Management of food allergy
Practical advice for general practitioners

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5 May 2016

Food allergy in Australia

1995-2005
Increase in hospital admissions for food anaphylaxis increased by 350%

Challenge-proven food allergy at 12 mo
Egg 8.9% (sensitisation 16.5%)
Peanut 3.0% (sensitisation 8.9%)
Sesame 0.8% (sensitisation 2.5%)

Osborne NJ et al., J Allergy Clin Immunol 2011; 127:668-76.e2

Food Hypersensitivity
Objective, reproducible symptoms initiated by a defined food component

Food Allergy
Immune-mediated

IgE-mediated
- Urticaria
- Angioedema
- Vomiting
- Anaphylaxis

Mixed IgE and non-IgE-mediated
- Atopic dermatitis
- Eosinophilic oesophagitis

Non-IgE-mediated
Food protein-induced
- Enteropathy
- Enterocolitis syndrome
- Proctocolitis

Food Intolerance
Not immune-mediated e.g. lactose intolerance

Cow’s milk allergy

Acute
IgE-mediated:
- Urticaria
- Angioedema
- Anaphylaxis

Chronic
Cow’s milk enteropathy
Infantile allergic proctocolitis

Cow’s milk proteins

Protein content 3.5%
- Caseins (~80%)
- Whey proteins (~20%)
- Fat globule membrane proteins
- Enzymes
- Other

8 major food allergens
Cow’s milk
Hen’s egg
Peanut
Wheat
Soya bean
Shellfish
Fish
Tree nuts
Acid precipitation

**Casein fractions:**
- $\alpha_{s1}$ casein: 32%
- $\alpha_{s2}$ casein: 10%
- $\beta$-casein: 28%
- $\kappa$-casein: 10%

Micelles (colloid calcium phosphate)

**Whey stabilise serum proteins**

**Whey fractions:**
- $\beta$-lactoglobulin (lipid binding protein)
- $\alpha$-lactalbumin
- Bovine serum albumin

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Dairy processing and allergenicity

Fresh milk > Yoghurt > Cheese > Baked milk

Lactose-free milk

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Beta-casein variants: A2 milk

Beta-casomorphin-7

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A2 milk is allergenic

- No difference in wheal diameter between A2 and standard milk (p=0.09)

We therefore caution that A2 milk should not be used by those with IgE-mediated cow's milk allergy, particularly those who have had recent severe reactions to milk.

[WB Smith et al. MJA 2004:181:574]

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Lactose

Glucose - Galactose
Lactose

- Main carbohydrate in mammalian milk
- Human milk contains 6.5-7.5% of lactose, compared to about 4.8% in cow’s milk
- Less sweet than glucose or fructose
- Lactose converted to lactic acid by bacteria (Streptococcus lactis and others)
- Malabsorbed lactase is fermented in colon to short-chain fatty acids (e.g. butyrate) and H₂

Clinical overlap

<table>
<thead>
<tr>
<th>Gastrointestinal cow’s milk allergy</th>
<th>Lactose malabsorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>+++</td>
</tr>
<tr>
<td>Vomiting</td>
<td>+</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>+</td>
</tr>
<tr>
<td>Perianal rash</td>
<td>++</td>
</tr>
<tr>
<td>Eczema</td>
<td>+</td>
</tr>
<tr>
<td>Poor weight gain</td>
<td>+++</td>
</tr>
</tbody>
</table>

Causes of lactose malabsorption

**Primary:**
- Congenital (Finnish type)
- Hypolactasia (adult-type)
- Intestinal dysplasia syndromes

**Secondary:**
- Gastroenteritis (viral, giardiasis)
- Cow’s milk enteropathy
- Coeliac disease
- Other

Secondary lactase deficiency

![Normal and Rotavirus gastroenteritis](image)

Postenteritic lactase deficiency

![Relative Activity Graph](image)

Cow’s milk allergy

**Acute**
- IgE-mediated:
  - urticaria
  - angioedema
  - anaphylaxis

**Chronic**
- Cow’s milk enteropathy
- Infantile allergic proctocolitis

FPIES

![FPIES Image](image)
### IgE-mediated food allergy

- **Urticaria**
- **Facial angioedema**

### Urticaria

- **CLINICAL PRESENTATION:**
  - Urticaria / rash
  - Facial angioedema and lip swelling
  - Acute vomiting and diarrhoea
  - Eczema flare
  - **Anaphylaxis**
    - Sneezing / rhinorrhoea
    - Wheeze
    - Stridor
    - Haemodynamic compromise / shock

### IgE-mediated cow’s milk allergy

- **CLINICAL PRESENTATION:**
  - Urticaria / rash
  - Facial angioedema and lip swelling
  - Acute vomiting and diarrhoea
  - Eczema flare
  - **Anaphylaxis**

### Gastrointestinal food allergy

- **Food protein-induced**
  - Enteropathy
  - Enterocolitis syndrome (FPIES)
  - Proctocolitis (FPIPC)

### Symptoms of non-IgE-CMA in infancy

- Abdominal pain / irritability
- Poor feeding / feeding refusal
- Vomiting / frequent regurgitation
- Persistent diarrhoea
- Abdominal distension / constipation
- Rectal bleeding
- Poor weight gain

### Problems

- Diagnostic criteria / phenotypes not clearly defined
- Lack of *in vitro* diagnostic markers
- Overlap with other common paediatric diseases
- Diagnostic elimination and challenge sequence cumbersome
- Need for endoscopic evaluation
Food protein-induced enteropathy

- Activation of mucosal T-lymphocytes:
  - T-helper cytokines (IFN-γ, TNF-α)
  - Villous atrophy
  - Secondary disaccharidase deficiency

- Chronic diarrhoea
- Osmotic diarrhoea
- Fat malabsorption
- Protein losing enteropathy
- Mast cell activation

Cow’s milk protein-induced enteropathy

- Chronic diarrhoea
- Vomiting
- Micronutrient deficiencies
  - iron
  - calcium
- Protein-energy malnutrition
- Growth failure

Food protein-induced proctocolitis

- Mild diarrhoea and bright rectal bleeding in first weeks of life
- Most common cause of rectal bleeding in infants
- Infant otherwise well
- May occur in breast- and bottle-fed infants
- Increase of intraepithelial T-lymphocytes and eosinophils in rectal mucosa (>10 eos/HPF)
- 65% respond to cow’s milk elimination alone
- Infants generally tolerant by 12 months

Cow’s milk-induced proctocolitis

- Main cause of rectal bleeding in infancy
- Endoscopy and biopsy generally not required
- In non-responder to hypoallergenic diet, consider:
  - Juvenile polyps
  - Chronic granulomatous disease
  - Severe viral infection in immuno-compromised infant (adenovirus, CMV)

Food protein-induced enterocolitis syndrome (FPIES)

- Often after ingestion of cow’s milk or soy formula
- Also occurs after solids (rice, wheat rye, chicken)
- Does not occur in breast-fed infants
- Severe vomiting with onset 2-4 after hrs
- May cause acute dehydration and shock (20%)
- No reliable in vitro diagnostic test
- Skin prick tests and food-specific IgE negative
- APT may be helpful in predicting challenge outcome
- Food challenge generally not before 2 yrs of age

Cow’s milk-induced proctocolitis

- Main cause of rectal bleeding in infancy
- Endoscopy and biopsy generally not required
- In non-responder to hypoallergenic diet, consider:
  - Juvenile polyps
  - Chronic granulomatous disease
  - Severe viral infection in immuno-compromised infant (adenovirus, CMV)

Table 2: Characteristics of rice versus cow’s milk/soy food protein-induced enterocolitis syndrome (FPIES) episodes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rice (n=29)</th>
<th>Cow’s milk/soy (n=30)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of episodes before correct diagnosis</td>
<td>4 (1-4)</td>
<td>2 (1-4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Clinical features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to reaction (h)</td>
<td>1.7 (1-11)</td>
<td>1.7 (1-11)</td>
<td>0.96</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20 (100%)</td>
<td>20 (100%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>5 (19%)</td>
<td>5 (19%)</td>
<td>0.94</td>
</tr>
<tr>
<td>Lethargy</td>
<td>23 (88%)</td>
<td>24 (80%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Pallor</td>
<td>16 (53%)</td>
<td>20 (67%)</td>
<td>0.95</td>
</tr>
<tr>
<td>“Physical” presentation</td>
<td>2 (9%)</td>
<td>3 (10%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Presentation to hospital</td>
<td>15 (53%)</td>
<td>19 (63%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Matters of reaction security</td>
<td>6 (20%)</td>
<td>9 (30%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Abdominal imaging performed</td>
<td>9 (39%)</td>
<td>13 (43%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Request for surgical consultation</td>
<td>6 (21%)</td>
<td>7 (23%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Sopic work-up</td>
<td>7 (27%)</td>
<td>7 (23%)</td>
<td>0.36</td>
</tr>
<tr>
<td>IF fluid before presentation</td>
<td>11 (42%)</td>
<td>5 (17%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Complications of GI food allergy

- Growth failure
  - poor feeding
  - persistent vomiting/regurgitation
  - chronic diarrhoea
- Micronutrient deficiencies
  - iron deficiency anaemia
  - vitamins, trace elements
- Aversive feeding behaviours
- Sleep pattern disturbance
- Family stress / parental exhaustion

Extended spectrum of food allergy

- Eczema
- Persistent crying/infantile colic
- Eosinophilic oesophagitis

Eczema in infancy

- Infantile eczema is closely associated with IgE-mediated food allergy
- Infants with eczema are 6 times more likely to have IgE-mediated egg allergy, and 11 times more likely to have peanut allergy at 12 mo

Eczema and non-IgE food allergy

- 208 DBPCFC performed in 139 children with eczema (median age 13 mo)
- 111 (53%) challenges deemed positive
  - 99 were IgE positive
  - 12 were IgE negative
- About 10% of positive challenges in infants with eczema were non-IgE-mediated (cow’s milk and wheat)

Atopic dermatitis in infancy: triggers

- Food allergy
- S. aureus
Persistent crying in infancy and CMA

- A subset of infants with persistent crying suffers from non-IgE-CMA
- Diagnosis depends on response to hypoallergenic diet
  - Maternal diet
  - Hypoallergenic formula
- Exact rate of non-IgE food allergy in infantile colic unclear

Normal crying curve

Eosinophilic oesophagitis (EoE)

- Presence of at least 15 eosinophils per HPF at 400x magnification
- Stomach and duodenum normal
- Symptoms attributable to upper GI dysfunction
- No improvement after PPI treatment

Clinico-pathological diagnosis of EoE

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Median Age (interquartile Range)</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeding disorder</td>
<td>2.0 (1.2–6.2)</td>
<td>14 (13.6)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8.1 (7.3–12.3)</td>
<td>27 (26.2)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12.0 (9.6–15.2)</td>
<td>27 (26.2)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>13.4 (10.0–16.7)</td>
<td>28 (27.2)</td>
</tr>
<tr>
<td>Food impaction</td>
<td>16.8 (11.7–19.6)</td>
<td>7 (6.8)</td>
</tr>
</tbody>
</table>

Noel et al., NEJM 2004: 351:940-1
**Investigation of food allergies**

- **Food specific IgE antibody (Immuno-CAP)**
- **Skin Prick Test**
- **Atopy Patch Test**
- **Food elimination and challenge**
- **BIOPSY**

**95% diagnostic SPT wheal diameters**

<table>
<thead>
<tr>
<th>Food item</th>
<th>Infants ≤ 2 years</th>
<th>Children &gt; 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cow milk</td>
<td>≥ 6 mm</td>
<td>≥ 8 mm</td>
</tr>
<tr>
<td>Egg</td>
<td>≥ 5 mm</td>
<td>≥ 7 mm</td>
</tr>
<tr>
<td>Peanut</td>
<td>≥ 4 mm</td>
<td>≥ 8 mm</td>
</tr>
</tbody>
</table>

*Sporik R et al., Clin Exp Allergy 2000; 30:1540-1546*

**Food-specific serum IgE antibodies**

<table>
<thead>
<tr>
<th>Positive predictive IgE levels (CAP-RAST), compared with DBPCFC:</th>
<th>PPV [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cow milk 32 kU/L/L</td>
<td>100</td>
</tr>
<tr>
<td>Egg 7 kU/L/L</td>
<td>98</td>
</tr>
<tr>
<td>Peanut 14 kU/L/L</td>
<td>100</td>
</tr>
<tr>
<td>Fish 20 kU/L/L</td>
<td>100</td>
</tr>
<tr>
<td>Soy 30 kU/L/L</td>
<td>73</td>
</tr>
<tr>
<td>Wheat 26 kU/L/L</td>
<td>74</td>
</tr>
</tbody>
</table>

*Sampson HA & HO D, J Allergy Clin Immunol 1997; 100:444-451*
*Sampson HA, J Allergy Clin Immunol 2001; 100:444-451*

**Diagnostic instruments for non-IgE-mediated food allergy**

- Parental report
- Clinical observations
- Other GI investigations
- Home challenge
- Open hospital challenge
- DBPCFC in hospital

**Diagnostic accuracy**

**Home food challenge procedure (non-IgE-mediated)**

- Patients with suspected non-IgE food allergy
- Skin prick test and/or CAP-RAST negative
- No previous anaphylaxis or FPIES
- Infants otherwise well
- Starting doses:
  - 1 ml liquid food / formula
  - 1/8th teaspoon solid food
- One daily morning dose
- Double dose on following day if previous dose tolerated
## Diagnostic approach GI food allergy

1. **Recognise allergic syndrome (phenotype)**
2. **Rule out other relevant gut pathology**
3. **Confirm diagnosis by elimination / challenge**
4. **Re-assess and monitor progress**

## General treatment principles

- Encourage breast feeding, if possible
- Maternal elimination diets, where appropriate (monitor nutritional adequacy of diet; supplements)
- Hypoallergenic formula - extensively hydrolysed - amino acid-based - soy in infants > 6 mo
- Specific food elimination (targeted or empirical)

## General treatment principles

- **Specific nutrient mix**
- **Psychosocial benefits/mother-infant relationship**
- **Nucleotides**
- **Growth factors**
- **Protection from respiratory and gastrointestinal infection (IgA)**
- **Immune modulation sIgA, TGF-β, LCPUFA**
- **Contains maternally ingested intact food allergens**

## Maternal elimination diet

- Encourage continued breast feeding
- Maternal elimination diet useful if ongoing allergic reactions while infant exclusively breast-fed
- Not required if infants tolerating breast milk while mother on unrestricted diet (e.g. previous reaction occurred to supplemental CM formula or dairy products)
- Maternal soy intake is often tolerated in CMA
- Monitor maternal protein and calcium intake (1.2 g calcium daily in divided doses) – **dietitian R/V**

## Breast milk

- **Specific nutrient mix**
- **Psychosocial benefits/mother-infant relationship**
- **Nucleotides**
- **Growth factors**
- **Protection from respiratory and gastrointestinal infection (IgA)**
- **Immune modulation sIgA, TGF-β, LCPUFA**
- **Contains maternally ingested intact food allergens**

## Epipen and anaphylaxis training

- **150 mcg**
- **300 mcg**

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**Maternal elimination diet**

- [Image: Maternal elimination diet]

**Breast milk**

- [Image: Breast milk]

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**Maternal elimination diet**

- [Image: Maternal elimination diet]

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**Epipen and anaphylaxis training**

- [Image: Epipen and anaphylaxis training]

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**Maternal elimination diet**

- [Image: Maternal elimination diet]
Hydrolysed and amino acid-based formulae

- pHF
- eHF
- AAF

BLG content in formula and human milk


Alternatives to cow’s milk-based formula

- Cross-reactivity with goat’s milk > 90%
- Role in infants > 6 months of age?
- Not suitable for treatment of CMA
- Extensively hydrolysed casein-based
- Extensively hydrolysed whey-based
- Amino acid-based

Progression to hypoallergenic formula

Progression to hypoallergenic formula

Kemp AS et al. MJA 2008; 188: 109-112
## Summary

- Strict avoidance of food allergens until tolerance has developed is the main treatment strategy in patients with food allergies.
- Maternal elimination diets and hypoallergenic formulae (eHF or AAF) provide the basis for the treatment of food allergy in infancy.
- Unrecognised GI food allergy may lead to protein-energy malnutrition, specific micronutrient deficiencies or behavioural feeding difficulties.
- A paediatric dietitian should be involved in the management of patients with complex food allergies in order to prevent nutritional deficiency states.
- Patients need to be reviewed regularly in order to avoid unnecessary dietary restrictions.