BEATING FOOD ALLERGY

Dr. John TAN
MBBS, FRACP, BSc, DCH
Paediatric Allergist and Immunologist
North Shore Paediatrics-Allergy Centre
Staff Specialist, Children’s Hospital at Westmead
Woolcock Institute

Allergy - what is it?

- allergy
  /ˈælərɡi/ Show Spelled [ˈælərɡi] Show IPA
- noun, plural -gies. 1. an abnormal reaction of the body to a previously encountered allergen introduced by inhalation, ingestion, injection, or skin contact, often manifested by itchy eyes, runny nose, wheezing, skin rash, or diarrhea.
  2. hypersensitivity to the reintroduction of an allergen. Compare anaphylaxis.
  3. Informal : a strong dislike or aversion, as toward a person or activity: He has an allergy to hard work.

Use allergy in a Sentence
See images of allergy
Search allergy on the Web

Dictionary.com Unabridged

What is Food Allergy?

- WAO (World Allergy organization)
- Atopy
  - Genetic predisposition to become sensitized and produce IgE antibodies in response to ordinary exposure to allergens
  - This in turn may lead to the development of allergic disease such as asthma, rhinoconjunctivitis eczema and food allergy

Immunity

Tolerance
Allergy

WHAT IS ALLERGY?

- Allergy is dysfunctional adaptation based on an error of recognition
- That error leads to the host immune system activating an aggressive adaptive response, against a harmless foreign substance with deleterious consequences for the host

Allergy on the rise

- Food allergy affects 10% of children up to 1 yr of age, 4-8% of children aged up to 5 yrs.
- Approximately 2% of adults
- Hospital admission for severe allergic reactions have doubled in the last decade in USA, UK and Australia
- In Australia, admission for food anaphylaxis in children age 0-4yrs have increased 5X in the last decade

Why the rise in food allergy?

- Hygiene hypothesis
- Methods of food processing foods
- Development of allergy to food via skin exposure
- Western diet
- Vitamin D
- Genetics
- Delayed introduction of solids food

Background – egg allergy

- Amongst the commonest food allergy worldwide
- Australia has highest prevalence rate – 8.9%
- Wide spectrum of severity, including anaphylaxis
- Natural history
  - early studies indicate tolerance to be achieved in most children – 50% by age 3yrs and 66% by age 5yrs.
  - More recent studies indicate that egg allergy is becoming more persistent with predicted tolerance of 4% by 4 yrs., 12% by 6 yrs., 37% by 10yrs and 68% by 16 yrs.
- Mx is egg avoidance which can be difficult
Primary prevention - food allergy

- The maternal diet in pregnancy and lactation.
- The use of Pro and Prebiotics
- The diet of infants – Breast milk or formula
- The timing, types, and forms of complementary foods

Solid introduction - The Established ‘norm’

- 1900 - late introduction of solids/CF - 1 yr.
- 1960’s - early introduction of solids/CF <4 months
- 1970’s - delayed solids/CF >4 months
- 1990 - delayed solids/CF >6 months
  - Delayed specific allergenic foods up to 3 years

Prevention of food allergy

- Despite early allergen avoidance for past 2 decades - increase not decrease in food allergy
- Low rates of peanut allergy in Israel - the ‘Bamba’ story
- Can early introduction prevent food allergy?

Primary prevention - early introduction of complementary foods

- LEAP
- EAT
- BEAT
- STEP
- HEAP

LEAP in short

- LEAP study – 7x decrease in peanut allergy in early exposure <1yr compared with delayed >5yr
- Early introduction of peanut can serve as an effective primary and secondary strategy for the prevention of peanut allergy.
- Criteria: at least 4 months and less than 11 months with eczema or egg allergy or both
- Participants were stratified in to 2 cohorts according to SPT
  - SPT 0mm
  - SPT 1-4 mm
- Randomly assigned peanut consumption or avoidance
- Those assigned to peanut consumption had open labelled peanut challenge
- Those who did not react to challenge had at least 1 per week until 60 months of age
- Challenge to peanut at 60 months of age
LEAP-on

- Persistence of tolerance to peanut study
- Would study subjects who consumed peanut for 4 years have lasting tolerance if they stopped having peanut in their diet?
- Followed 556 of the 640 subjects for 1 yr. peanut avoidance (274 consumers, 282 avoiders)
- 4.8% of peanut consumers were allergic compared to 18.6% of peanut avoiders.

EAT

- Early introduction of 6 food vs. delayed introduction
- 1300 BF infants
- Rice, egg, cow's milk, peanut, sesame, fish
- 4g of protein per week
- Follow up at 3 yrs.
- Failed to show any significance at ITT analysis but PP analysis of individual foods showed significance

Beating Egg Allergy Trial

- Aim
  - To determine if the introduction of dietary egg between 4-6 months of age in infant at high risk of developing allergic disease reduces sensitisation to egg.
- Study design
  - Single site, parallel, two arm, double blind, placebo controlled randomized controlled trial (RCT)
  - Intervention: 350mg whole pasturised egg daily from successful first weaning food (4-6 months) until 8 months
- Primary outcome
  - The proportion of infants in each group at 12 months of age with sensitisation to egg white (as defined as skin prick test (SPT) ≥ 3mm)
- Secondary outcomes
  - Egg allergy at 12 months, eczema at 12 months, Immunological parameters including, IgG4, IgG4/IgE to whole egg, ovalbumin and Ovomucoid at 12 months

BEAT – In press JACI

A randomized trial of egg introduction from 4 months of age in infants at risk for egg allergy

John Wei-Liang Tan, Carolina Valerio, Elizabeth H. Barnes, Paul J. Turner, Peter A. Van Asperen, Alysion M. Kakakios, Dianne E. Campbell on behalf of the Beating Egg Allergy Trial (BEAT) Study Group
Publication stage: In Press Corrected Proof
Journal of Allergy and Clinical Immunology
Published online: October 11, 2016
**Inclusion criteria**
- First degree relative with a history of atopy. (asthma, eczema, hay fever or food allergy)

**Exclusion criteria**
- Evidence of IgE sensitisation to egg at 4 months
- Unable to meet study requirements

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**Primary outcome - sensitisation at 12 months**

*Figure 2*

![Graph showing odds ratio of 0.46 (95% CI: 0.22-0.95) (p=0.03)]

- Placebo: 20.5%
- Egg: 10.7%

**Secondary outcome - IgG4,IgG4/IgE**

*Figure 8*

<table>
<thead>
<tr>
<th>IgG4</th>
<th>IgG4/IgE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>20.5%</td>
</tr>
<tr>
<td>Egg</td>
<td>20.5%</td>
</tr>
</tbody>
</table>

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**Table 1: Baseline characteristics at randomisation**

<table>
<thead>
<tr>
<th>Male</th>
<th>Egg (n%)</th>
<th>Rice (n%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>166 (52%)</td>
<td>84 (51%)</td>
<td>82 (53%)</td>
</tr>
<tr>
<td>62%</td>
<td>37 (23%)</td>
<td>45 (29%)</td>
</tr>
<tr>
<td>Father born in Australia</td>
<td>98 (59%)</td>
<td>109 (71%)</td>
</tr>
<tr>
<td>65%</td>
<td>104 (63%)</td>
<td>104 (67%)</td>
</tr>
<tr>
<td>Mother born in Australia</td>
<td>53 (17%)</td>
<td>25 (15%)</td>
</tr>
<tr>
<td>111 (35%)</td>
<td>60 (33%)</td>
<td>60 (37%)</td>
</tr>
<tr>
<td>Delivery by caesarean section</td>
<td>150 (91%)</td>
<td>139 (90%)</td>
</tr>
<tr>
<td>42 (27%)</td>
<td>42 (27%)</td>
<td></td>
</tr>
<tr>
<td>First born</td>
<td>42 (27%)</td>
<td>42 (27%)</td>
</tr>
</tbody>
</table>

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**BEAT - Recruitment**

- Via maternity units, postpartum
- Families personally approached
- Approximately 4500 families approached
- 1434 families showed interest
- Follow up call made to book initial appointment
- Initial appointment at CHW 4/12 of age
- 332 infants screened
Secondary outcomes

- There was no difference in probable egg allergy between rice and egg groups at 12 months when analysed (13 compared with 8 infants).
- PP analysis, a significant difference was found between 2 groups (11 compared with 2; p=0.013).
- The rate of sensitization to peanut at 12 months was high at 8.6% (SPT≥ 3), but there was no difference between the two groups (p=0.49).
- There was no difference in the prevalence or severity of eczema between groups at 8 (p=0.52, p=0.77) or 12 months respectively.

Safety

- 15 reacted to initial introduction of powder
- 14 had egg powder and had mild to moderate reactions (Urticaria, vomiting, angioedema)
- No cardiovascular or respiratory involvement
- No adrenaline required
- 1 case of FPIES to rice powder

Conclusion

- Decrease in sensitisation at 12 months
- No significant decrease in egg allergy (larger numbers needed)
- Safe
- No increase in eczema in treatment group
- No effect on other foods at 12 months

Guidelines – Then and NOW

- 1900- late introduction of solids/CF - 1 yr.
- 1960's - early introduction of solids/CF < 4 months
- 1970's - delayed solids/CF > 4 months
- 1990 - delayed specific allergenic foods up to 3 years
- 2008 - introduction of solids from 4-6 months (ASCIA)
- 2012 - NHMRC - introduction of solids from around 6 months
- 2016 - Revised ASCIA feeding advice
- Specific recommendations for infants at high risk of peanut allergy
- 2016 - CFAR - consensus recommendations

ASCIA Infant Feeding Advice 2008-2016

<table>
<thead>
<tr>
<th>ASCIA 2008</th>
<th>ASCIA 2016</th>
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<tbody>
<tr>
<td>Maternal diet</td>
<td>Maternal diet</td>
</tr>
<tr>
<td>- Pregnancy</td>
<td>no dietary restrictions</td>
</tr>
<tr>
<td>- Breast feeding</td>
<td>no dietary restrictions</td>
</tr>
<tr>
<td>Healthy Maternal diet</td>
<td>recommended</td>
</tr>
<tr>
<td>Infant diet</td>
<td>Infant diet</td>
</tr>
<tr>
<td>Breast milk</td>
<td>yes</td>
</tr>
<tr>
<td>EHf or HA formula</td>
<td>yes</td>
</tr>
<tr>
<td>Soy</td>
<td>no</td>
</tr>
<tr>
<td>Complementary feeding</td>
<td>should not be delayed</td>
</tr>
<tr>
<td></td>
<td>developmentally ready</td>
</tr>
<tr>
<td></td>
<td>more research needed</td>
</tr>
<tr>
<td>Allergens</td>
<td>no advice</td>
</tr>
</tbody>
</table>
Unanswered questions-

- Benefit for introduction of allergenic foods between 4-6 months vs. 6-8 months
- Risk of reducing total breastfeeding duration by “early” introduction of solids
  - Not observed in EAT (duration of BF or weight gain)
  - Not observed in HealthNuts
- Benefit of pre-probiotics for infants
- Sequence of allergenic food introduction
- Benefit of exclusive vs. continuing breastfeeding between 4-6 months or beyond?

Acknowledgements

- Prof Dianne Campbell
- A/P Alyson Kakakios
- Prof Peter Van Asperen
- Carol Valerio
- Liz Barnes
- BEAT study group

CASE

- 11 year old asthmatic girl wheezy throughout day requiring ventolin
- Had had URTI symptoms few days prior
- At 1800hrs, developed respiratory distress, tachypnoea, chest pain, initially relieved by ventolin
- At 2100hrs, worsening respiratory distress and chest pain
- Driven to hospital by aunt, loss consciousness in car

ANAPHYLAXIS

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LOCAL ED

- Cyanosed and GCS 3
- SaO2 73% room air
- Decreased air entry bilaterally with widespread wheeze
- Bag and mask, high flow oxygen
- IV methylprednisolone
- IV salbutamol infusion and continuous nebs
- Transferred directly to PICU on IV salbutamol

CHW PICU

- By time of arrival had improved
- GCS 14
- 24 hours in PICU
- IV methylprednisolone q6h
- Weaned off salbutamol infusion
- Transferred to ward on 90minly salbutamol nebulisers

PAST HISTORY

- Asthma
  - Since 2 years of age
  - Normally infrequent episodic
  - Not on any preventer
  - Last ED presentation 12 months prior
- Mild eczema
- No history of any immediate IgE mediated food allergy

ON THE WARD @ CHW

- 2 days after transferred to ward:
  - Admitted to medical staff ½ hour prior to having acute respiratory deterioration had eaten Cornetto ice-cream with peanuts
  - Had had Cornetto ice-cream with peanuts before; but would remove peanuts. This would still often cause her tongue to be “sore”
  - Had gone to Thai restaurant in past – developed lip angioedema relieved by oral antihistamines
  - Never assessed by immunologist/Allergist

Definition – Anaphylaxis

Anaphylaxis is a rapidly evolving, generalised multi-system reaction characterized by one or more symptoms or signs of respiratory, cardiovascular and other systems such as the skin and/or gastrointestinal tract.

ASCIA

Anaphylaxis Definition: ASCIA

“Potentially life threatening, severe allergic reaction”
Mild to Moderate Allergic Reactions

- Hives / Welts
- Swelling of face, eyes, lips
- Abdominal cramps
- Feeling sick, vomiting
- Diarrhoea

Anaphylaxis

- Difficulty/ noisy breathing
- Swelling of tongue (drooling)
- Swelling/ tightness in throat (fingers down throat)
- Stridor
- Difficulty talking and/ or hoarse voice
- Wheeze or persistent cough (staccato)
- Loss of consciousness and/ or collapse
- Pale and floppy (young children)

IgE-mediated Anaphylaxis

- Type I hypersensitivity
- 2 distinct stages:
  1. Sensitization stage
  2. Subsequent exposure to allergen causing an anaphylactic response

Mast Cell

- Has high affinity for IgE molecules (105 IgE/cell)
- Originates in the bone marrow, reside in connective tissues
- Increases host response to parasitic infections
- Contain immunological mediators in granules
- 2 populations that vary in granule content and activity:
  - Connective tissue
  - Mucosal
Sensitisation

Re-exposure

Mediators
- Inflammatory ‘soup’:
  - Histamine
  - Leukotrienes
  - Tumour necrosis factor
  - Cytokines…
- "Mast cell leukocyte cytokine cascade"

Clinical Manifestations
- Skin:
  - Flushing
  - Pruritus
  - Urticaria
  - Angioedema
- Cardiovascular system:
  - Tachycardia (bradycardia)
  - Hypotension/shock (Pale/floppy child)
  - Dysrhythmias
  - Ischaemia, chest pain
**Key clinical features**

- Generalized allergic reaction with respiratory and/or cardiovascular involvement
  - Respiratory much more prevalent in children
- Involvement of many parts of the body
- Rapid onset and progression.

**Course and progression**

- May appear within seconds, or as late as 2 hours after ingestion of trigger food.
- In children, > 90% have cutaneous symptoms first
- All fatal food-induced anaphylactic reactions cause respiratory difficulties
- Up to one third have a biphasic reaction:
  - Initial symptoms -> apparent resolution -> recurrence of symptoms after 1-3 hours
  - Protracted symptoms occasionally occur – persisting for up to 3 weeks.

**Risk factors for death from food induced Anaphylaxis**

- Asthma (even well controlled)
- Previous allergic reaction to same food
- Biphasic course
- Not at home when reaction occurs
- Non-timely delivery of adrenaline

Sampson et al, NEJM (1992)

**Acute Management**

**H1-antihistamines**

Act against histamine release by blocking Histamine H1 receptors
### Acute Management

#### H1-antihistamines

- Act against histamine release by blocking Histamine H1 receptors
- Slow onset of action
- Don’t inhibit all actions of histamine (other receptors)
- Appear to be mostly active against skin symptoms (little effect on CVS / RS)
- Don’t inhibit other mediators released
- Cannot inhibit “Mast cell leukocyte cytokine cascade”
- Can be useful to treat urticaria and pruritus
- More effective if combined with H2 antagonists
- May have prophylactic value (eg before IT)

#### Steroids

- “They do everything”
- (Glucocorticosteroids)
  - Onset of action 4 - 6 hours
  - Will inhibit the “Mast cell leukocyte cytokine cascade”
  - Administer only after initial stabilisation
  - Potentially influence biphasic response
  - Benefit
    - Patients with asthma (steroid responsive diseases)
    - Decrease Risk of biphasic reactions
  - Potentially influence biphasic response

### Acute Management

#### Bronchodilators

<table>
<thead>
<tr>
<th>Bronchodilators (Ventolin)</th>
</tr>
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<tbody>
<tr>
<td>Causes bronchodilatation</td>
</tr>
<tr>
<td>i.e. works against wheeze</td>
</tr>
</tbody>
</table>
Acute Management

Salbutamol (Ventolin)
- Fails to treat all the other symptoms of anaphylaxis
- Will not inhibit the "Mast cell leukocyte cytokine cascade"
- Will not prevent further deterioration
- Administer only after initial stabilisation i.e. if the onset of wheeze might be due to anaphylaxis, give adrenaline.

Acute Management

Salbutamol (Ventolin)
- Fails to treat all the other symptoms of anaphylaxis
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Acute Management

Adrenaline
(Epinephrine)
Direct-acting adrenergic agonist acting at α- and β-receptors

Role of Adrenaline (epinephrine)
- α1-adrenergic effects:
  - Vasoconstriction
  - Increased peripheral vascular resistance
  - Decreased mucosal oedema
- β2-adrenergic effects:
  - Bronchodilatation
  - Decreased mediator release from mast cells and basophils

1st line drug of choice

Where & how
- IM anterolateral thigh > IM or SC deltoid

Ref: 1. These plasma epinephrine concentrations versus time after i.m. injections of epinephrine indicate very significant and after injection of epinephrine administered in i.m. children.
(Simons et al. JACI 1989)
Dose

0.01 ml/kg (1 mg/kg)
1:1000 Adrenaline

OR

Risks and side effects of adrenaline

- WELL TOLERATED in children as well as adults
- Transient adverse effects include anxiety, fear, restlessness, headache, dizziness, palpitations, pallor, and tremor
- Benefits in anaphylaxis outweigh the risks

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dose</th>
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<tr>
<td>&lt; 1 yr</td>
<td>0.05 - 0.1 ml</td>
</tr>
<tr>
<td>1 – 2 yrs</td>
<td>0.1 ml</td>
</tr>
<tr>
<td>2 – 3 yrs</td>
<td>0.15 ml</td>
</tr>
<tr>
<td>4 – 6 yrs</td>
<td>0.2 ml</td>
</tr>
<tr>
<td>7 – 10 yrs</td>
<td>0.3 ml</td>
</tr>
<tr>
<td>10 – 12 yrs</td>
<td>0.4 ml</td>
</tr>
<tr>
<td>&gt; 12 yrs</td>
<td>0.5 ml</td>
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