



Cow's Milk Allergy

.....of the trickier kind

Ingrid Roche
Accredited Practising Dietitian



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.

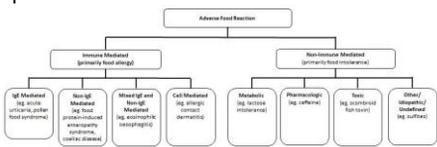


The confusing world of food allergy

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



IgE mediated food allergy



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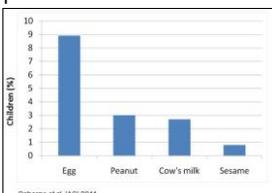
    graph TD
      A[Allergic Food Reaction] --> B[Immune Mediated  
(primarily food allergy)]
      A --> C[Non-Immune Mediated  
(primarily food intolerance)]
      B --> B1[IgE Mediated  
(IgE levels critical in severe food syndrome)]
      B --> B2[Non-IgE Mediated  
(IgE level protein-induced enteropathy, syndrome, celiac disease)]
      B --> B3[Mixed IgE and Non-IgE Mediated  
(IgE, eosinophilic enteropathy)]
      C --> C1[Cell Mediated  
(IgE, allergy, dermatitis)]
      C --> C2[Mucosal  
(IgE, stress, intolerance)]
      C --> C3[Pharmacologic  
(IgE, caffeine)]
      C --> C4[None  
(IgE, intolerance, lactose)]
      C --> C5[Oral  
(absorption/ digestion)  
(IgE, caffeine)]
    
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IgE mediated food allergy can result in mild, moderate or severe (anaphylaxis) reactions

Source: Adapted from Boyce et al. JACI, 2010.



Food allergy



Food	Children (%)
Egg	~9
Peanut	~3
Cow's milk	~3
Sesame	~1

In Australia:

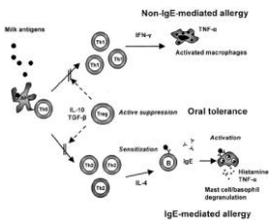
- Children < 1 yr: 10%
- Children < 5 yrs: 4-8%
- Adults: up to 2%

Ref: Osborne et al. JACI, 2011.



A food allergy

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



The diagram illustrates the pathways of food allergy. Milk antigens can lead to a Non-IgE-mediated allergy (involving TNF-α and activated macrophages) or an IgE-mediated allergy (involving sensitization, active suppression, oral tolerance, and activation leading to histamine release and mast cell/basophil degranulation). It also shows the role of IL-10 and TGF-β in active suppression.



Crittenden et al, 2006

	IgE mediated	Non IgE mediated
Time to symptoms	Immediate seconds – 30 mins	Delayed 1-48 hours
Diagnosis	Clinical history SPT, sIgE (RAST) +ve OFC	Clinical history SPT, sIgE (RAST) –ve Elimination and trial
Skin		
• Urticaria	✓	
• Angioedema	✓	
• Eczematous rash	✓	✓
Gastrointestinal		
• Pain	✓	✓
• Vomiting	✓	✓
• Diarrhoea	✓	✓
Respiratory		
• Throat tightness	✓	
• Shortness of breath	✓	
• Wheezing	✓	
Anaphylaxis	✓	

Non IgE Mediated Cows Milk Allergy

- Cows Milk Proctocolitis
- FPIES (Food Protein Induced Enterocolitis)
- Cows Milk Enteropathy
- Reflux
- 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
- Foods: cows milk most common, followed by soy, egg, wheat, corn.



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



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

(Nowak-Węgrzyn et al., 201¹)



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

(Nowak-Węgrzyn et al., 2017)



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%

Meyer, De Koker, et al., 2014

Nutritional Management in FPIES

- Most infants in Australia have FPIES to only one food

Triggering food	Other foods to avoid	Alternative foods considered to be safe to introduce at home
Rice	+/- Oats (risk cross-reactivity < 20%)	Wheat, rye, barley, corn, quinoa, millet, buckwheat
Soy	+/- legumes +/- cow's milk	
Cow's milk	+/- soy	
Egg	Whole egg and baked egg	
Chicken	All poultry	Beef, lamb, pork
Fish	All fish	Currently no data available to determine if shellfish is safe
Fruits and vegetables		Introduce other fruits and vegetables at home

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

The screenshot shows the ASCIA website with the following sections visible:

- ascia Information FOR PARENTS, CONSUMERS AND CARERS**
- ascia Information FOR PATIENTS, CONSUMERS AND CARERS**
- Dietary Guide for introducing your child with food protein-induced enteropathy to new foods**
- ascia ACTION PLAN FOR FPIES** (with a sub-header: "Your doctor's advice")
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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 triggers: 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 Hirschsprungs, 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.

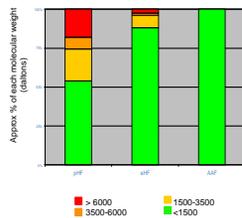


Summary: Infant Formula for cows milk allergy

	Breastfeeding	Extensively hydrolysed formula (including rice based)	Amino acid formula
Anaphylaxis	No maternal diet elimination	X	✓ (soy > 6 months)
Proctocolitis	Maternal diet elimination	✓	If no improvement on eHF
FPIS	No maternal diet elimination	✓ Not rice based	If eHF not tolerated
Enteropathy	Maternal diet elimination	✓	If growth failure or If no improvement on eHF
Constipation	Maternal diet elimination	✓ (soy > 6 mo)	
Reflux	Maternal diet elimination	✓	If no improvement on eHF



Partially hydrolysed, extensively hydrolysed and Amino Acid formula



Amino Acid Formula



>12 month preparations



Caution: 1.0kcal/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

Product	Energy (kJ)	Protein (g)	Fat (g)	Calcium (mg)
Breast milk	296	1.3	4.0	26.4
Cow's milk	195	3.3	3.6	125
Soy drink	170 – 303	2.3 – 4.2	0.9 – 4.7	120 – 160
Cereal drinks	210 – 270	0.5 – 2.5	0.8 – 1.8	1.0 – 120
Almond drink	382	1.1	3.7	3.0
Infant formula (standard and specialised)	280 – 298	1.8 – 2.2	3.5 – 4.5	40 – 80
Amino acid preparation >1yr	417 – 418	2.9 – 3.0	4.0 – 4.6	109 – 120

Ref: Nutrient Reference Values for Australia and New Zealand, 2005. Kemp et al, MJA, 2008.



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) |



