

Diagnosis and Management of Food Allergy

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**ACT AGAINST
ALLERGY**

Food Allergy: Outline

- **Definitions**
- **Prevalence**
- **Clinical manifestations**
- **Diagnosis**
- **Treatment**
- **Natural History**

Adverse Reactions to Foods

True Food Allergy

Food Intolerance

Food Toxicity

Food Aversion

ADVERSE REACTIONS TO FOODS

Toxic Reactions

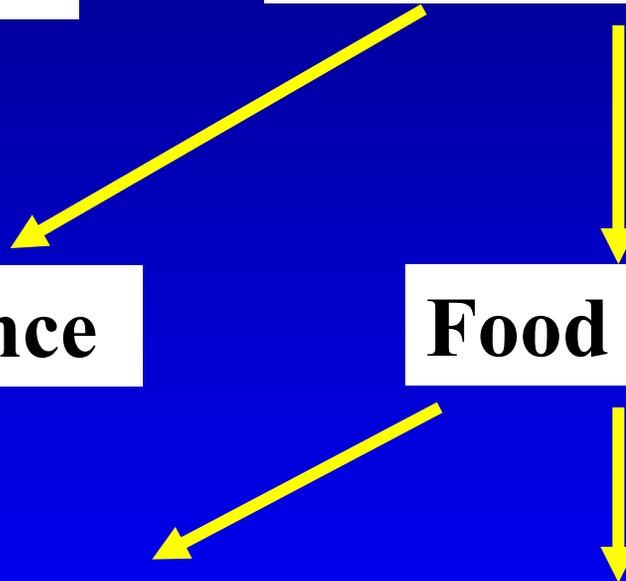
Non-Toxic Reactions

Food Intolerance

Food Allergy

IgE/TH₂-Mediated

Non-IgE-Mediated



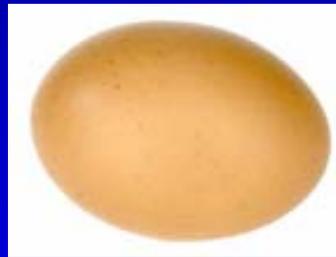
Prevalence of Food Allergy

- Perception by public: 20-25%
- Confirmed allergy (oral challenge)
 - Adults: 1-2%
 - Infants/Children: 6-8% (~1/4 million births)
- Dye/preservative allergy (rare)
- Specific Allergens
 - Dependent upon societal eating pattern
 - Milk (infants)- 2.5%
 - Peanut/nuts in general population- 1.1%

8 Major Food Allergens



COWS' MILK



HENS' EGG



PEANUT



TREE NUTS



SOYA BEAN



SHELLFISH



FISH



WHEAT

“SECOND TIER” FOODS

- 10% reactions to foods
- 160 foods
- Fruits
- Vegetables
- Seeds (sesame, sunflower, poppy)
- Spices

Food Allergy in Children

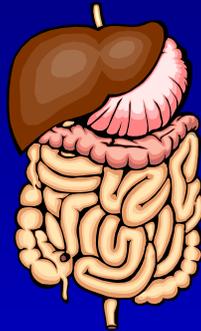
International



Pathophysiology: Allergens

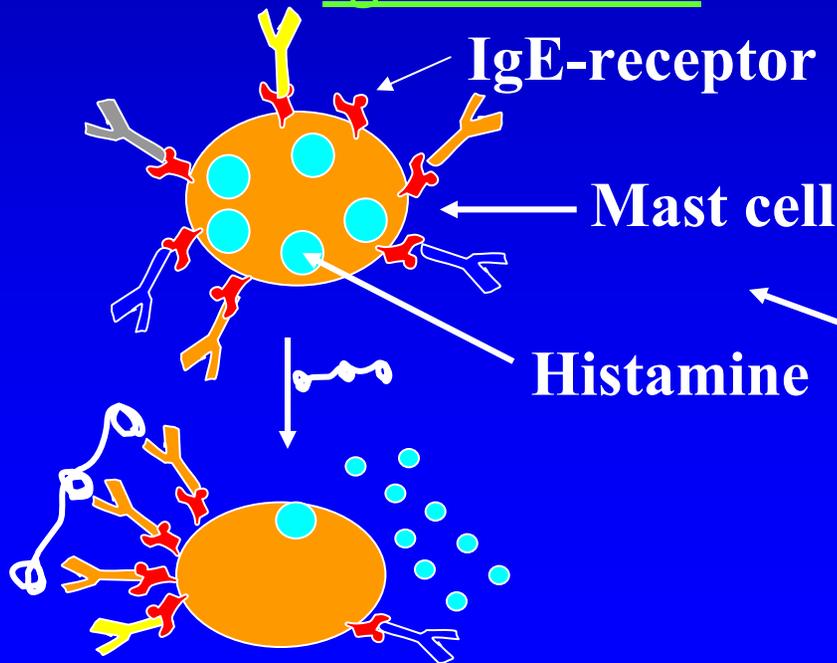
- **Proteins (not fat/carbohydrate)**
 - 10-70 kD glycoproteins
 - Heat resistant, acid stable
- **Major allergenic foods (>85% of allergy)**
 - Children: **milk**, egg, soy, wheat and below
 - Adults: peanut, nuts, shellfish, fish
- **Single food > many food allergies**
- **Characterization of epitopes underway**
 - Linear vs conformational epitopes
 - B-cell vs T-cell epitopes

Pathophysiology: Immune Mechanisms

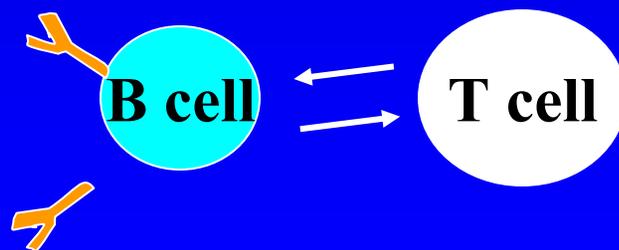


- Protein digestion
- Antigen processing
- Some Ag enters blood

IgE-Mediated



Non-IgE-Mediated



- TNF- α
- IL-5

Adverse Reactions to Food

A. Nonimmunologic

Toxic/Pharmacologic

- Bacterial food poisoning
- Heavy metal poisoning
- Scombrotoxic fish poisoning
- Caffeine
- Tyramine
- Histamine

Non-Toxic/Intolerance

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

Adverse Reactions to Food

B. Immunologic Spectrum

IgE-Mediated



Non-IgE Mediated

- Oral Allergy Syndrome
- Anaphylaxis
- Urticaria

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

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

Signs and Symptoms

Skin	IgE	Non-IgE	Acute	Chronic
Urticaria	<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Angioedema	<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>	
Atopic dermatitis	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Respiratory				
Throat tightness	<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>	
Rhinitis	<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Asthma	<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Gut				
Vomit	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Diarrhea	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Pain	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Anaphylaxis	<input checked="" type="checkbox"/>		<input checked="" type="checkbox"/>	

IgE-mediated: Oral Allergy Syndrome (OAS)

- Oral pruritus, rapid onset, rarely progressive
- Usually fresh fruits and vegetables
- Heat labile: cooked forms, no reaction
- Cause: cross reactive proteins pollen/food



POLLEN

FOODS

Birch

Apple, apricot, carrot, cherry, kiwi, plum

Ragweed

Banana, cucumber, melon, watermelon

Grass

Cherry, peach, potato, tomato

IgE-mediated: Urticaria



- Acute urticaria ✓
- Chronic urticaria ✗

IgE – mediated: Anaphylaxis

- **Food-induced anaphylaxis**
 - Rapid-onset
 - Multi-organ system involvement
 - Potentially fatal
 - Any food, highest risk:
 - peanut, nut, seafood
- **Food-associated, exercise-induced**
 - Associated with a particular food
 - Associated with eating any food

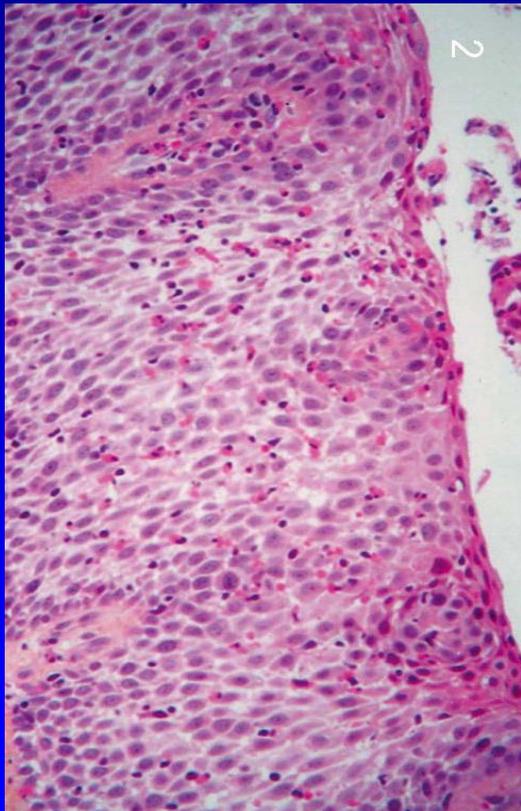
Fatal Food Anaphylaxis

- **Frequency: ~ 100 deaths/yr**
- **Risk:**
 - Underlying asthma
 - Delayed adrenaline
 - Symptom denial
 - Previous severe reaction
- **History: known allergic food**
- **Key foods: peanut/nuts/shellfish**
- **Biphasic reaction**
- **Lack of cutaneous symptoms**

Mixed IgE/Non-IgE mediated: GI Syndromes of Children/Adults

- **Eosinophilic esophagitis, gastritis, gastroenteritis**
 - Eosinophilic infiltration
 - Poor growth, pain, vomit, diarrhea, reflux
 - **Multiple food allergy, IgE and non-IgE-mediated**
 - May affect varying regions of gut
- **Celiac Disease (Gluten-sensitive enteropathy)**
 - Anti-gliadin IgG, anti-endomysial IgG, IgA
 - Villus atrophy, malabsorption, pain, associated CA

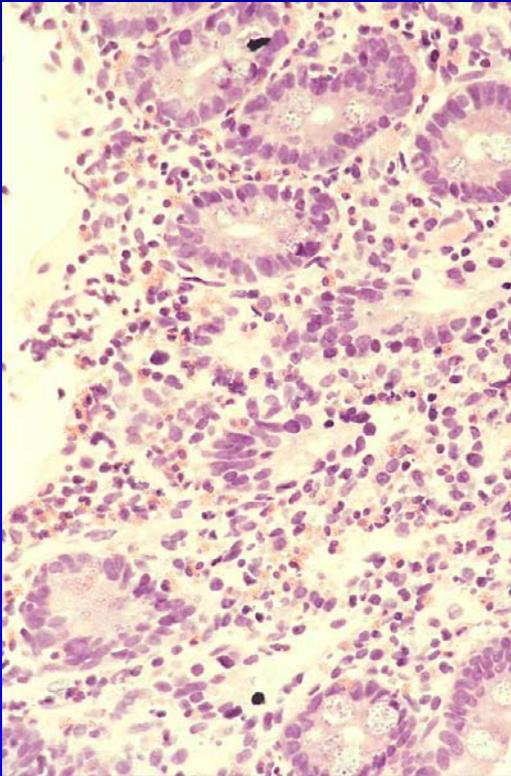
Mixed IgE/Non-IgE mediated: Allergic Eosinophilic Esophagitis (AEE)



- Dysphagia
- Abdominal pain
- Poor response to anti - reflux drugs
- Biopsy:Eosinophils ++++
- Respond to L-AAF
- Respond to steroids
- ? Anti-IL5 therapy
- ?anti-reflux pro-kinetic effect

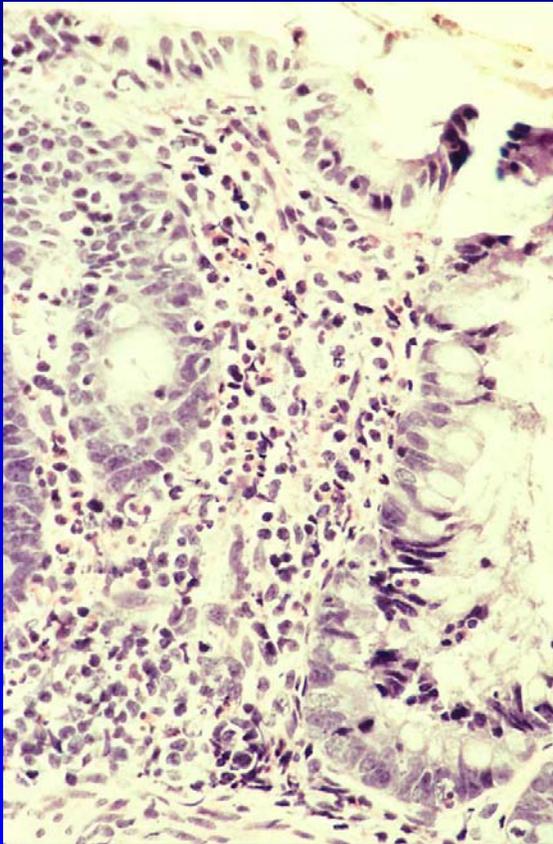
More than 20 eosinophils per HPF
Similar appearance in upper and lower oesophagus

Mixed IgE/Non-IgE mediated: Allergic Eosinophilic Gastroenteritis (AEG)



- Weight loss, FTT+/_oedema
- Vomiting, diarrhoea (post-prandial)
- Blood loss
- Iron deficiency
- Protein/iron- losing enteropathy
- ↑ TH2 in blood and mucosa
- ↑ Mast cells, Eosinophils in mucosa
- Persistent food hypersensitivity at 5yr FU.

Non-IgE mediated: Food protein-induced proctocolitis



- Mild diarrhoea and bright rectal bleeding in first weeks of life ;infant otherwise well
- Challenge onset:<72hours
- May occur in breast- and bottle-fed infants
- Increase of intraepithelial T-lymphocytes in rectal mucosa;CD8+
- 65% respond to **cow's milk exclusion**, the remainder may require more extensive dietary elimination diets
- Usually tolerant by 12 months – prognosis excellent
- **Milk**, egg, corn and soy frequent in breast fed infants

Non-IgE mediated: Pediatric Gastrointestinal Syndromes

	<u>Enterocolitis</u>	<u>Enteropathy</u>	<u>Proctitis</u>
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

- Typically **milk** and soy induced
- Spectrum may include colic, constipation and occult GI blood loss

Non-IgE-mediated Syndromes Affecting the Skin and Lung

- **Dermatitis Herpetiformis**
 - Vesicular, pruritic eruption
 - Gluten-sensitive
 - Associated with Celiac Disease
- **Heiner's Syndrome**
 - Infantile pulmonary hemosiderosis
 - Anemia, failure to thrive
 - **Cow's milk-associated**
 - Precipitating antibodies to cow's milk

Disorders Not Proven to be Related to Food Allergy

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

Food Allergy Prevalence in Specific Disorders

Disorder	Food Allergy Prevalence
Anaphylaxis	35-55%
Oral allergy syndrome	25-75% in pollen allergic
Atopic dermatitis	37% in children (rare in adults)
Urticaria	20% in acute (rare in chronic)
Asthma	5-6% in asthmatic or food allergic children
Chronic rhinitis	Rare

Diagnosis: History/Examination

- **History: symptoms, timing, reproducibility**
 - Acute reactions vs chronic disease
- **Diet details/symptom diary**
 - Specific causal food(s)
 - **“Hidden” ingredient(s)**
- **Physical examination: evaluate disease severity**
- **Identify general approach**
 - Allergy vs intolerance
 - **IgE versus non-IgE mediated**

When to Suspect a Food Allergy

- **Set of symptoms with ingested food**
 - GI (mouth itching, vomiting, diarrhea, pain)
 - Skin (rash, eczema, hives, swelling)
 - Respiratory (nasal sx, cough, wheeze, SOB)
 - Generalized (low BP, shock)
- **Symptoms typical within min to hrs**
- **Symptoms recur with repeat ingestion**

Diagnosis: Laboratory Evaluation

- **Suspect IgE-mediated**
 - Prick skin tests (fresh extract if OAS)
 - RAST
- **Suspect non-IgE-mediated**
 - Consider endoscopy, biopsy of gut, skin
- **Suspect non-allergic, consider:**
 - Breath hydrogen
 - Sweat test

Skin Prick Testing (SPT)

- Wheal size (3mm)
Bock et al. JACI
1978;62:327-334
- Predictive accuracy :
Neg > Pos
Negative < 3mm
Positive \geq 3mm
- Inhalant allergens



Prick – Prick Test



Skin Prick Testing

100% Postive Predictive values (PPV)

Food	100%PPV ≥ 3 yrs (wheal diameter)	100% PPV ≤ 2 yrs (wheal diameter)
Cow's milk	≥ 8 mm	6mm
Egg	≥ 7 mm	5mm
Peanut	≥ 8 mm	4mm

Reference: Sporik et al. Clin Exp Allergy 2000;30:1540-6

PHARMACIA CAP[®]-FEIA

- Quantitation of specific IgE
(0.35-100.000KU/L)
- Inhalant vs Food Allergens
- Higher concentration of specific IgE predictive of clinical reactivity?

Performance of CAP-System FEIA 90% Specificity Decision Points

Allergen	Decision Pt kU _A /L)*	PPV	Sens.	Spec.
Egg	7	98%	61%	98%
≤ 2 yr old	≥2.0**			
Milk	15	95%	57%	94%
≤ 2 ys old	≥5.0 ***			
Peanut	14	100%	57%	100%
Soy	65	73%	44%	94%
Wheat	80	74%	61%	92%

* **Reactive if ≥ this value (no challenge needed)** Sampson *JACI* 2001; 107:891

** Boyanao- Martinez et al 2001

*** Garcia-Ara et al 2001

Interpretation of Laboratory Tests

- **Positive prick test or RAST**
 - Indicates presence of IgE antibody NOT clinical reactivity (~50% false positive)
- **Negative prick test or RAST**
 - Essentially excludes IgE antibody (>95%)
- **ID skin test with food**
 - Risk of systemic reaction & not predictive
- **Unproven/experimental tests (useless)**
 - Provocation/neutralization, cytotoxic tests, applied kinesiology, hair analysis, IgG₄

Diagnosis: Elimination Diets and Food Challenges

- **Elimination diets (1 to 6 weeks)**
 - Eliminate suspected food(s), or
 - Prescribe limited “eat only” diet, or
 - Elemental diet
- **Oral challenge testing (Physician supervised, ER meds available)**
 - Open
 - Single-blind
 - Double-blind, placebo-controlled (DBPCFC)

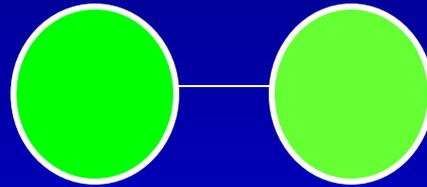
Basic Elimination Diet: (ALLOWED Foods)

- **Rice**
- **Fruit: Pear, Apple, Grape**
- **Meat: Lamb, Chicken**
- **Vegetables: Asparagus, Beetroot, Carrots, Lettuce, Sweet potatoes, Butternut, Squash**
- **Other: Black Tea, Rooibos**
- **Olive oil, Sunflower oil, Sugar, Salts**

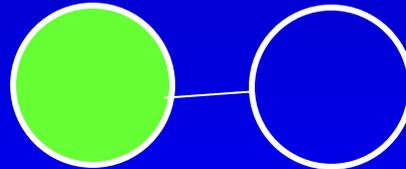
NB: No Preservatives, No tinned or packet foods

Types of challenge testing

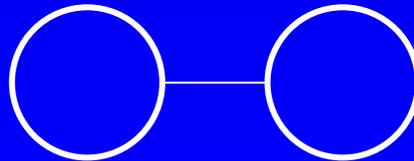
- **Double -blind**



- **Single Blind**



- **Open**



Diagnosis of Non-IgE Mediated Food Allergy

- Reaction: slower onset
- Difficult to distinguish from food intolerance
- Elimination - challenge testing (DBPCFC)
- Ancillary Tests (endoscopy, biopsy)
- In-vitro tests : little progress (APT, CAST?)

CELLULAR ALLERGEN STIMULATION TEST (CAST®-ELISA)

- Commercially available
- Basophil-based assay
sulphidoleukotrine (SLT) release
- Non-IgE-mediated reactions, food
intolerance, IgE mediated reactions

Crockard et al. Clin Exp Allergy 2001;31:345-350

Available CAST Allergens

Inhalants

grasses, weeds, trees, moulds, mites, animals

Insects

honey bee, wasps, cockroach, flea

Foods

Wide range of foods

Food additives

Tartrazine, Sodium Benzoate, Sodium Nitrate,
Potassium, Metabisulphite Food colourants

Antibiotics

Penicillin

Analgesics

Aspirin

Anaesthetics/Muscle relaxants

Vecuronium, Atracurium

Occupational

Formaldehyde, Latex, alpha amylase

Food intolerance reactions to additives and preservatives

- **Sodium Benzoate**
- **Sodium Metabisulphite**
- **Nitrates**
- **Monosodium glutamate**
- **Yellow dyes**
- **Red dyes**

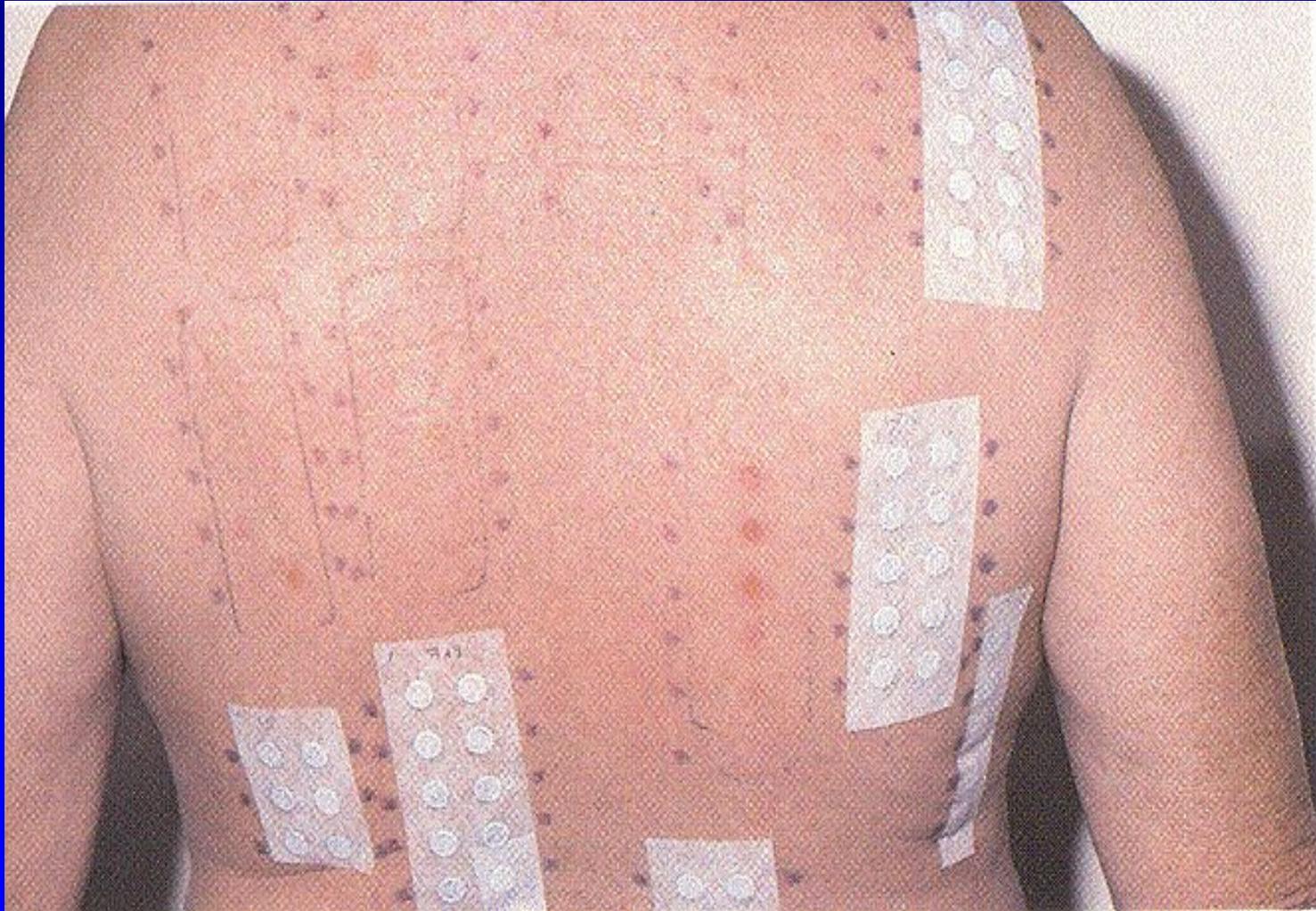
New technical cut off values

	Pg/ml
Sodium Benzoate	90
Sodium Metabisulphite	40
Food Colourant	160
Latex	200

Requesting a CAST test

- Fresh sample, 2 x 4ml specimens of EDTA blood
- Test to be done within 3 hours
- Conduct test 3 weeks after adverse reaction
- No oral or injected steroids within 2 weeks

Atopy Patch Test (APT)



Predictive values of SPT & APT vs DBPCFC in patients with atopic dermatitis

Technique	PPA	NPA
SPT(early reaction)	69%	95%
SPT (late-phase reaction)	41%	81%
APT	81%	93%

NPA = Negative predictive accuracy

PPA = Positive predictive accuracy

Niggemann et al. Allergy 2000;55:281-285

Treatment of food allergy

- Dietary elimination
- Pharmacotherapy
- Immunotherapy (future)

Treatment: Dietary Elimination

- Hidden ingredients (peanut in sauces or egg rolls)
- Labeling issues (“spices”, changes, errors)
- Cross contamination (shared equipment)
- **“Code words” (“Natural flavor” may be CM)**
- Seeking assistance
 - **Registered dietitian: (www.eatright.org)**
 - **Food Allergy Network (www.foodallergy.org;
800-929-4040)**

Example: Milk Elimination

Artificial butter flavor, butter, butter fat, buttermilk, **casein, caseinates** (sodium, calcium, etc.), cheese, cream, cottage cheese, curds, custard, Half&Half®, **hydrolysates** (casein, milk, **whey**), **lactalbumin**, lactose, milk derivatives (protein, solids, malted, condensed, evaporated, dry, whole, low-fat, non-fat, skim), nougat, pudding, rennet casein, sour cream, sour cream solids, sour milk solids, whey (delactosed, demineralized, protein concentrate), yogurt. **MAY contain milk:** brown sugar flavoring, natural flavoring, chocolate, caramel flavoring, high protein flour, margarine, Simplese®.

Substitute Infant Formulas

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

*CMA=cow's milk allergy

Treatment:

Emergency Medications

- **Adrenaline: first line treatment**
 - Self-administered adrenaline readily available
 - Train patients: indications/technique
- **Antihistamines: secondary therapy**
- **Written emergency plan**
 - Schools, spouses, caregivers, mature sibs/friends
- **Medic – Alert bracelet**

Treatment: Follow-Up

- Re-evaluate for tolerance periodically
- Interval and decision to re-challenge:
 - Type of food allergy
 - Severity of previous symptoms
 - Allergen
- Ancillary testing
 - Skin prick test/RAST may remain positive
 - Reduced concentration specific-IgE (RAST) encouraging

Natural History

- **Dependent on food & immunopathogenesis**
- **~ 85% CM, egg, wheat, soy allergy remit by 3 yrs**
 - Declining/low levels of specific-IgE predictive
 - IgE binding to conformational epitopes predictive
- **Allergy to peanut, nuts, seafood typically persist**
- **Non-IgE-associated GI allergy**
 - Infant forms resolve 1-3 years
 - Toddler/adult forms more persistent

Reasons for Allergy Referral

- **Identification of causative food**
- **Institution of elimination diet**
- **Education on food avoidance**
- **Development of action plan**
- **Prevention of other allergies**

Summary

- **History and examination paramount**
- **IgE & non-IgE mediated conditions exist**
- **Diagnosis by elimination and challenge**
- **Avoidance/education/preparation for emergencies are current therapies**
- **Periodic re-challenge to monitor tolerance as indicated by history, allergen, and level of food specific-IgE**