به نام خدا

Food Allergy

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Adverse Food Reactions

Non-immunologic

Toxic / Pharmacologic

- **Bacterial food poisoning**
- **Heavy metal poisoning**
- **Scombroid fish poisoning**
- **Caffeine**
- **Alcohol**
- **Histamine**

Non-Toxic / Intolerance

- **Lactase deficiency**
- **Galactosemia**
- **Pancreatic insufficiency**
- **Gallbladder / liver disease**
- **Hiatal hernia**
- **Gustatory rhinitis**
- **Anorexia nervosa**

Adverse Food Reactions

Immunologic

IgE-Mediated (most common)

- Systemic (Anaphylaxis)
- Oral Allergy Syndrome
- Immediate gastrointestinal allergy
- Asthma/rhinitis
- Urticaria
- Morbilliform rashes and flushing

Non-IgE Mediated Cell-Mediated

- Eosinophilic esophagitis
- Eosinophilic gastritis
- Eosinophilic gastroenteritis
- Atopic dermatitis

- Protein-Induced Enterocolitis
- Protein-Induced Enteropathy
- Eosinophilic proctitis
- Dermatitis herpetiformis
- Contact dermatitis

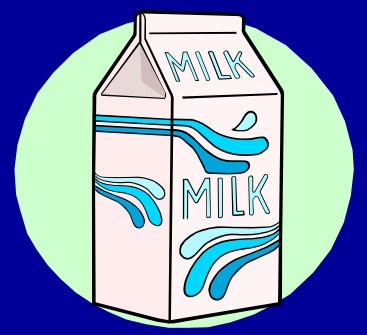
Allergens

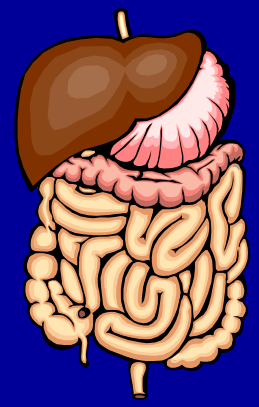
- Proteins or glycoproteins (not fat or carbohydrate)
  - Generally heat resistant, acid stable
- Major allergenic foods (>85% of food allergy)
  - Children: milk, egg, soy, wheat, peanut, tree nuts
  - Adults: peanut, tree nuts, shellfish, fish, fruits and vegetables

Pan-allergens

- Proteins in food, pollen or plants that possess homologous IgE binding epitopes across species
- Tropomyosins: crustacea, dust mites, cockroach, mollusks
- Parvalbumins: fish
- Bovine IgG: beef, lamb, venison, cow's milk
- Lipid transfer protein: fruits (peach, apple), vegetables, peanut, tree nuts
- Profilin: fruits, vegetables
- Class 1 chitinases: fruits, wheat, latex

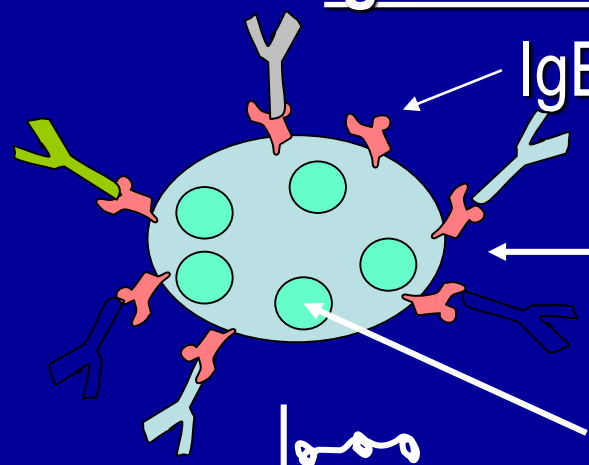
Immune Mechanisms

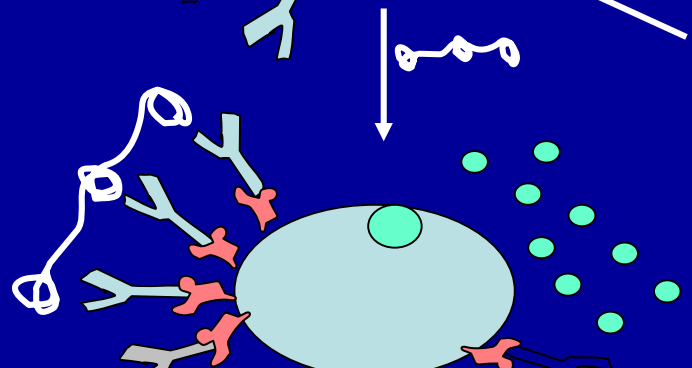


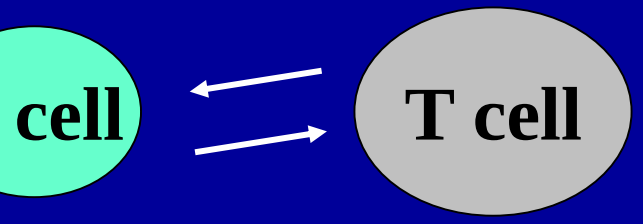


- Protein digestion
- Antigen processing
- Some Ag enters blood

IgE-Mediated







Non-IgE Mediated

- TNF-α
- IL-5

Risk Factors for Development of Food Allergy

Local Factors (Rodent Models)	Host Factors
• Genetic susceptibility •Pepsin digestion • Gastrointestinal infections? • Malabsorption • Rate of absorption • Antigen processing • Nature and dose of Ag	• Age (esp neonates) • Genetic susceptibility • FHx of atopy • FHx of food allergy • Atopic dermatitis • Transdermal food exposure (peanut)

Signs and Symptoms

	IgE	Non-IgE	Acute	Chronic
Skin				
Urticaria	✓		✓	
Angioedema	✓		✓	
Atopic dermatitis	✓	✓	✓	✓
Respiratory				
Throat tightness	✓		✓	
Rhinitis	✓		✓	(✓)
Asthma	✓		✓	✓
Gut				
Vomit	✓	✓	✓	✓
Diarrhea	✓	✓	✓	✓
Pain	✓	✓	✓	✓

Food Allergy Disorders

Anaphylaxis Syndromes

- Food-induced anaphylaxis
  - Food allergy = #1 cause of anaphylaxis in the ED
  - Rapid-onset, up to 30% biphasic
  - May be localized (single organ) or generalized
  - Potentially fatal
  - Any food, highest risk:
    - peanut, tree nut, seafood (cow's milk and egg in young children)
- Food-dependent, exercise-induced: 2 forms
  - Specific foods (wheat, celery most common)
  - Any food (post-prandial)

Fatal Food Anaphylaxis

- Frequency: ~ 150 deaths / year
- Clinical features:
  - Biphasic reaction can contribute –initially better, then recurs
  - Cutaneous symptoms may not be present
  - Respiratory symptoms prominent
- **Risk factors:**
  - **Underlying asthma**
  - **Delayed epinephrine**
  - **Symptom denial**
  - **Previous severe reaction**
  - **Adolescents, young adults**
- History: known food allergen
- Key foods: ***peanuts and tree nuts dominate (~90% of fatalities)***, fish,crustaceans
- Most events occurred away from home

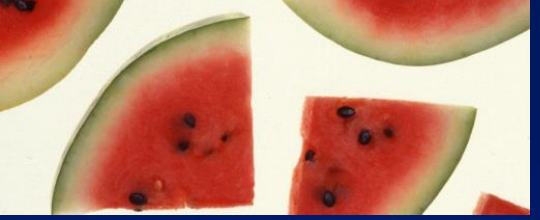
Cutaneous Reactions

- Acute urticaria/angioedema – common
- Contact urticaria - common
- Food allergy rarely causes chronic urticaria/angioedema
- 1/3 of children with moderate to severe atopic dermatitis may have food allergy (especially cow's milk, egg, soy, wheat). Morbilliform rashes may be seen in these children upon food challenge.
- Contact dermatitis (food handlers)

Respiratory Responses

- Upper and lower respiratory tract symptoms may be seen (rhinoconjunctivitis, laryngeal edema, asthma)
- Rarely isolated, usually accompany skin and GI symptoms
- Inhalational exposure may cause respiratory symptoms that can be severe
  - Occupational
  - Restaurants
  - Kitchen/Home

Example:



Pollen-Food Syndrome or Oral Allergy Syndrome

- Clinical features: rapid onset oral pruritus, rarely progressive
- Epidemiology: prior sensitization to pollens
- Key foods: raw fruits and vegetables
- Allergens: Profilins and pathogenesis–related proteins
  - Heat labile (cooked food usually OK)
- Cause: cross reactive proteins pollen/food

Birch → Apple, carrot, celery, cherry, pear, hazelnut
Ragweed → Banana, cucumber, melons
Grass → Melon, tomato, orange
Mugwort → Melon, apple, peach, cherry

Latex-Fruit Syndrome

- 30-50% of those with latex allergy are sensitive to some fruits due to cross-reactive IgE
- Most common fruits: banana, avocado, kiwi, chestnut but other fruits and nuts have been reported
- Can clinically present as anaphylaxis to fruit
- Warn latex-sensitive patients of potential cross-reactivity
- Some fruit-allergic patients may be at risk for latex allergy

Pediatric Gastrointestinal Syndromes

	Enterocolitis	Enteropathy	Proctitis
Age Onset:	Infant	Infant/Toddler	Newborn
Duration:	12-24 mo	? 12-24 mo	9 mo-12 mo
Characteristics:	Failure to thrive Shock Lethargy Vomit Diarrhea	Malabsorption Villous atrophy Diarrhea	Bloody stools No systemic sx Eosinophilic

- Non-IgE-mediated, typically milk and soy induced
- Spectrum may include colic, constipation and occult GI blood loss

GI Syndromes of Children and Adults:

Celiac Disease (Gluten-sensitive enteropathy)

- In children:
  - **FTT, or weight loss**
  - **Malabsorption, diarrhea, abdominal pain**
  - **May be subtle**
- In adults, average 10 years of nonspecific symptoms:
  - Diarrhea, abdominal pain
  - GERD
  - Malabsorption
  - May present atypically with osteoporosis, infertility, neurologic sx

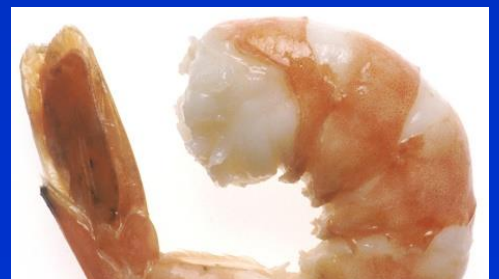
Pathophysiology: an immune-mediated enteropathy triggered by gluten peptides in genetically predisposed patients (DQ2 or DQ8)

- Lymphocytic infiltration of small bowel
- Villus atrophy

GI Syndromes of Children and Adults

Gastrointestinal Anaphylaxis or Immediate Gastrointestinal Allergy

- IgE-mediated
- Acute emesis/diarrhea/abdominal pain
- Can present without other signs or symptoms of an allergic reaction to food



GI Syndromes of Children and Adults

Eosinophilic Gastrointestinal Disorders: eosinophilic esophagitis/gastritis/gastroenteritis

- Prevalence increasing, eosinophilic esophagitis is the most common syndrome, all rare in adults
- Symptoms
  - Post-prandial N/V/D/abdominal pain, weight loss
  - FTT in infants and young children, irritability, sleep disturbance
  - GER, often refractory, may be seen
  - In teens/adults: dysphagia, food impaction

Eosinophilic Gastrointestinal Disorders: eosinophilic esophagitis/gastritis/gastroenteritis cont'd:

- Diagnosis
  - Biopsy: eos infiltration (mucosa → serosa): >20/HPF
  - Presence of eos doesn't necessarily invoke food allergy
  - May affect esophagus to rectum
- Response to specific food elimination found in a subset of patients (especially eosinophilic esophagitis): can screen for food allergy with prick/in vitro IgE, patch testing with food is currently under investigation

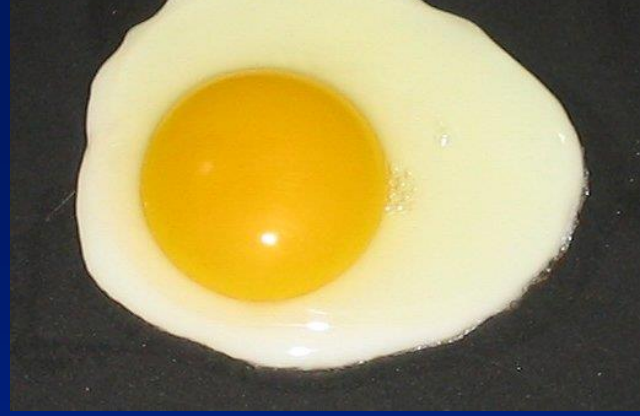
Non-IgE-Mediated Syndromes of the Skin and Lung

- Dermatitis Herpetiformis
  - Associated with Celiac Disease
  - Gluten-sensitive, improves on diet
  - Vesicular, pruritic eruption sacrum, extensor knees and elbows
- Heiner's Syndrome
  - Precipitating antibodies to cow's milk
  - Infantile pulmonary hemosiderosis
  - Anemia, failure to thrive

Disorders Not Proven to be Related to Food Allergy

- Migraines
- Behavioral / Developmental disorders
- Arthritis
- Seizures
- Inflammatory bowel disease

Prevalence of Food Allergy



- Perception by public: 20-25%
- Confirmed allergy (oral challenge)
  - Adults: 2-3.5%
  - Infants/young children: 6-8%
- Specific Allergens
  - Dependent upon societal eating and cooking patterns
- Prevalence higher in those with:
  - Atopic dermatitis
  - Certain pollen allergies
  - Latex allergy
- Prevalence seems to be increasing

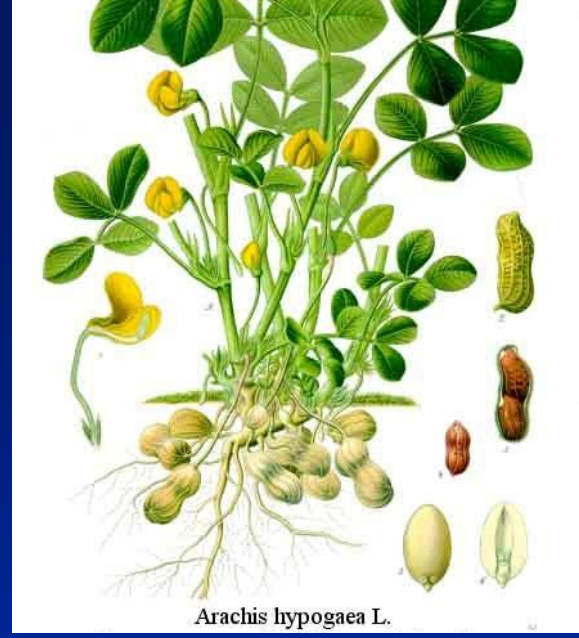
Estimated Prevalence of Food Allergy

Food	Children (%)	Adults (%)
Cow's milk	2.5	0.3
Egg	1.3	0.2
Soy	0.3-0.4	0.04
Peanut	0.8	0.6
Tree nut	0.2	0.5
Crustaceans	0.1	2.0
Fish	0.1	0.4

Natural History

- Dependent on food & immunopathogenesis
- ~ 85% of cows milk, soy, egg and wheat allergy remit by age 3 yrs
  - Declining/low levels of specific-IgE predictive
  - IgE binding to conformational epitopes predictive
- Non-IgE-mediated GI allergy
  - Infant forms resolve in 1-3 years
  - Toddler / adult forms more persistent

Natural History (cont'd)



- Allergies to peanuts, tree nuts, seafoods, and seeds typically persist
- ~20% of cases of peanut allergy resolve by age 5 years.

  Prognostic factors include:
  - PST <6mm
  - ≥2 years avoidance
  - History of mild reaction
  - Few other atopic diseases
  - Low levels of peanut-specific IgE
  - Rarely re-develop allergy: role for regular

Evaluation: History & Physical Exam

- History: most important
  - Symptoms, timing, reproducibility, treatment and outcome
  - Concurrent exercise, NSAIDs, EtOH
- Diet details / symptom diary
  - Subject to recall
  - “Hidden” ingredient(s) may be overlooked
- Physical exam: assess for other allergic and alternative disorders
- Identify general mechanism
  - Allergy vs intolerance
  - IgE versus non-IgE mediated

Evaluation of Food Allergy

- Suspect IgE-mediated
  - Panels/broad screening should NOT be done without supporting history because of high rate of false positives.
  - Prick skin tests (prick-prick with fresh food if pollen-food syndrome)
  - In vitro tests for food-specific IgE
- Suspect non-IgE-mediated
  - Consider biopsy of gut, skin
- Suspect non-immune, consider:
  - Breath hydrogen
  - Sweat test
  - Endoscopy

Evaluation: Interpretation of Laboratory Tests

- Positive prick test or specific IgE
  - Indicates presence of IgE antibody NOT clinical reactivity
  - ~90% sensitivity
  - ~50% specificity
  - ~50% false positives
  - Larger skin tests/higher IgE correlates with likelihood of reaction but not severity

- Negative prick test or specific IgE
  - Essentially excludes IgE antibody (>95% specific)

Specific IgE Levels Associated with 95% Risk of Reaction

Age Group	Food	Serum IgE (kU/L)
Child	Egg	≥ 7
<2 years	Egg	≥ 2
Child	Cow Milk	≥ 15
<2 years	Cow Milk	≥ 5
Child	Peanut	≥ 14
Child	Fish	≥ 20

Evaluation:
Elimination Diets & Food Challenges

- Elimination diets (1 - 6 weeks) most useful for chronic disease (eg. AD, GI syndromes)
  - Eliminate suspected food(s) or
  - Prescribe limited “eat only” diet or
  - Elemental diet
- Oral challenge testing (MD supervised, emergency meds available)
  - Open
  - Single-blind
  - Double-blind, placebo-controlled (DBPCFC)

Diagnostic Approach: IgE-Mediated Allergy

- If test for specific-IgE antibody is
  - Negative: reintroduce food*
  - Positive: start elimination diet
- If elimination diet is associated with
  - No resolution: reintroduce food*
  - Resolution
    - Open / single-blind challenges to “screen”
    - DBPCFC for equivocal open challenges

Diagnostic Approach: Non-IgE-Mediated Disease or those with unclear mechanism

- Elimination diets (may need elemental diet)
- Oral Challenges
  - Timing/dose/approach individualized for disorder
    - Enterocolitis syndrome can induce shock
    - Eosinophilic gastroenteritis may need prolonged feedings before symptoms develop
  - DBPCFCs preferred
  - May require ancillary testing (endoscopy/biopsy)

Optimizing the Diagnosis of Food Allergy

- Accurate diagnosis of food allergies is vital to identify patients who may have severe, life threatening allergic reactions, and to exclude suspected allergies that could lead to unnecessary dietary restrictions.

Molecular Allergy Diagnosis
component-resolved diagnostics (CRD)

- Peanut reactivity and tolerance : Ara h 2
- Hazelnut allergy : Cor a 1

- Exercise-induced wheat anaphylaxis : Omega-5 gliadin

Management of Food Allergy

- Complete avoidance of specific food trigger
- Ensure nutritional needs are being met
- Education
- Anaphylaxis Emergency Action Plan if applicable
  - most accidental exposures occur away from home

This frozen dessert could have peanut, tree nut, cow's milk, egg, wheat

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Management: Dietary Elimination

- Hidden ingredients in restaurants/homes (peanut in sauces,egg rolls)
- Labeling issues (“spices”, changes, errors)
- Cross contamination (shared equipment)
- Seeking assistance
  - Food allergy specialist
  - Registered dietitian: (www.eatright.org)
  - Food Allergy & Anaphylaxis Network (www.foodallergy.org; 800-929-4040) and local support groups

Management: Infant Formulas

- Soy (confirm soy IgE negative)
  - <15% soy allergy among IgE-CMA
  - ~50% soy allergy among non-IgE CMA
- Cow's milk protein extensive hydrolysates
  - >90% tolerance in IgE-CMA
- Partial hydrolysates
  - Not hypoallergenic!
- Elemental amino acid-based formulas
  - Lack allergenicity

Management: Emergency Treatment of Anaphylaxis

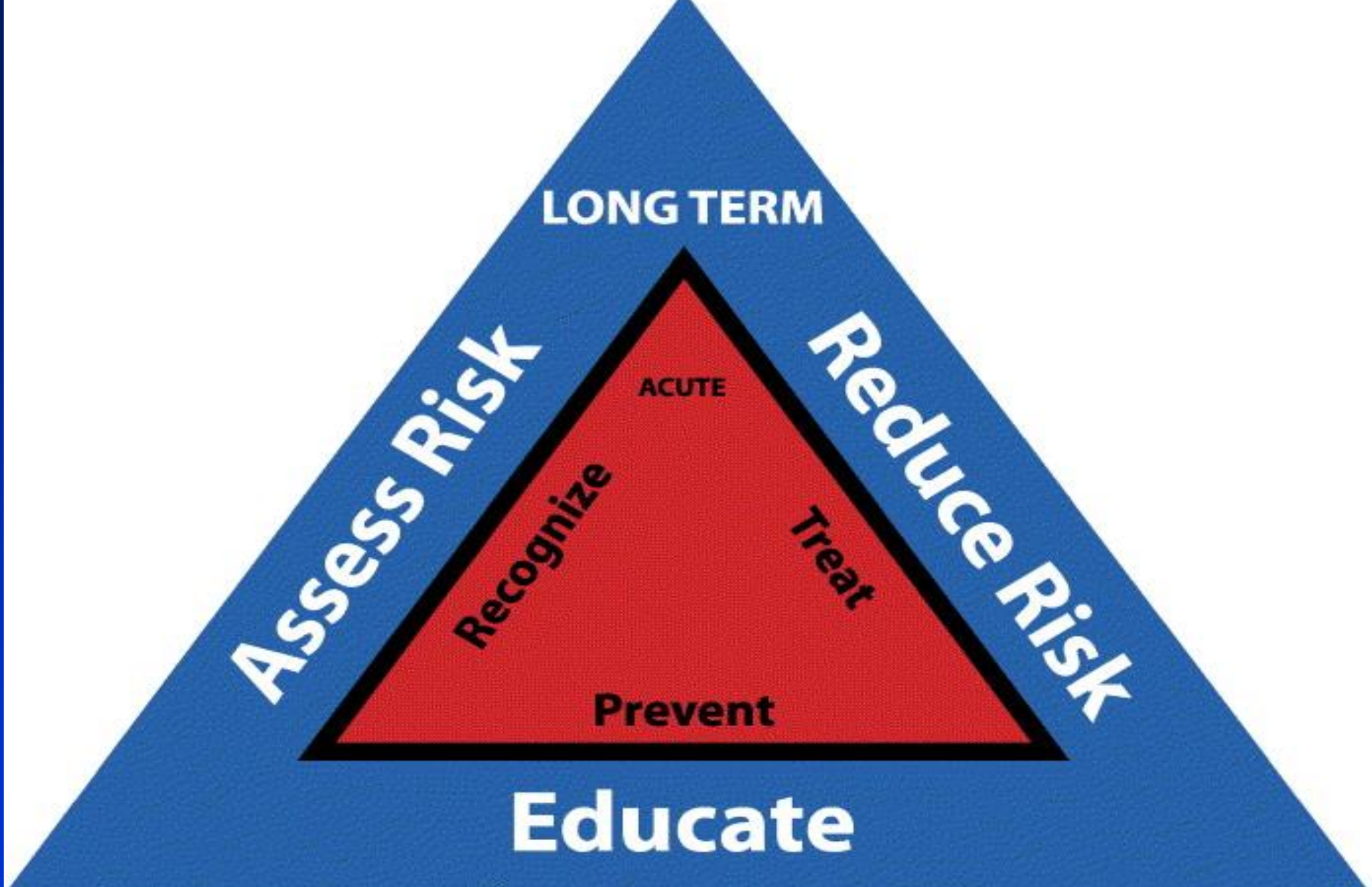
- Epinephrine: drug of choice
  - Self-administered epinephrine readily available at all times
  - If administered, seek medical care IMMEDIATELY
  - Train patients, parents, contacts: indications/technique
- Antihistamines: secondary therapy only: WILL NOT STOP ANAPHYLXAXIS
- Written Anaphylaxis Emergency Action Plan
  - Schools, spouses, caregivers, mature sibs / friends
- Emergency identification bracelet

Accidents Are Never Planned

Emergency medications and a treatment plan must be immediately available and accessible at all times!

Respond Quickly!

- Administer epinephrine quickly
- Activate EMS – 911
- Then, call emergency contacts


LONG TERM
Assess Risk
Reduce Risk
ACUTE
Recognize
Treat
Prevent
Educate

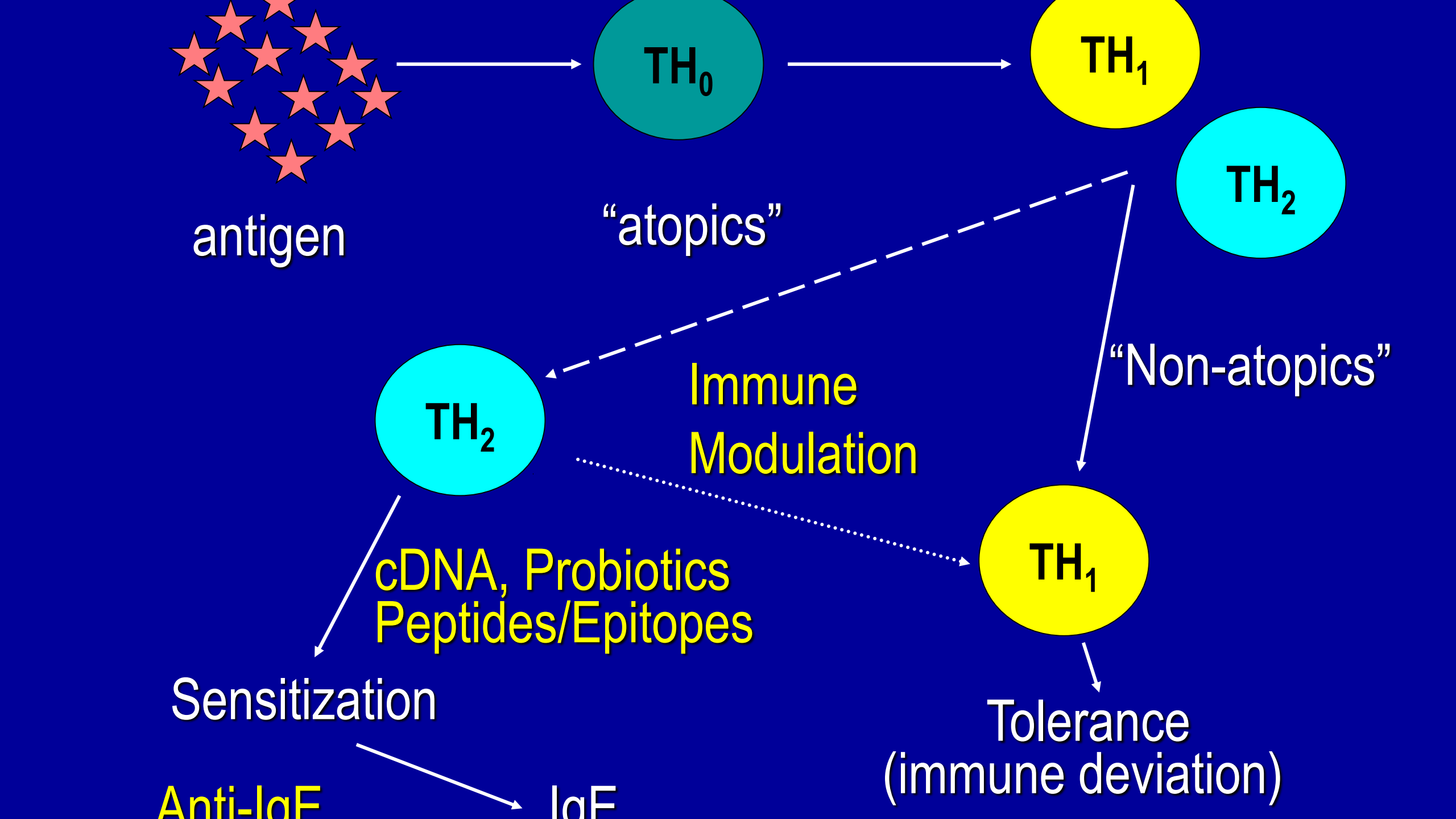
Management: Follow-Up

- Re-evaluate for tolerance periodically
- Interval and decision to re-challenge:
  - Type of food allergy (IgE vs non-IgE)
  - Severity of previous symptoms
  - Allergen/Prognosis (cow's milk vs peanut)
- Ancillary testing
  - Skin prick test/in vitro specific IgE may remain positive
  - Decline in concentration of food specific-IgE is suggestive of development of tolerance

Future Approaches

Future Immunomodulatory Approaches

- Recombinant anti-IgE antibody
- Gene (naked DNA) immunization
- Mutated B-cell epitopes
- Minimal T-cell epitopes
- Immune-modulating adjuvants (ISS)
- Probiotics
- T lymphocyte manipulation to induce tolerance
- Chinese herbal remedies (Food Allergy Herbal Formula)


antigen
TH0
TH1
TH2
"atopics"
"Non-atopics"
TH2
Immune
Modulation
TH1
cDNA, Probiotics
Peptides/Epitopes
Sensitization
Tolerance
(immune deviation)
Anti-IgE
IgE

Role of the Allergist

- Identification of causative food
- Institution of elimination diet
- Education on food avoidance
- Development of an Anaphylaxis Emergency Action Plan
- Prevention of other allergies
- Follow-up to ascertain tolerance

Summary and Conclusions

- IgE & non-IgE-mediated conditions exist
- The history and physical are paramount
- Elimination diets, skin testing, in vitro assays, and food challenges also have roles in diagnosis
- Avoidance, education, and preparation for emergencies are the pillars of current management
- Periodic re-challenge to monitor tolerance as indicated by history, allergen, and level of food-specific IgE is an important part of ongoing follow-up