IgE-mediated Food Allergy - an overview

Dr Claudia Gray

Friday morning allergy meeting, April 2012
Background

1. Food allergies are common:
   - Infants: 6-8%; children 2-3%, adults 1% true food allergy
   - Higher prevalence in children: many food allergic children develop immune tolerance
Background ctd

2. Food allergies are increasing:
   • Peanut allergy in UK doubled in 1-2 decades: 1.8%
Background

3. Spectrum changing:

- Multiple food allergies increasing
- “Rare” food allergies are increasing
e.g. Eosinophilic oesophagitis; FPIES
Background

4. Genetics-environmental interplay

- Genetic predisposition and environmental factors may abrogate oral tolerance, leading to FA
- Disease outcomes are determined by triggering allergen, and characteristics of the immune response
Allergenic Foods

- Prevalence of food allergies influenced by geography and diet; egg and milk allergy universally common
- Major food allergens are water-soluble glycoproteins (plant or animal sources); generally stable to heat, acid, proteases:
- “Class 1 allergens”
Allergenic Foods

- Relatively small number of food types cause the majority of reactions:

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Allergenic Foods

Young Children
- Cow’s milk
- Hen’s Egg
- Wheat
- Soya
- Peanut
- Treenut
- Sesame
- Kiwi
- (* persistence likely)

Adults
- Fin-fish
- Shellfish
- Treenut
- Peanut
- Fruit and vegetables
Allergenic Foods

- A single food allergen can induce a range of allergic reactions e.g. wheat
Classification of adverse reactions to food

Adverse Reaction to food

May occur in all individuals if they eat sufficient quantity

- Toxic (e.g. scromboid)
- Pharmacological e.g. tyramine
- Microbiological e.g. food poisoning

Occurs only in some susceptible individuals

- Food aversion
- Food hypersensitivity
Classification of adverse reactions to food

Food Hypersensitivity

Non-allergic food hypersensitivity
- Unknown mechanism
- Metabolic e.g. lactose intolerance

Food Allergy
- IgE-mediated
- Mixed IgE- and non IgE-mediated
- Non IgE-mediated
Definitions

• *Food hypersensitivity* has also been described as any reproducible, abnormal, non-psychologically mediated reaction to food.

• *Food allergy* is an immune-mediated food hypersensitivity reaction
Mechanisms of food allergies

FOOD ALLERGY

IgE mediated
- General
- Anaphylaxis
- Cross reactivity syndromes

Mixed IgE and non-IgE mediated
- Eosinophilic oesophagitis
- Eosinophilic gastroenteritis
- Dietary protein enteropathy
- Asthma
- Atopic eczema

Non-IgE mediated
- Allergic proctocolitis
- FPIES
- Coeliac disease
- Contact dermatitis
- Heiner’s syndrome
- GI motility disorders
Mechanisms of food allergies

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IgE mediated allergic reactions

- Majority of food-induced reactions.
- Initial sensitisation to food allergen via oral route OR skin/inhaled route
- Subsequent exposure to food→cross links IgE molecules bound to mast cells
- Release of histamine and mediators from mast cells and basophils produce immediate symptoms
Food allergy

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Diagram:
- IgE Antibody
- Allergen
- Mast Cell Basophil
- Histamine containing granules
- Degranulation
- Inflammatory mediators
- Symptoms such as rashes, wheezing, vomiting.
IgE mediated allergic reactions

- By definition, IgE mediated reactions occur within minutes to 2 hours after exposure.
- Some evidence for role of IgE-mediated reaction in intermediate and late symptoms e.g. in atopic dermatitis.
- Can involve several organ systems - most common skin and GIT.
- Most severe form = anaphylaxis.
IgE-mediated allergic reactions

- Large variability in dose/route of exposure required to induce reaction
- Symptoms of FA should occur consistently following ingestion of the causative food allergen, but →
  - small, sub-threshold quantities of a food allergen/extensively baked, heat-denatured foods may be tolerated
  - modifying factors e.g. exercise, alcohol, NSAIDs, viral illness
Overview of IgE mediated Food Allergies

1. Manifestations
2. Diagnosis
3. Management
4. Novel Strategies
1. Manifestations of food allergies

**FOOD ALLERGY**

- **IgE mediated**
  - General
  - Anaphylaxis
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- **Mixed IgE and non-IgE mediated**
  - Eosinophilic oesophagitis
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- **Non-IgE mediated**
  - Allergic proctocolitis
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  - GI motility disorders
IgE mediated: Skin manifestations

AFTER FOOD INGESTION:

- Urticaria and/or angioedema
- Pruritis, erythema and flushing
- Morbilliform rash
- Immediate worsening of eczema
IgE mediated: Skin manifestations

AFTER CONTACT WITH FOOD

- Morbilliform rashes and erythema after skin contact to fruit and vegetables (tomato, citrus and berries)

- Acute localised urticaria after contact with food (e.g. seafood, eggs)
IgE-mediated: Gastrointestinal

UPPER GIT

- Angioedema of the lips, tongue, or palate
- Oral pruritis
- Tongue swelling
- Oral allergy syndrome
IgE-mediated: Gastrointestinal

LOWER GIT

- Nausea
- Colicky abdominal pain
- Reflux
- Vomiting
- Diarrhoea
IgE-mediated: Respiratory

UPPER RESPIRATORY TRACT

- Nasal congestion
- Pruritus
- Rhinorrhea
- Sneezing
- Laryngeal oedema → stridor*
- Hoarseness
- Dry staccato cough
IgE-mediated: Respiratory

LOWER RESPIRATORY TRACT*

- Cough
- Chest tightness
- Dyspnoea
- Wheezing**
- Intercostal retractions
- Accessory muscle use

*can be sign of anaphylaxis
**wheeze is seldom in isolation; usually with skin signs
IgE-mediated: Ocular

- Pruritus
- Conjunctival erythema
- Tearing
- Periorbital edema
IgE-mediated: Neurological

- Change in activity level
- Anxiety
- Feeling of impending doom
- Dizziness, LOC
IgE-mediated: Cardiovascular

- Tachycardia (occasionally bradycardia in anaphylaxis)
- Hypotension
- Dizziness
- Fainting
- Loss of consciousness
IgE-mediated: Other

- Metallic taste in mouth
- Uterine cramping
- Urinary urgency
Manifestations of food allergies

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IgE-mediated: Anaphylaxis

- Acute life-threatening allergic reaction, typically IgE-mediated
- Any food; most common peanut, tree nut, shellfish
- Multiorgan involvement
IgE-mediated: Anaphylaxis

- Acute onset of illness (80-90% skin signs) + at least one of:
  - respiratory compromise (70%)
  - cardiovascular compromise (↓BP/ hypotonia, syncope, incontinence) (35%)
  - persistent abdominal symptoms (40%)

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IgE-mediated: Anaphylaxis

- Usually immediate (within 2 hours) and *uniphasic*
- 20% *biphasic* (second reaction 8-72 hours after initial reaction subsided)
- Rarely *protracted* over hours to days
IgE-mediated: Anaphylaxis

Risk factors for severe anaphylaxis:

- Previous severe reaction
- Adolescents
- Asthma, especially poorly controlled
- Delayed/no adrenaline
IgE-mediated: Anaphylaxis

Factors modifying severity of reaction:

- Amount of allergen ingested
- Raw vs heated
- Amount and type of other food ingested
- Presence of acute viral illness
- Stress
- Chronic disease: Chronic cardiovascular/respiratory disease/Adrenal insufficiency
- Drugs eg β-blockers
- Alcohol
- Exercise*
IgE-mediated: anaphylaxis

Food-dependent exercise-induced anaphylaxis

- Rare condition in which symptoms develop if food is eaten within 2 hours prior to exercising. (These foods are tolerated in the diet when exercise is not involved)

- Altered splanchnic flow/ pro-inflammatory mediators/ autonomic dysregulation/ and increased intestinal permeability during exercise

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Manifestations of food allergies

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IgE-mediated: Cross reactivity

- **Cross-reactivity** = reaction on exposure to a second antigen after sensitisation to the first, because of similar antibody binding epitopes

- E.g peanut → **treenut**

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IgE-mediated: Cross reactivity

- **Co-reactivity**: independent sensitisation to more than one allergen

- egg allergy

- peanut allergy
IgE-mediated: Cross reactivity

Oral allergy syndrome:
- Cross reaction of airborne allergens with plant proteins (profilins, PR-10 proteins: often Bet v 1 analogues)
- E.g. birch pollen-hazelnut/apple/pear/peach/carrot/cherry/nectarine
- Grass pollen-melon/tomato/orange
IgE-mediated: cross reactivity

Oral allergy syndrome:
- Onset usually in 2\textsuperscript{nd} decade after pollen sensitisation
- Allergens destroyed by acid and heat:
- Symptoms usually mild oropharyngeal

- Rarely systemic symptoms and even anaphylaxis (1.7%)
- Can be reduced by peeling/heat
IgE-mediated: Cross reactivity

Latex Fruit Syndrome

- Latex products
- Fruits (banana, papaya, avo, kiwi, chestnut)
- Shared enzyme chitinase

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2. Diagnosis of IgE mediated Food Allergy
1. Accurate History

- A food previously tolerated in the diet should be continued regardless of test results
Accurate History

- Suspected food allergens?
- Timing of reaction post exposure?
- Description of allergic symptoms
  - Remember food aversion
  - Differential e.g. anxiety/HAE/chronic urticaria
  - Local irritation e.g. tomato, berries
- Possible co and cross reactivity
- Route of exposure
- Factors influencing reactivity e.g. amount/processing/exercise/medication
2. Physical Examination

- Atopic appearance
- Concomitant conditions
- Nutritional status
3. Skin Prick Tests

- Standardised extracts and methodology
- Should be performed in experienced hands to increase reliability
Skin Prick Test

- Selective for allergens suspected from history
- Using fresh food may produce more reliable results eg fruit
- Well defined allergens eg egg, milk: useful to perform extracts + fresh product to help define phenotype
Skin Prick Test

• **Plus Points:**
  • Quick, cheap, point of care test with good demonstrability
  • High negative predictive value
  • Generally, larger wheal size → greater chance of true allergy
  • Useful to monitor patient over time to look for possible development of tolerance
Skin Prick Tests

- **Pitfalls:**
  - Difficult on severely eczematous skin
  - Patient needs to have antihistamine wash out
  - Positive indicates sensitisation and not always allergy
  - Size does not indicate severity of reaction
  - Small risk systemic reactions
  - Intra- and inter user variability
SPT: 95% positive predictive values

<table>
<thead>
<tr>
<th>&gt;95% PPV for foodstuff</th>
<th>Average wheal diameter (mm)</th>
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<tbody>
<tr>
<td>MILK</td>
<td></td>
</tr>
<tr>
<td>&gt; 2 years</td>
<td>8</td>
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<tr>
<td>&lt; 2 years</td>
<td>6</td>
</tr>
<tr>
<td>EGG</td>
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<td>&gt; 2 years</td>
<td>7</td>
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<tr>
<td>&lt; 2 years</td>
<td>5</td>
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<tr>
<td>PEANUT</td>
<td></td>
</tr>
<tr>
<td>&gt; 2 years</td>
<td>8</td>
</tr>
<tr>
<td>&lt; 2 years</td>
<td>4</td>
</tr>
</tbody>
</table>
4. Specific IgE tests

- Standardised immunofluorescence techniques used to quantify food-specific IgE levels
- Initially only to crude allergens - more recently to allergen components and even epitopes
- Native (n...) vs recombinant (r...) allergens
- Especially useful in severe reactions, patient on antihistamines, dermatographism/severe eczema
sIgE: 95% positive predictive values

<table>
<thead>
<tr>
<th>Foodstuff</th>
<th>&gt;95% specific IgE level (kU/L)</th>
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<tbody>
<tr>
<td>MILK</td>
<td>&gt; 2 years: 15</td>
</tr>
<tr>
<td></td>
<td>&lt; 2 years: 5</td>
</tr>
<tr>
<td>EGG</td>
<td>&gt; 2 years: 7</td>
</tr>
<tr>
<td></td>
<td>&lt; 2 years: 2</td>
</tr>
<tr>
<td>PEANUT</td>
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<tr>
<td></td>
<td>&lt; 2 years:</td>
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5. Component resolved diagnostics

- IgE responses to more specific components of the allergen
- Helps explain primary sensitisation vs cross reactivity
- Eg ara h1, arah2, arah3 for peanut vs arah8, arah9
- Also identifies people at risk of severe or persistent allergy
Component resolved diagnostics
Epitopes on Arah1
6. Microarrays

- Large number of molecular allergens on a single chip requiring minimal blood volume
- Eg ISAC (immuno solid phase allergen chip)
- Useful for allergic patients with complex symptomatology eg eczema, unstable asthma, chronic urticaria
- Semi quantitative
- Not as sensitive as CAP tests
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7. Oral Food Challenges

- **Indications:**
  - Diagnostic uncertainty e.g. discrepancy between history and investigations
  - Positive allergy tests but never consumed food before
  - To check for development of tolerance
  - Sometimes in idiopathic anaphylaxis to try establish cause

1. Make an accurate diagnosis
2. Characterise the “phenotype” of the food allergic child
3. Assess allergic co-morbidity
4. Assess ancillary factors which may alter reaction outcome:
5. Targeted dietary elimination
6. Education and training of caregivers and child
7. Pharmacotherapy
8. Regular Follow-up visits
9. Decision on timing and method of re-introduction of food

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2. Characterise the phenotype of the allergic child
2. Characterise the “phenotype” of the food allergic child

1. Severity of previous reactions:
   - anaphylaxis/trace amounts/inhaled vapour) and involvement of several target organs → persistence more likely
   - milder reactions (milk, egg) → increased likelihood of eventual resolution

2. Delayed versus immediate symptoms:
   - in CMPA: delayed reactions seem to outgrow quicker

3. Intercurrent asthma, eczema, AR, co-sensitisation to other foods → persistence

4. Tolerance of baked goods (egg and milk):
   - good prognosis (conformational epitopes)
2. Characterise the “phenotype” of the food allergic child

5. Peak food specific IgE levels:
   - > 50 kU/L for milk and egg → likely persistence
   - < 2kU/L → likely to outgrow early

6. Faster decline in sIgE → more likely to outgrow

- Clark AT et al. British Society for Allergy and Clinical Immunology Guidelines for the management of Egg Allergy. *Clin Exp Allergy* 2010; 40: 1116-29
- Fiocchi A et al. WAO Diagnosis and rationale for Action against Cow’s Milk Allergy Guidelines. *WAO Journal* April 2010
2. Characterise the “phenotype” of the food allergic child

7. Component resolved diagnostics:
   - Egg – *ovomucoid* (Gald1) → persistence
   - Milk- *casein* (Bosd8) → persistence
     (casein and ovomucoid: heat resistant sequential epitopes)
   - Peanut- *Arah2* → clinical severity/relevance
2. Characterise the “phenotype” of the food allergic child

8. Peptide microarray studies:
   - determines affinity of IgE binding to sequential epitopes on major food allergens
   - determine severity and persistence

3. Assess allergic co-morbidity

- Food allergy - 2-4 X more likely to develop other allergic conditions and asthma
- Atopic dermatitis - 30-40% have associated food allergy
- Egg allergy + eczema - asthma in up to 90%
- Food allergy and asthma - higher risk of anaphylaxis
- Food allergy + co-morbidity - food allergy perseverance
- Cross reactivity vs co-reactivity
3. Cross reactivity

- Peanut - most beans: 5%
- Peanut - tree nut: 60%
- Tree nut - other tree nut: 35%
- Fish - other fish: 50%
- Shellfish - other shellfish: 75%
- Grains - other grains: 50%
- Cow’s milk - beef: 10%
- Cow’s milk - goat/sheep milk: 90%
4. Assess ancillary factors which may affect reactions

- Intercurrent viral illness
- Sub-optimally controlled asthma
- Timing of dose after food
- Exercise
- Dosing during menses
- NSAIDs, alcohol
5. Targeted Dietary Elimination

- Cornerstone of food allergy management
- Requires knowledge of “hidden sources” of relevant allergens, and cross-reactivity
- Need to ensure a nutritionally complete diet
- ROLE OF DIETICIAN CRUCIAL
- Breastfed babies: mother asked to avoid the offending foods from her diet as proteins are detectable in the breastmilk.
5. Targeted Dietary Elimination

- **Labelling**

- Label reading, alternative names:
  - Milk: casein, whey, lactalbumin, lactose…
  - Egg: ovomucoid, lecithin, meringue…

- **Labelling**: EU directive: packaged foods must clearly identify major allergenic foods

- “May contain traces of..” – unquantifiable risk of manufacturing carry-over of allergens: AVOID in those with exquisite sensitivity to small amounts; previous anaphylaxis; severe asthma
How to Read a Label for a Milk-Free Diet

All FDA-regulated manufactured food products that contain milk as an ingredient are required by U.S. law to list the word “milk” on the product label.

Avoid foods that contain milk or any of these ingredients:
- butter, butter fat, butter oil, butter and butterfat
- buttermilk, cream
- casein, casein hydrolyzate, caseinate (in all forms)
- cheese, cottage cheese
- cream, cream cheese, curd
- diacetyl, ghee
- half and half, buttermilk, bromelain, lactalbumin, lactalbumin phosphate, lactofructose, lactose
- milk protein hydrolyzate, whey protein hydrolyzate
- milk, buttermilk, sour cream, sour cream solids, milk solids, milk solids-reefed, milk solids-reamed, whole milk
- milk protein, milk protein isolate
- milk solids, whey protein isolate

Milk is sometimes found in the following:
- flavored butters: flavor
- baked goods: margarine
- candy, candies: mints
- chocolate: morsels
- alcoholic beverages: rum, aperol
- vegetable and other flavors: curry
- seasoning products: MSG, msg

How to Read a Label for a Peanut-Free Diet

All FDA-regulated manufactured food products that contain peanut as an ingredient are required by U.S. law to list the word “peanut” on the product label.

Avoid foods that contain peanuts or any of these ingredients:
- artificial nuts: monosodium glutamate
- beer nuts: malt
- cooked, fried, spiced, or baked peanuts:
- ground nuts: peanut butter, peanut flour, peanut protein hydrolysate
- mixed nuts

Peanut is sometimes found in the following:
- nuts: hazelnuts, pecans, pine nuts, Brazilian nuts, cashews
- baked goods: cookies, pretzels
- candy (including chocolate candy): nuts

Keep the following in mind:
- Mollusks are peanuts cooked in alcohol.
- The FDA exempts highly refined peanut oil from being labeled as an allergen.
- A study showed that unlike other legumes, there is a strong possibility of cross-reaction between peanuts and lupins.
- Sesame oil is peanut oil.
- Many experts advise patients allergic to peanuts to avoid tree nuts as well.
- Sunflower seeds are often produced on equipment shared with peanuts.
## Which milk for CMPA?

<table>
<thead>
<tr>
<th>TYPE OF MILK</th>
<th>INDICATIONS/COMMENTS</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breastmilk</td>
<td>- May be continued, eliminating maternal CMP intake</td>
<td></td>
</tr>
</tbody>
</table>
| Partially hydrolysed       | - No role in CMPA  
- Do not meet criteria for hypoallergenicity  
- May have a role in reduction of atopic eczema/food allergy in babies at high risk of atopy who are unable to breastfeed                                                                                   | Nan-HA            |
| formula                     |                                                                                                                                                                                                                    |                   |
| Extensively hydrolysed     | - By definition need to be tolerated by 90% of CMPA children  
- Contain peptides with molecular weight 3000 Daltons  
- First line for mild to moderate CMA                                                                                                               | Similac Alimentum  
Nan Alfare  
Nutricia Pepticate |
| formulae                   |                                                                                                                                                                                                                    |                   |
| Amino acid formulae        | - Severe CMA/anaphylaxis  
- Severe eczema  
- Eosinophilic oesophagitis  
- If symptoms do not improve after 2-4 weeks EHF                                                                                                        | Neocate           |

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<td>Soya milk</td>
<td>• not hypoallergenic-risk of soya sensitization</td>
<td>Infasoy</td>
</tr>
<tr>
<td></td>
<td>• cross reactivity milk-soya up to 50% of patients with non IgE- mediated CMA</td>
<td>Isomil</td>
</tr>
<tr>
<td></td>
<td>• concern re phytooestrogens</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• no place &lt; 6 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• palatable and affordable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• place in &gt; 6 months with immediate cow’s milk allergy and no soy sensitisation</td>
<td></td>
</tr>
<tr>
<td>Goat’s /Ewe’s milk</td>
<td>- Substantial structural homology with cow’ milk- not recommended</td>
<td></td>
</tr>
</tbody>
</table>
6. Education & Training of Caregivers & Child

- Food allergies lead to a significant decrease in quality of life and uncertainty.
- Regular dialogue with caregivers and tell them of prognosis and plans.
- Nursery and school staff should receive training on allergy avoidance as well as recognition and treatment of food-induced allergic reactions.
6. Education & Training of Caregivers & Child

- Personalised allergy action plan, clearly outlining steps to be taken in case of accidental ingestion and emergency contact details
- Action plan + emergency drugs must be accessible at all times.
I am allergic to:

My medic alert number is:

**MINOR REACTION**

Face and Skin – itching, redness, hives (“bomets”), swelling of face, eyes, hands and feet

Stomach – stomach pain, vomiting, diarrhoea

**MAJOR REACTION**

Airway – difficulty breathing, coughing, wheezy, choking, noisy breathing, voice change

Total body – change of colour, floppy, sense of impending doom, loss of consciousness, sleepy

**MINOR REACTION**

(Face / Stomach / Skin)

GIVE: ____________________________

DOSE: __________________________

If asthmatic give Asthavent 4-6 puffs via spacer

Consult your doctor as soon as possible

**MAJOR REACTION**

(Airway / Total Body)

 BREATHING DIFFICULTY OR CHANGE OF CONSCIOUSNESS

GIVE: ADRENALINE / EPIPEN

DOSE: ________________

IMMEDIATELY

If asthmatic give Asthavent 4-6 puffs via spacer

CALL 10111

say “ANAPHYLAXIS”

Get to closest doctor/clinic/hospital immediately

If no improvement in 5-10 minutes give a second dose of adrenaline

---

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6. Education & Training of Caregivers & Child

- Medic alert bracelet

**MedicAlert®**

HOW TO BECOME A MEMBER
Please complete this form and **mail with your payment** details to: MedicAlert, P O Box 4841, Cape Town, 8000. or [info@medicalert.co.za](mailto:info@medicalert.co.za) - Print or type clearly.
For more information call Medic Alert on (021) 425-7328 or fax (021) 425-6654
7. Pharmacotherapy

- "Preventative" medicines e.g chromoglycates/ketotifen/anti-histamines/pre and probiotics: unproven effect
- Acute treatment of mild reactions: antihistamine
- Severe reactions: IM adrenaline
- Concomitant asthma: salbutamol inhaler and oral corticosteroid
7. Pharmacotherapy
7. Pharmacotherapy

**Indications for Adrenaline Auto-Injector**

- Life threatening (cardiovascular or respiratory) reaction with foods
- Generalised (skin, cardiovascular or respiratory) reaction with insect venom (and consider immunotherapy)
- Food allergy and asthma
- Generalised (but not life threatening) reaction to small amount of food
- Generalised (but not life threatening) reaction to peanuts / tree nuts / seafood (>5 yrs)
8. Regular Follow-Up

- 6-12 monthly (more frequent in < 1 years)
- Assess growth and nutritional intake
- Reiterate diet
- Repeat SPT +/- sIgE
- Enquire about “accidental” ingestion
9. Decision on timing and method of re-introduction of food

Decisions on re-introduction are based on:

- History of dietary indiscretions - ? reaction
- Serial IgE and SPT levels
- Knowledge of natural history of allergy for various syndromes/allergens
9. Decision on timing and method of re-introduction of food

- Seems reasonable to attempt re-introduction if there has been no significant recent clinical reaction accompanied by a reduction in SPT size/sIgE over time.
- Reintroduction: Initial supervised oral food challenge for IgE-mediated and non-IgE-mediated allergies.
9. Decision on timing and method of reintroduction of food

Natural History:

- Peanut/treenut/fish and shellfish: only 20% chance of outgrowing;
- Milk, egg, wheat, soya: natural history = spontaneous resolution over time
Milk natural history:

- Initial studies indicated that 50% outgrow milk allergy by 2 years, 80-90% by 4 years
- Subsequent studies a bit more cautious: 50% outgrow by 54 months, 80% by 16 years
- Finnish study: % outgrown

<table>
<thead>
<tr>
<th></th>
<th>2 yrs</th>
<th>3 yrs</th>
<th>4 yrs</th>
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<tbody>
<tr>
<td>Delayed reactions</td>
<td>64</td>
<td>92</td>
<td>96</td>
</tr>
<tr>
<td>Immediate reactions</td>
<td>31</td>
<td>53</td>
<td>63</td>
</tr>
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9. Decision on timing and method of re-introduction of food

- Saarinen et al. Clinical course and prognosis of cow’s milk allergy are dependent on milk-specific IgE status. *JACI* 2005; 116: 869-75
- Skripak JM et al. The natural history of IgE mediated cow’s milk allergy. *JACI* 2007;120: 1172-7
9. Decision on timing and method of reintroduction of food

EGG: natural history

- Resolution of well cooked egg twice as quick as resolution to uncooked egg.
- Median time to tolerance of raw egg: 35 months
- 66% resolved by 5 years

- Clark A et al. A longitudinal study of resolution of allergy to well cooked and uncooked egg. *Clin Exp Allergy* 2011; 41: 706-712
New Concepts in the Treatment of Food Allergies
New Concepts in the Treatment of Food Allergies

- Current management of FA limited to dietary restriction and emergency treatment of adverse reactions
- Several new strategies looking at treatment/“cure” of food allergies
- Most needed by those at high risk for severe anaphylaxis, and those unlikely to outgrow food allergy spontaneously
### New Concepts in the Treatment of Food Allergies

<table>
<thead>
<tr>
<th>NON-SPECIFIC</th>
<th>FOOD SPECIFIC</th>
</tr>
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<tbody>
<tr>
<td>Humanized monoclonal IgE</td>
<td>Baked egg and Milk diet</td>
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<tr>
<td>Traditional Chinese medicine</td>
<td>Oral immunotherapy</td>
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<td>Anti-IL-5</td>
<td>SLIT</td>
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<td>SCIT</td>
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<td>Immunotherapy with modified recombinant engineered food proteins</td>
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</table>
Oral Immunotherapy (SOTI)

- Protocols to administer increasing doses of causative food orally over time → altering immune response to allergen

- Ultimate aim = permanent oral tolerance → looking for immunological deviation away from TH2 response, ↓ food specific IgE, ↑ IgG4
Oral Immunotherapy (SOTI)

- **Desensitisation:**
  - temporary clinical state in which allergen exposure fails to cause allergic symptoms
  - protects against life-threatening anaphylaxis to trace doses

- **Tolerance:**
  - clinical non-reactivity to allergen exposure even after long periods of abstinence
  - more permanent state
Oral Immunotherapy (SOTI)

General approach to OIT:
- Initial rush escalation
- Slow graded increase towards maintenance dose
- Maintenance phase
- Abstinence followed by rechallenge

desensitisation
tolerance

Food allergy Gray April 2012
<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Success rate</th>
<th>Comments</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Staden et al 2008</td>
<td>Milk=14, Egg=11, Control=20</td>
<td>36% tolerance, 12% desensitised, 16% partial responders</td>
<td></td>
<td>Staden U et al. <em>Allergy</em> 2007; 62:1261.</td>
</tr>
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<tr>
<td></td>
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<td></td>
<td>2x IM adrenaline</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>10% withdrew</td>
<td></td>
</tr>
<tr>
<td>Varshney et al 2011</td>
<td>Peanut=19 Placebo=9</td>
<td>All 16 peanut patients who completed the maintenance phase were able to tolerate 5g peanut</td>
<td>3 withdrew in peanut group</td>
<td>Varshney Pet al. J Allergy Clin Immunol 2009; 124:1351.</td>
</tr>
</tbody>
</table>
Summary: Oral Immunotherapy

- Initial rush escalation
  \[(10-20\% \text{ fail})\]

- Slow graded increase towards maintenance dose
  \[(10-20\% \text{ do not reach full maintenance})\]

- Maintenance phase
  \[(50-75\% \text{ achieve and maintain maintenance dose})\]

- Abstinence followed by rechallenge
  \[(about \ 35\% \text{ tolerant, needs further studies})\]
“OIT is not ready to be translated into everyday clinical practice and should be used in controlled research setting only”
SLIT

- Several small studies with hazelnut, peanut, milk
- Preliminary results success in 50%
Epicutaneous IT

- Delivery of milk allergen in epicutaneous patch 3x/week in 18 children- ↑ threshold of tolerance

Abandoned - some fatalities with peanut
Immunotherapy with modified recombinant engineered food proteins

- Aim: to decrease immediate reactions of immunotherapy
- Modified food allergens combined with bacterial adjuvants to enhance TH1 skewing
- Peptide immunotherapy-sequence of peptides which is too short to be able to cross link IgE molecules
Baked Egg and Milk Diet

- Up to 80% of children with egg and milk allergy tolerate extensively heated milk and egg products
- Preliminary study: baked milk and egg products added to diet of tolerant children:
  - No ↑ allergic reactions
  - No ↑ severity of atopic disease
  - No negative effect on growth
  - Trend towards accelerated tolerance induction
  - ↑IgG4 and ↓ food specific IgE →
Baked Egg and Milk Diet

“Natural oral immunotherapy”

Humanised anti-IgE (omalizumab)

- Leung et al 2003: 84 adults with peanut allergy treated with regular anti-IgE →
  ↑ reaction threshold in 75% of patients
- Nadeau et al 2011: Rapid milk OIT combined with anti-IgE: 9/11 children reached threshold maintenance dose of daily milk consumption


Traditional Chinese Medicine

- Food allergy herbal formula 1 (FAHF1) has shown promising effects in mouse peanut anaphylaxis and is now moving into human trials.
Summary: IgE mediated Food Allergy

- Food allergies are increasing and affect quality of life of families significantly
- The mainstay of food allergy management is correct diagnosis, targeted supervised dietary elimination and planned treatment of allergic reactions
- Knowledge of the “phenotype” of the allergic child and natural history of food allergies is vital in management planning.
- Patients need to be reviewed periodically to prevent unnecessary prolongation of dietary avoidance
- Food challenges are vital in the initiation of reintroduction
- Novel strategies in food allergy treatment are on the horizon yet still experimental
THANK YOU
Recommended Reading


- Leonard S. Food Allergy: What you need to know. *Medscape Allergy and Clinical Immunology* 15/11/2010

- Jackson, William F. Food Allergy. *International Life Sciences Institute Europe*, Belgium 2003