Diagnosis & Rationale for Action against CMA: DRACMA
Chi è il bambino allergico al latte di mucca

Come si diagnostica

DRACMA

Esiste una prima scelta?

implementazione delle linee-guida

Scelta della formula e storia naturale della APLV
CM hypersensitivity

CM allergy  Nonallergic CM hypersensitivity (lactase deficit….)

IgE-mediated food allergy  Non-IgE-mediated CMA allergy (CM intolerance)

Fiocchi A, Schunemann H. Diagnosis and Rationale for Action against Cow’s Milk Allergy. The WAO DRACMA guideline. WAO Journal & Pediatr Allergy Immunol 2010; S1 (April), 1-105.
### Immediate allergic reactions

<table>
<thead>
<tr>
<th>I- anaphylaxis</th>
<th>OAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>II - GI</td>
<td>Immediate GI (vomting, bloody stools)</td>
</tr>
<tr>
<td></td>
<td>CMA in short bowel syndrome</td>
</tr>
<tr>
<td>III-respiratory</td>
<td>After ingestion</td>
</tr>
<tr>
<td></td>
<td>After inhalation</td>
</tr>
<tr>
<td>IV-cutaneous</td>
<td>Acute urticaria</td>
</tr>
<tr>
<td></td>
<td>Contact urticaria</td>
</tr>
</tbody>
</table>

Fiocchi A, Schunemann H. Diagnosis and Rationale for Action against Cow’s Milk Allergy. The WAO DRACMA guideline. WAO Journal & Pediatr Allergy Immunol 2010; S1 (April), 1-105.
### Delayed allergic reactions

<table>
<thead>
<tr>
<th>Category</th>
<th>Disease/Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I- Cutaneous</td>
<td>Atopic dermatitis</td>
</tr>
<tr>
<td>II - GI</td>
<td>GERD</td>
</tr>
<tr>
<td></td>
<td>Cryco-pharyngeal spasm</td>
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<tr>
<td></td>
<td>Pyloric stenosis</td>
</tr>
<tr>
<td></td>
<td>Allergic Eosinophil Oesophagitis</td>
</tr>
<tr>
<td></td>
<td>FPIES</td>
</tr>
<tr>
<td></td>
<td>Cow’s Milk Protein-Induced Enteropathy</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
</tr>
<tr>
<td></td>
<td>Severe Irritability (Colic)</td>
</tr>
<tr>
<td>III-respiratory</td>
<td>Milk-Induced Chronic Pulmonary Disease (Heiner’s Syndrome)</td>
</tr>
</tbody>
</table>

Fiocchi A, Schunemann H. Diagnosis and Rationale for Action against Cow’s Milk Allergy. The WAO DRACMA guideline. WAO Journal & Pediatr Allergy Immunol 2010; S1 (April), 1-105.
Proportion of children with persistent CMA: IgE-positive vs. IgE-negative

Saarinen KM. Clinical course and prognosis of cow’s milk allergy are dependent on milk-specific IgE status. J Allergy Clin Immunol. 2005;116:869-75
Quale latte

Chi è il bambino allergico al latte di mucca

DRACMA

Come si diagnostica

Esiste una prima scelta?

implementazione delle linee-guida

Scelta della formula e storia naturale della APLV
No recent guidelines on diagnosis and treatment of CMA


POSITION STATEMENT

Guidelines for the use of infant formulas to treat cows milk protein allergy: an Australian consensus panel opinion

Andrew S Kemp,* David J Hill,* Katrina J Allen, Kym Anderson, Geoffrey P Davidson, Andrew S Day, Ralph G Heine, Jane F Peake, Susan I Prescott, Albert W Shugg and John K Sinn

ABSTRACT

- Three types of infant formula (soy, extensively hydrolysed and amino acid) may be appropriate for treating cows milk protein allergy.
- Selection of a formula depends on the allergy syndrome to be treated.
- Extensively hydrolysed formula is recommended as first choice for infants under 6 months of age for treating immediate cows milk allergy (non-anaphylactic), food protein-induced enterocolitis syndrome, atopic eczema, gastrointestinal symptoms and food protein-induced proctocolitis.
- Soy formula is recommended as first choice for infants over 6 months of age with immediate food reactions, and for those with gastrointestinal symptoms or atopic dermatitis in the absence of failure to thrive.
- Amino acid formula is recommended as first choice in anaphylaxis and eosinophilic oesophagitis.
- If treatment with the initial formula is not successful, use of an alternative formula is recommended.

Guidelines for the diagnosis and management of cow’s milk protein allergy in infants

Yvan Vandenplas, Martin Brueton, Christophe Dupont, David Hill, Erika Isolauri, Sibylle Koletzko, Arnold P Oranje, Annamaria Staiano

This paper is freely available online under the BMJ Journals unlocked scheme, see http://adc.bmj.com/info/unlocked.dtl

Arch Dis Child 2007;92:902–908. doi: 10.1136/adc.2006.110999
Goat’s milk

26 children with CMA
SPT with goat’s milk: 100% positive
Challenge with goat’s milk: 24/26 positive
Blotting cross-inhibition: 100%

Rice hydrolysate

- Hypoallergenic

Piacentini GL. Allergenicity of a hydrolyzed rice infant formula in a guinea pig model. Ann Allergy Asthma Immunol 2003; 91:61-4

- Tolerated by polyallergic

Fiocchi A. Tolerance to a rice hydrolysate formula in children allergic to cow's milk and soy. Clin Experim Allergy 2003; 33:1576-80

- Tolerated in CMA

Fiocchi A. Children allergic to cow's milk tolerate a rice hydrolysate formula. Clin Exp Allergy 2006; 36:311-6

- Nutritionally adequate

The pediatrician faces CMA

- Time pressure
- Fatigue
- Lack of expertise
- Hostile patients or families
- Societal lack of the figure of the paediatric allergist
- Dominance by individuals with powerful personalities in scientific policy forums

WAO guidelines

Recommendations for standardization of clinical trials with Allergen Specific Immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce.

Allergy 2007: 62: 317–324
Implementing & disseminating DRACMA

- Publication in WAO journal
- Distribution to the WAO audience
- Presentation at the World Allergy Congress, BA December 2009
- Release at the Milan Congress, February 4°- 6°, 2010
- Generation of powerpoint presentations for different countries worldwide
- Implementation with educational events at national levels

WAO Special Committee on Food Allergy

Lead by Prof. Alessandro Fiocchi, the WAO Special Committee on Food Allergy brings together experts in the field from all over the world.

WAO Food Allergy Special Committee

- Chair: Alessandro Fiocchi, Italy
- Sami Bahna, USA
- Barbara Ballmer-Weber, Switzerland
- Martin Bozzola, Argentina
- Chng Hiok Hee, Singapore
- Motohiro Ebisawa, Japan
- Maria Antonieta Guzman, Chile
- Ralf Heine, Australia
- Gideon Lack, United Kingdom
- Haiqi Li, China
- Hugh Sampson, USA
- Stefan Vieths, Germany

The WAO Food Allergy Special Committee is in the process of developing an evidence-based document:

Cow’s Milk Allergy (CMA) in infancy and childhood: from suspicion to treatment

Why this document and why now?

A new CMA Document is necessary because:

- The current documents on CMA treatment are not global in scope
- The existing documents are not up-to-date
- Much of the existing research is not evidence-based

Format & Methodology:

This will be an evidence-based document using GRADE methodology. The authors of the document are supported by the WAO Evidence Based Medicine Special Committee. The GRADE methodology ensures the best grading of evidence and
CM allergy diagnosis and treatment

- Method: GRADE guidelines
- Setting: WAO
- Targets: Allergist, Paediatric allergist, General Paediatrician, Gastroenterologist, Dermatologist, Dietician, Food Chemist.
- Diagnosis and Rationale for Action against Cow’s Milk Allergy (DRACMA)
World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow’s Milk Allergy (DRACMA) Guidelines

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

Fiocchi A, Schunemann H. Diagnosis and Rationale for Action against Cow’s Milk Allergy. The WAO DRACMA guideline. WAO Journal & Pediatr Allergy Immunol 2010; S1 (April), 1-105.
# DRACMA: the document

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>Introduction and CMA epidemiology</td>
</tr>
<tr>
<td>2.</td>
<td>CM allergens</td>
</tr>
<tr>
<td>3.</td>
<td>Mechanisms of CMA</td>
</tr>
<tr>
<td>4.</td>
<td>Clinical presentation (history and symptoms)</td>
</tr>
<tr>
<td>5.</td>
<td>What do preceding guidelines say?</td>
</tr>
<tr>
<td>6.</td>
<td>Milk elimination in the diagnostic process of CMA</td>
</tr>
<tr>
<td>7.</td>
<td>GRADE questions on diagnosis</td>
</tr>
<tr>
<td>8.</td>
<td>When and how should oral food challenges be performed?</td>
</tr>
<tr>
<td>9.</td>
<td>Natural history</td>
</tr>
<tr>
<td>10.</td>
<td>What do preceding guidelines say?</td>
</tr>
<tr>
<td>11.</td>
<td>When can milk proteins be eliminated from the diet without substitute?</td>
</tr>
<tr>
<td>12.</td>
<td>GRADE questions on treatment</td>
</tr>
<tr>
<td>13.</td>
<td>Other milks (goat’s, ewe’s, mare’s, donkey’s, camel’s, …)</td>
</tr>
<tr>
<td>14.</td>
<td>Nutritional considerations</td>
</tr>
<tr>
<td>15.</td>
<td>Which is the 1st choice formula?</td>
</tr>
<tr>
<td>16.</td>
<td>GRADE questions on OIT</td>
</tr>
<tr>
<td>17.</td>
<td>Unmet needs. Recommendations for research. Recommendation for the implementation of the DRACMA guidelines. Periodical update of DRACMA.</td>
</tr>
</tbody>
</table>
The DRACMA worked with the GRADE members on this panel the clinical questions and their scope after various fine-tuning stages. The GRADE panelists independently searched the relevant literature for sections 9, 14, 18. Their analysis was independent of the other panel lists. For question formulation, guideline panel members explicitly rated the importance of all outcomes on a scale from 1–9, where the upper end of the scale (7–9) identifies outcomes of critical importance for decision making, ratings of 4–6 represent outcomes that are important but not critical and ratings of 1–3 are items of limited importance. Evidence summaries were prepared following the GRADE Working Group’s approach\(^1\)–\(^6\) based on systematic reviews done by an independent team of the GRADE Working Group members (JLB and HJS supported by 5 research associates).

Fiocchi A, Schunemann H. Diagnosis and Rationale for Action against Cow’s Milk Allergy. The WAO DRACMA guideline. WAO Journal & Pediatr Allergy Immunol 2010; S1 (April), 1-105.
Chi è il bambino allergico al latte di mucca

DRACMA

Come si diagnostica

Esiste una prima scelta?

implementazione delle linee-guida

Scelta della formula e storia naturale della APLV
Guidelines for diagnosis

• **Question 1.** Should *skin prick tests* be used to exclude IgE-mediated CMA in patients with low pre-test probability of CMA?

• **Question 2.** Should *in vitro specific IgE determination* be used to exclude IgE-mediated CMA in patients with low pre-test probability of CMA?

• **Question 3.** Should *in vitro specific IgE determination* be used to exclude IgE-mediated CMA in patients with low pre-test probability of CMA and a positive result of a skin prick test?

• **Question 4.** Should *in vitro specific IgE determination* be used to confirm the diagnosis of IgE-mediated CMA in patients with high pre-test probability of CMA?

• **Question 5.** Should *allergen microarrays* be used to confirm or exclude IgE-mediated CMA in patients with low pre-test probability of CMA?

• **Question 6.** Should *component-resolved diagnostics* be used to confirm or exclude IgE-mediated CMA in patients with low pre-test probability of CMA?

Records identified through database searching (all study designs)

EMBASE = 2203
MEDLINE = 2261
Total n = 4464
Records identified through database searching (all study designs) EMBASE = 2203 MEDLINE = 2261 Total n = 4464

Additional records identified through other sources (n = 0)

Records after duplicates removed (n = 3877)

Records screened (n = 3877)

Records excluded (n = 3619)

Full-text articles awaiting assessment (n = 15)

Full-text articles excluded, with reasons (n = 207)

Studies included in qualitative synthesis (n = 36)

Studies included in quantitative synthesis (meta-analysis) (n = 31)

CMA diagnosis

PRISMA diagram

Should skin prick tests be used for the diagnosis of IgE-mediated CMA in patients suspected of CMA?

Fiocchi A, Schunemann H. WAO Special Committee on Food Allergy. Diagnosis and Rationale for Action against Cow’s Milk Allergy. The DRACMA guideline. WAO Journal 2010; S1 (April), 1-105
Questions of diagnosis

Should skin prick tests be used for the diagnosis of IgE-mediated CMA in patients suspected of CMA?

Should in vitro specific IgE determination be used for the diagnosis of IgE-mediated CMA in patients suspected of CMA?

Should in vitro specific IgE determination be used for the diagnosis of IgE-mediated CMA in patients suspected of CMA and a positive SPT?

Should allergen microarrays or component resolved diagnostics be used for the diagnosis of IgE-mediated CMA in patients suspected of CMA and a negative SPT?

Fiocchi A, Schunemann H. WAO Special Committee on Food Allergy. Diagnosis and Rationale for Action against Cow’s Milk Allergy. The DRACMA guideline. WAO Journal 2010; S1 (April), 1-105
• In settings where oral food challenge is considered a requirement for making a diagnosis of IgE-mediated cow’s milk allergy, we recommend using oral food challenge with cow’s milk as the only test without performing a skin prick test as a triage or an add-on test to establish a diagnosis (strong recommendation | very low quality evidence).

**Underlying values and preferences**

• This recommendation places a relatively high value on avoiding resource consumption and the risk of anaphylactic reactions at home in patients who would be misclassified by a skin prick test alone. It places a lower value on anaphylactic reactions in a controlled setting that can be managed by experienced personnel when oral food challenge is performed. This recommendation also places a high value on avoiding any unnecessary treatment in patients who would be incorrectly classified by a skin prick test as allergic to cow’s milk.

**Remark**

• This recommendation applies to clinical practice settings. In research settings there may be compelling reasons to perform skin prick tests even though a food challenge test with cow’s milk is always being done.

Fiocchi A, Schunemann H. WAO Special Committee on Food Allergy. Diagnosis and Rationale for Action against Cow’s Milk Allergy. The DRACMA guideline. WAO Journal 2010; in press
APPENDIX 2. Question 1, Profile 1. Should Skin Prick Tests Be Used for the Diagnosis of IgE-Mediated CMA in Patients Suspected of CMA? Cut-Off ≥3 mm/All Populations

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Studies</th>
<th>Study Design</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Reporting Bias</th>
<th>Final Quality</th>
<th>Effect Per 1000&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positives (patients with CMA)</td>
<td>23 studies (2302 patients)</td>
<td>Consecutive or nonconsecutive series</td>
<td>Serious&lt;sup&gt;+&lt;/sup&gt;</td>
<td>None</td>
<td>Serious&lt;sup&gt;+&lt;/sup&gt;</td>
<td>None</td>
<td>Unlikely</td>
<td>@&lt;sup&gt;0&lt;/sup&gt;O low</td>
<td>Prev 80%: 536 Prev 40%: 268 Prev 10%: 67</td>
<td>Critical</td>
</tr>
<tr>
<td>True negatives (patients without CMA)</td>
<td>23 studies (2302 patients)</td>
<td>Consecutive or nonconsecutive series</td>
<td>Serious&lt;sup&gt;+&lt;/sup&gt;</td>
<td>None</td>
<td>Serious&lt;sup&gt;+&lt;/sup&gt;</td>
<td>None</td>
<td>Unlikely</td>
<td>@&lt;sup&gt;0&lt;/sup&gt;O low</td>
<td>Prev 80%: 108 Prev 40%: 324 Prev 10%: 486</td>
<td>Critical</td>
</tr>
<tr>
<td>False positives (patients incorrectly classified as having CMA)</td>
<td>23 studies (2302 patients)</td>
<td>Consecutive or nonconsecutive series</td>
<td>Serious&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Serious&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Serious&lt;sup&gt;+&lt;/sup&gt;</td>
<td>None</td>
<td>Unlikely</td>
<td>@&lt;sup&gt;0&lt;/sup&gt;O very low</td>
<td>Prev 80%: 92  Prev 40%: 276  Prev 10%: 414</td>
<td>Critical</td>
</tr>
<tr>
<td>False negatives (patients incorrectly classified as not having CMA)</td>
<td>23 studies (2302 patients)</td>
<td>Consecutive or nonconsecutive series</td>
<td>Serious&lt;sup&gt;+&lt;/sup&gt;</td>
<td>None</td>
<td>Serious&lt;sup&gt;+&lt;/sup&gt;</td>
<td>None</td>
<td>Unlikely</td>
<td>@&lt;sup&gt;0&lt;/sup&gt;O low</td>
<td>Prev 80%: 264 Prev 40%: 132 Prev 10%: 33</td>
<td>Critical</td>
</tr>
<tr>
<td>Inconclusive&lt;sup&gt;5&lt;/sup&gt;</td>
<td>1 study (310 patients)</td>
<td>Nonconsecutive series</td>
<td>—</td>
<td>—</td>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Important</td>
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<tr>
<td>Complications</td>
<td>Not reported</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Not important</td>
</tr>
<tr>
<td>Cost</td>
<td>Not reported</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Not important</td>
</tr>
</tbody>
</table>

<sup>*Based on combined sensitivity of 67% (95% CI: 64–70) and specificity of 74% (95% CI: 72–77).
</sup>1<sup>Most studies enrolled highly selected patients with atopic eczema or gastrointestinal symptoms, no study reported if an index test or a reference standard were interpreted without knowledge of the results of the other test, but it is very likely that those interpreting results of one test knew the results of the other; all except for one study that reported withdrawals did not explain why patients were withdrawn.
</sup>2<sup>Estimates of sensitivity ranged from 10 to 100%, and specificity from 14 to 100%; we could not explain it by quality of the studies, tests used or included population.
</sup>3<sup>There is uncertainty about the consequences for these patients; in some a diagnosis of other potentially serious condition may be delayed.
</sup>4<sup>One study in children <12 months of age reported 8% inconclusive challenge tests but did not report number of inconclusive skin prick tests.
</sup>
• In settings where oral food challenge is not considered a requirement in all patients suspected of IgE-mediated cow’s milk allergy, in patients with high pre-test probability of CMA we suggest using a skin prick test with a cut-off value of ≥3 mm as a triage test to avoid oral food challenge in those in whom the result of a skin prick test turns out positive (weak recommendation | low quality evidence).

Underlying values and preferences
• This recommendation places a relatively high value on avoiding burden, resource use and very likely anaphylactic reactions during the oral food challenge test (~50–70% food challenges avoided). It places a lower value on unnecessary treatment of around 1 in 20 patients misclassified as allergic to cow’s milk (5–6% false positive results).

Remark
• A high pre-test probability of CMA (~80%) can be estimated based on the history and would represent, for instance, patients who experienced an anaphylactic reaction in the past.

Fiocchi A, Schunemann H. WAO Special Committee on Food Allergy. Diagnosis and Rationale for Action against Cow’s Milk Allergy. The DRACMA guideline. WAO Journal 2010; in press
If SPT positive:

unnecessary treatment of 1 in 20 patients misclassified as CMA (5–6% false positive results).

Fiocchi A, Schunemann H. WAO Special Committee on Food Allergy. Diagnosis and Rationale for Action against Cow’s Milk Allergy. The DRACMA guideline. WAO Journal 2010; S1 (April), 1-105
• In settings where oral food challenge is not considered a requirement in all patients suspected of IgE-mediated cow’s milk allergy, in patients with low pre-test probability of CMA we suggest using a skin prick test with a cut-off value of ≥3 mm as a triage test to avoid oral food challenge in those in whom the result of a skin prick test turns out negative (weak recommendation | low quality evidence).

Underlying values and preferences: This recommendation places a relatively high value on avoiding burden and resource use with an oral food challenge test (~70% challenges avoided). It places a lower value on avoiding an allergic reaction (possibly a mild one) in around 1 in 25–50 patients misclassified as not having cow's milk allergy while they would actually be allergic to cow’s milk (2–4% false negative results).

Remark: A low pre-test probability of CMA (~10%) can be estimated based on the history and would represent, for instance, patients with unexplained gastrointestinal symptoms (e.g. gastroesophageal reflux).

Fiocchi A, Schunemann H. WAO Special Committee on Food Allergy. Diagnosis and Rationale for Action against Cow’s Milk Allergy. The DRACMA guideline. WAO Journal 2010; in press
If SPT negative: allergic reaction (possibly mild) in 1 in 25–50 patients misclassified as not having cow’s milk allergy while they would actually be allergic to cow’s milk (2–4% false negative results).
Recommendation 1.3

• In settings where oral food challenge is not considered a requirement for making a diagnosis of IgE-mediated cow’s milk allergy, in patients with average pre-test probability of CMA we suggest using an oral food challenge test with cow’s milk as the only test without performing a skin prick test with a cut-off value of ≥3 mm as a triage or an add-on test to establish a diagnosis.

Underlying values and preferences
• This recommendation places a high value on avoiding resource consumption and the risk of anaphylactic reactions at home in large proportion of patients who would be incorrectly classified by a skin prick test alone. It places a lower value on anaphylactic reactions in a controlled setting that can be managed by experienced personnel when oral food challenge is performed. This recommendation also places a high value on avoiding any unnecessary treatment in patients who would be incorrectly classified by a skin prick test as allergic to cow’s milk.

Remark: An average pre-test probability of CMA (~40%) can be estimated based on the history and presenting symptoms and would represent the majority of situations.

Fiocchi A, Schunemann H. WAO Special Committee on Food Allergy. Diagnosis and Rationale for Action against Cow’s Milk Allergy. The DRACMA guideline. WAO Journal 2010; in press.
If SPT positive: unnecessary treatment of 8 in 20 patients misclassified as CMA (40% false positive results).

Fiocchi A, Schunemann H. WAO Special Committee on Food Allergy. Diagnosis and Rationale for Action against Cow’s Milk Allergy. The DRACMA guideline. WAO Journal 2010; S1 (April), 1-105
Quale latte

Chi è il bambino allergico al latte di mucca

Come si diagnostica

DRACMA

Esiste una prima scelta?

implementazione delle linee-guida

Scelta della formula e storia naturale della APLV
<table>
<thead>
<tr>
<th>Informal Question</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Should <strong>extensively hydrolysed cow’s milk formulae</strong> be used in patients with</td>
<td>soy, rice, amino acid formula, other cow’s milk hydrolysed formula</td>
<td>symptoms, quality of life of a patient &amp; caregivers, failure to thrive,</td>
</tr>
<tr>
<td>CMA?</td>
<td></td>
<td>iron, calcium, vitamin D deficiency, protein, fats and other minerals and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>vitamins</td>
</tr>
<tr>
<td>Should <strong>soy-based formulae</strong> be used in patients with CMA?</td>
<td>other soy-based formula, rice, amino acid, cow’s milk hydrolysed formula</td>
<td>deficiency, weight/height, excessive weight gain, anthropometric values</td>
</tr>
<tr>
<td>Should <strong>rice hydrolysate</strong> be used in patients with CMA?</td>
<td>soy, amino acid, cow’s milk hydrolysed formula</td>
<td>secondary sensitization to that formula, allergic reaction (milk hydrolyzed formula), allergic reaction to soy, other adverse effects</td>
</tr>
<tr>
<td>Should <strong>amino acid formulae</strong> be used in patients with CMA?</td>
<td>soy, rice, cow’s milk hydrolysed formula</td>
<td>unpleasant taste, resource utilization (cost), burden for parents, cross-reactivity with cow’s milk (soy formula)</td>
</tr>
</tbody>
</table>

Fiocchi A, Schunemann H. WAO Special Committee on Food Allergy. Diagnosis and Rationale for Action against Cow’s Milk Allergy. The DRACMA guideline. WAO Journal 2010; in press
<table>
<thead>
<tr>
<th>Condition Description</th>
<th>RH</th>
<th>ML</th>
<th>ME</th>
<th>MG</th>
<th>AM</th>
<th>AS</th>
<th>AF</th>
<th>MB</th>
<th>JB</th>
<th>HS</th>
<th>KB</th>
<th>SB</th>
<th>GL</th>
<th>SV</th>
<th>m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe symptoms of CMA (severe laryngeal edema, severe asthma, anaphylaxis)</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>8</td>
<td>9</td>
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<td>8</td>
<td>9</td>
<td>8</td>
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<td>9</td>
</tr>
<tr>
<td>Allergic reaction to protein in the formula</td>
<td>8</td>
<td>4</td>
<td>8</td>
<td>6</td>
<td>9</td>
<td>5</td>
<td>9</td>
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<td>Moderate symptoms of CMA (mild laryngeal edema, mild asthma)</td>
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<td>Failure to thrive</td>
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<td>Enteropathy, enteropathy/proctocolitis</td>
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<td>Protein and fats deficiency</td>
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<td>Iron, calcium, vitamin D, and other minerals and vitamins deficiency</td>
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<td>Weight/height</td>
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<tr>
<td>Mild symptoms of CMA (erythema, urticaria, angioedema, pruritus, vomiting, diarrhoea, rhinitis, conjunctivitis)</td>
<td>9</td>
<td>7</td>
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Fiocchi A, Schunemann H. WAO Special Committee on Food Allergy. Diagnosis and Rationale for Action against Cow’s Milk Allergy. The DRACMA guideline. WAO Journal 2010; in press.
<table>
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<tr>
<th></th>
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<th>MB</th>
<th>JB</th>
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<th>SB</th>
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<td>duration of CMA</td>
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<td>9</td>
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<td>8</td>
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<td>unpleasant taste (child may refuse to take the formula)</td>
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<td>quality of life of caregivers</td>
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<td>anthropometric values</td>
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<td>cross-reactivity with cow’s milk</td>
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<td>development of secondary sensitization to proteins present in a formula</td>
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<td>6</td>
<td>4</td>
<td>1</td>
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<td>excessive weight gain</td>
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<td>7</td>
<td>3</td>
<td>7</td>
<td>5</td>
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<tr>
<td>burden for parents: need to change from bottles to beakers (milk hydrolysed, rice, and amino acid formulas are high in sugar)</td>
<td>5</td>
<td>2</td>
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<td>7</td>
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<td>sexual maturation (development of secondary and tertiary sexual traits)</td>
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<td>3</td>
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<td>8</td>
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<td>7</td>
<td>4</td>
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</table>

Fiocchi A, Schunemann H. WAO Special Committee on Food Allergy. Diagnosis and Rationale for Action against Cow’s Milk Allergy. The DRACMA guideline. WAO Journal 2010; in press
<table>
<thead>
<tr>
<th>Milk/formula</th>
<th>Cost per liter [US$ (Euro)]</th>
<th>Cost per 6 months [US$ (Euro)]</th>
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<tr>
<td>normal cow’s milk</td>
<td>1.2 (0.9)</td>
<td>100 (75)</td>
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<tr>
<td>normal formula</td>
<td>2.5 (2.0)</td>
<td>230 (160)</td>
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<tr>
<td>extensively hydrolysed formula</td>
<td>9 (6)</td>
<td>800 (550)</td>
</tr>
<tr>
<td>soy formula</td>
<td>7 (5)</td>
<td>750 (450)</td>
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<tr>
<td>rice formula</td>
<td>9 (6)</td>
<td>800 (550)</td>
</tr>
<tr>
<td>amino acid formula</td>
<td>20 (14)</td>
<td>1800 (1250)</td>
</tr>
</tbody>
</table>

Fiocchi A, Schunemann H. WAO Special Committee on Food Allergy. Diagnosis and Rationale for Action against Cow’s Milk Allergy. The DRACMA guideline. WAO Journal 2010; in press
Guidelines for replacement formula choice

- **Question 7.** Should *cow’s milk hydrolysed formulae* be used in patients with CMA?
- **Question 8.** Should *soy-based formulae* be used in patients with CMA?
- **Question 9.** Should *rice hydrolysate* be used in patients with CMA?
- **Question 10.** Should *amino acid formulae* be used in patients with CMA?
- **Question 11.** Can *immunotherapy* be used in patients with CMA?

Records identified through database searching (all study designs)

- EMBASE = 724
- MEDLINE = 574
- CENTRAL = 908

(Total n = 2206)
Records identified through database searching (all study designs)
- EMBASE = 724
- MEDLINE = 574
- CENTRAL = 908
(Total n = 2206)

Additional records identified through other sources (n = 0)

Records after duplicates removed (n = 1579)

Records screened (n = 1579)

Records excluded (n = 1525)

Full-text articles assessed for eligibility (n = 54)

Full-text articles excluded, with reasons (n = 44)

Studies included in qualitative synthesis (n = 10)

Studies included in quantitative synthesis (meta-analysis) (n = 7)

Should extensively hydrolysed milk, soy, amino acid or extensively hydrolysed rice formula be used in patients with cow’s milk allergy?

Fiocchi A, Schunemann H. WAO Special Committee on Food Allergy. Diagnosis and Rationale for Action against Cow’s Milk Allergy. The DRACMA guideline. WAO Journal 2010; S1 (April), 1-105
• In children with IgE-mediated cow’s milk allergy at high risk of anaphylactic reactions (prior history of anaphylaxis and currently not using extensively hydrolysed milk formula), we suggest amino acid formula rather than extensively hydrolysed milk formula (conditional recommendation | very low quality evidence).

Underlying values and preferences

• This recommendation places a relatively high value on avoiding possible anaphylactic reactions and a lower value on avoiding the direct cost of amino acid formula in settings where the cost of amino acid formulas is high.

Remark

• In controlled settings a trial feeding with an extensively hydrolysed milk formula may be appropriate

Fiocchi A, Schunemann H. WAO Special Committee on Food Allergy. Diagnosis and Rationale for Action against Cow’s Milk Allergy. The DRACMA guideline. WAO Journal 2010; S1 (April), 1-105
Expensive, but necessary

Fiocchi A, Schunemann H. WAO Special Committee on Food Allergy. Diagnosis and Rationale for Action against Cow’s Milk Allergy. The DRACMA guideline. WAO Journal 2010; S1 (April), 1-105
In children with IgE-mediated cow’s milk allergy at low risk of anaphylactic reactions (no prior history of anaphylaxis or currently on extensively hydrolysed milk formula), we suggest extensively hydrolysed milk formula over amino acid formula (conditional recommendation | very low quality evidence).

Underlying values and preferences
This recommendation places a relatively high value on avoiding the direct cost of amino acid formula in settings where the cost of amino acid formula is high. In settings where the cost of amino acid formula is lower the use of amino acid formula may be equally reasonable.

Remark
Extensively hydrolysed milk formula should be tested in clinical studies before being used. (American Academy of Pediatrics Committee on Nutrition 2000 [19]) If a new formula is introduced, one should carefully monitor if any adverse reactions develop after first administration.

Fiocchi A, Schunemann H. WAO Special Committee on Food Allergy. Diagnosis and Rationale for Action against Cow’s Milk Allergy. The DRACMA guideline. WAO Journal 2010; S1 (April), 1-105
- Controlled risk of sensitisation
  - less expensive
  - low risk of anaphylactic reactions
• In children with IgE-mediated cow’s milk allergy, we suggest extensively hydrolysed milk formula rather than soy formula (conditional recommendation | very low quality evidence).

Underlying values and preferences
• This recommendation places a relatively high value on avoiding adverse reactions to soy formula, and a relatively low value on an inferior acceptance of the extensively hydrolysed formula and resource utilization. In settings where relative importance of resource expenditure is lower an alternative choice may be equally reasonable.

Remark
• Soy should not be used in first 6 months of life, because of nutritional risks.
• Growth, (length and weight for age z-score) adequate, but trend towards improved growth in extensively hydrolysed formula compared to soy formula.

• Fewer children had allergic reaction to extensively hydrolysed formula than to soy formula (relative risk: 0.18; 95% CI: 0.05 to 0.71).

• Fewer children developed secondary sensitization to eHF than to soy formula.

Fiocchi A, Schunemann H. WAO Special Committee on Food Allergy. Diagnosis and Rationale for Action against Cow’s Milk Allergy. The DRACMA guideline. WAO Journal 2010; S1 (April), 1-105
Recommendation 7.4

- In children with IgE-mediated cow’s milk allergy, extensively hydrolysed milk formula rather than extensively hydrolysed rice formula.

  (conditional recommendation | very low quality evidence).

*Underlying values and preferences*

- This recommendation places a relatively high value on wide availability of extensively hydrolysed milk formulae relative to hydrolysed rice formulae.

Fiocchi A, Schunemann H. WAO Special Committee on Food Allergy. Diagnosis and Rationale for Action against Cow’s Milk Allergy. The DRACMA guideline. WAO Journal 2010; S1 (April), 1-105
Rice milk is a perfect substitute for people with a lactose, dairy or soy intolerance or allergy. It is lactose free, dairy free, soy free and kosher. Our rice milk powder is made from milling sound broken long grain white rice, and blended with the remaining ingredients to produce the final product. Used as a substitute for milk and milk powder.

**Ingredients:** Rice Flour, Maltodextrin, Vegetable fat, Fructose, Xanthan Gum, Salt, Vitamin & mineral supplement, Nature Identical flavour.
Generalized edema more evident (A) in the face and (B) in the legs (fovea sign)
<table>
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<tr>
<th>Clinical Presentation</th>
<th>1st Choice</th>
<th>2nd Choice</th>
<th>3rd Choice</th>
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<tr>
<td>Anaphylaxis</td>
<td>AAF*</td>
<td>eHF*</td>
<td>SF</td>
</tr>
<tr>
<td>Immediate gastrointestinal allergy</td>
<td>eHF†</td>
<td>AAF†/SF**</td>
<td></td>
</tr>
<tr>
<td>Food protein-induced enterocolitis syndrome</td>
<td>eHF†</td>
<td>AAF†</td>
<td></td>
</tr>
<tr>
<td>Asthma and rhinitis</td>
<td>eHF‡</td>
<td>AAF‡</td>
<td></td>
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<tr>
<td>Acute urticaria or angioedema</td>
<td>eHF‡</td>
<td>AAF‡</td>
<td></td>
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<tr>
<td>Atopic dermatitis</td>
<td>eHF‡</td>
<td>AAF‡</td>
<td></td>
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<tr>
<td>Gastroesophageal reflux disease (GERD)</td>
<td>eHF†</td>
<td>AAF†</td>
<td></td>
</tr>
<tr>
<td>Allergic eosinophilic oesophagitis</td>
<td>AAF†</td>
<td>eHF†</td>
<td></td>
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<tr>
<td>Cow’s milk protein-induced enteropathy</td>
<td>eHF‡</td>
<td>AAF‡</td>
<td></td>
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<tr>
<td>Constipation</td>
<td>eHF†</td>
<td>AAF†</td>
<td>Donkey milk§§</td>
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<td>Severe irritability (colic)</td>
<td>eHF†</td>
<td>AAF†</td>
<td></td>
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<td>CM protein-induced gastroenteritis and proctocolitis</td>
<td>eHF†</td>
<td>AAF†</td>
<td></td>
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<tr>
<td>Milk-induced chronic pulmonary disease (Heiner’s syndrome)**</td>
<td>AAF§§</td>
<td>SF</td>
<td>eHF</td>
</tr>
</tbody>
</table>

*Recommendation 7.1.
†Recommendation 7.2.
‡If AAF refusal.
§Subject to local availability, HRF can be considered instead than eHF (7.4).
||§§Subject to negative SPT with the specific formula (panel recommendation).
||§*AAF if a relatively high value on avoiding sensitization by SF and/or a low value on resource expenditure are placed.
||§‡SF if a relatively low value on avoiding sensitization by SF and/or a high value on resource expenditure are placed.
||§†Subject to local availability.
||§‡This suggestion attributes a high value on avoiding exposure to even residual antigenic cow’s milk proteins.
||§§Based on reports from one case series (section 15).
||**Given that more than 50% of such children are allergic to soy, a careful clinical evaluation is necessary (panel recommendation).
Guidelines for the use of infant formulas to treat cows milk protein allergy: an Australian consensus panel opinion

Andrew S Kemp,* David J Hill,* Katrina J Allen, Kym Anderson, Geoffrey P Davidson, Andrew S Day, Ralph G Heine, Jane E Peake, Susan L Prescott, Albert W Shugg and John K Sinn

2 Formula feeding in syndromes associated with cows milk protein allergy*

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Onset of reaction</th>
<th>Maternal elimination of CMP if breastfeeding?</th>
<th>Choice of formula</th>
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<tr>
<td>Immediate reaction</td>
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<td>First†</td>
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<tr>
<td>Immediate food allergy</td>
<td>&lt; 1 h</td>
<td>Yes</td>
<td>eHF (&lt; 6 months)</td>
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<td></td>
<td></td>
<td></td>
<td>Soy (&gt; 6 months)</td>
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<tr>
<td>Anaphylaxis</td>
<td>&lt; 1 h</td>
<td>Yes</td>
<td>AAF (followed by urgent consultation with paediatric allergist)</td>
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<tr>
<td>Food protein-induced enterocolitis syndrome</td>
<td>1–3 h</td>
<td>No</td>
<td>eHF</td>
</tr>
</tbody>
</table>

# Position Statement

Guidelines for the use of infant formulas to treat cows milk protein allergy: an Australian consensus panel opinion

Andrew S Kemp,* David J Hill,* Katrina J Allen, Kym Anderson, Geoffrey P Davidson, Andrew S Day, Ralph G Heine, Jane E Peake, Susan L Prescott, Albert W Shugg and John K Sinn

<table>
<thead>
<tr>
<th>Delayed reaction</th>
<th>Hours to days</th>
<th>Yes</th>
<th>eHF (&lt;6 months or &gt;6 months with FTT)</th>
<th>AAF</th>
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</thead>
<tbody>
<tr>
<td>Atopic eczema</td>
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<td>eHF (&lt;6 months or &gt;6 months with FTT)</td>
<td>AAF</td>
<td>—</td>
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<tr>
<td>Soy (&gt;6 months, no FTT)</td>
<td></td>
<td></td>
<td>eHF (&lt;6 months or &gt;6 months with FTT)</td>
<td>AAF</td>
<td>—</td>
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<tr>
<td>Gastrointestinal syndromes, GORD, allergic eosinophilic gastroenteritis, food</td>
<td></td>
<td></td>
<td>eHF (&lt;6 months or &gt;6 months with FTT)</td>
<td>AAF</td>
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<tr>
<td>protein-induced enteropathy, constipation, severe irritability (colic)</td>
<td></td>
<td></td>
<td>eHF (&lt;6 months or &gt;6 months with FTT)</td>
<td>AAF</td>
<td>—</td>
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<tr>
<td>Soy (&gt;6 months, no FTT)</td>
<td></td>
<td></td>
<td>eHF (&lt;6 months or &gt;6 months with FTT)</td>
<td>AAF</td>
<td>—</td>
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<tr>
<td><strong>Food protein-induced proctocolitis</strong></td>
<td></td>
<td></td>
<td></td>
<td>AAF</td>
<td>—</td>
</tr>
<tr>
<td>Formula-fed</td>
<td>&gt;24 h</td>
<td>—</td>
<td>eHF</td>
<td>—</td>
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<td>Breastfed</td>
<td>&gt;24 h</td>
<td>—</td>
<td></td>
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<tr>
<td>Eosinophilic oesophagitis in infants</td>
<td>Days to weeks</td>
<td>Yes</td>
<td>AAF</td>
<td>—</td>
<td>—</td>
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How to Use These Recommendations

The DRACMA guidelines are not intended to impose a standard of care for individual countries and jurisdictions. They should, as any guideline, provide a basis for rational decisions for clinicians and their patients about the management of cow’s milk allergy. Clinicians, patients, third-party payers, institutional review committees, other stakeholders, or the courts should never view these recommendations as dictates. Strong recommendations based on high quality evidence will apply to most patients for whom these recommendations are made, but they may not apply to all patients in all circumstances. No recommendation can take into ac-

Fiocchi A, Schunemann H. Diagnosis and Rationale for Action against Cow’s Milk Allergy. The WAO DRACMA guideline. WAO Journal & Pediatr Allergy Immunol 2010; S1 (April), 1-105.
Quale latte

Chi è il bambino allergico al latte di mucca

Come si diagnostica

DRACMA

Esiste una prima scelta?

Implementazione delle linee-guida

Scelta della formula e storia naturale della APLV
Next steps - 1

1. DRACMA publication: WAO Journal, April 2010 – PAI, May 2010
2. Milan Meeting proceedings: JACI 2010
3. GLORIA educational modules
4. World allergy societies endorsement & input sought
5. World sister societies endorsement & input sought
6. DRACMA symposia during allergy and nutrition society meetings
7. Outreach towards patient organisations
8. Creation of an international bureau for dissemination and update
Next steps - 2

The international bureau for dissemination and update:

a. Translation and publication
b. Educational materials
c. Translational updates to link-up with basic & clinical R&D and the industry
d. Communication with government agencies and NGOs
e. Cultural adaptation
Quale latte

Chi è il bambino allergico al latte di mucca

Come si diagnostica

DRACMA

Esiste una prima scelta?

Implementazione delle linee-guida

Scelta della formula e storia naturale della APLV
<table>
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<th>Year (author)</th>
<th>Publication type</th>
<th>Title</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999 - Host</td>
<td>Joint position statement ESPACI-ESPGHAN</td>
<td>Dietary products used in infants for treatment and prevention of food allergy.</td>
<td>Primary Treatment</td>
</tr>
<tr>
<td>2000</td>
<td>Position statement (AAP)</td>
<td>Hypoallergenic Formulas</td>
<td>Primary</td>
</tr>
<tr>
<td>2004 - Muraro</td>
<td>Literature review (EAACI)</td>
<td>Dietary prevention of allergic diseases in infants and small children.</td>
<td>Primary</td>
</tr>
<tr>
<td>2006 – Adverse Reactions to Foods Committee</td>
<td>Literature review (ACAAI)</td>
<td>Food allergy and the introduction of solid foods to infants: a consensus document</td>
<td>Primary</td>
</tr>
</tbody>
</table>

# Recommendations for avoidance or delayed introduction of allergenic foods

<table>
<thead>
<tr>
<th>Year (author)</th>
<th>Publication type</th>
<th>Title</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006 - Osborne</td>
<td>Cochrane systematic review</td>
<td>Formulas containing hydrolysed protein for prevention of allergy and food protein intolerance in infants.</td>
<td>Primary</td>
</tr>
<tr>
<td>2006 - Kramer</td>
<td>Cochrane systematic review</td>
<td>Maternal dietary antigen avoidance during pregnancy and/or lactation, or both, for preventing or treating atopic disease in the child.</td>
<td>Primary</td>
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<tr>
<td>2007 - Prescott</td>
<td>Position statement ASCIA</td>
<td>Primary allergy prevention in children</td>
<td>Primary</td>
</tr>
</tbody>
</table>

Pregcott S, Fiocchi A. Avoidance or exposure to foods in prevention and treatment of food allergy? Corr Opin Allergy Clin Immunol 2010;10:258–66
Exposures associated with peanut allergy

“Baked-Milk” Study

• 100 milk-allergic subjects enrolled
  - mean age: 6.7 yrs; range: 2.6 – 17.3 yrs
  - 62% males
• Challenged with baked muffin, waffle & uncooked milk [~ 3 oz milk protein/baked product]
• Milk challenges:
  - 77 HCM tolerant [baked-milk products only]
  - 23 Allergic [could not tolerate milk in any form]
“Baked Milk” Study

Re-challenge

 HM-Reactive
N=23

HM- Reactive
N=23

Strict avoidance for 12 months

HM OFC
N=100

Not challenged to NHM due to highly predictive test results;
N=34

HM-Tolerant
N=77

NHM OFC
N=43

NHM Reactive
N=34

NHM-Tolerant
N=9

HM Diet*

3 mo

48 mo

*The subjects in the HM Diet group will be followed every 6 months for up to 48 months or until become cow’s milk-tolerant.

Changes in Milk-specific PST, IgE & IgG₄ in HCM-Tolerant Subjects

Milk PST decreases and casein-specific IgG₄ increases

Eliciting dose at diagnostic challenge in 112 CMA children

<table>
<thead>
<tr>
<th>ED</th>
<th>n</th>
<th>%</th>
<th>Epinephrine?</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 mL</td>
<td>14</td>
<td>12.5</td>
<td>12.5</td>
</tr>
<tr>
<td>0.4 mL</td>
<td>10</td>
<td>8.9</td>
<td>21.4</td>
</tr>
<tr>
<td>1.4 mL</td>
<td>20</td>
<td>17.9</td>
<td>39.3</td>
</tr>
<tr>
<td>4.4 mL</td>
<td>20</td>
<td>19.6</td>
<td>60.7%</td>
</tr>
<tr>
<td>14.4 mL</td>
<td>12</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td>44.4 mL</td>
<td>14</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>144.4 mL</td>
<td>100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A vastly altered approach to food allergy management

1. The change from a milk avoidance diet to a milk-limited diet could provide a substantial improvement to the quality of life of milk-allergic individuals.

2. The frequency of prolonged or permanent milk allergy may be reduced if this type of diet can augment the development of tolerance.

3. These children receiving limited, extensively heated milk essentially reported no acute milk-induced allergic reactions as a result of this diet.

Modification of allergenicity as a promoter of tolerance?

Protection on CMA with hypoallergenic formula in high risk infants: seen for both partially and extensively hydrolysed formula.

not allergen avoidance

but

allergen modification?

In vivo (skin prick test and/or challenge) studies on residual allergenicity of CM hydrolysates

<table>
<thead>
<tr>
<th>Hydrolysate</th>
<th>Sampson</th>
<th>Wahn</th>
<th>Ragno</th>
<th>Hill</th>
<th>Giampietro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutramigen</td>
<td>P</td>
<td>P</td>
<td>-</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Pregestimil</td>
<td>-</td>
<td>P</td>
<td>-</td>
<td>N</td>
<td>-</td>
</tr>
<tr>
<td>Alimentum</td>
<td>P</td>
<td>-</td>
<td>P/C</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Profylac</td>
<td>-</td>
<td>P/C</td>
<td>-</td>
<td>P/C</td>
<td>C</td>
</tr>
<tr>
<td>Nutrilon Pepti</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>P/C</td>
<td>C</td>
</tr>
<tr>
<td>Alfarè</td>
<td>-</td>
<td>P/C</td>
<td>-</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Nan HA</td>
<td>-</td>
<td>-</td>
<td>P/C</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

P= skin prick-positive; C= challenge positive; N= negative; - = not tested

Terracciano L. Use of hydrolysates in the treatment of cow’s milk allergy
Ann Allergy Asthma Immunol 2002; 89 (Suppl), 86-90
Loss of tolerance after an exclusion diet

The anecdote

At the age of 18 she inadvertently entered a dairy shop and inhaled milk proteins experiencing a fatal reaction (asthma, urticaria, angioedema).

The non sequitur

In our case the temporal link between the diet and the development of symptoms is suggestive for a causal relationship between the two.

The literature


Barbi et al. Allergy 2004;59:668
Acute allergic reactions to CM after elimination in children with AEDS?

• 11 children with eczema and prolonged cow's milk (CM) elimination
• Retrospective evaluation of the exposure to CM, sensitization and reactions to accidental ingestion
• Before the elimination period all children consumed CM without acute reactions.
• During the elimination period, eight of 11 children developed severe acute allergic reactions to CM after accidental ingestion.

“There is a considerable chance of developing acute allergic reactions to CM after elimination in children without previous problems after CM intake”.

Flinterman AE. Acute allergic reactions in children with AEDS after prolonged cow’s milk elimination diets. Allergy 2006; 61:370-4
Wrongful conviction: allergens found guilty of allergy epidemic

Prescott S, Fiocchi A. Avoidance or exposure to foods in prevention and treatment of food allergy? Curr Opin Allergy Clin Immunol 2010,10:258–66
There is a considerable chance of developing acute allergic reactions to CM after elimination in children without previous problems after CM intake.

There is a considerable chance of developing tolerance to CM after elimination in children with previous problems after CM intake.
At least a subset of children treated with SOTI acquire definitive tolerance.

Food-specific IgE levels decrease over 24 months.

Such studies have been interpreted as not lending support for the proposition that continued exposure to allergen will increase the IgE level or delay the acquisition of tolerance.


MiCMAC cohort: survival curve

Profile of the child with long-term CMA

1. Presenting with asthma
2. CM sensitisation at ImmunoCAP®
3. Co-sensitisation to foods at SPT
4. Co-sensitisation to beef
5. Co-sensitisation to grass and dog dander
6. Co-sensitisation to less prevalent allergens (soy)

Methods: randomisation

Children breastfed, or symptomatic despite soy formula prescription were switched to a different formula:

Jan – Apr: SF

May – Aug: eHF

Sept – Dec: HRF

An elemental formula (Neocate®, SHS, UK) was administered as rescue therapy
Results: mean duration of CMA

\[ \mu_40.2 \]
\[ \mu_24.3 \]

\[ \mu_24.3 \]

\[ P = 0.018; \text{log-rank test} \]
Polysensitised children are insensitive to avoidance.

Profile of the child with long-term CMA

1. Presenting with asthma
2. CM sensitisation at ImmunoCAP®
3. Co-sensitisation to foods at SPT
4. Co-sensitisation to beef
5. Co-sensitisation to grass and dog dander
6. Exposed to CM proteins
7. Co-sensitisation to less prevalent allergens

Exposure and natural history

Is it neutral?

... decrease tolerance?

..increase tolerance?
LEAP Study – Immune Tolerance Network

Recruitment:
- 4-8 month old children with eczema and/or egg allergy

Randomisation/Stratification:
- Intervention group: Peanut consumed 3 times per week (n≈240)
- Control Group (n≈240): Peanut avoidance

Age:
- 4-8 months
- 1 yr
- 2.5 yr
- 5 yr

WAO Meeting Bangkok 2007 - Courtesy of Stephen Durham,
WAO Meeting Bangkok 2007 - Courtesy of Stephen Durham,
dilemmas that have not yet been addressed. Based on the currently available evidence, there can only be one verdict beyond any reasonable doubt: to uphold the current approaches until such time that there is sufficient evidence to indicate that these should be changed. Again, the burden of proof lies with those who are proposing change, and so far clear evidence has not been produced.

Prescott S, Fiocchi A. Avoidance or exposure to foods in prevention and treatment of food allergy? Curr Opin Allergy Clin Immunol 2010,10:258–66
Prescott S, Fiocchi A. Avoidance or exposure to foods in prevention and treatment of food allergy? Curr Opin Allergy Clin Immunol 2010, 10:258–66
Prescott S, Fiocchi A. Avoidance or exposure to foods in prevention and treatment of food allergy? Curr Opin Allergy Clin Immunol 2010,10:258–66
Diet therapy: not for everybody suspicious – not for all the sensitised. Just for the challenge+

Strict avoidance:
  a. Prevents severe reaction risk
  b. Does not worsen food allergy
  c. Helps some to reach tolerance

Some avoidance:
  a. Possible in some cases
  b. Could expose to severe reactions
  c. Could modulate food allergy: tolerance? persistence?

Does OIT modify natural history?
We look forward to seeing you in Dubai!