Food Allergy and Other Adverse Food Reactions

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GENERAL PRINCIPLES

Definition

• Adverse food reaction: Any abnormal reaction due to ingestion of a food. This includes immunologic (allergy) as well as nonimmunologic reactions (food intolerances, e.g., lactose intolerance).¹
• Food allergy (FA): Also referred to as food hypersensitivity, is an adverse health effect arising from a specific immunologic response that occurs reproducibly on exposure to a given food. This includes both immunoglobulin E (IgE)-mediated and non–IgE-mediated immunologic reactivity to specific foods.
  ○ IgE-mediated FAs are FAs mediated by IgE. This requires both the presence of food antigen-specific IgE and the development of specific signs and symptoms upon exposure to a specific food.
  ○ Non–IgE-mediated FAs are conditions that are immunologically mediated processes with reproducible signs and symptoms on exposure to a food but without IgE sensitization.

Classification

• The various forms of FA are presented in Table 16-1.
• Food intolerances are non–immune-mediated adverse reactions to food. Intolerance may result from metabolic, toxic, pharmacologic, or other causes.
• Food-induced anaphylaxis is an IgE-mediated, rapid-onset, serious systemic reaction which may result in shock and/or respiratory compromise.
• Gastrointestinal (GI) food allergies:
  ○ Immediate GI hypersensitivity: IgE-mediated FA with upper GI symptoms within minutes (most commonly vomiting) and lower GI symptoms that are either immediate or delayed up to several hours.
  ○ Eosinophilic esophagitis (EoE): Localized eosinophilic inflammation of the esophagus involving both IgE- and non–IgE-mediated mechanisms. Symptoms include vomiting, reflux, abdominal pain, dysphagia, and food impaction. Food avoidance frequently results in resolution.
  ○ Eosinophilic gastroenteritis: Like EoE, but involving portions of the GI tract distal to the esophagus.
  ○ Dietary protein–induced proctitis/proctocolitis: Presents in infants who seem healthy but have visible blood in the stool. This process is generally non–IgE-mediated, and differentiated from other GI food allergies with similar stool findings by lack of systemic symptoms. There is no specific testing, so the causal role of food allergens is inferred from a characteristic history on exposure.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Subtype</th>
<th>Symptoms</th>
<th>Epidemiology</th>
<th>Diagnostic tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE-mediated food allergy</td>
<td>Anaphylaxis</td>
<td>Hypotension, shock</td>
<td>All ages</td>
<td>SPT, <em>in vitro</em> antigen-specific IgE, OFC</td>
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<td></td>
<td>Cutaneous</td>
<td>Minutes to 2 hours: urticaria, angioedema, flushing, acute morbilliform rash, acute contact urticaria</td>
<td>All ages</td>
<td>SPT, <em>in vitro</em> antigen-specific IgE, OFC</td>
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<td>Respiratory</td>
<td>Acute rhinoconjunctivitis, acute bronchospasm</td>
<td>All ages</td>
<td>SPT, <em>in vitro</em> antigen-specific IgE, OFC</td>
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<td></td>
<td>Acute gastrointestinal hypersensitivity</td>
<td>Minutes to 2 hours: nausea, emesis, diarrhea, typically with cutaneous and/or respiratory symptoms</td>
<td>All ages</td>
<td>SPT, <em>in vitro</em> antigen-specific IgE, OFC</td>
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<td>Oral allergy syndrome</td>
<td>Pruritus, tingling, erythema or angioedema of the lips, tongue, oropharynx; immediately on contact of raw fruit with oral mucosa</td>
<td>All ages, most common in birch pollen-allergic young adults</td>
<td>SPT or OFC with raw fruits or vegetables</td>
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<tr>
<td>IgE- and cell-mediated food allergy</td>
<td>Allergic eosinophilic esophagitis</td>
<td>Chronic/intermittent GE reflux, emesis, dysphagia, abdominal pain, food impaction</td>
<td>All ages, but especially infants, children, adolescents</td>
<td>50% have positive SPT and/or food-IgE; endoscopy and biopsy for conclusive diagnosis</td>
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<td>Allergic eosinophilic gastroenteritis</td>
<td>Chronic/intermittent abdominal pain, emesis, poor appetite, failure to thrive, weight loss, anemia, protein-loss</td>
<td>All ages</td>
<td>50% have positive SPT and/or food-IgE; endoscopy and biopsy for conclusive diagnosis</td>
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<td>Asthma</td>
<td>Chronic cough, wheezing, dyspnea</td>
<td>All ages</td>
<td>SPT, <em>in vitro</em> antigen-specific IgE, OFC</td>
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<tr>
<td>Non–IgE-mediated food allergy</td>
<td>Atopic dermatitis</td>
<td>Relapsing pruritic vesiculopapular rash</td>
<td>Infants and children; 60–80% significantly improve/resolve by adolescence</td>
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<td>Allergic proctocolitis</td>
<td>Blood-streaked or occult blood positive stools, otherwise healthy-appearing</td>
<td>Infants &lt;6 months, often breast-fed; usually outgrown by age 1</td>
<td></td>
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<td>Food protein-induced enterocolitis syndrome</td>
<td>Subacute repetitive emesis, dehydration, diarrhea</td>
<td>Young infants, breastfeeding is protective; usually outgrown by age 1–3 years</td>
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<td>Dietary protein-induced enteropathy</td>
<td>Protracted diarrhea, emesis, failure to thrive, often anemia</td>
<td>Young infants; usually outgrown by age 1–2 years</td>
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<td>Celiac disease</td>
<td>Chronic diarrhea, malabsorption, abdominal distention, flatulence, failure to thrive or weight loss, possibly oral ulcers and/or dermatitis herpetiformis</td>
<td>All ages</td>
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<td>Contact dermatitis</td>
<td>Relapsing pruritic eczematous rash, often to hands or face; occupational food contact</td>
<td>All ages, more common in adults</td>
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IgE, immunoglobulin E; SPT, skin prick test; OFC, oral food challenge; GE, gastroesophageal.
○ Food protein–induced enterocolitis syndrome (FPIES): Non–IgE-mediated disorder presenting in infants with very severe vomiting and diarrhea, most commonly caused by cow’s milk, soy, or grains.
○ Oral allergy syndrome (OAS): Localized IgE-mediated allergy to fresh fruits or vegetables, with itching, tingling, and/or swelling of the lips, tongue, roof of the mouth, and throat. This affects patients with pollen allergy and is also referred to as pollen-associated FA syndrome.

• Cutaneous reactions to foods:
  ○ Acute urticaria: A common manifestation of IgE-mediated FA, especially in the setting of anaphylaxis, with rapid development of polymorphic, round, or irregularly shaped pruritic wheals after ingestion of the problem food.
  ○ Angioedema: Typically IgE-mediated when food-induced and usually in combination with urticaria. This is a nonpitting, nonpruritic, well-defined swelling of the subcutaneous tissues, abdominal organs, or upper airway. Also a common feature of anaphylaxis.
  ○ Atopic dermatitis (AD): Because this disease involves complex interaction between skin barrier dysfunction and environmental factors, the role of FA in its pathogenesis remains controversial. In some sensitized patients, food allergens can aggravate AD.
  ○ Acute contact dermatitis: A form of AD caused by cell-mediated allergic reactions to chemical haptens in foods, resulting in pruritus, erythema, papules, vesicles, and edema.
  ○ Contact urticaria: Can be either immunologic (IgE-mediated) or non-immunologic (direct histamine release).

• Respiratory manifestations: These are important components of anaphylaxis but are uncommon in isolation.

Epidemiology

• Food allergies are over-reported by patients, which is one of many obstacles in establishing the true prevalence of FA.
• Objective measurements are necessary to make an accurate FA diagnosis.
• Milk, egg, and peanut account for the vast majority of allergic reactions in young children.
• Peanut, tree nuts, and seafood account for the vast majority of reactions in teenagers and adults.
• The following data are drawn from a recent meta-analysis of 51 publications:
  ○ Self-reported FA to cow’s milk, hen’s eggs, peanuts, fish, or crustacean shellfish: 13% for adults, 12% for children.
  ○ When objective measures were employed, including skin test, serum IgE, or food challenge, the overall prevalence dropped to 3% for all ages.
• US prevalence rates for specific foods:
  ○ Peanut allergy: 0.4–0.8%.
  ○ Tree nut allergy: 0.4%.
  ○ Seafood allergy: 0.6% in children, 2.8% in adults.
• Most children with FA will eventually tolerate cow’s milk, egg, wheat, and soy but far fewer eventually tolerate peanut and tree nuts.
• Allergy to seafood most commonly develops in adulthood and usually persists.
• A high initial level of allergen-specific IgE to a food is associated with a lower resolution rate over time.
• The resolution of AD is a useful marker for the onset of tolerance to food allergens.
A decrease in the level of allergen-specific IgE is often associated with the ability to tolerate foods.

**Pathophysiology**
- In the normal mature gut, about 2% of ingested food antigens penetrate the GI tract barrier and enter the circulation.\(^3\)  
- The majority of individuals develop what is known as oral tolerance to these antigens, which is a state of immunologic unresponsiveness.  
- A failure to develop tolerance or a breakdown in this process results in excessive production of food-specific IgE antibodies.  
- When food allergens penetrate the mucosal barriers and reach these antibodies bound to mast cells or basophils, mediators are released, which result symptoms of immediate hypersensitivity, including vasodilation, smooth muscle contraction, and mucus secretion (type I hypersensitivity).  
- These cells also may release cytokines and other mediators that contribute to a late-phase response.  
- The clinical manifestations of IgE-mediated hypersensitivity are widely variable but depend on various host and antigen factors.  
- As for non–IgE-mediated food reactions, pathogenic factors are not well defined, but, like IgE-mediated FA, likely involve a break in oral tolerance resulting in an inappropriate immune response to orally ingested antigens.

**Risk Factors**
- Biologic parents or siblings with existing, or history of, allergic rhinitis, asthma, AD, or FA increase risk of FA.  
- Presence of AD, especially when severe with early onset, is associated with increased risk of food sensitization.  
- Asthma is the risk factor most commonly identified with the greatest severity of allergic reactions to foods.  
- Complementary factors that affect the absorption of a food allergen may increase the severity of a reaction and should be taken into account. These include concomitant alcohol consumption, use of nonsteroidal anti-inflammatory drugs (NSAIDs), and exercise.

**Prevention**
The following are not recommended, as there is insufficient evidence to support the idea that such practices prevent the development or clinical course of FA:  
- Limited exposure to non-food allergens (e.g., dust, pollen, pet dander) even for those patients considered to have increased risk for the development of FA.  
- Routine FA testing prior to the introduction of allergenic foods.  
- Maternal diet restriction during pregnancy or lactation.  
- Use of soy infant formula instead of cow’s milk infant formula in at-risk infants.  
- Delayed introduction of solid foods beyond 4–6 months of age.

**Associated Conditions**
- Children with FA are 2.3 times more likely to have asthma, 2.3 times more likely to have AD, and 3.6 times more likely to have respiratory allergies than children without FA.\(^1\)  
- Asthmatics that also have FA are more likely to have increased rates of emergency department visits and hospitalization in an intensive care unit for their asthma than non-food allergic asthmatics.
• EoE is frequently associated with FA.
• Exercise-induced anaphylaxis in adults is triggered by foods about one-third of the time, according to patient report.

**DIAGNOSIS**

**Clinical Presentation**
- Manifestations of an immune-mediated reaction to food can vary widely.
- Most IgE-mediated reactions are considered to be immediate, meaning they occur within minutes to a few hours.
- Delayed responses occur within several hours to a few days and are thought to involve cellular mechanisms.
- **Food-induced anaphylaxis** (see Chap. 13) is the most common, serious consequence of FA.
  - Typically IgE-mediated and believed to involve systemic mediator release from sensitized mast cells and basophils.
  - Significantly under-recognized and under-treated.
  - Prompt recognition and management is essential to ensure a favorable outcome.
  - Fatalities can occur within 30 minutes of exposure and usually result from respiratory compromise.

**Differential Diagnosis**
- Acute allergic reactions triggered by other allergens, such as medications or insect stings.
- AD flares triggered by other irritants.
- Chronic GI symptoms due to reflux, infection, anatomical abnormalities, or metabolic disorders.
- Chemical and irritant effects of foods, such as gustatory rhinitis due to neurologic responses to temperature or capsaicin.
- Gustatory flushing syndrome is an erythematous band on the cheek in the distribution of the auriculotemporal nerve, triggered by tart foods.
- Food poisoning due to bacterial toxins or scombroid poisoning.
- For those with eosinophilic GI disorders, other diagnoses such as parasitic infections, GI reflux disease (GERD), systemic eosinophilic disorders, and vasculitis should be considered.
- Mental/behavioral disorders resulting in food aversion.
- Pharmacologic effects such as tryptamine in tomatoes and food additives may mimic allergic symptoms of the skin and GI tract.

**Diagnostic Testing**
- Diagnostic testing is based on a comprehensive history, which should suggest whether or not the reaction was IgE- or non–IgE-mediated. This determines the kind of testing to pursue and the possible foods involved.
- **Testing should not be comprised of general broad panels of food allergens.**

**Laboratories**
- **Total serum IgE:**
  - Although it is often elevated in atopic individuals, it **not a sensitive and specific test for FAs.**
Obtaining this study for the purpose of providing a ratio of food-specific IgE to total IgE offers no advantage over food-specific IgE alone in the diagnosis of FA.

- **Food allergen-specific serum IgE:**
  - Formerly measured using the radioallergosorbent test (RAST), specific IgE levels are now measured by more sensitive fluorescence enzyme-labeled assays.
  - Similar to skin prick test (SPT) in the sense that these tests are useful in identifying foods that may be provoking IgE-mediated food allergic reactions but are **not diagnostic of FA alone**.
  - Very useful in detecting allergic sensitization, meaning the presence of allergen-specific antibodies; sensitization does not always correlate with clinical allergy.
  - Especially useful when SPT cannot be done, either due to clinical contraindications or failure to discontinue antihistamines prior to the test.
  - Studies support the idea that specific IgE antibody levels directly correlate with likelihood of clinical reactivity.\(^4\)

- **Mast cell and basophil mediators:**
  - Histamine and tryptase are rarely used to support the diagnosis of food-induced anaphylaxis.
  - Tryptase lacks specificity and may not be elevated in food-induced anaphylaxis.

### Diagnostic Procedures

#### Skin Prick Test

- SPT assists in the identification of foods that potentially induce IgE-mediated reactions but is **not diagnostic of FA when used alone**.
- It reflects the IgE bound to cutaneous mast cells.
- SPT has a **low positive predictive value**, as many patients have IgE to certain foods without clinical FA.
- When the patient provides a history very suspicious for FA, SPTs are valuable in identifying the foods responsible, and therefore have **high sensitivity and a high negative predictive value** in this clinical setting.
- Results are immediately available, making SPT the most commonly performed procedure in the evaluation of IgE-mediated FA.
- The patient **must be off all antihistamine medications for 1 week** prior to the procedure to insure the reliability of the test.

#### Intradermal Tests

- This method is not more sensitive than SPT in detecting food protein–induced allergic reactions.
- The risk of systemic adverse allergic reactions is greater compared to SPT.
- Intradermal tests are **rarely indicated** for the evaluation of FA.

#### Other

- **Oral food challenges:**
  - The double-blind placebo-controlled food challenge is the gold standard for diagnosing FA, but its use is limited by time and expense.
  - Single-blind and open food challenges are frequently used to screen patients for FA.
  - Should be designed and performed under medical supervision and avoided in patients with a recent life-threatening reaction to a particular food.
Food elimination diets:
- Cutting out one or a few specific foods may be useful in the diagnosis of FA, especially in the setting of non–IgE-mediated disorders such as FPIES.
- Prolonged elimination diets consisting of multiple foods are not recommended.

TREATMENT

Medications

Epinephrine
- Prompt and rapid IM epinephrine after onset of symptoms of anaphylaxis is first-line therapy.
- Benefits of epinephrine far outweigh the risks and delays in epinephrine administration are associated with increased morbidity and death.
- Dosing:
  - Autoinjector (IM): 0.15 mg for individuals 10–30 kg; 0.3 mg for those >30 kg.
  - Epinephrine IM 1:1,000 solution: 0.1 mg/kg, maximum dose of 0.3 mg.
- The anterior-lateral thigh is the preferred injection site.
- IV epinephrine is recommended for patients who do not respond to IM epinephrine and whose fluid status may not be adequate for muscle perfusion.
- Repeated epinephrine dosing is required up to 20% of the time and can be done every 5–15 minutes in patients with ongoing or progressive symptoms.
- After epinephrine administration, the patient should be transferred to an emergency facility for observation for at least 4–6 hours and possible further treatment.

Adjunctive Treatment
- Epinephrine is the only first-line treatment for anaphylaxis, and there is no substitute.
- The following treatments are adjunctive, and there are little or no data demonstrating their effectiveness:
  - Inhaled β2-agonist every 20 minutes or continuously as needed.
  - Antihistamines: Diphenhydramine 1–2 mg/kg/dose, maximum 50 mg IV or oral (preferably liquid for ready absorption); ranitidine 1–2 mg/kg/dose, max 150 mg oral and IV.
  - Prednisone 1 mg/kg oral or methylprednisolone 1 mg/kg IV, maximum 60–80 mg for both.
  - Oxygen therapy.
  - Large volume IV fluids.
  - Recumbent positioning with lower extremities elevated.
  - In the hospital setting, vasopressors or glucagon can be given for refractory hypotension.

Discharge Therapy
- Epinephrine autoinjector prescription/instructions, allergen avoidance education, follow-up with primary care physician, consider referral to an allergist.
- Adjunctive over the next 48–72 hours: Diphenhydramine every 6 hours, ranitidine twice daily, and prednisone.
- There are no medications that are currently recommended for the prevention of IgE- or non–IgE-mediated food allergic reactions.
**Milder Food Allergic Reactions**

- Symptoms such as flushing, urticaria, mild angioedema, or OAS can be treated with antihistamines.
- If progression is noted, epinephrine should be given immediately.
- If the patient has a history of prior severe allergic reaction, epinephrine should be given earlier in the course.

**Immunotherapy for Food Allergy**

While allergen-specific immunotherapy has been shown to improve clinical symptoms of FA for some patients, it is not recommended at this time because of the risk of severe reaction combined with unclear long-term efficacy in preventing future food-allergic reactions.

**Lifestyle/Risk Modification**

**Diet**

- Allergen avoidance is currently the safest strategy for managing IgE-mediated and non-IgE-mediated FA.
- Food allergen avoidance in patients with documented FA may reduce the severity of associated comorbid conditions such as AD and EoE.

**SPECIAL CONSIDERATIONS**

**Vaccinations in Patients with Egg Allergy**

- Many vaccines are grown in chick embryos and may contain small, variable amounts of egg protein.
- The MMR (measles, mumps, and rubella) and MMRV (measles, mumps, rubella, and varicella) vaccines are safe in egg-allergic children, even in those with a history of severe reaction to egg.
- Influenza:
  - Either the inactivated or live-attenuated vaccine should **not** be given to children with history of:
    - Egg-allergic symptoms with co-existent asthma or
    - Systemic anaphylaxis to egg.
  - Unless:
    - The vaccine contains <1.2 μg/mL of ovalbumin or
    - The patient has had a negative result on skin prick testing with the vaccine.
  - In the case of positive SPT, the vaccine can be given but the dose should be divided: One-tenth followed by the remainder if the initial dose is tolerated.
- Rabies and yellow fever vaccines should **not** be given to patients with egg allergy, unless an allergy evaluation and testing to the vaccine has been done.

**PATIENT EDUCATION**

**Food Labeling**

- Patients with FAs and their caregivers must be educated on the interpretation of ingredient lists on food labels to optimize trigger avoidance.
- In 2004, a law was passed by the US Congress requiring that **products containing any of the eight major food allergens must clearly list them on the label in simple English.** This includes peanut, tree nuts, egg, milk, soy, wheat, fish, and shellfish.
Emergency Management

- Patients with FAs and their caregivers should be informed on the risk of anaphylaxis and should be able to recognize signs and symptoms early.
- Families should be equipped with the knowledge and skills to handle such medical emergencies, including understanding of and ready access to an anaphylaxis emergency action plan.
- Epinephrine autoinjector teaching should be done in the office and the clinician should ensure that the patients/caregivers are familiar with the sequence of events according to the action plan.
- Patients should wear medical identification jewelry or carry an anaphylaxis wallet card.

MONITORING/FOLLOW-UP

- Annual testing is reasonable to evaluate whether a patient has outgrown allergy to those foods that are likely to resolve over time (e.g., milk, egg, wheat, and soy), assuming the patient has not had a recent reaction to those foods.
- Testing for ongoing allergy to peanut, tree nuts, fish, and shellfish should not be performed more frequently than every 2 to 3 years since allergy to these foods is not typically outgrown quickly.

REFERENCES