Food allergy: prevention and treatment

H. Szajewska (PL)
Food allergy: prevention and treatment

Cow’s milk allergy

Prof. Hania Szajewska
The Medical University of Warsaw
Department of Paediatrics
How much will you remember in 24 h?

① 90%
② 75%
③ 50%
④ 25%
⑤ 5%
Average recall after 24 h

- Listening: 5%
- Discussing: 50%
- Teach others: 90%

The Learning Pyramid

Learning objectives

- To summarize recent evidence on CMA.

- Preference is given to evidence and recommendations from scientific societies published in the last 5 years (2009-2014).
World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow’s Milk Allergy (DRACMA) Guidelines

Alessandro Fiocchi, (Chair), Jan Brozek, Holger Schünemann, (Chair), Sami I. Bahna, Andrea von Berg, Kirsten Beyer, Martin Bozzola, Julia Bradsher, Enrico Compalati, Motohiro Ebisawa, Marta Antonietta Guzman, Haig Li, Ralf G. Heine, Paul Keith, Gideon Lack, Massimo Landi, Alberto Martelli, Fabienne Rancé, Hugh Sampson, Airton Stein, Luigi Terracciano, and Stefan Vieths

Diagnostic Approach and Management of Cow’s-Milk Protein Allergy in Infants and Children: ESPGHAN GI Committee Practical Guidelines

*S. Koletzko, †B. Niggemann, ‡A. Arato, §J.A. Dias, ||R. Heuschkel, ¶S. Husby, **M.L. Mearin, ***A. Papadopoulou, ¶¶F.M. Ruemmele, §§A. Staitano, §§§M.G. Schäppi, and §§§§Y. Vandenplas

BSACI guideline for the diagnosis and management of cow’s milk allergy

D. Luyt¹, H. Ball¹, N. Makwana², M. R. Green¹, K. Bravin¹, S. M. Nasser³ and A. T. Clark³

¹University Hospitals of Leicester NHS Trust, Leicester, UK; ²Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK and ³Cambridge University Hospital NHS Foundation Trust, Cambridge, UK
## Terminology

Revised and up-dated by the WAO

### Food hypersensitivity

#### Food allergy

- Immunologic mechanisms

#### Non-allergic food hypersensitivity

- Non-immune mediated

### IgE-mediated

- Urticaria/angioedema
- Oral allergy syndrome
- Rhinitis, asthma
- Immediate GI hypersens
- Anaphylaxis

### Non-IgE-mediated

- FPIES
- FPI-allergic proctocolitis

### Mixed

- Atopic dermatitis
- Eosinophilic gastroenteropathies

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Example

Lactose intolerance

Prevalence of CMA
CMA is the most common food allergy in infancy

• Formula-fed infants
  – 2-3%

• Breastfed infants
  – 0.5%

• Problems
  – A lack of uniformity of the criteria for making a diagnosis
  – Unclear whether the prevalence is increasing

Chafen et al. JAMA 2010;303;1848-56.
### Major allergens

**Table 4-1. The Proteins of Cow’s Milk**

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Protein</th>
<th>Allergen10</th>
<th>g/L</th>
<th>% Total Protein</th>
<th>MW (kDa)</th>
<th># AA</th>
<th>pI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caseins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>αs1-casein</td>
<td>Bos d 8</td>
<td>~30</td>
<td>80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>αs2-casein</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>β-casein</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>γ1-casein</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>γ2-casein</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>γ3-casein</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>κ-casein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whey proteins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alpha-lactalbumin</td>
<td>Bos d 4</td>
<td>~5.0</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Beta-lactoglobulin</td>
<td>Bos d 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immunoglobulin</td>
<td>Bos d 7</td>
<td>0.6–1.0</td>
<td>3</td>
<td>160.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>BSA*</td>
<td>Bos d 6</td>
<td>0.1–0.4</td>
<td>1</td>
<td>67.0</td>
<td>583</td>
<td>4.9–5.1</td>
</tr>
<tr>
<td></td>
<td>Lactoferrin</td>
<td></td>
<td>0.09</td>
<td>Traces</td>
<td>800.0</td>
<td>703</td>
<td>8.7</td>
</tr>
</tbody>
</table>

* Bovine serum albumin.

**4 casein fraction proteins & 2 whey proteins**

Clinical manifestations
# Signs and symptoms of CMA

CMA mainly affects children during the first 2 y of life

- Affected children present with symptoms usually within the first 6 mo of life

- Very rarely, the onset after 12 mo

*Most often seen immediately after exposure and IgE-mediated*
Natural history

- **CMA is frequently outgrown**
  - Data on the resolution of CMA vary
- **Non-IgE-mediated CMA**
  - More likely to be transient
- **IgE-mediated CMA**
  - More likely to persist longer

- **More likely to have persistent disease**
  - Highly elevated milk-specific IgE
  - Multiple food allergies
  - Concomitant asthma and/or allergic rhinitis

Diagnosis

### A comparison of diagnostic approaches proposed by various organisations

<table>
<thead>
<tr>
<th></th>
<th>WAO 2010</th>
<th>ESPGHAN 2012</th>
<th>BSACI 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Physical exam</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Oral food challenge</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Specific IgE</strong></td>
<td>+</td>
<td>+</td>
<td>sIgE ≥0.35 kU/L to support a clinical dx</td>
</tr>
<tr>
<td><strong>Skin prick test</strong></td>
<td>+</td>
<td>+</td>
<td>Wheal ≥5(≥2) mm - predictive</td>
</tr>
<tr>
<td><strong>Total IgE</strong></td>
<td>NA</td>
<td>No benefit over specific IgE</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Atopy patch test</strong></td>
<td>NA</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Intradermal tests</strong></td>
<td>NA</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Specific IgG/IgG subclasses</strong></td>
<td>NA</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

NA = not addressed
### IgE levels that predict which patients will react (95% predictive value*)

<table>
<thead>
<tr>
<th>Allergen</th>
<th>IgE Level (kU$_A$/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg</td>
<td>&gt;7</td>
</tr>
<tr>
<td>Milk</td>
<td>&gt;15</td>
</tr>
<tr>
<td>Peanuts</td>
<td>&gt;15</td>
</tr>
<tr>
<td>Soy</td>
<td>&gt;65</td>
</tr>
<tr>
<td>Wheat</td>
<td>&gt;80</td>
</tr>
</tbody>
</table>

* Younger children sometimes have lower IgE levels in the 95% predictive range, so thresholds for some allergens are lower for infants and toddlers.

All tests – skin and IgE – need to be interpreted in the context of the clinical picture.
Management of CMA

• Breastfed infants
  – Continuation of BF
  – Mother – dairy-free diet

• Non-breastfed infants
  – EH formula
  – AA formula
  – Soy formula
  – Rice EH formula
  – Soy EH formula
# Reference guide to the recommendations

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>1st choice</th>
<th>2nd choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylaxis</td>
<td>AAF</td>
<td>eHF</td>
</tr>
<tr>
<td>Acute urticaria or angioedema</td>
<td>eHF</td>
<td>AAF/SF</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>eHF</td>
<td>AAF/SF</td>
</tr>
<tr>
<td>Immediate GI allergy</td>
<td>eHF</td>
<td>AAF/SF</td>
</tr>
<tr>
<td>Allergic eosinophilic esophagitis</td>
<td>AAF</td>
<td></td>
</tr>
<tr>
<td>GERD</td>
<td>eHF</td>
<td>AAF</td>
</tr>
<tr>
<td>CMP-induced enteropathy</td>
<td>eHF</td>
<td>AAF</td>
</tr>
<tr>
<td>FPIES</td>
<td>eHF</td>
<td>AAF</td>
</tr>
<tr>
<td>CMP-induced gastroenteritis/proctocolitis</td>
<td>eHF</td>
<td>AAF</td>
</tr>
<tr>
<td>Severe irritability (colic)</td>
<td>eHF</td>
<td>AAF</td>
</tr>
<tr>
<td>Constipation</td>
<td>eHF</td>
<td>AAF</td>
</tr>
</tbody>
</table>
What is new?

To examine whether formula selection affects the development of tolerance

<table>
<thead>
<tr>
<th>Design</th>
<th>RCT, open</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>N=260, CMA, age 1-12 mo</td>
</tr>
<tr>
<td>Intervention</td>
<td>5 different formulas</td>
</tr>
<tr>
<td></td>
<td>• Ext Hydr Casein</td>
</tr>
<tr>
<td></td>
<td>• Ext Hydr Casein + LGG</td>
</tr>
<tr>
<td></td>
<td>• Hydr rice</td>
</tr>
<tr>
<td></td>
<td>• Soy formula</td>
</tr>
<tr>
<td></td>
<td>• Amino acid formula</td>
</tr>
<tr>
<td>Outcome</td>
<td>Development of tolerance at 12 mo (SPT, APT, DBPCFC)</td>
</tr>
</tbody>
</table>

What is new?

To examine whether formula selection affects the development of tolerance

EHF + LGG was the most effective in promoting cow’s milk protein tolerance
Not recommended for the management of CMA

- Partially hydrolyzed formula
- Soy formula during the first 6 mo of life
- Milk of other mammalian species
  - Sheep, buffalo, horse, goat
- Unmodified soy or rice milk
- ‘Milk beverages’
  - Based on almond, coconut, hazelnut, oat, potato, rice, soya
Duration of milk exclusion diet

• Re-assessment every 6-12 mo from 12 mo of age
  - To assess the possibility of reintroduction of cow’s milk
Start with baked milk products
Baking reduces allergenicity
More allergenic products only in subjects who have achieved full tolerance to baked

Oral tolerance induction
Repetitive, increasing doses of daily milk for treatment of milk allergy

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Full desensitization</td>
<td>5</td>
<td>196</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>6.61 [3.51, 12.44]</td>
</tr>
<tr>
<td>2 Full desensitization - Subgroup analysis of patients 4 years and older</td>
<td>4</td>
<td>136</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>14.94 [3.86, 57.90]</td>
</tr>
<tr>
<td>3 Full desensitization - Subgroup analysis of patients without a history of anaphylaxis</td>
<td>4</td>
<td>136</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>5.68 [2.98, 10.85]</td>
</tr>
<tr>
<td>4 Partial desensitization</td>
<td>5</td>
<td>196</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>9.34 [2.72, 32.09]</td>
</tr>
</tbody>
</table>

↑ full tolerance to cow’s milk!

Yeung et al. Cochrane Review 2012
Oral tolerance induction

• Problems/limitations
  – Long-term tolerance?
  – Risk of adverse effects
    • Although mostly mild and self-limiting

Currently under research
No desensitisation guidelines have been established at this point.
Growth and nutritional concerns in children with food allergy

Studies have raised concerns about poor diet and nutritional deficiencies in children following avoidance diets.

Monitoring growth and guiding food allergic patients in choosing appropriate alternatives is crucial.

Mehta et al. Curr Opin Allergy Clin Immunol 2013
Mehta et al. J Pediatr 2014
Early nutritional strategies for preventing allergic disease

- Exclusive breastfeeding
- Use of dietary products with reduced allergenicity
- Early vs. delayed introduction of complementary foods
- Probiotics, prebiotics
Breastfeeding & Allergy
What is the evidence?

- No association
- A reduced risk
- An increased risk

The issue remains controversial
Why inconsistent results?

- Confounding factors
  - gender, age (asthma!), socioeconomic status, family history of atopy, parental smoking, and presence of furry animal in the home
- Recruitment and reporting biases
- Inability to randomize and blind
- Many studies do not make the distinction between ‘exclusive breastfeeding’ and ‘any breastfeeding’
- Imprecise definitions
- Reverse causality
  - infants at the highest risk of allergy might be breastfed for longer periods

What to advice?

Exclusive breastfeeding (in all infants) for about 6 mo is a desirable goal

AAP. Pediatrics 2012;129;e827
## Hydrolyzed formula Recommendations

<table>
<thead>
<tr>
<th>Organisation</th>
<th>Risk</th>
<th>Recommendation (if not breast-fed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EAACI 2014</td>
<td>At-risk</td>
<td>Hydrolyzed formula</td>
</tr>
<tr>
<td>CSACI 2013</td>
<td>At-risk</td>
<td>Hydrolyzed formula</td>
</tr>
<tr>
<td>AAAAI 2013</td>
<td>At-risk</td>
<td>Hydrolyzed formula</td>
</tr>
<tr>
<td>US NIAID 2010</td>
<td>At-risk</td>
<td><strong>Hydrolyzed formula</strong> Practical and cost considerations of eHF may limit their use</td>
</tr>
<tr>
<td>EAACI 2008</td>
<td>At-risk</td>
<td>Formula with documented reduced allergenicity for ≥4 mo</td>
</tr>
<tr>
<td>AAP 2008</td>
<td>At-risk</td>
<td>Hydrolyzed formula Not all HF provide the same degree of protective benefit</td>
</tr>
</tbody>
</table>

CSACI = Canadian Society of Allergy and Clinical Immunology
AAAAAI = American Academy of Allergy, Asthma & Immunology
NIAID = National Institute of Allergy & Inf Dis
EAACI = European Academy of Allergy and Clinical Immunology
AAP = American Academy of Pediatrics

Chan et al. 2013
Boyce et al. JACI 2010;126:S1-S58
## Timing of introduction of allergenic foods to infants

### Recommendations

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Solid food</th>
<th>Avoidance or delay of potentially allergic foods</th>
</tr>
</thead>
<tbody>
<tr>
<td>EAACI 2014</td>
<td>4 to 6 mo</td>
<td>Np</td>
</tr>
<tr>
<td>CSACI 2013</td>
<td>4 to 6 mo</td>
<td>Np</td>
</tr>
<tr>
<td>AAAAI 2013</td>
<td>4 to 6 mo</td>
<td>Np</td>
</tr>
<tr>
<td>US NIAID 2010</td>
<td>4 to 6 mo</td>
<td>No</td>
</tr>
<tr>
<td>AAP 2008</td>
<td>Not before 4 to 6 mo</td>
<td>No</td>
</tr>
<tr>
<td>ESPGHAN 2008</td>
<td>After 17 wk (≈4 mo), but not later than 26 wk (≈6 mo)</td>
<td>No</td>
</tr>
</tbody>
</table>

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**All recommendations agree:**

- No convincing scientific evidence that the avoidance or delayed introduction of potentially allergenic foods beyond 4-6 mo reduces allergies.
## Ongoing RCT

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EAT</strong>&lt;br&gt;UK</td>
<td>General population</td>
<td>BF 3 mo, then CM, egg, wheat, sesame, fish, peanut</td>
<td>Excl BF 6 mo, no allergenic foods before 6 mo</td>
<td>IgE mediated food allergy 1-3 y</td>
</tr>
<tr>
<td><strong>LEAP</strong>&lt;br&gt;UK</td>
<td>High risk</td>
<td>Peanut from 4-10 mo</td>
<td>Peanut avoidance</td>
<td>Peanut allergy at 5 y</td>
</tr>
<tr>
<td><strong>HEAP</strong>&lt;br&gt;Germany</td>
<td>General population</td>
<td>Hen’s egg powder from 4-6 mo</td>
<td>Placebo</td>
<td>IgE mediated food allergy at 12 mo</td>
</tr>
<tr>
<td><strong>STAR</strong>&lt;br&gt;Australia</td>
<td>High-risk infants</td>
<td>Egg powder from 4-8 mo; cooked egg from 8 mo</td>
<td>Placebo. Cooked egg from 8 mo</td>
<td>IgE-mediated egg allergy</td>
</tr>
<tr>
<td><strong>STEP</strong>&lt;br&gt;Australia</td>
<td>At risk</td>
<td>Egg powder from 4-6 mo until 10 mo. Cooked egg from 10 mo</td>
<td>Placebo. Cooked egg from 10 mo</td>
<td>IgE-mediated egg allergy</td>
</tr>
</tbody>
</table>

The results are expected in 2014/2015.

### Other interventions

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probiotics</td>
<td>No</td>
<td>WAO 2012</td>
</tr>
<tr>
<td>N-3 LC-PUFA</td>
<td>During pregnancy better than during lactation</td>
<td>Makrides 2013</td>
</tr>
<tr>
<td>Antioxidants</td>
<td>No intervention studies; role unclear</td>
<td></td>
</tr>
<tr>
<td>Folate</td>
<td>No intervention studies; role unclear</td>
<td></td>
</tr>
<tr>
<td>Vitamin D</td>
<td>No</td>
<td>ESPGHAN 2013</td>
</tr>
</tbody>
</table>
Take home messages

- **Cow’s milk allergy**
  - the most common food allergy in children

- **Diagnosis**
  - history, diagnostic elimination diets, SPT, specific IgE, and oral food challenges.

- **Treatment**
  - strict avoidance of the offending allergen

- **Oral immunotherapy**
  - not yet recommended for routine practice
Take home messages

• Prevention
  – Exclusive breastfeeding
    • 6 mo is a desirable goal (at least 4 mo)
  – Protein hydrolysates
    • only formulas with documented effect
  – Complementary foods
    • start at 4-6 months
    • no delayed introduction of allergenic foods
  – Probiotics, LCPUFA, vitamins, etc.
    • no specific recommendations; more studies needed
A final comment...
A final comment...

'Half of what you are taught as medical students will in ten years have been shown to be wrong, and the trouble is, none of your teachers knows which half…'

Thank you for your attention
A starting comment....

‘Medical science has made such tremendous progress that there is hardly a healthy human left...’

Aldous Huxley
Case presentation
A 2-year old boy with persistent eczema
Case presentation

• A 2-year old boy is brought to the ED because he has had **persistent eczema** since infancy

• His mother is concerned that the eczema is due to a food allergy

• He recently had a **reaction after eating peanut butter**
Allergy testing?

Allergy tests should be done only if clinically indicated.

For food allergies, patient history is the most important factor in determining whether testing is needed.
His eczema is persistent but relatively mild and is well controlled with intermittent use of a low-potency topic corticosteroid.
He had facial urticaria after eating scrambled eggs at age 1 year, but has eaten egg in baked foods without obvious reaction.
He had never eaten peanut before recent episode, which included vomiting and hives that occurred just a few minutes after his first peanut exposure.
He has had no apparent reaction to milk, soy, wheat or other common allergens.
Case presentation
A 2-year old boy with persistent eczema

- Physical examination
  - A well-appearing 2-year-old with normal growth.
  - His examination findings were normal except for mild, scattered eczema in antecubital and popliteal fossae.
## Serum IgE results

<table>
<thead>
<tr>
<th>Test</th>
<th>Result (kU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg</td>
<td>2.0</td>
</tr>
<tr>
<td>Milk</td>
<td>5.5</td>
</tr>
<tr>
<td>Peanuts</td>
<td>4.0</td>
</tr>
<tr>
<td>Soy</td>
<td>&lt;0.35</td>
</tr>
<tr>
<td>Wheat</td>
<td>9.5</td>
</tr>
</tbody>
</table>

The mother was advised to remove all egg, milk, and peanut from the child’s diet.

A represents allergen-specific antibodies
Serum IgE results

<table>
<thead>
<tr>
<th>Tests results</th>
<th>95% predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg</td>
<td>2.0 kU\textsubscript{A}/L</td>
</tr>
<tr>
<td>Milk</td>
<td>5.5 kU\textsubscript{A}/L</td>
</tr>
<tr>
<td>Peanuts</td>
<td>4.0 kU\textsubscript{A}/L</td>
</tr>
<tr>
<td>Soy</td>
<td>&lt;0.35 kU\textsubscript{A}/L</td>
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<tbody>
<tr>
<td>Egg 2.0 kU A/L</td>
<td>&gt;7 kU A/L</td>
</tr>
<tr>
<td>Milk 5.5 kU A/L</td>
<td>&gt;15 kU A/L</td>
</tr>
<tr>
<td>Peanuts 4.0 kU A/L</td>
<td>&gt;15 kU A/L</td>
</tr>
<tr>
<td>Soy &lt;0.35 kU A/L</td>
<td>&gt;65 kU A/L</td>
</tr>
<tr>
<td>Wheat 9.5 kU A/L</td>
<td>&gt;80 kU A/L</td>
</tr>
</tbody>
</table>

All tests – skin and IgE – need to be interpreted in the context of the clinical picture.

Oral food challenge

- Oral food challenges are the only definitive test if the diagnosis is not clear based on the history and test results.

- Oral food challenges can be used to establish whether a patient has outgrown a food allergy.
Case presentation

A 5-week old girl with bloody diarrhea
Case presentation

- Mary, a five-week-old girl,
- admitted to the ED with a 2-week history of worsening bloody diarrhea
Case presentation
A 5-week old girl with bloody diarrhea

For 2 weeks

Soy-based formula

Bloody diarrhea

CMF

No improvement
Case presentation
A 5-week old girl with bloody diarrhea

• No history of fever, vomiting, exposure to sick contacts

• No history of travel
Case presentation
A 5-week old girl with bloody diarrhea

<table>
<thead>
<tr>
<th>Past medical history</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>Normal</td>
</tr>
<tr>
<td>Perinatal</td>
<td>Normal</td>
</tr>
<tr>
<td>Delivery</td>
<td>No complications, BW 3.47 kg</td>
</tr>
<tr>
<td>Infancy</td>
<td>Meconium within 24 h</td>
</tr>
<tr>
<td>Immunizations</td>
<td>Up-to-date</td>
</tr>
<tr>
<td>Surgical history</td>
<td>No</td>
</tr>
<tr>
<td>Medical history</td>
<td>Nothing reported</td>
</tr>
<tr>
<td>Medications</td>
<td>No</td>
</tr>
<tr>
<td>Allergies</td>
<td>None known</td>
</tr>
</tbody>
</table>
Case presentation
A 5-week old girl with bloody diarrhea

• Family/social history
  – 1 older sister healthy
  – No one in the family with similar symptoms
  – Father (-)
  – Mother (-)
Case presentation
A 5-week old girl with bloody diarrhea

• On examination
  – Weight 3.6 kg (10 pc)
  – Afebrile
  – Abdomen soft with no massess
  – No hepatosplenomegaly
  – No anal fissures visible
  – The remainder of the examination was normal
Case presentation
A 5-week old girl with bloody diarrhea

- **Differential diagnosis**
  - Infectious enteritis
  - Cow’s milk allergy
  - Enterocolitis with Hirschsprung’s disease
  - NEC
  - Infectious enterocolitis
  - Intussusception
  - Volvulus
  - Meckel’s diverticulum
  - Duplication cysts
  - Bleeding diathesis
Case presentation
A 5-week old girl with bloody diarrhea

<table>
<thead>
<tr>
<th>Laboratory investigations</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>90 g/L</td>
</tr>
<tr>
<td>While blood cell count</td>
<td>16.8 x 10^9 /L</td>
</tr>
<tr>
<td>Platelets</td>
<td>675 x 10^9/L</td>
</tr>
<tr>
<td>Albumin</td>
<td>21 g/L</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>Normal</td>
</tr>
<tr>
<td>Renal function tests</td>
<td>Normal</td>
</tr>
<tr>
<td>Coagulation studies</td>
<td>Normal</td>
</tr>
</tbody>
</table>
**Case presentation**
**A 5-week old girl with bloody diarrhea**

<table>
<thead>
<tr>
<th>Laboratory investigations</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal radiograph</td>
<td>Normal gas pattern, no pneumatosis, diluted loops of bowel, or air/fluid levels</td>
</tr>
<tr>
<td>Stool cultures for bacteria, ova and parasites</td>
<td>Negative</td>
</tr>
<tr>
<td>Stool viruses</td>
<td>Negative</td>
</tr>
<tr>
<td>Abdominal ultrasound</td>
<td>Normal</td>
</tr>
<tr>
<td>Meckel’s scan</td>
<td>Normal</td>
</tr>
</tbody>
</table>
Case presentation
A 5-week old girl with bloody diarrhea

For 2 weeks

Soy formula

The response to the EHF was highly suggestive of CMA
Case presentation
A 5-week old girl with bloody diarrhea

If no response to the EHF, other causes of bloody diarrhea should be considered.
Case presentation

A 2-mo old boy with generalised redness of the skin
Case presentation
A 2-mo old boy with generalised redness of the skin

- A 2-month old boy
- Brought to the ED after developing generalised redness of the skin.
Case presentation
A 2-mo old boy with generalised redness of the skin

At 1 month

Clinical presentation
• Symptoms of infantile colic
  – a dairy-free diet for the mother was recommended

Exclusive breastfeeding
Case presentation
A 2-mo old boy with generalised redness of the skin

At 2 months

Clinical presentation
• 3 h later
  – generalised flushing of the skin

A cow milk based formula for the first time

Brought to the ED
Case presentation
A 2-mo old boy with generalised redness of the skin

• Uncomplicated term pregnancy
• BW 3.125 kg

• On physical examination
  • A well-appearing infant
  • Temperature 37.9°C
  • HR 193/min, BP 103/58
  • Weight 5.1 kg
  • The remainder of the examination was normal
Case presentation
A 2-mo old boy with generalised redness of the skin

Your diagnosis?

Testing?
Case presentation
A 2-mo old boy with generalised redness of the skin

• Laboratory tests
  – CBC
  – Electrolytes
  – Creatinine
  – Urinalysis

• All normal
Case presentation
A 2-mo old boy with generalised redness of the skin

<table>
<thead>
<tr>
<th>Allergy testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPT</td>
</tr>
<tr>
<td>• using an extract of cow milk protein and fresh milk</td>
</tr>
<tr>
<td>Milk-specific IgE levels</td>
</tr>
</tbody>
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**Case presentation**

A 2-mo old boy with generalised redness of the skin

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<th>Allergy testing</th>
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<tr>
<td><strong>SPT</strong></td>
<td></td>
</tr>
<tr>
<td>• using an extract of cow milk protein and fresh milk</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>Milk-specific IgE levels</strong></td>
<td>&lt;0.1 kU/l</td>
</tr>
<tr>
<td><strong>Open challenge with CMF</strong></td>
<td>Your decision?</td>
</tr>
</tbody>
</table>
**Case presentation**
A 2-mo old boy with generalised redness of the skin

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<th>Allergy testing</th>
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<td><strong>SPT</strong></td>
<td>Negative</td>
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<td>• using an extract of cow milk protein and fresh milk</td>
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</tr>
<tr>
<td><strong>Milk-specific IgE levels</strong></td>
<td>&lt;0.1 kU/l</td>
</tr>
<tr>
<td><strong>Open challenge with CMF</strong></td>
<td>Within 5 min of drinking 5 ml of the formula, the infant developed generalised hives</td>
</tr>
</tbody>
</table>
Case presentation
A 2-mo old boy with generalised redness of the skin

Your diagnosis?

Cow’s milk allergy

Learning point
CMA can present in infancy with a negative skin test
Case presentation
A 6-mo old boy referred due to suspected CMA
Case presentation

• A 6-mo old boy referred due to suspected CMA
Case presentation
A 6-mo old boy with suspected CMA

The first 2 mo of life
Fed with a CMF

Clinical presentation
• episodes of crying or fussing
• most frequently after a feeding
• infantile colic (?)
**Case presentation**

A 6-mo old boy with suspected CMA

**The first 2 mo of life**

Fed with a CMF

**Clinical presentation**

- episodes of crying or fussing
- most frequently after a feeding
- infantile colic (?)

- At 2 mo
  - EHF (Nutramigen)
Case presentation
A 6-mo old boy with suspected CMA

At 5 months

Clinical presentation
• Within minutes
  – facial flushing
  – hives
  – angioedema of the wrists and ankles

Given twice CMF & cereals
Case presentation
A 6-mo old boy with suspected CMA

Current visit

Clinical presentation

Father accidentally touched infant’s face after adding milk to his coffee
**Case presentation**

* A 6-mo old boy with suspected CMA

### Summary

<table>
<thead>
<tr>
<th>0-2 mo</th>
<th>2 mo</th>
<th>5 mo</th>
<th>6 mo (at visit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMF</td>
<td>Infantile colic (?)</td>
<td>Cereals &amp; CMF</td>
<td>Accident with milk</td>
</tr>
<tr>
<td>EHF (Nutramigen)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Images of skin condition](image1.jpg) ![Images of skin condition](image2.jpg)
Case presentation
A 6-mo old boy with suspected CMA

Your diagnosis?
Case presentation
A 6-mo old boy with suspected CMA

• SPT with milk extract
  – 8 mm wheal size compared with control
Case presentation
A 6-mo old boy with suspected CMA

Your diagnosis?

Cow’s milk allergy
Case presentation
A 6-mo old boy with suspected CMA

- Differential diagnosis

- Flushing and/or hives
  - Allergy
  - Infections
  - Malignancy
Treatment

- Avoidance of cow milk and dairy products

**When to consider an oral challenge to cow’s milk?**

Re-assessment every 6-12 mo from 12 mo of age to assess the possibility of reintroduction of cow’s milk
Case presentation
A 2-mo-old boy with failure to thrive
Case presentation
A 2-mo-old boy with failure to thrive

• A 2-month-old boy presented to the ED with failure to thrive.
Case presentation
A 2-mo-old boy with failure to thrive

- From birth to 1 mo
  - **CMF**; gained weight appropriately
- Then,
  - Spitting-up, gasping
  - Feeding prolonged, sometimes up to 2 h
  - Hungry?
- At around 1.5 mo, various CMFs
- Around 2 mo (10 d prior to admission)
  - CMF + infant cereal

<table>
<thead>
<tr>
<th>0-1 mo</th>
<th>1 to 1.5. mo</th>
<th>2 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMF</td>
<td>Various CMF</td>
<td>CMF + infant cereal</td>
</tr>
</tbody>
</table>
Case presentation
A 2-mo-old boy with failure to thrive

- On examination
  - Weight 2.8 kg
  - Temp 35.7°C
  - HR 139/min
  - RR 42/min
  - O₂ satur 98%
Case presentation
A 2-mo-old boy with failure to thrive

<table>
<thead>
<tr>
<th>Past medical history</th>
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<td>Immunizations</td>
</tr>
<tr>
<td>Surgical history</td>
</tr>
<tr>
<td>Medical history</td>
</tr>
<tr>
<td>Medications</td>
</tr>
<tr>
<td>Allergies</td>
</tr>
</tbody>
</table>
Case presentation
A 2-mo-old boy with failure to thrive

- Family history
  - Atopy
    - asthma, eczema, food allergy, penicillin allergy, allergic rhinitis and latex rhinitis in a number of family members
Case presentation
A 2-mo-old boy with failure to thrive

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete blood count</td>
<td>20% eosinophilis</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>normal</td>
</tr>
<tr>
<td>Renal function</td>
<td>normal</td>
</tr>
<tr>
<td>Glucose</td>
<td>2.8 mmol/l (50.5 mg%)</td>
</tr>
<tr>
<td>Albumin</td>
<td>21 g/l</td>
</tr>
<tr>
<td>CRP</td>
<td>52 mg/l</td>
</tr>
<tr>
<td>Liver function</td>
<td>normal</td>
</tr>
<tr>
<td>Thyroid, metabolic screen, sweat chloride</td>
<td>normal</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>6-8 WBC, 3-5 RBC/</td>
</tr>
<tr>
<td>Stool – microbiology</td>
<td>negative</td>
</tr>
</tbody>
</table>
Case presentation
A 2-mo-old boy with failure to thrive

Your diagnosis?

Cow’s milk allergy?
Hospitalization
Growth parameters

- **CMF**
  - Difficulties in gaining weight

- **EHF**
  - Quick recovery

- Discharged from the hospital on EHF, gaining weight steadily, with a diagnosis of CMA.

- No solid foods until 6 mo
- A dairy-free, soy-free diet
After discharge...

Numerous visits to the ED due to **severe vomiting and diarrhea** leading to dehydration
Case presentation
A 2-mo-old boy with failure to thrive

At 6 months

A teaspoon of an organic brown rice cereal

Clinical presentation

• Within 45 min
  – Vomiting
    • Continued for most of the day
  – Severe diarrhea

• Well next day

• Weight 9.07 kg (>50 pc)
• SPT to cow’s milk, rice, soybean, soymilk – all negative
Case presentation

A 2-mo-old boy with failure to thrive

At 6 months

A teaspoon of an organic brown rice cereal

Outcome

- Food protein-induced enterocolitis syndrome (rice, milk hypersensitivity?)
- Carrot, sweet potato, peas, green beans
  - Consumed with no problems
Case presentation
A 2-mo-old boy with failure to thrive

At 6 months

Clinical presentation

- 2 h later
  - Severe vomiting
  - Diarrhea

- A few days later, a small amount of oat given

- 1 h later
  - Vomiting
  - Bloody, profuse diarrhea

A teaspoon of an oat cereal
Case presentation
A 2-mo-old boy with failure to thrive

At 6 months

A teaspoon of an oat cereal

Outcome
- Gradual improvement over the following 24 h

Avoidance of oat recommended
Case presentation
A 2-mo-old boy with failure to thrive

At 6 months

Clinical presentation

- 2 h later
  - Profuse vomiting
  - Severe diarrhea
    - IV rehydration

- Next morning
  - Improvement

Avoidance of barley recommended

A small amount of barley
Case presentation
A 2-mo-old boy with failure to thrive

At 11 months
- Hospitalisation for a week for open food challenges
- Passed
  - Beef
  - Chicken
- Failed
  - Wheat
  - Corn
  - Potato
  - Egg

Oral food challenge
- Positive if there is repetitive vomiting, without other symptoms of an IgE-mediated reaction,

Avoidance of beef, chicken recommended

Case presentation
A 2-mo-old boy with failure to thrive

At 12 months

Clinical presentation
• After 1 h
  – Vomiting
  – No treatment was necessary

Avoidance of cow’s milk recommended
Case presentation
A 2-mo-old boy with failure to thrive

Your diagnosis?
Cow’s milk allergy?
Differential diagnosis

• Viral gastroenteritis
• Sepsis
• NEC
• Ileus
• Hirschsprung disease
• Intussusception
• Metabolic disorders
• GERD

• IgE-mediated reaction?
• Non-IgE-mediated reaction?
Learning points
Food protein-induced enterocolitis syndrome

- FPIES is a non–IgE-mediated GI food hypersensitivity
- Classic symptoms
  - profuse, repetitive vomiting, often with diarrhea, leading to acute dehydration and lethargy or weight loss and failure to thrive if chronic.
- Clinical diagnosis
  - Allergy tests not helpful
- Offending foods
  - CM protein, soy, rice,
  - also meats, grains, poultry, egg, fruits (and more)
- Prognosis
  - good

Learning points
Food protein-induced enterocolitis syndrome

- Classic symptoms
  - profuse, repetitive vomiting, often with diarrhea, leading to acute dehydration and lethargy or weight loss and failure to thrive if chronic.
Summary of growth parameters prior to diagnosis and after intervention
Take home messages

• Cow’s milk allergy
  – the most common food allergy in children

• Diagnosis
  – history, diagnostic elimination diets, SPT, specific IgE, and oral food challenges.

• Treatment
  – strict avoidance of the offending allergen

• Oral immunotherapy
  – not yet recommended for routine practice
Take home messages

• Prevention
  – Exclusive breastfeeding
    • 6 mo is a desirable goal (at least 4 mo)
  – Protein hydrolysates
    • only formulas with documented effect
  – Complementary foods
    • start at 4-6 months
    • no delayed introduction of allergenic foods
  – Probiotics, LCPUFA, vitamins, etc.
    • no specific recommendations; more studies needed
Clinical manifestations
Clinical manifestations
Clinical manifestations
Clinical manifestations
Clinical manifestations