr>
<td>Lethargy, limpness (&quot;septic appearance&quot;)</td>
<td>Mucous, blood in stools</td>
</tr>
<tr>
<td>15% go into shock</td>
<td>Intermittent emesis</td>
</tr>
<tr>
<td>15% with methemoglobinemia</td>
<td>Low albumin and total protein</td>
</tr>
<tr>
<td>6–8 hours later: diarrhea</td>
<td>Failure to thrive, poor growth</td>
</tr>
<tr>
<td>Onset: usually under 12 months; Fish/Shellfish: children, adults</td>
<td>Onset: first 1–3 months of life</td>
</tr>
<tr>
<td>Symptoms resolve within 24 hrs</td>
<td>Symptoms resolve within days–weeks, may require TPN</td>
</tr>
<tr>
<td>Cow’s milk, soy, rice, oat, vegetables</td>
<td>Cow’s milk, soy</td>
</tr>
</tbody>
</table>

methemoglobinemia
## Distinguishing FPIES, FPIAP, and FPE

<table>
<thead>
<tr>
<th></th>
<th>Main clinical features</th>
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</thead>
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<tr>
<td><strong>FPIES</strong></td>
<td>Delayed repetitive vomiting, pallor, lethargy</td>
</tr>
<tr>
<td><strong>FPIAP</strong></td>
<td>Benign blood in stool, baby thriving</td>
</tr>
<tr>
<td></td>
<td>Average age at onset lower: 2 months vs 4-6 months in FPIES, no acute symptoms upon food ingestion</td>
</tr>
<tr>
<td><strong>FPE</strong></td>
<td>Chronic diarrhea, malabsorption, low weight gain, no acute symptoms upon food ingestion</td>
</tr>
</tbody>
</table>

FPIAP, food protein-induced allergic proctocolitis; FPE, food protein-induced enteropathy.

Oral Food Challenge: What You Need to Know

• Oral food challenge (OFC) can confirm the diagnosis
• OFC is the *only* currently available diagnostic test
• FPIES diagnosis is based on consistent clinical features with improvement following withdrawal of suspected causal protein
• Physician-supervised OFC is necessary to evaluate for FPIES resolution
• Keep child away from food until challenge is done
• OFC is standardized
ER Letter—Individualized Allergy Action Plans

- Letter every parent should carry (see course downloads)
  - Provide letter to ER—What to do with accidental exposure
  - Letter includes:
    - Clinical features (it is this)
    - How this child is being treated for FPIES
    - Avoid medicine (eg, do not give antihistamine or epinephrine)
    - Foods this child has FPIES reaction(s) to

- How to Treat—Best treatment is rehydration in ER
  - Rehydration [with intravenous fluids]
  - Single dose of intravenous methylprednisolone given in severe reactions
  - Ondansetron iv/im/po may be useful in mild-moderate reactions

IV, intravenous; IM, intramuscular; PO, Per os (orally).
Management While Breastfeeding

FPIES can happen in exclusively breastfed infants, although rarely

- Do not restrict maternal diet unless infant is symptomatic (acute or chronic), or is not thriving
- Majority are asymptomatic and thriving during breastfeeding
- Rarely have acute or chronic symptoms been reported in breastfed infants, attributed to foods in maternal diet
- Maternal dietary avoidance vs stopping
- Substitute for breast milk: Hypoallergenic formula
  - Extensively hydrolyzed casein or amino acid formula [up to 40%]
## Selecting Safe Nutritional Alternatives

<table>
<thead>
<tr>
<th>Ages and Stages</th>
<th>Lower-risk foods*</th>
<th>Moderate-risk foods*</th>
<th>Higher-risk foods*</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 to 6 months (per AAP, CoN)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• If developmentally appropriate, and safe and nutritious foods are available:</td>
<td>Broccoli, cauliflower, parsnip, turnip, pumpkin</td>
<td>Squash, carrot, white potato, green bean (legume)</td>
<td>Sweet potato, green pea (legume)</td>
</tr>
<tr>
<td>• Begin with smooth, thin, purees and progress to thicker purees</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Choose foods that are high in iron</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Add vegetables and fruits</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months (per WHO)</td>
<td>Blueberries, strawberries, plum, watermelon, peach, avocado</td>
<td>Apple, pear, orange</td>
<td>Banana</td>
</tr>
<tr>
<td>• Complementary feeding should begin no later than 6 months of age.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• In the breastfed infant, high-iron foods or supplemental iron (1 mg/kg/day) is suggested by 6 months of age.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Continue to expand variety of fruits, vegetables, legumes, grains, meats, and other foods as tolerated.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Risk assessment is based on the clinical experience and the published reports of FPIES triggers.

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<tr>
<td><strong>8 months of age or when developmentally appropriate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Offer soft-cooked and bite-and-dissolve textures around 8 months of age or as tolerated by infant.</td>
<td>Lamb, fortified quinoa cereal, millet</td>
<td>Beef, fortified grits and corn cereal, wheat (whole wheat and fortified), fortified barley cereal</td>
<td>Higher iron foods: Fortified, infant rice and oat cereals.</td>
</tr>
<tr>
<td><strong>12 months of age or when developmentally appropriate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Offer modified tolerated foods from the family table: chopped meats, soft cooked vegetables, grains, and fruits.</td>
<td>Tree nuts and seed butters* (sesame, sunflower, etc)</td>
<td>Peanut, other legumes (other than green pea)</td>
<td>Milk, soy, poultry, egg, fish</td>
</tr>
</tbody>
</table>

*Risk assessment is based on the clinical experience and the published reports of FPIES triggers.

FPIES Resources

- FPIES.org [https://www.fpies.org](https://www.fpies.org)

- Help track frequency of FPIES occurrence
  - ICD-10 code: K52.2 [https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20Management/finances-coding/FPIES-Codes-ICD-10.pdf](https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20Management/finances-coding/FPIES-Codes-ICD-10.pdf)
EoE: Allergic Histopathology

Allergen exposure $\rightarrow$ Allergic inflammatory response $\rightarrow$
Infiltration of the esophagus with eosinophils and other inflammatory cells

- Eosinophils
- Activated eosinophils
- Mast cells
- CD4 lymphocytes
- CD8 lymphocytes
- Dendritic cells
EoE: Immunopathogenesis
EoE: Endoscopic Diagnosis

Furrows

Plaques

Rings

Stricture
EoE: Histological Diagnosis

- Normal (0 eos/HPF)
- EoE (≥15 eos/HPF)
EoE: Histological Diagnosis

- Eosinophil superficial layering and microabscesses
- Eosinophilic degranulation
EoE: Course With Increasing Duration of Symptoms

EoE: Inflammatory Phenotype

- Seen more often in early disease
- Seen more often in children

- Furrows
- Plaques
- Plaques along furrows
EoE: Fibrostenotic Phenotype

- Seen more often in late disease
- Seen more often in adults
Pediatric EoE: Fibrosis can be reversed with diet or topical corticosteroids

EOE Patient
Pre-treatment

EOE Patient
Post-treatment

Trichrome stain

### EoE: Histological response to topical corticosteroids in children

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
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</tr>
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<tbody>
<tr>
<td>No. subjects</td>
<td>36</td>
<td>80</td>
<td>24</td>
<td>42</td>
</tr>
<tr>
<td>Drug</td>
<td>fluticasone</td>
<td>fluticasone</td>
<td>budesonide</td>
<td>fluticasone</td>
</tr>
<tr>
<td>μg/day</td>
<td>880</td>
<td>880/1760</td>
<td>1000/2000</td>
<td>1760</td>
</tr>
<tr>
<td>Control group</td>
<td>placebo</td>
<td>prednisone</td>
<td>placebo</td>
<td>placebo</td>
</tr>
<tr>
<td>Blinding</td>
<td>DB</td>
<td>open</td>
<td>DB</td>
<td>DB</td>
</tr>
<tr>
<td>Rx duration</td>
<td>12 weeks</td>
<td>4 weeks</td>
<td>12 weeks</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

**DB, double-blind**

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### Graphs

**Graph 1:** Comparison of Eos/HPF pre-Rx and post-Rx for different RCTs. 
- **Pre-Rx:**
  - Konikoff Gastro 2006: 80
eosinophils/HPF
  - Schaefer CGH 2008: 80
eosinophils/HPF
  - Dohil Gastro 2010: 80
eosinophils/HPF
  - Butz Gastro 2014: 80
eosinophils/HPF

**Graph 2:** Comparison of Eos/HPF post-Rx for different RCTs.
- **Post-Rx:**
  - Konikoff Gastro 2006: 10 eosinophils/HPF
  - Schaefer CGH 2008: 10 eosinophils/HPF
  - Dohil Gastro 2010: 10 eosinophils/HPF
  - Butz Gastro 2014: 10 eosinophils/HPF

**Graph 3:** Comparison of Eos/HPF post-Rx for different RCTs.
- **Post-Rx:**
  - Konikoff Gastro 2006: 10 eosinophils/HPF
  - Schaefer CGH 2008: 10 eosinophils/HPF
  - Dohil Gastro 2010: 10 eosinophils/HPF
  - Butz Gastro 2014: 10 eosinophils/HPF

**Graph 4:** Comparison of Eos/HPF post-Rx for different RCTs.
- **Post-Rx:**
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