

# Food Allergy

Food Toxicology

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## Learning Objectives

- Understand the types of adverse food reactions.
- Differentiate food allergy and food sensitivity.
- Understand the role of IgE (Immunoglobulin E) in allergic reaction.
- Explore the types of IgE and non-IgE mediated food allergy.
- Summarize the series of events in allergic reaction.

## Learning Objectives

- Examine symptoms of allergic reaction including local and systemic anaphylaxis.
- Summarize the approach to food allergy diagnosis.
- Survey common food allergens.

## Adverse Reactions to Food

- 30% of population report family member with food “allergy”
- Actual % estimates vary <1-7%
- Subpopulations/ethnic groups differ markedly

## Most Common Allergic Foods/Groups

- Cows milk
- Crustacea
- Eggs
- Fish
- Peanuts
- Soybean
- Tree nut
- Wheat

## Adverse Food Reactions

### Allergy – Sensitivity - Intolerance

- General terms that can be applied to any clinically abnormal response to food or food additives.
- Many symptoms are similar.

## Types of Adverse Food Reactions

- Allergy
- Non-immune anaphylaxis (anaphylactoid)
- Intolerance
- Metabolic
- Idiosyncrasy
  
- Pharmacological (drug interaction)
- Toxicity

## Types of Food Sensitivities and Allergies

- True food allergy
- Food sensitivities
  - Anaphylactoid reactions
  - Metabolic food disorders
  - Idiosyncratic reactions
- Some in several classes
- Food aversions
  - Mimic sensitivity but no blinded response

### Food Allergy: Hypersensitivity

- Immune-mediated reaction
- Can be triggered by very small amounts of food
- Occurs on second exposure or to a cross reacting antigen
- Anaphylaxis and cutaneous reactions most common

### Food Allergies: History

- Observed since early Greeks and Romans
  - Hippocrates documents milk sensitivity
- Injected normal person with fish extract - no effect (1921)
  - Injected serum of sensitive person, then fish extract - allergic reaction
- Researchers discovered IgE (Immunoglobulin E, antibody subclass) in serum was cause (1966)

### Food Allergy Epidemiology

- Affect ~ 6% of children < 3 years old
  - Milk & soy
- Cow's milk: 2.5%
  - Over 80% tolerant by 5<sup>th</sup> birthday
- Egg allergy: 1.5%
  - Over 85% tolerant by 3<sup>rd</sup> birthday
- Peanut allergy: 0.5%
  - Clinical tolerance reached in a minority
  - Prevalence may be increasing in children

### Epidemiology

- Small subpopulation at risk <1%
- 65% of susceptible people have close relative with allergy
- Increased intestinal permeability to macromolecules predisposes
  - Viral gastroenteritis, premature birth, cystic fibrosis
  - Leaky gut syndrome (LGS)

### Epidemiology

- Higher in children with other *atopic* disorders
  - 35% of children with moderate to severe atopic dermatitis (eczema)
  - 6% of asthmatic children
- Adverse reactions to food additives 0.5-1% of children

### Pathophysiology

- GI tract forms a barrier to outside environment
- GALT inhibits responses to non-dangerous antigens while mounting responses to pathogens
  - Gut-Associated Lymphoid Tissue
- Oral tolerance = unresponsiveness
- Intact food antigens may penetrate the GI tract but not cause clinical symptoms
- Develop in genetically predisposed individuals when oral tolerance fails

### Types of Hypersensitivity

- Type I: Immediate hypersensitivity
- Type II: Antibody dependent cytotoxicity
- Type III: Antigen-antibody complex mediated

- Type IV: Cell-mediated hypersensitivity
- ### IgE Mediated
- Type I: Immediate hypersensitivity
    - Failure in oral tolerance leads to excessive food-specific IgE antibodies
    - These bind receptors on many cells (esp basophils and mast cells)
    - Food allergens penetrate mucosal barrier and bind these IgE antibodies
    - Cellular mediator release

### IgE Mediated

- Cutaneous
  - Urticaria (hives)
  - Angioedema (welts)
  - Morbilliform rashes
  - Flushing
- Gastrointestinal
  - Lip, tongue, and palatal pruritis and swelling
  - Laryngeal edema
  - Vomiting and diarrhea

### IgE Mediated

- Respiratory
  - Upper
    - Ocular pruritus and tearing
    - Nasal congestion
  - Lower
    - Bronchospasm/wheezing
- Generalized
  - Anaphylactic shock

### Non-IgE Mediated

- Type II: Antibody dependent cytotoxicity
  - Specific antibody binds to a surface tissue antigen and induces complement activation (system of serum immunoproteins which interact in a cascade)
  - Complement → inflammatory mediators → tissue damage
  - Milk-induced thrombocytopenia

### Non-IgE Mediated

- Type III: Antigen-antibody complex mediated
  - Complement activation
  - Has been implicated in food related complaints
  - Can be found in sera of normal patients

- IgE-food antigen complexes are more commonly found in patients with food hypersensitivity
- Little support for causing disease

## Non-IgE Mediated

- Type IV: Cell-mediated hypersensitivity
  - Mediated by sensitized CD4+ T lymphocytes which process antigens and release lymphokines.
  - The lymphokines promote a reaction mediated through macrophages beginning in hrs but reaching a peak in 2 to 3 days.
  - Implicated in foods with delayed onset of sx
  - Likely to contribute to a number of GI disorders
  - Ingestion of sensitizing antigen may cause mucosal lesions

## Non-IgE Mediated

- Cell Mediated Hypersensitivity
  - Cutaneous
    - Contact dermatitis
    - Dermatitis herpetiformis
  - Gastrointestinal
    - Food protein-induced enterocolitis
    - Food protein-induced proctocolitis
    - Food protein-induced enteropathy syndromes
    - Celiac disease
  - Respiratory
    - Food-induced pulmonary hemosiderosis (Heiner syndrome)
    - Intra-alveolar bleeding

## Mixed IgE and Cell Mediated

- Cutaneous
  - Atopic dermatitis
- Gastrointestinal inflammation
  - Allergic eosinophilic esophagitis
  - Allergic eosinophilic gastroenteritis
- Respiratory
  - Asthma

## Allergic Response Type I Hypersensitivity

- The food is eaten.
- 4 Reaches the stomach and small intestine where the proteins are not digested correctly
- 4 Intact proteins cross the small intestine and reach the blood and lymph system.

- 4 The immune system makes antibodies against the proteins
- 5 Allergic people make Immuglobulin E (IgE) which non allergic people don't .
- 7 IgE binds to the surface of mast cells or basophils which sensitizes them.

### Allergic Response: Second Exposure

- 1 The person eats the food a second time.
- 2 The protein enters the body
- 3 Binds to and cross-links two to IgE antibodies.
- 4 Causes the mast cell or basophil to degranulate.
- 5 Granules contain 40 different substances that cause allergic reactions.
  - Histamine, prostaglandins, leukotrienes

### IgE Mediated Food Allergy Summary

- Production of IgE antibodies
- IgE bind to surface of mast cells or basophils
- Second exposure to allergen
- Allergen cross-links IgE on surface
- Release of histamine, bradykinin, leukotrienes, TNF
- Inflammation and swelling via capillary leakage and wbc
- Allergic reaction

### Mast Cell Sensitization

### Food Allergy: Symptoms

- Respiratory = asthma, wheezing, bronchospasms, dyspnea (shortness of breath)
- Cutaneous = urticaria (hives), eczema, rash, pruritis
- Gastrointestinal = vomiting, diarrhea, abdominal pain
- Inflammation, vasoconstriction, hypotension, chest pain, nausea

### Food Allergy: Symptoms

- Other = anaphylaxis
- Mild and annoying to fatal
- Depend on amount ingested and length of time from initial exposure
- Not all symptoms in all people

## Food Allergens

- Almost all natural food proteins
- Papain - only known additive - meat tenderizer additive - enzyme
- Penicillin contaminants in meat and dairy products are potential hazard

## Local Anaphylaxis (atopy)

- About 10% of people have "atopy" (atopic syndrome) and are easily sensitized to allergens that cause a localized reaction when inhaled or ingested.
  - This can produce hay fever, hives, asthma, etc.

## Generalized Systemic Anaphylaxis

- Accounts for 1/3 of all anaphylaxis seen in emergency rooms
- Symptoms
  - Skin – urticaria / angioedema
  - Respiratory – rhinitis, bronchial hyperreactivity
  - Cardiac – hypotension, arrhythmias, vascular collapse
  - GI – nausea, vomiting, abdominal cramping, diarrhea
- Dx by history and demonstration of food specific IgE

## Fatal Food-Induced Anaphylaxis (32 cases)

- Most were adolescents or young adults
- History of prior reaction to implicated food
- Only 10% had epinephrine available
- Peanuts and tree nuts for majority (94%)

## Exercise-Induced Anaphylaxis (EIA)

- Rare form occurring when patient exercises 2-4 hrs after ingestion of specific food
- Without exercise, food no problem
- Most common in women 15-35 y.o.
  - Sx more pronounced just prior to menstruation
  - Dx based on history and evidence of specific IgE

- Common offenders: wheat, celery, shellfish, fish, fruits, milk

## Diagnosis of Food Allergy

- Self/parental often erroneous
- Food diary-when/what/how much
- Double-blind food challenge(DBFC)
  - Neither patient nor doctor know if placebo or allergen (crossover)
- Skin prick test
- RAST

### Skin Prick Test

- To determine if IgE involved
- Usually preliminary test
- Apply allergen extract to skin
- Scratch to increase access to blood
- Inflammation results from release of histamine, edema and swelling
- Positive control = histamine
- Result in ~ 20 min

### Radio-Allergosorbent Test (RAST)

- Also test for IgE
- Apply crude extract of allergen to solid phase (tissue culture plate)
- Add patient serum
- IgE (if present) binds allergen
- Add anti-IgE radiolabeled antibody
- Measure binding

### Common Allergenic Foods: Infants/Children

- Cow's milk - most common
- Eggs
- Legumes
  - peanuts
  - soybean
- Wheat

### Common Allergenic Food: Adults

- Legumes - peanuts, soybean
- Crustacea - shrimp, crab, lobster

- Molluscs - clams, oyster, scallop
- Fish
- Tree nuts
- Eggs
- Wheat

## Food Allergens

- Most food allergens contain multiple proteins which are allergenic

## Protein Allergens

- Milk - casein, lactoglobulins, lactoalbumins
  - No reduction by pasteurization, condensation, evaporation, and drying
- Eggs - ovalbumin, conalbumin, lipoprotein
  - Egg white more allergenic
  - No reduction by cooking
- Peanuts - arachin, lectin-reactive glycoprotein, Peanut I
  - Very heat stable, trace sensitivity

## Allergen M

- Common protein allergen in fish
- Muscle protein - parvalbumin
- These proteins are conserved in fish species
- Very cross-reactive
- Very stable in processing

## Allergenic Proteins

- Not many specific allergens have been identified
- Peanuts - 30% protein
- Soybeans - 42% protein
- Difficult to isolate specific moieties
- Groups - albumins, lipoproteins, globulins, glycoproteins, S-fractions

## Food Allergen Proteins

- Cow milk
- Egg yolk
- Peanuts
- Soybeans
- Codfish
- Green peas
- Rice

- Tomatoes
- $\beta$ -lactoglobulin
- Lipoprotein
- Peanut I + others
- Glycinin + others
- Allergen M
- Albumin
- Glutelin/globulins
- Glycoproteins

## Food Allergens

- Allergens such as chocolate, strawberries and citrus often do not show positive on double blind studies

## Treatment of Food Allergy

- Total avoidance of specific allergen
- No level is safe
- Very small doses can elicit
  - Distinguishes from other food sensitivities
- Cross reactivity is constant worry