FOOD ALLERGIES

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FOOD ALLERGIES

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Hippocrates is credited with first recognizing that food could be responsible for adverse symptoms and even death in some individuals.
Guidelines for the Diagnosis and Management of Food Allergy in the United States: Summary of the NIAID-Sponsored Expert Panel Report

Primary Authors: Joshua A. Boyce, MD, Amal Assa’ad, MD, A. Wesley Burks, MD, Stacie M. Jones, MD

ICON: Food allergy

Food allergy is an “adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food.” This definition encompasses immune responses that are: IgE mediated, non-IgE mediated or a combination of both.

Food intolerance is an “nonimmune reaction that include metabolic, toxic, pharmacologic, and undefined mechanisms.”
Food Intolerance versus Food Allergy

Comparison between food intolerance, IgE mediated food allergy and non IgE mediated food allergy.

<table>
<thead>
<tr>
<th>Food reactions</th>
<th>Food Intolerance</th>
<th>Food Allergy: Immediate IgE reactions</th>
<th>Food Allergy: Non IgE reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic Mechanism</td>
<td>Difficulty in digesting or metabolizing a particular food</td>
<td>Food specific IgE antibodies releasing histamine</td>
<td>T lymphocyte cell mediated</td>
</tr>
<tr>
<td>Onset of Symptoms</td>
<td>Hours</td>
<td>Seconds to minutes and rarely upto 2 hours</td>
<td>Often within 2 hours or more</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Not serious</td>
<td>Maybe serious leading to anaphylaxis</td>
<td>Unpredictable. May involve skin and mucus membranes, respiratory, cardiovascular and gastrointestinal symptoms.</td>
</tr>
<tr>
<td>Examples</td>
<td>Lactose, fructose, alcohol, Flavourings and preservatives</td>
<td>Seafood allergy, peanut allergy</td>
<td>Protein induced enterocolitis</td>
</tr>
</tbody>
</table>
Common clinical features of food allergy by organ system

**Cutaneous**
- Erythema
- Pruritus
- Urticaria
- Morbilliform eruption
- Angioedema

**Generalised (systemic)**
- Anaphylaxis (with all its complications, including cardiovascular symptoms and generalised collapse)

**Gastrointestinal**
- Angioedema of the lips, tongue, or palate
- Oral pruritus
- Tongue swelling
- Nausea
- Colicky abdominal pain
- Reflux
- Vomiting
- Diarrhea

**Respiratory**
- Nasal congestion
- Pruritus
- Rhinorrhea
- Sneezing
- Laryngeal edema
- Hoarseness
- Dry staccato cough
- Cough
- Chest tightness
- Dyspnea
- Wheezing
- Intercostal retractions
- Accessory muscle use

**Ocular**
- Pruritus
- Conjunctival erythema
- Tearing
- Periorbital edema

**Cardiovascular**
- Tachycardia (occasionally bradycardia in anaphylaxis)
- Hypotension
- Dizziness
- Fainting
- Loss of consciousness

**Miscellaneous**
- Uterine contractions
- Sense of “impending doom”
TOP FOOD ALLERGIES AMONG CHILDREN UNDER 18 AROUND THE WORLD

Cows’s milk allergy highest 🔺 in UK and The Nederlands (1%), lowest 🔻 in Lithuania, Germany and Greece (0.3%)

Egg allergy highest 🔺 in UK (2.18%) and lowest 🔻 in Greece (0.07%)

The highest 🔺 rates of food allergy are noted in Australia

Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management

Scott H. Sicherer, MD, and Hugh A. Sampson, MD  New York, NY

- The prevalence of food allergy is high, up to 10% of the population, and has likely increased in the past decades
- Numerous genetic and environmental risk factors have been identified.
- Industrialized/westernized regions
- More common in children compared with adults
- Children with parent or sibling with allergic disease are at increase risk.

How Common and Severe are Food Allergies Among US Adults?

- Prevalence of Food Allergy
  - 10.8% (95% CI 10.4%-11.1%)
- Most Common Food Allergies
  - Shellfish 2.9% (2.7%-3.1%)
  - Milk 1.9% (1.8%-2.1%)
  - Peanut 1.8% (1.7%-1.9%)


J ALLERGY CLIN IMMUNOL 2017 VOLUME 141, NUMBER 1
Some food allergies have a high rate of resolution in childhood with continued resolution into adolescence:
- milk (>50% by age 5-10 years)
- egg (approximately 50% by ages 2-9 years)
- wheat (50% by age 7 years)
- soy (45% by age 6 years)

Other food allergies typically persist or have low rates of childhood resolution:
- peanut allergy (20% by age 4 years),
- tree nut allergy (10%)
- fish, and shellfish
Food allergy etiology

Genetic enivronment interactions
- Variant in serine peptidase inhibitor Kazal typ 5 (SPINK5)
- Genetic variation in the IL-13 gene
- Genetic determinants of challenge-confirmed peanut allergy in alleles at the HLA-DRB1 locus

Early-life gastrointestinal microbiota
- The early-life gut microbiota and resolution of Cow’s Milk allergy (Clostridia and Firmicutes)

Hygiene hypothesis
- Number of siblings
- Antibiotic use
- Infection history
- Pet exposure
- Child care exposure
- Maternal-child factors

Novel hypothesis
- High levels of dietary advanced glycation end-products from cooked meats, oils and cheese in the presence of high sugar concentration – promote proallergenic innate immune responses

A.M. Scurlock J Allergy Clin Immunol 2018;141: 2002-14
Adverse Food Reaction

Immune Mediated Food Allergy

IgE Mediated
- Acute urticaria/angioedema
- Contact urticaria
- Anaphylaxis
- Food-associated, exercise-induced anaphylaxis
- Oral allergy syndrome
- Immediate gastrointestinal hypersensitivity

Non-IgE Mediated
- Food protein induced enterocolitis syndrome
- Food protein induced proctocolitis syndrome
- Food protein induced enteropathy syndrome

Mixed IgE and Non-IgE Mediated
- Eosinophilic esophagitis
- Eosinophilic gastroenteritis

Cell Mediated
- Allergic contact dermatitis
- Celiac disease
Food-dependent, exercise-induced anaphylaxis
Food-dependent, exercise-induced anaphylaxis

- First reported in 1979 triggered by a combination of shellfish ingestion and exercise.
- Patients only develop symptoms when ingestion of culprit food is followed within a few hours by exertion or exercise.
- Time between meal and exercise is usually between 30 and 120 min and the duration of exercise before the onset of symptoms lasts 10-50 min.
- Symptoms do not develop if the food is eaten at rest.
- Causative foods: shellfish, wheat products, vegetable, fruits, nuts, egg, cow’s milk.
Oral Allergic Syndrom OAS
Oral Allergic Syndrom OAS

- Cross-reaction between pollen antigen and fruit or vegetable antigen
- More specific term „pollen food allergy syndrom”
- Estimated about 5% of general population in central Europe
- Affects up to 50-70% of adults suffering from pollen allergy (birch, regeweed)
- Symptoms: itchiness or mild swelling of the mouth, face, lip, tongue and throat (within minutes after eating raw fruits or vegetables)
- Cooked fruits and vegetables do not elicit the symptoms
- Common triggers are: melon, banana, apple, kiwi, tommato and celery
- Mild form of food allergy
Unusual form of IgE-mediated food allergy
Unusual form of IgE-mediated food allergy

- Caused by sensitization to alergen galactose-alpha-1,3-galactose (alpha-gal)
- This form of meat allergy is distinguished by a delayed onset, with symptoms appearing 3 to 6 h after ingestion (sometimes in the middle of the night)
- Symptoms: urticaria, angioedema or anaphylaxis with GI symptoms or hypotension
- Allergy due to sensitization to alpha-gal is described in an increasing number of countries (USA, Australia, Germany, Spain, Japan)
- Patients become sensitized to alpha-gal through tick bites
## Anaphylaxis definitions

<table>
<thead>
<tr>
<th>AAAAI/AACAAI Guidelines (Liberman et al., 2010)</th>
<th>NIAID (Sampson et al., 2006)</th>
<th>EAACI Guidelines (Muraro et al., 2014)</th>
<th>WAO Guidelines (Simons et al., 2011)</th>
<th>ASCIA Practice Essentials (Brown et al., 2006)</th>
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<tbody>
<tr>
<td>&quot;an acute life-threatening systemic reaction with varied mechanisms, clinical presentations, and severity that results from the sudden release of mediators from mast cells and basophils&quot;</td>
<td>&quot;a serious allergic reaction that involves more than one organ system (e.g. skin, respiratory tract, and/or gastrointestinal tract). It can begin very rapidly, and symptoms may be severe or life-threatening&quot;</td>
<td>&quot;a severe life-threatening generalized reaction or systemic hypersensitivity reaction&quot;</td>
<td>&quot;a serious life-threatening generalized or systemic hypersensitivity reaction&quot; and &quot;a serious allergic reaction that is rapid in onset and might cause death&quot;</td>
<td>&quot;a serious, rapid-onset, allergic reaction that may cause death&quot;</td>
</tr>
</tbody>
</table>
Review article: the diagnosis and management of food allergy and food intolerances

J. L. Turnbull*, H. N. Adams† & D. A. Gorard†

Diagnostic criteria for anaphylaxis

Anaphylaxis is highly likely when any 1 of the following three criteria sets is fulfilled:

1. Onset of illness in minutes to several hours with involvement of the skin or mucosa (urticaria, itching or flushing, swollen lips-tongue-uvula) and one of:
   a. Respiratory compromise (dyspnoea, wheeze, stridor, reduced peak expiratory flow, hypoxia)
   b. Reduced blood pressure or associated symptoms of end organ dysfunction (eg syncope, incontinence)

2. Known allergy and likely exposure to allergen for that patient and with rapid symptoms including two of:
   a. Skin/mucosa involvement (urticarial, itching/flushing, swollen lips-tongue-uvula)
   b. Respiratory compromise (dyspnoea, wheeze, stridor, hypoxia)
   c. Reduced blood pressure or associated symptoms (collapse, syncope, incontinence)
   d. Persistent gastrointestinal symptoms (cramping, abdominal pain, vomiting)

3. Reduced blood pressure after exposure to known allergen for the patient:
   - Adult: systolic pressure <90 mmHg or >30% lower than patient’s baseline
   - Child: refer to age-specific centile charts
Food-Induced Anaphylaxis

Anaphylaxis is a severe, life-threatening allergic reaction that can be caused by food. Private insurance claim lines with diagnoses of anaphylactic food reactions increased 377% percent from 2007 to 2016.

Anaphylactic Food Reaction Claim Lines by Type of Food, 2007-2016

- Anaphylactic reaction to nuts: 7%
- Anaphylactic reaction to fish: 2%
- Anaphylactic reaction to allergenic foods: 1%
- Anaphylactic reaction to fruits/vegetables: 2%
- Anaphylactic reaction to milk products: 5%
- Anaphylactic reaction to tree nuts/peanuts: 18%
- Anaphylactic reaction to other specific foods: 33%
- Anaphylactic reaction to cow's milk: 6%
- Anaphylactic reaction to other specific foods: 26%

Source: FAIR Health’s NPIC® database of more than 23 billion privately billed medical and dental healthcare claims from more than 60 contributors nationwide.
Diagnosis of Food Allergy

Clinical History

- Possible casual food/foods
- Form in which ingested (raw, semicooked, cooked or baked)
- Quantity ingested
- Nature of reactions
- Ancillary factors (exercise or ingestion of aspirin or alcohol)

Physical Examination

Additional Testing
Additional Testing

Key diagnostic tools
- Allergen specific IgE
  - SPTs (Skin Prick Tests)
  - Immunoassays of Food-specific IgE antibody level (immunoCAP, Immulite and HYTEC-288)
- Oral Food Challenge
  - GOLDEN STANDARD
  - Double-blind placebo-controlled food challenge (DBPCFC)
  - Single blind food challenge
  - Open food challenge

Future diagnostic tests
- Component-Resolved Diagnostics CRD measures IgE to individual allergen proteins
  - Epitope Binding
  - T-Cell Responses
  - Basophil Activation
  - PAF and PAF Acetylhydrolase

Nonstandardized tests
- Facial thermography
- Gastric Juice analysis
- Endoscopic allergen provocation
- Hair analysis
- Applied kinesiology
- Provocation neutralization
- Allergen-specific IgG4
- Cytoxicity assays
- Electrodermal test (Vega)
Food allergy diagnostic algorithm

History and physical exam: obtain information to identify the likely pathophysiologic basis of the adverse reaction

IgE-Mediated Food Allergy:
Targeted SPT and/or RAST testing based on possible food triggers, avoidances, and whether or not a food had been previously tolerated.

Does the diagnosis of a food allergy remain in doubt?

Yes: Consider further testing such as components or oral food challenge.

No: Recommend introduction or avoidance of foods.

Non-IgE-Mediated Food Allergy:
If clinical history is not compelling for making a presumptive diagnosis, consider elimination diets and oral food challenges.

Mixed IgE and Non-IgE-Mediated Food Allergy:
Elimination and reintroduction challenge of food in question. Endoscopy + biopsy to determine the response to dietary foods from the diet.

If recommending food avoidance, patient should be re-evaluated periodically to assess disease course and possible allergy resolution. The timing of retesting of varies based on the history, patient age, the trigger, and the type of illness that led to the recommendation of avoidance.
Food Allergy Management

- Absence of a cure
- Effective management of food allergy requires avoidance of ingestion and prompt treatment in the event of an allergic reaction
- The role of dietitians is key – replacement foods or supplements
- High level of education
- Allergy education of restaurants staff

half of the staff reported any food allergy training, deficit in their knowledge about hidden ingredients and cross-contact

- Understanding how to read a food label

S.H.Sicherer J ALLERGY CLIN IMMUNOL JANUARY 2018
Countries have different labelling practices and laws

USA: The most common eight allergens are mandated to be labeled in “contains” statements: sesame, molluscan shellfish (snails, octopus, clams and scallops), mustard and sulfites (a preservative).

Canada: Additional allergens are mandated to be labeled in “contains” statements:

In Japan: buckwheat, peanut, milk, egg, shrimp and crab must be labeled.
Food Allergy Management

- Some individuals with egg and cow’s milk allergy may be able to tolerate extensively heated egg or cow’s milk products in their diet without having any allergic reaction.
- The decision to introduce such foods should only be done so in consultation with a clinical immunology/allergy specialist.
- There are currently a few studies which suggest that regular ingestion of these extensively heated products might assist with outgrowing the egg or cow’s milk allergy.

A recent meta-analysis found that early feeding with **egg and peanut** but not other potentially allergenic foods, led to a significant reduction in egg and peanut allergy.
Prevention of Egg allergy with Tiny amount Intake PETIT

Randomized, placebo-controlled trial
218 infants 4-5 months of age with eczema

Aggressive treatment of eczema

Egg powder
- 50 mg of heated egg powder daily 6-9 months of age
- 250 mg heated egg powder daily 9-12 months of age

Placebo

9% Egg allergy

38% Egg allergy

O Natsume, Lancet 2017;389:276e86.
Allergen specificity of early peanut consumption and effect on development of allergic disease in the Learning Early About Peanut Allergy study cohort

George du Toit, MB, BCh, FRCPCH, a Peter H. Sayre, MD, PhD, c Graham Roberts, FRCPCH, DM, d Kaitie Lawson, MS, f

- Early introduction of peanut to high-risk infants can reduce the risk of peanut allergy.
- Prevention of peanut allergy through early peanut consumption is allergen specific and allergic disease specific.
- Regular consumption of peanut containing products starting in infancy would promote a protective immune response and dietary tolerance to peanut.
Introduction of peanuts

Risk categories infants

Highest
- Severe eczema
- Egg allergy
- Or both
- Allergy testing should be performed
  Peanut should be introduced as early as possible 4-6 months of age

Moderate
- Mild or moderate eczema
- Required no allergy testing
  Peanut introduction around 6 months of age

Low risk
- Without eczema
- Or food allergy
- Peanut introduction together with other complementary food

A.M. Scourlock J Allergy Clin Immunol 2018;141:2002-14
## Selected therapeutic strategies with clinical trials

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Benefits</th>
<th>Limitations</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>OIT</td>
<td>Robust, possible sustained unresponsiveness</td>
<td>Time-consuming, side effects</td>
<td>Peanut in phase 3</td>
</tr>
<tr>
<td>SLIT</td>
<td>Minor side effects, brief exposure</td>
<td>Less robust than OIT</td>
<td>Peanut in phase 3, milk in phase 2</td>
</tr>
<tr>
<td>EPIT</td>
<td>Minor side effects</td>
<td>Less robust than OIT; more effective in younger age group</td>
<td></td>
</tr>
<tr>
<td>Subcutaneous immunotherapy with chemically modified, aluminum hydroxide-adsorbed peanut proteins</td>
<td>Convenience</td>
<td>Injection</td>
<td>Safety and efficacy largely unknown, phase 1</td>
</tr>
<tr>
<td>Intradermal/intramuscular immunotherapy with lysosome-associated membrane protein DNA vaccine</td>
<td>Convenience, presumed safety</td>
<td>Unexplored</td>
<td>Safety and efficacy largely unknown, phase 1</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>Multiple foods</td>
<td>Cost, IgE levels/weight limitations</td>
<td>More studies to characterize efficacy</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>Multiple foods (?)</td>
<td></td>
<td>Potential largely unknown; might need OIT in combination</td>
</tr>
<tr>
<td>Traditional Chinese medicine</td>
<td>Safe</td>
<td>No effect in phase 2, poor adherence</td>
<td>Trial with OIT underway</td>
</tr>
<tr>
<td>Omalizumab plus OIT</td>
<td>Fewer reactions, faster updosing</td>
<td>Cost, convenience, OIT side effects</td>
<td>Trials underway</td>
</tr>
<tr>
<td>OIT and probiotics and other adjuvants</td>
<td>Potential to increase efficacy, persistence of effect</td>
<td>As per OIT</td>
<td>Trials underway</td>
</tr>
</tbody>
</table>

2017 American Academy of Allergy, Asthma & Immunology
Double-blind, placebo-controlled randomized trial of the probiotic
*Lactobacillus rhamnosus CGMCC 1.3724* and peanut OIT in children (1-10 years) with peanut allergy.

*Was effective in modulation of the peanut-specific immune response.*

- Induced high rates of desensitization (90%)
- Reduced peanut skin test reactivity
- Decreased peanut-specific IgE
- Increased peanut-specific IgG4 levels
- Well tolerated
Early-life gut microbiome composition and milk allergy resolution

Supinda Bunyavanich, MD, MPH\textsuperscript{1,2,*}, Nan Shen, PhD\textsuperscript{1}, Alexander Grishin, PhD\textsuperscript{2}, Robert

- Gut microbiota may play a role in the natural history of cow’s milk allergy.
- Milk allergy resolved by age 8 years in 128 (56.6\%) of the 226 children which gut microbiome composition at age 3–6 mo was enriched with Clostridia and Firmicutes.
- Clostridia and Firmicutes could be studied as probiotic candidates for milk allergy therapy.

ICON: Food allergy

A. Wesley Burks, MD, a Mimi Tang, MBBS, PhD, b Scott Sicherer, MD, c Antonella Muraro, MD, PhD, d Philippe A. Eigenmann, MD, e Motohiro Ebisawa, MD, PhD, f Alessandro Fiocchi, MD, g Wen Chiang, MBBS, MRCPCH, h Kirsten Beyer, MD, i Robert Wood, MD, j Jonathan Hourihane, MB, DM, MRCP, FRCPCH, k Stacie M. Jones, MD, l Gideon Lack, FRCPath, m and Hugh A. Sampson, MD n

Chapel Hill, NC, Parkville, Australia, New York, NY, Padua and Milan, Italy, Geneva, Switzerland, Kanagawa, Japan, Singapore, Berlin, Germany, Baltimore, Md, Cork, Ireland, Little Rock, Ark, and London, United Kingdom

In an outpatient setting

- First-line treatment
  - Epinephrine, IM: autoinjector or 1:1000 solution
    - Weight, 10-25 kg: 0.15-mg epinephrine autoinjector, IM (anterior-lateral thigh)
    - Weight >25 kg: 0.3-mg epinephrine autoinjector, IM (anterior-lateral thigh)
  - Epinephrine (1:1000 solution [IM]), 0.01 mg/kg per dose: maximum dose, 0.5 mg per dose (anterior-lateral thigh)
  - Epinephrine doses might need to be repeated every 5-15 min

- Adjunctive treatment
  - Place the patient in recumbent position if tolerated, with the lower extremities elevated
  - Bronchodilator (β2-agonist): albuterol
    - MDI (child: 4-8 puffs; adult: 8 puffs) or
  - Nebulized solution (child: 1.5 mL; adult: 3 mL) every 20 min or continuously as needed
  - H1 antihistamine: less-sedating second-generation antihistamines recommended

In a hospital-based setting

- Corticosteroids
  - Prednisone at 1 mg/kg with a maximum dose of 60-80 mg orally or
  - Methylprednisolone at 1 mg/kg with a maximum dose of 60 to 80 mg IV

- Vasopressors (other than epinephrine) for refractory hypotension, titrate to effect

- Glucagon for refractory hypotension, titrate to effect
Current perspectives

ICON: Food allergy

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United Kingdom

To instruct to patients at discharge

- First-line treatment
  - Epinephrine autoinjector prescription (2 doses) and instructions
  - Education on avoidance of allergen and emergency action plan
  - Follow-up with primary care physician
  - Consider referral to an allergist if first presentation or of unknown cause

- Adjunctive treatment
  - H1 antihistamine: diphenhydramine every 6 h for 2-3 d; alternate dosing with a non-sedating second-generation antihistamine
  - H2 antihistamine: ranitidine twice daily for 2-3 d
  - Corticosteroid: prednisone daily for 2-3 d
Among children with convincing food allergy...

Epinephrine (2 doses) must be available at all times for patients at risk

42% visited the emergency department 1 or more times in their lifetime.

Of this, 19% of children had visited the emergency department 1 or more times in the past year.

However, only 40.7% of children with convincing FA reported a current prescription for an epinephrine autoinjector.
Take-home message

- The prevalence of food allergy is high, up to 10% of the population.
- Numerous genetic and environmental risk factors have been identified.
- Diagnosis depends on combining a knowledge of pathophysiology and epidemiology with patient history and test results.
- Management currently requires attention to allergen avoidance and emergency treatment.
- Early introduction of peanut and egg to high-risk infants can reduce the risk of peanut and egg allergy.
- Numerous clinical trials are underway, therapies are likely to reach clinics soon.
"What is food to one, to another is rank poison,"
Titus Lucretius Cato (99-55 BC)