Update: Cows Milk Allergy

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Durban

Paediatric Refresher Course 2011
Epidemiology

• Hippocrates first observed and wrote about negative reactions to *cow's milk* around 370 BC, and since then the prevalence, awareness and understanding has increased.

• Much higher reported than actually proven

• Food allergy was reported by 40% of 5- to 16-year-olds but confirmed by challenge in only 5% of cases.

• More than 20 studies have dealt with self-perceived or parentally perceived CMA over the last 20 years in preschoolers, school-aged children (5-16 years), and young adults. Self-reported prevalence varies between 1% and 17.5% in preschoolers, 1% and 13.5% in 5- to 16-year-olds, and 1% and 4% in adults.

• No SA data
Self/Parental report of CMA JACI Dec 10
Prevalence of Symptoms & sensitization (SPT/IgE) JACI Dec 10
Adverse Food Reactions

Non-immunologic

**Toxic / Pharmacologic**
- Bacterial food poisoning
- Heavy metal poisoning
- Scombroid fish poisoning
- Caffeine
- Alcohol
- Histamine

**Non-Toxic / Intolerance**
- Lactase deficiency
- Galactosemia
- Pancreatic insufficiency
- Gallbladder / liver disease
- Hiatal hernia
- Gustatory rhinitis
- Anorexia nervosa
- Idiosyncratic

Adverse Food Reactions

**Immunologic**

IgE-Mediated (most common)

- Systemic (Anaphylaxis)
- Oral Allergy Syndrome
- Immediate gastrointestinal allergy
- Asthma/rhinitis
- Urticaria
- Morbilliform rashes and flushing
- Contact urticaria

- Eosinophilic esophagitis
- Eosinophilic gastritis
- Eosinophilic gastroenteritis
- Atopic dermatitis

Non-IgE Mediated Cell-Mediated

- Protein-Induced Enterocolitis
- Protein-Induced Enteropathy
- Eosinophilic proctitis
- Contact dermatitis

Major allergens

20 sensitizing proteins found in CM, major allergens identified in

1. α Lactalbumin
2. β lactoglobulin
3. Casein
4. Serum albumin
Unusual routes of exposure

CMA often presents before ingestion of cows’ milk suggesting possible mechanisms

- Skin contact
- Mucous membrane exposure
- Inhalation
Environmental exposure

- Poor food labeling
- Hidden in foods or contamination
- Hidden or contamination of medications.
IgE mediated reactions
anaphylaxis

• life-threatening
• Can occur any time to within minutes and up to 2 hours after ingestion of dairy products.
• Like any food-induced anaphylactic reaction, CMA can present with skin, respiratory tract, and gastrointestinal symptoms
• Cardiovascular collapse, syncope, or incontinence are the hallmarks of the most severe forms.
• Food-dependent exercise-induced anaphylaxis has also been reported in children with previous milk allergy, either after achieving tolerance or after oral desensitization protocols.
IgE-mediated skin reactions

Acute urticaria or angioedema
- Urticaria is a feature of most anaphylactic reactions to cow’s milk.
- Urticaria with inhalation or accidental skin contact is often severe.

Contact urticaria
- Pattern varies from irritant to allergic contact dermatitis.
- Generalized eczematous rash (systemic contact dermatitis) is present.
- Contact reactions are frequent in patients with AD.
IgE-mediated respiratory reactions

- Reactions rarely occur in isolation.
- Rhinitis occurs in 70% of patients during oral cow’s milk challenge, and asthma occurs in less than 8%.
- Reactions correlate with severe CMA.
- Asthma makes for the worst prognosis in children with anaphylaxis.
- Asthma in patients with CMA is of particular severity.
- Respiratory symptoms in patients with CMA can progress to respiratory allergy.
- Inhalation of milk vapor has been associated with severe respiratory tract reactions.
IgE mediated GIT reactions

• Oral allergy syndrome (rare in pediatric patients)
• Lip swelling is a commonly observed manifestation during food challenge procedures.
• Vomiting (described in children both isolated and as part of allergic/anaphylactic reactions)
• Diarrhea (usually in, but not limited to, delayed reactions)
Non IgE mediated Late-onset reactions

• Symptoms not IgE mediated, therefore often delayed
• Mostly localized in the gastrointestinal tract
• Typically develop 1hr to several hours or even days after ingestion
• No reliable laboratory tests to diagnose late-onset CMA:
  • IgE test results are negative
Non IgE mediated Late onset reactions

Skin
• AD

Gastrointestinal tract
• Gastroesophageal reflux disease
• Allergic eosinophilic esophagitis
• Food protein–induced enterocolitis syndrome
• Cow’s milk protein–induced enteropathy
• Constipation
• Severe irritability (colic)
• Food protein–induced gastroenteritis and proctocolitis

Respiratory system
• Milk-induced chronic pulmonary disease
• Heiner syndrome
AD

• AD is most often present as an eczematous lesion (after ingestion or contact).
• AD can involve both IgE-mediated and non–IgE-mediated skin responses.
• Less than 30% of children with moderate-to-severe AD have food allergy, and CMA is the second most common food allergy in this population.
• The earlier the age of onset, the greater the severity and frequency of high of cow’s milk sIgE levels.
• Appropriate diagnosis and elimination diets can lead to symptom improvement, but often not very effective.
GIT manifestations

• Gastroesophageal reflux disease
• Allergic eosinophilic esophagitis
• Food protein–induced enterocolitis syndrome
• Cow’s milk protein–induced enteropathy
• Constipation
• Severe irritability (colic)
• Food protein–induced gastroenteritis and proctocolitis
Non – IgE- Mediated

Allergic Eosinophilic Esophagitis (AEE)

- Dysphagia, symptoms of GERD
- Abdominal pain
- Poor response to reflux drugs
- Biopsy: Eosinophils ++++
- Respond to swallowed ICS

More than 20 eosinophils per HPF
Similar appearance in upper and lower oesophagus
Non – IgE- Mediated

Allergic Eosinophilic Gastroenteritis (AEG)

Weight loss, FTT+/-oedema
Vomiting, diarrhoea (post-prandial)
Blood loss
Iron deficiency
Protein/iron- losing enteropathy
TH2 in blood and mucosa
Mast cells, Eosinophils in mucosa
Persistent food hypersensitivity at 5yr FU.

Chehade M et al JPGN 2006;42;516-521
Non-IgE Mediated: Food Protein-Induced Enteropathy Syndrome (FPIES)

- Occurs from 0 - 24 months
- Diarrhea (mild to moderate steatorrhea in about 80% of cases)
- Food implicated: milk, cereals, egg, fish
- Poor weight gain
- Diagnosis:
  - Biopsy shows patchy villous atrophy with prominent mononuclear round cell infiltrate, few eosinophils,
  - Response to exclusion diet,
  - Challenge test
- Resolved at 2 - 3 years old

Adapted from J Allergy Clin Immunol. 2004; 113:808-809
Non – IgE- Mediated

Food protein-induced proctocolitis

- Mild diarrhoea and bright rectal bleeding in first weeks of life; infant otherwise well and thriving
- Challenge onset:<72hours
- May occur in breast- and bottle-fed infants
- Increase of intraepithelial T-lymphocytes in rectal mucosa; CD8+
- 65% respond to cow’s milk exclusion, the remainder may require more extensive dietary elimination diets
- Usually tolerant by 12 months – prognosis excellent

Örmälä T et al., J Pediatr Gastroenterol Nutr 2001;33;133-138
Lake AM, J Pediatr Gastroenterol Nutr 2001;30 (Suppl.);S58-S60
Arvola T et al, Pediatr. 2006;117:e760-e768
# Pediatric Gastrointestinal Syndromes

<table>
<thead>
<tr>
<th></th>
<th>Enterocolitis</th>
<th>Enteropathy</th>
<th>Proctitis</th>
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<tbody>
<tr>
<td><strong>Age Onset:</strong></td>
<td>Infant</td>
<td>Infant/Toddler</td>
<td>Newborn</td>
</tr>
<tr>
<td><strong>Duration:</strong></td>
<td>12-24 mo</td>
<td>? 12-24 mo</td>
<td>9 mo-12 mo</td>
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<tr>
<td><strong>Characteristics:</strong></td>
<td>Failure to thrive</td>
<td>Malabsorption</td>
<td>Bloody stools</td>
</tr>
<tr>
<td></td>
<td>Shock</td>
<td>Villous atrophy</td>
<td>No systemic sx</td>
</tr>
<tr>
<td></td>
<td>Lethargy</td>
<td>Diarrhea</td>
<td>Eosinophilia</td>
</tr>
<tr>
<td></td>
<td>Vomit</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Diarrhea</td>
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- Non-IgE-mediated, typically milk and soy induced
- Spectrum may include colic, constipation and occult GI blood loss
Prevention of CMA

• Breast feeding
• GINI study: use of pHF and eHF.
• Early exposure to CMP as a supplement to breast-feeding might promote tolerance.

Katz et al JACI 2010;126:77-82.
Katz et al. JACI 2010, 126,77-82
Diagnostic approach

- History
- Clinical characteristics
- Elimination/challenge testing depending on the clinical characteristics.
- DPPCFC
- Open challenges Recommended by DRACMA
- Biopsies.
Diagnostic approach: History

- History very important
- What is the food allergen?
- Timing of reaction?
- Symptoms?
- Route of exposure?
- Symptom severity
- Concomitant disease such as asthma, AR, AD.
## Diagnostic cut off values for SPT & RAST

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<tr>
<th></th>
<th>&gt;KU/l</th>
<th>&gt;PPV</th>
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<tbody>
<tr>
<td>Predictive value of CM specific IgE levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All children</td>
<td>15</td>
<td>95</td>
</tr>
<tr>
<td>Infants &lt;2yrs</td>
<td>5</td>
<td>95</td>
</tr>
<tr>
<td>Wheal size</td>
<td>PPV</td>
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<tr>
<td>Predictive value of SPT</td>
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<tr>
<td>Children &gt;2yrs</td>
<td>8</td>
<td>95</td>
</tr>
<tr>
<td>Infants &lt;2yrs</td>
<td>6</td>
<td>95</td>
</tr>
</tbody>
</table>
RAST testing

• Can be performed to many of the components of CMP: α lactalbumin, β-lactoglobulin, BSA, casien & d-lactoferrin.

• Patients may react to one or more of these components.

• Each component has certain characteristics.

• Casein is heat stable and resistant to peptide digestion, variable clinical reactivity.
APT

• Role is yet undefined
• Not well validated
• Used only in research centers
Management of CMA

• Avoidance of all CMP. Breast milk preferred.
• Diet must fulfill the nutritional needs of individual patients. Dietary interventions must be individually tailored according to patients needs. Done with dietician.
• Must teach parents to read food labels
• Some children may tolerate extensively heated milk product eg. Baked foods.
Management of CMA

- Patient and carers should be educated and empowered to recognize and respond to reactions.
- Individualised emergency plan.
- Antihistamines
- Epinephrine auto-injector
- Presence of asthma major risk for severe reactions.
Hypoallergenic formula

- Clinical Definitions: should be tolerated by 90% of CMA infants with a 95% CI.
  - pHF
  - eHF
  - AAF
Hypoallergenic formula

Partially hydrolysed (MW 3-1000Da)
- Nan –HA 80.00 400g
- Similac advance HA 78.00 400g
- Novolac HA 72.00 400g

Extensively hydrolysed formula (<3000 Da)
- Alimentum (hydrolysed casein) 140.00 450g
- Nutramigen (hydrolysed casien) 128.00 400g
- Alfare (hydrolysed whey) 240.00 400g
- Pepticate (hydrolysed whey) 200.00 400g
- Allernova 185.00 400g

Amino acid based formula
- Neocate 500.00 400g
- Neotricia 200.00 400g
Hypoallergenic formula

pHF
• not suitable for the treatment of CMA
• May have a role in the prevention of CMA

eHF : used for the treatment of CMA
• Can be used for both IgE and non-IgE mediated reactions.
• Cost & taste are problems
• 2-10% of CMA infants may react to eHF and will need AAF. This is due to residual β lactoglobulin detected in EHF.

AAF : no known reaction . Taste can be problem. Cost. very useful in elimination diets to resolve symptoms before challenges . More useful for non IgE mediated CMA.
HF & AAF

• Hill et al in systematic review found that EHF are efficacious at relieving the symptoms of CMA in the majority of infants.

• Infants with non-IgE-mediated food-induced gastro-enterocolitis and proctitis syndromes with faltering growth, severe atopic eczema, or with symptoms during exclusive breast feeding were more likely overall to benefit from AAF.

• AAF must be used in patients with CMA anaphylaxis
Soy formulae

- No evidence that it has any effect on the prevention of CMA
- Not hypoallergenic. Still popular in RSA.
- Can be used for Rx of IgE mediated CMA.
- Children with IgE CMA can develop soy allergy as well (10-14%).
- Soya allergy more common in Non IgE mediated (up to 50%)
- In Katz study found very little soya allergy
- Concern about phytoestrogens, high level of phytates and aluminium. (animal studies)
Close homology between mammalian milk and CM

Journal of Allergy and Clinical Immunology 2010; 126:1119-1128.e12
Every food has its own story...

- cow’s milk
- hen’s egg
- peanuts, fish, seafood, ...

![Graph showing prevalence over age for different foods.](image)
Suspicion of cows' milk protein allergy (CMPA)

Clinical assessment
- Clinical findings
- Family history (risk factor)

Suspicion of mild to moderate CMPA
One or more of the following symptoms:
- Gastrointestinal: frequent regurgitation, vomiting, diarrhoea, constipation (with/without perianal rash), blood in stool, iron deficiency anaemia
- Dermatological: atopic dermatitis, swelling of lips or eye lids (angio-oedema), urticaria unrelated to acute infections, drug intake or other causes
- Respiratory: runny nose, chronic cough, wheezing (all unrelated to infection)
- General: persistent distress or colic (≥3 h per day wailing/irritable) at least 3 days/week over a period of >3 weeks
- Others (rare)

Elimination diet

Improvement
- Open challenge†
  Cows' milk formula under clinical observation
  - No CMPA symptoms
  - Resume CMP in diet and monitor

No improvement
- Elimination diet with AAF*
  - CMPA symptoms
    - Maintain CMP elimination diet until 9–12 months of age, and for at least 6 months
    - Repeat challenge
- Resume CMP in diet

Testing for CMPA
Consider the following:
- Skin tests: prick test, patch test for CMP
- Blood: total IgE, specific IgE (RAST) for CMP

Suspicion of severe CMPA
One or more of the following symptoms:
- Gastrointestinal: failure to thrive due to chronic diarrhoea, and/or regurgitation/vomiting and/or refusal to feed; iron deficiency anaemia due to occult or macroscopic blood loss; protein-losing enteropathy (hypoalbuminaemia); endoscopic/histologically confirmed enteropathy or severe ulcerative colitis
- Dermatological: exudative or severe atopic dermatitis with hypoalbuminaemia-anaemia or failure to thrive or iron deficiency anaemia
- Respiratory: acute laryngoedema or bronchial obstruction with difficulty breathing
- Systemic reactions (anaphylactic shock – needs immediate referral to hospital for management)

Elimination diet
Amino acid formula (AAF) for a minimal 2–4 weeks*

No improvement
- Referral to paediatric specialist

Improvement
- Paediatric specialist diagnostic procedures

† According to results of control testing in IgE-mediated allergy

* Amino acid formula (AAF), depending on cost/benefit ratio and/or if the child refuses to drink eHF
References

• Du Toit et al Identifying & managing cow`s milk protein allergy: Arch Dis Child Educ Pract Ed published online August 5, 2010

• Alessandro Fiocchi et al Diagnosis and Rationale for Action against Cow’s Milk Allergy (DRACMA): A summary report : JACI Dec 2010

• Yvan Vandenplas :Guidelines for the diagnosis & management of CMPA in infants :Arch Dis Child 2007, 92:902-8

• Cas Motala: Cow`s milk allergy in children. CME 2010, 28:412-6
Prof Cas Motala