Cow’s Milk Allergy
......of the trickier kind

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Declarations

• Chair of Dietitian Committee – ASCIA (Australasian Society for Clinical Immunology and Allergy)
• Member FSANZ Food Allergy & Intolerance Scientific Advisory Group
• Delivered talks at PD events sponsored by Nutricia, Abbott, Nestle – no personal honorarium received.

The confusing world of food allergy

• IgE mediated or non IgE mediated?
• Which syndrome?
• Maternal elimination?
• Which formula?
• Ongoing management?

IgE mediated food allergy

IgE mediated food allergy can result in mild, moderate or severe (anaphylaxis) reactions

Food allergy

In Australia:
• Children < 1 yr: 10%
• Children < 5 yrs: 4-8%
• Adults: up to 2%

A food allergy ....

• is a reaction to a food protein caused by immune antibodies or cells
• Can cause immediate or delayed reactions

References:

Crittenden et al, 2006
Osborne et al, JACI 2011.
### Non-IgE Mediated Cows Milk Allergy

- **Cows Milk Proctocolitis**
- **FPIES (Food Protein Induced Enterocolitis)**
- **Cows Milk Enteropathy**
- **Reflex**
- **Constipation**
- **Multiple Food Protein Intolerance of Infancy**
- **Eosinophilic Oesophagitis**

### Case 1: Hilda

- Born term, fully breastfed
- 7 weeks of age – presents with bloody streaks in stools
- Happy baby
- Sleeping and feeding well
- Growing

### Differential Diagnosis

- Anal fissure
- Necrotising enterocolitis
- Intussusception
- Infection
- Meckel’s diverticulum
- FPIES
- Food protein enteropathy
- Swallowed maternal blood, vascular malformation, early IBD, volvulus
- Usually present as unwell

### Food Protein Induced Proctocolitis

- Presents 2-8 weeks of age
- Common cause of rectal bleeding (18-64%)
- >50% breastfed (generally present later than formula fed)
- Otherwise well

#### Management

**Breastfed:**
- Maternal elimination of cows milk (strict)
- Usually blood clears up 72-96 hours but occasionally takes 2-3 weeks
- If no improvement take out soy, egg, wheat, corn
- Refer to gastro if no improvement
- Some babies have to be weaned to specialised formula

**Formula fed** (cow or soy):
- Switch to extensively hydrolysed formula
- If no improvement use amino acid formula

### Skin

- **Urticaria**
- **Angioedema**
- **Eczematous rash**

### Gastrointestinal

- **Pain**
- **Vomiting**
- **Diarrhoea**

### Respiratory

- **Throat tightness**
- **Shortness of breath**
- **Wheezing**

Anaphylaxis

<table>
<thead>
<tr>
<th>IgE mediated</th>
<th>Non-IgE mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to symptoms</td>
<td>Immediate seconds – 30 mins</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Clinical History SPT, sIgE (RAST) +ve OFC</td>
</tr>
</tbody>
</table>
Resolution of Proctocolitis

- 50% of cases resolve by 6 months of age; 95% by 9 months

Breastfed:
- 30ml milk in maternal diet, increase by 30ml a day x 5 days

Formula fed:
- Trial of 5ml standard formula or fresh milk, increase to 30-60ml days 2 and 3.
- If ongoing symptoms retrial every 3 months

Case 2: Three month old Larry

- Fully breastfed, thriving.
- Mum and dad are having their first night out and grandma is looking after Larry.
- Mum has expressed breastmilk and has left some formula ‘just in case’ he needs more.
- Grandma gives Larry the EBM and some of the formula and puts him to sleep.
- 2.5 hours later Larry wakes with severe vomiting, and goes pale and floppy.

Differential Diagnosis

- Acute gastroenteritis
- Sepsis
- Other infectious diseases
- Surgical emergency
- Food allergy

Food protein induced enterocolitis syndrome (FPIES)

- Presents around 3 – 6 months but can be earlier in formula fed infants
  - Major triggers cows milk and soy
- FPIES to solid foods from 4-7 months of age
  - Rice, oats, chicken, eggs, legumes
  - Profuse vomiting, lethargy, pallor, diarrhoea, hypothermia and/or hypovolaemia +/- growth faltering
  - Occurs within 1 – 4 hours after exposure to offending food
  - Diarrhoea may occur 4 – 8 hours later
  - IgE tests negative although up to 30% develop IgE over time

Larry – what to do

- Advise mum to keep breastfeeding, maternal elimination of dairy not necessary.
- Extensively hydrolysed formula if needed
  - Progress to amino acid formula if not tolerated
- Advice on solids introduction
  - Dairy and soy free (20-50% of CM FPIES also triggered by soy)
  - Introduce foods more likely to be tolerated
  - Most children in Australia have FPIES to only one food
  - Close monitoring over time - feeding difficulties occur in 30 – 40%

Nutritional Management in FPIES

- Most infants in Australia have FPIES to only one food

<table>
<thead>
<tr>
<th>Triggering food</th>
<th>Other foods to avoid</th>
<th>Alternative foods considered to be safe to introduce at home</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rice +/- oats (risk cross-reactivity &lt; 20%)</td>
<td>Wheat, rye, barley, corn, quinoa, millet, buckwheat</td>
<td></td>
</tr>
<tr>
<td>Soy +/- legumes</td>
<td>Cane’s milk +/- soy</td>
<td></td>
</tr>
<tr>
<td>Cane’s milk +/- soy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chicken</td>
<td>All poultry</td>
<td>Beef, lamb, pork</td>
</tr>
<tr>
<td>Fish</td>
<td>All fish</td>
<td>Currently no data available to determine if shellfish is safe</td>
</tr>
<tr>
<td>Fruits and vegetables</td>
<td></td>
<td>Introduce other fruits and vegetables at home</td>
</tr>
</tbody>
</table>

ASCIA, 2016
Natural history of FPIES

- Most grow out of FPIES 3-4 years of age
- Supervised oral food challenge in hospital or doctor’s rooms is recommended as the way to diagnose when a child has outgrown FPIES

ASCIA resources

Case 3: Two month old Billy

- Born term, Breastfed
- Increasingly unsettled and irritable, more crying and less sleep
- “colicky”
- Diarrhoea – watery stools, sometimes green and explosive, sometimes yellow
- Mild eczema
- Faltering growth

Differential diagnosis

- Infectious diarrhoea/gastroenteritis
- Lactose intolerance
- Autoimmune enteropathy
- Giardiasis
- Coeliac disease (older child)
- Food allergy

Food protein-induced enteropathy

- **Age**: < 3 years, usually early infancy
- **Symptoms**: vomiting, diarrhoea, poor growth, poor nutrition, may have anaemia, abdominal distention, malabsorption, oedema
- **Onset**: 1-3 days after exposure to offending food
- **Major trigger**: cows milk and soy most common; also wheat and egg
- **Exposure route**: via breast milk or infant diet

Food protein-induced enteropathy - management

- If breastfeeding
  - Continue and eliminate major triggers from maternal diet – cows milk then soy, egg, wheat
- If formula fed
  - Eliminate food and/or formula from infant’s diet
  - Extensively hydrolysed formula usually tolerated
  - Use amino acid formula if no improvement seen or poor growth
- Improvement usually seen 3-7 days (occasionally 1-4 weeks)
- If child improves - challenge 1 food/week
- Modified diet thereafter
- Breastfeeding mothers may need nutritional support
- Re-assess and possibly re-challenge around 12 months of age (usually home challenge)
Severe Food Protein-Induced Enteropathy or multiple food protein intolerance/allergy?

- Multiple symptoms: vomiting, diarrhoea, irritability, eczema, poor sleep & poor growth from early infancy
- CMPA – good resolution with maternal elimination or amino acid formula
- Symptoms return with introduction of solids
- 50% unable to tolerate more than 5 individual foods before 12 months in a case series of 24 children
- Many dependent on amino acid formula
- Many experience ongoing symptoms until age 4 years
- Need a lot of dietetic support

(McWilliam, Tang, Heine, & Allen, 2015)

Reflux

- Thickener, reassurance, time, ?reflux meds
- Up to 40% of infants with GORD may have CMA (Iacono, 1996)
- Breastfeeding – maternal elimination for 2-4 weeks and challenge to confirm if improvement
- Formula – trial of extensively hydrolysed
- If improvement, trial reintroduction around 6 month and 3 monthly after that if tolerated
- Reintroduce if no effect

Constipation

- CMA may be indicated if:
  - Onset at time of weaning from breastmilk to formula
  - Constipation coinciding with introduction of solid food that includes dairy.
  - Rule out Hirschprungs, anorectal malformations
  - Cows milk elimination effective in 28-78% (Sopo, 2014)
  - Eliminate dairy for 2-4 weeks, if no resolution put back in diet
  - If constipation improves, challenge with dairy to confirm.
  - If causal, retry every 6 months.

Summary: Infant Formula for cows milk allergy

<table>
<thead>
<tr>
<th></th>
<th>Breastfeeding</th>
<th>Extensively hydrolysed formula (including rice based)</th>
<th>Amino acid formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylaxis</td>
<td>No maternal diet elimination</td>
<td>✗</td>
<td>✓ (soy &gt; 6 months)</td>
</tr>
<tr>
<td>Proctocolitis</td>
<td>Maternal diet elimination</td>
<td>✓</td>
<td>If no improvement on eHF</td>
</tr>
<tr>
<td>EHF</td>
<td>No maternal diet elimination</td>
<td>✓ (not rice based)</td>
<td>If eHF not tolerated</td>
</tr>
<tr>
<td>Enteropathy</td>
<td>Maternal diet elimination</td>
<td>✓</td>
<td>If growth failure or if no improvement on eHF</td>
</tr>
<tr>
<td>Constipation</td>
<td>Maternal diet elimination</td>
<td>✓ (soy &gt; 6 mo)</td>
<td>If no improvement on eHF</td>
</tr>
<tr>
<td>Reflux</td>
<td>Maternal diet elimination</td>
<td>✓</td>
<td>If no improvement on eHF</td>
</tr>
</tbody>
</table>

Partially hydrolysed, extensively hydrolysed and Amino Acid formula

Approx % of each molecular weight (daltons)

- > 6000
- 3500-6000
- 1500-3500
- <1500

Approx % of each molecular weight

- 0%
- 25%
- 50%
- 75%
- 100%

Amino Acid Formula

- All PBS
>12 month preparations

Caution: 1.0 kcal/ml formula can interfere with solids intake
Flavoured versions useful for older infants

Extensively Hydrolysed Formula

- PBS
  - Over counter
  - Contains Lactose

New kid off the block

- Rice based formula + tryptophan & lysine
- Made to infant formula standards (FSANZ)
- Studies show supports growth
- Same indication as other extensively hydrolysed formula
- Caution with FPIES
- Useful to trial while waiting for specialist appointment
- Still recommend AAF for anaphylaxis

Not recommended for CMA

Infant Formula:
- Cows milk based including anti-reflux, A2, lactose free
- Partially hydrolysed (pHF) cow’s milk based (labelled HA)
- Goat milk/other animal milk based formula

Older children:
- A2 (cows) milk – cross reactivity
- Other mammalian milks – cross reactivity
- Cereal and nut drinks (oat, rice, almond) – nutritional concerns

Nutritional composition

<table>
<thead>
<tr>
<th>Product</th>
<th>Energy (KJ)</th>
<th>Protein (g)</th>
<th>Fat (g)</th>
<th>Calcium (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast milk</td>
<td>256</td>
<td>1.3</td>
<td>4.0</td>
<td>26.4</td>
</tr>
<tr>
<td>Cow’s milk</td>
<td>166</td>
<td>3.3</td>
<td>3.9</td>
<td>125</td>
</tr>
<tr>
<td>Soy drink</td>
<td>170 - 200</td>
<td>2.3 - 4.2</td>
<td>0.9 - 4.7</td>
<td>120 - 160</td>
</tr>
<tr>
<td>Cereal drinks</td>
<td>210 - 270</td>
<td>0.5 - 2.5</td>
<td>0.8 - 1.8</td>
<td>1.0 - 1.20</td>
</tr>
<tr>
<td>Almond milk</td>
<td>360</td>
<td>1.1</td>
<td>3.7</td>
<td>30</td>
</tr>
<tr>
<td>Infant formula (standard)</td>
<td>320</td>
<td>2.7</td>
<td>1.3</td>
<td>80</td>
</tr>
<tr>
<td>Infant formula (specialised)</td>
<td>280 - 285</td>
<td>1.8 - 2.2</td>
<td>3.5 - 4.5</td>
<td>40 - 80</td>
</tr>
</tbody>
</table>

Nutritional deficiencies in children with cow’s milk allergy or multiple food allergies are at increased risk of:

- Macro- and micronutrient deficiencies (Christie, Hine, Parker, & Burks, 2002)
- Short stature (Mehta, Groetch, & Wang, 2013)
- Faltering growth (Meyer, De Koker et al. 2014)
- Severe malnutrition (Alvares et al., 2013)
- Nutritional Rickets (Fox, Du Toit, Lang, & Lack, 2004)
- Kwashiorkor (Mori et al., 2015)
- Low bone mineral density (Mailhot et al., 2016)
- Iodine deficiency (Seward, 2016)
Main food allergens and their nutritional content

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Nutrients involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cow’s milk</td>
<td>Protein, CHO, fat, vitamin A, vitamin D, riboflavin, pantothenic acid, vitamin B12, calcium, magnesium, phosphate, iodine</td>
</tr>
<tr>
<td>Egg</td>
<td>Protein, riboflavin, biotin, vitamin A, vitamin B12, vitamin D, vitamin E, pantothenic acid, selenium, iodine, folate</td>
</tr>
<tr>
<td>Peanut</td>
<td>Protein, fat, vitamin E, niacin, magnesium</td>
</tr>
<tr>
<td>Tree nuts</td>
<td>Protein, fat, vitamin E, niacin, magnesium, omega-3 and omega-6 fatty acids</td>
</tr>
<tr>
<td>Wheat</td>
<td>CHO, protein, fibre, thiamin, riboflavin, niacin (iron &amp; folate if fortified)</td>
</tr>
<tr>
<td>Fish</td>
<td>Protein, iodine (if bones – calcium, phosphorus, fluoride)</td>
</tr>
<tr>
<td>Oily fish</td>
<td>Protein, fat, vitamin A, vitamin D, omega-3 fatty acids</td>
</tr>
</tbody>
</table>

Maternal dietary restriction

Need support especially if taking out more than one protein

Breastfeeding = 500 additional calories required

Dairy recommendation = 2.5 serves = 300 calories / 15-20g protein

So potentially have to provide 800 calories extra on restricted diet

Calcium supplementation – 1000mg, 2 x ~ 500mg doses

Multivitamin with iodine

What’s the role of the gut microbiome?

Gut microbiota:
- Modulate immune programming,
- Promote oral tolerance
- Important inhibiting the development of the allergic phenotype
- Early stages of research – more in atopy/IGE mediated allergy

Of likely benefit:
- Maternal diet in pregnancy
- Vaginal birth
- Breastfeeding (microbes, oligosaccharides)
- Lactobacillus rhamnosus GG, reuteri

Summary

- IGE mediated food allergies can be complex
- Cow’s milk is major trigger for GI allergy, followed by soy
- Confirm by elimination and retriial
  - Proctocolitis, enteropathy, reflux; constipation; multiple symptoms
- FPIES – needs supervised challenge
- Refer to specialist
- Nutritional support is important
- Follow up and reintroduction
  - From 6 months for Proctocolitis, reflux
  - From 12 months for enteropathy
- FPIES – supervised challenge 2-5 years of age

Further Information