IgE-Mediated Food Allergy

Review of clinical presentation, diagnosis, potential therapies and new perspectives.
Adverse Food Reactions

- **Toxic:**
  - Will occur in all individuals exposed to a sufficient dose.

- **Nontoxic:**
  - Caused by individual susceptibility.
Case Report:

- 25-yr-old man presents with flushing eruption that began 30 min. prior.
- Complained also of headache, dizziness, abdominal pain.
- Symptoms started 1 hr after lunch, he had eaten a serving of tuna.
- One hour after presentation & without any treatment the eruption resolved.
Scrombroid food poisoning

Nontoxic Adverse Food Reactions

Food Allergies: (immunologic)
- IgE-Mediated
- Non-IgE-Mediated

Food Intolerances: (non-immunologic)
- Enzymatic
  - lactase deficiency
- Pharmacological
- Idiosyncratic

Food Allergies/ Hypersensitivities

IgE-Mediated

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

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

Non-IgE Mediated

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

IgE-Mediated Food Allergy

- Prevalence
- Pathophysiology
- Clinical manifestations
- Diagnosis
- Treatment
- Prevention strategies
Prevalence: IgE-Mediated Food Allergy

- Public perception 20- 25%
- Confirmed allergy:
  - Adults 2 to 4%
  - Children (< 4 yrs) 6 to 8%
- Higher if other atopic disease:
  - Eczema
  - Allergic rhinitis
  - Asthma

90% Reactions Caused by 7 Allergen Groups:

Children
- Egg
- Cow milk
- Peanut
- Wheat
- Soy
- Tree nuts/ seeds

Adults
- Peanut
- Tree nuts/ seeds
- Fin fish
- Shellfish
- (fruits & vegetables: food-pollen syndrome)
Pathophysiology: Allergens

- Proteins or glycoproteins
  - 10-70 kD
  - heat resistant, acid stable

- Epitopes: antigenic determinant
  - Conformational: dependant on folding
  - Linear/sequential: not dependent on folding

- Identification of specific epitopes
  - Guide therapy?
  - Predict outcomes?
IgE-Mediated Immune Mechanisms

- Protein digestion
- Antigen processing
- Some Ag enters blood

Clinical Manifestations

- Skin (> 85%)
  - Urticaria/ angioedema
  - Eczema

- Respiratory
  - Rhinitis
  - Cough/ wheeze; asthma flare

- GI symptoms
  - Nausea/ vomiting
  - Diarrhea
  - Abdominal cramping

- Anaphylaxis
Eczema

- Food allergy: 20-30% severe cases in children
- Atopic sensitization high
  - Aeroallergens (70-90%)
  - Food allergens (50-70%)
- High rates of asthma & allergic rhinitis
- Epidermal barrier function
  - Filaggrin defect?

Case Report:

- 55 yr old women referred for evaluation of “shrimp allergy”.
- History is of hives after shrimp ingestion.
- On review of history- it was determined that she ingested shrimp the evening prior with onset of hives the next day.
- Hives lasted for a couple of days.
Food-Induced Anaphylaxis

- Leading cause of anaphylaxis in children.
- ~30,000 cases seen in ED yearly.
- ~150 deaths per year.
- Severe/fatal anaphylaxis:
  - >90% are due to peanut/tree nuts.
  - >85% have asthma.

Case Report:

- 22 yr. old presents with complaint of itchy mouth/ palate, slight swelling of the tongue/ lips with ingestion of fresh fruits.
- Typically occurs with apples, peaches, cherries, pears- can ingest all of these when cooked/ processed.
Pollen-Food Syndrome (Oral Allergy Syndrome)

- Clinical features: rapid onset of pruritus & occasional hives or swelling of lips, tongue, palate, throat; usually mild.
- Epidemiology: prior sensitization to pollens.
- Key foods: raw fruits & vegetables.
- Allergens: homologous plant derived proteins in pollen and vegetables/ fruits/ nuts; heat labile.

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

- **Clinical history:** most important
  - Symptoms, timing, reproducibility, PMH, FH
- **Physical exam:**
  - Assess for other atopic disease
- **Specific IgE tests:**
  - Skin prick test (SPT)
  - *In vitro* serum immunoassays (ImmunoCAP, Phadia)
- **Controlled food challenge**
Food specific IgE tests

Negative (patients > 2 yrs):
- SPT: >98% NPV
- ImmunoCAP: 70 – 80% NPV

Positive: less predictive-
- 50-70% pts. with + test are not clinically allergic
- History
- Value (larger result correlates with true allergy)

Correlate food-specific IgE value with ingestion challenge outcome.

Probability curve of likely reaction with a specific IgE level.

Reduces the requirement for oral food challenge tests.

Specific IgE Levels Associated with 95% Risk of Reaction

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Food</th>
<th>Serum IgE (kU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child</td>
<td>Egg</td>
<td>≥ 7</td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>Egg</td>
<td>≥ 2</td>
</tr>
<tr>
<td>Child</td>
<td>Cow Milk</td>
<td>≥ 15</td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>Cow Milk</td>
<td>≥ 5</td>
</tr>
<tr>
<td>Child</td>
<td>Peanut</td>
<td>≥ 14</td>
</tr>
<tr>
<td>Child</td>
<td>Fish</td>
<td>≥ 20</td>
</tr>
</tbody>
</table>

Unproven Diagnostic Procedures

- Food-specific IgG or IgG4 tests
- Cytotoxic food tests
- Nambudripad's Allergy Elimination Technique (NAET)
- Electrodermal testing

Niggeman, B., et. al., Allergy 2004;59:806-808.
**Standard Food Panel: IgG/IgE**

**Physician:**

**Patient:**

**Age:** 29

**Sex:** F

**Collected:** 2000-03-10

**Received:** 2000-03-11

**Completed:** 2000-03-19

**CLIA #:** 50D0066861 © US BioTek Laboratories

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**Dairy**

- Caser
- Cheese, Cheddar
- Cheese, Cottage
- Cheese, Mozzarella
- Milk
- Milk, Goat
- Whey
- Yogurt

**Fruits**

- Apple
- Apricot
- Banana
- Blueberry
- Cranberry
- Grape, Red
- Grapefruit
- Lemon
- Orange
- Papaya
- Peach
- Pear
- Pineapple
- Plum
- Raspberry, Red
- Strawberry

**Meat/Fowl**

- Beef
- Chicken
- Egg White, Chicken
- Egg Yolk, Chicken
- Lamb
- Pork
- Turkey

**Fish/Crustacea/Mollusk**

- Cam, Manila
- Cod, Atlantic
- Crab, Dungeness
- Halibut
- Lobster, American
- Oyster
- Red Snapper
- Salmon, Pacific
- Shrimp, Western
- Zuke
- Turf, Yellowfin

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**Reaction Class**

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>None</strong></td>
<td>No Reaction</td>
<td>Very Low</td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
<td>Very High</td>
<td>Extremely High</td>
</tr>
</tbody>
</table>

*This test does not identify anaphylaxis. Low allergen IgE cannot justify secondary exposure in food except in inducing anaphylaxis as it may prove fatal.*

*This test is not intended to diagnose, treat, cure, or prevent any disease or replace the medical advice and/or treatment obtained from a qualified healthcare practitioner.*

US BioTek’s proprietary ELISA analysis is a semi-quantitative assessment for specific Total IgG antibodies 1, 2, 3, 4 and IgE antibodies.

The classification of 0 to VI denotes the level of IgG and/or IgE antibodies detected through specrophotometric analysis.

US BioTek Laboratories has developed and determined the performance characteristics of this test. This test has not been evaluated by the U.S. Food and Drug Administration.

IgG antibodies may be associated with Delayed-Onset Hypersensitivity Reactions. IgE antibodies may be associated with Immediate-Onset Hypersensitivity Reactions.

*This antigens in this panel are subject to changes without prior notice.*
Case Report:

- 8 yr old girl referred for evaluation of multiple food allergy/ on very restricted diet for past year.
- IgG testing + for cow milk, wheat, egg, soy, chocolate, peanut, tree nuts, others.
- Symptoms were mild eczema/ itch, nasal congestion & constipation/ stomach aches.
- Was undergoing “NAET acupressure therapy”.
- Patient seemed to improve initially, then symptoms returned.
Diagnosis: Oral Food Challenges

- “Gold standard”: Double blind placebo controlled food challenge (DBPCFC).
- Open challenges may have false positive results (20 – 70%).
- Positive placebo reactions during DBPCFCs are as high as 35%.

Eckman, J., et. al., Allergy, Asthma, Clin Immunol 2009;5:1-7;
Natural History

- Majority of children with cow milk, egg, soy, & wheat allergy will eventually develop clinical tolerance.

- Seafood, peanut, tree nut allergy rarely resolves.
Component Resolved Diagnostics (CRD)

- Correlates clinical expression of allergy with IgE binding to specific epitopes.
- Identification & characterization of clinically relevant allergen components is necessary for this new methodology.
- Novel methods being developed: peptide microarray technology.

CRD: Peanut Allergy

Manchester Asthma and Allergy Study

- 110/933 (11.8%) sensitized at age 8 yrs.
- 22.4% of sensitized patients had clinical allergy.
- CRD (peptide microarray)- marked difference in pattern recognition between peanut allergic & tolerant pts.
  - Tolerant- higher grass-specific IgE, CCDs, Arah8 epitope
  - Allergic- higher binding to 3 specific epitopes (Arah1, Arah2, Arah3)

“Oh no! Is that a peanut?”

As soon as it touched his lips, we panicked.
Before the test, we were always guessing.
Now we no longer have to live in fear.
● Marketed directly to patients.
● Cost $300 - patients pay; not insurance.
● Component resolved diagnostics:
  – Arah1, Arah2, Arah3, Arah9: claim “severe” risk
  – Arah8, CCD: “low” risk
● No challenge evidence!
Current Therapeutic Approaches

- No curative treatment currently available.
- Strict avoidance only option.
  - Avoid unsubstantiated elimination diets
- Reactions to accidental exposures can be severe.
  - Emergency management/ epinephrine
Novel Therapeutic Approaches

Non-specific:
- Monoclonal anti-IgE antibody
- Chinese herbal medicine

Allergen specific:
- Heat-denatured protein introduction
- Oral immunotherapy
- Sublingual immunotherapy
- Recombinant protein immunotherapy
Chinese Herbal Medicine

- Food Allergy Herbal Formula (FAHF-2) protected peanut-allergic mice against anaphylaxis to peanut.
  - Nine specific herbs - all appear essential for effect.
  - Protected 36 weeks after treatment discontinued.
  - Peanut-specific IgE levels decreased, IgG levels increased.
  - Increase in interferon-gamma producing CD 8+ T cells.

- Human clinical trials in progress.

Li. X., Mount Sinai Journal of Medicine 2011; 78(5):697-716.
Heat-Denatured Protein Introduction

- “Expert Opinion”- strict avoidance of food allergen needed for development of tolerance.
- Patients with milk- or egg- specific IgE against conformational epitopes may tolerate heated (baked) products.
  - Improve quality of life
  - ? Change on development of tolerance
Literature Case Reports:

- 87/94 (93%) egg allergic children (med. age 24 mo) tolerated 1.5 g egg protein baked.
- SPT/ CAP not significantly differ. betw. - & + challenge groups.
- 83/87 patients actively ingesting baked egg daily for 6 months passed open fresh egg challenge.

- 68/91 (75%) milk allergic children (med. age 7.5 yrs) tolerated 1.3 g milk protein baked.
- SPT/ CAP significantly higher in pts. with + challenge.
- Active ingestion group had significantly lower SPT/ CAP at 3 mo. compared to baseline.

Oral Immunotherapy

- Employs the concept that allergen interaction with gut-associated lymphoid system leads to induction of tolerance.
  - **Induction phase**: begin with minute amount of allergen and gradually increase to set maintenance dose.
  - **Maintenance phase**: daily ingestion of specific amount.
Twelve million Americans, including a growing number of children, suffer from them...

What You Can Do About Food Allergies

By Sean Flynn

published: 04/18/2007

“Every night, Nate’s mom snips open a small packet of peanut powder that, because he’s 8 years old, he would prefer she sprinkle over ice cream. Usually, though, she mixes it with water or Kool-Aid or yogurt, and then Nate swallows it all down. “Two dot four,” Nate dutifully says, or 1,200 milligrams of powder weighing 2.4 grams—the equivalent of four peanuts.

It is something of a minor miracle: Nate Alexander was born with severe—possibly deadly—peanut allergy… “

OIT: Early Results Promising

- Effective in majority of pts. (>75%): (egg, milk, fish)
  - Tolerating full are partial set dose

- Relatively safe:
  - ~ 10% -20% stopped due to side effects
  - Majority had side effects- usually mild.

- Problems:
  - small numbers, uncontrolled, variable protocols, variable pt. populations.

Oral Immunotherapy

● Desensitization:
  – raises the threshold dose of the food allergen required to cause an allergic reaction; dependent on ongoing antigen exposure.

● Tolerance:
  – permanent loss of allergic reactivity to the food allergen; not dependent on ongoing antigen exposure.
Peanut OIT: Protocol Example

- **Initial day escalation phase:**
  - Start 0.1 mg peanut, double ~ q 30 min. until reach 50 mg or highest dose tolerated.

- **Buildup phase:**
  - Ingested tolerated dose daily
  - Dose increased by 25 mg q 2 weeks until 300 mg reached.

- **Maintenance phase:**
  - Continued on 300mg daily dose until OFC

- **Oral Food Challenge:**
  - 3.9 g peanut protein

Peanut OIT: Early Results (n=29)

- 95% have side effects
  - Hives, congestion, mouth pruritus, wheeze
  - 10% required epinephrine

- Initial phase, buildup doses done in hospital center
  - 3.5% of home doses had reactions (2 Epinephrine doses)

- 93% successfully desensitized
  - Passed OFC of 3.9 g peanut
  - Plan is 3 year maintenance regimen before stopping daily maintenance therapy - see if tolerant.

Lack of Evidence Based Studies

Current projects aimed to provide reliable data:

- Consortium of Food Allergy Research (CoFAR)
- Immune Tolerance Network
- EuroPrevall consortium (EU)

Nurmatov U., et.al., 2012; Cochrane Database of Systemic Reviews,9:CD009014.
Egg OIT: CoFAR study

*Jones S, J Allergy Clin Immunol 2010;125:L6*

- 55 patients, 5 to 18 yr. age
  - 40 active, 15 placebo
- 3 phases: initial escalation, build-up, maintenance (2000 mg)
- OFC at 44 wks (5g): 21/40 OIT passed; 0/15 placebo passed
- Significant decrease in egg specific- IgE & -basophil activation seen in OIT group.

Sublingual Immunotherapy

- Small amt of milk allergen under tongue for 2 to 3 minutes, either spit out or swallow.
  - Initial: 0.000167 mg advance to 0.067 mg
  - Build up 4 times weekly at home to maintenance of 7 mg.
- Appears safe:
  - only 5% had side effects
  - oral pharyngeal; no systemic
- Efficacy still unknown

Keet C, et. al., J Allergy Clin Allergy 2010;125:506.
Recombinant Protein Immunotherapy

- Develop a “hypoallergenic” allergen
  - Decrease risk of side effects (anaphylaxis) while maintaining immunologic effect on tolerance development.

- EMP-123
  - E. coli-encapsulated recombinant modified peanut proteins Arah1, Arah2, Arah3.
  - Prevented peanut-induced anaphylaxis in mouse model.

- CoFAR study: currently in Phase I trial

Li X, et. al., J Allergy Clin Immunol 2003;112:159-67.

Pochard P, et. al., J Allergy Clin Immunol, 2009;123:S211-S211
Strict avoidance of food allergens by infants may reduce the risk or prevent IgE-mediated sensitization.

- In 2000- Am. Acad. Pediatrics (AAP) recommended for “at risk” infants:
  - Breast feed or hypoallergenic formula for first year.
  - Delay solids > 6 mos.
  - Delay cow milk > 12 mos., egg > 24 mos., peanut/ tree nuts/ seafood > 36 mos. age.

- Recommendations were not “evidence based”.

Case Report:

- 6 yr old boy with history of egg and milk allergy, now resolved.
- Strictly avoided peanut in order to “prevent” allergy.
- Decided to try before starting Kindergarten—had one small bite, complained of “burning” sensation in mouth; onset of generalized urticaria, vomiting, respiratory difficulties within 10 minutes.
Current Evidence:

- Cochrane review of maternal dietary antigen avoidance during pregnancy, and/or lactation:
  - No effect on prevention of atopic disease.

- Literature review of hypoallergenic formula:
  - No evidence of effect on atopic sensitization.

- Delaying solids > 6 mo:
  - No protective effect on development of eczema/common food allergen sensitization.

Current Evidence:

- Prospective randomized controlled studies that removed food allergens from maternal diet during pregnancy, lactation & from infant’s diet in first 3 years of life:
  - No significant reduction in food allergy seen.

Does early exposure actually prevent allergy?

- **Timing of initial wheat exposure:**
  - Significant higher wheat allergy if initial exposure > 6 mos.

- **Introduction of egg < 6 mos.** had less egg allergy.

- **Peanut allergy in Jewish children in Israel (0.17%) vs. UK (1.85%):**
  - Israeli infants ingest significantly higher amount of peanut.

Prevention: “New Concept”

Early and regular exposure to food allergens may decrease rather than increase the risk of subsequent food allergy.

- Learning Early About Peanut Allergy (LEAP study) ([http://www.leapstudy.co.uk/](http://www.leapstudy.co.uk/))
  - 4 to 10 mo. old infants with eczema & sensitization to egg (SPT/CAP)
  - Randomly placed in avoidance until > 36 mo or regular ingestion 3 times weekly (6g / week).
  - Outcome measured at age 5 yr.
AAP Recommendations: 2008

- ‘At present, there are insufficient data to document a protective effect of any dietary intervention beyond 4 to 6 months of age for the development of atopic disease.”

- Still encourage exclusive breast milk in first 4 months.

Conclusion: New Perspectives

- Eczema (skin barrier breakdown/ filaggrin defect) predisposes for allergic sensitization.
- New diagnostic techniques (CRD):
  - Separate sensitized/tolerant from allergic.
  - Predict severity, persistence of allergy.
  - Identify pts. for immune modulation therapy.
- Food allergen interaction with the gut-associated lymphoid system may lead to induction of tolerance.
- Early, regular exposure to food allergens may decrease risk of subsequent food allergy.