Diagnosis and Rationale for Action against Cow’s Milk Allergy

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Diagnosis and Rationale for Action against Cow’s Milk Allergy

World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow’s Milk Allergy (DRACMA) Guidelines

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WAO Journal, Abril 2010
Pediatr Allergy Immunol 2010;21, S21:1-125
Cow’s Milk Allergy (CMA)

- More than 60% of children with CMA, will develop moderate to severe eczema, respiratory allergy and asthma.

Newborns with early introduction of milk formulas have increased risk of more severe cow’s milk allergy.

Terraciano Clin Exp Allergy 2010 apr 40(4):637-42
Outcome

- 85% children with CMA develop clinical tolerance at 5 years old

- Direct relationship with decrease of specific IgE.

Outcome

- Food tolerance is faster in children who have late reactions to those who have immediate reactions.

Vanto T. J Pediatr 2004;144:218-22
Outcome (tolerance)

- **CMP:** 62% → 12 years
- **Egg:** 37% → 10 years
- **Wheat:** 65% → 12 years
- **peanut:** 20% → 10 years
- **Nut:** 9% → 10 years

Diagnosis

- Time of elimination diet:
  - acute reactions: 2 weeks.
  - Gastrointestinal late reactions: 4 weeks
Diagnostic elimination diet is suggested before allergy skin tests in patients with atopic dermatitis to improve skin inflammation.
Diagnosis

- When doing oral challenge in patients with atopic dermatitis, is considered positive when the SCORAD increases 10 or more points.
Oral Food Challenge

- Start with 0.1 ml increments every 20 to 30 minutes (total 145 ml)
  - 0.1 ml
  - 0.3 ml
  - 1.0 ml
  - 3.0 ml
  - 10 ml
  - 30 ml
  - 100 ml
Skin prick test

- +Test = papule > 3 mm
- excellent negative predictive value
- positive predictive value:
  - If no previous history = 50%
- In Vitro Test: (Phadiatop)

+ Test = specific IgE > 2.5 KU/L

- peanut: 14 KU/L
- milk: 15 KU/L
- egg: 7 KU/L

95%
Not validated tests:

- Provocation / Neutralization
- Cytotoxic tests
- Capillary analysis
- IgG$_4$ / IgG
- Endoscopic provocation test

Boyce et al. JACI 2010; 126 (6): S1-S57
Patch tests

- Patch test in atopic disease:
  - Hypersensitivity type I
  - IgE non mediated (T lymphocytes)
  - Aeroalergens, foods
  - Atopic dermatitis, contact dermatitis
  - Eosinophilic oesophagitis

Boyce et al. JACI 2010; 126 (6): S1-S57
Cow’s Milk Allergy Treatment

- Total elimination
- Written indications
- Identify lactose and casein
- Symptoms by inhalation or skin contact
Milk free diet

- Cream, cheese
- Butter, yoghurt, yakult, milk shakes, ice cream, pizzas, cheese popcorn, other desserts and drinks prepared with milk products
- Milk candies, chocolates, peanut butter, bread, cookies, dressings
- Baby products prepared with milk
Good labeling of foods and products for personal consumption

- Often incomplete information on labels
- Processed foods or pre packaged may inadvertently contain milk
- Requires better regulation at global level on mandatory information.
Cow’s Milk Allergy Treatment

• Strict adherence to the diet affects quality of life for the patient and their family members
Cow’s Milk Allergy

- Patients with allergy to beef proteins, often are also allergic to cow's milk proteins.
- Patients with allergy to cow's milk protein, 10% have allergy to beef.
Cow’s Milk Allergy Treatment

- Safe and balanced diet
  - Provide protein, energy, calcium, vitamin D and micronutrients
  - Nutricionist assistance
Cow’s Milk Allergy Treatment

- Frequent medical visits
- Annual oral challenges to prevent prolonged elimination diets
Cow’s Milk Allergy Treatment

- When the oral challenge to small doses of milk indicate tolerance, it is not necessary to implement an strict elimination diet

- Boiled milk, stove milk can be good options
Cow’s Milk Allergy Treatment

- In children less than 2 years old with allergy to cow's milk proteins, that are still fed with breast milk:
  - Mother: milk free diet and provide calcium supplementation
    - 1000 mg/day (quarterly)
Cow’s Milk Allergy Treatment

- In children older than 2 years old* with Cow’s milk allergy:
  - It is not necessary to replace with special formulas

* Cover requirements for calcium 600 - 800 mg/day
Cow’s Milk Allergy Treatment

- In children under 2 years with allergy to cow’s milk proteins and not fed with breast milk:
  - Use special formulas (highly recommended)
Cow’s Milk Allergy Treatment

- Onset of signs and symptoms with accidental intake → (+) oral challenge
- Oral challenge next year
Cow’s Milk Allergy Treatment

- Severe Cow’s milk allergy with accidental intake:
  - Consider tolerance induction
  - Oral immunotherapy
  - Anti IgE
Cow’s Milk Allergy Treatment

- Special formulas (GRADE):
  - Extensively hydrolyzed (eHF)
    - Casein (eHcF)
    - Whey (eHwF)
  - Soy (SF)
  - Hydrolyzed rice (HRF)
  - Amino acids (AAF)
Cow’s Milk Allergy Treatment

- 90% Of children with cow's milk allergy tolerate eHF

- 10% that cannot tolerate:
  - Amino acid formula
  - Hydrolyzed rice formula
Conformational epitopes vs sequential epitopes

Conformational epitopes vs sequential epitopes

Tolerance

Sensitization persists

Cow’s Milk Allergy Treatment

- Milk from other species and hydrolyzed soy formula were not subjected to GRADE.

- Individual analysis
### Reference Guide: WAO 2010

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<th>2&lt;sup&gt;nd&lt;/sup&gt; Choice</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; Choice</th>
<th>Observations</th>
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<td>AAF</td>
<td>eHF HRF</td>
<td>SF</td>
<td>SPT (-) to eHF</td>
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<td>Acute urticaria angioedema</td>
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<td>AAF SF</td>
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<td>Immediate gastrointestinal allergy</td>
<td>eHF HRF</td>
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<td>GERD</td>
<td>eHF</td>
<td>AAF</td>
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<tr>
<td>CMP induced enteropathy</td>
<td>eHF, HRF</td>
<td>AAF</td>
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<tr>
<td>Food protein induced enterocolitis Sx (FPIES)</td>
<td>eHF</td>
<td>AAF</td>
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<th>3(^{rd}) Choice</th>
<th>Observations</th>
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<td>Severe irritability (colic)</td>
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<tr>
<td>Constipation</td>
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<td>AAF</td>
<td>Donkey milk</td>
<td>Based on reports from one case series</td>
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<td>Milk-induced chronic pulmonary disease (Heiner’s Syndrome)</td>
<td>AAF</td>
<td>eHF</td>
<td>SF</td>
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Cow’s milk allergy treatment

- With each new formula, check adverse effects after the first administration.
Cow’s milk allergy treatment

- Designed more rigorous, randomized studies, comparing different formulas to long term, and not only one dose challenges, in patients with CMA are required
- Evaluate evolution and adverse side effects
Cow’s milk allergy treatment

- Start with eHF or AAF before 6 months of age, after 6 months old it can be changed to SF if the SPT or specific IgE to soy are negatives.

Extensively Hydrolyzed Formulas

- **Whey:**
  - Alfaré
  - Althéra
  - Friso Intensive HA
  - Pepti Junior
Extensively Hydrolyzed Formulas

- **Casein:**
  - Alimentum
  - Friso Allergy Care
  - Pregestemil
  - Nutramigen
Amino acid Formulas

- Under 12 months old:
  - Neocate LCP
  - Elecare

- Older than 12 months old:
  - Neocate advance
  - Pepti Jr
  - Vivonex
Soy Formulas

- Isomil Advance
- Nan Soya
- Nursoy
- Prosobee

Proteins:
- Conglycine (180 000 D)
- Glycine (320 000 D)
Partially Hydrolyzed Rice Formula

- Blemil plus arroz
- Alternative treatment
- Molecular weight: 2000 to 5000 Daltons
Milks from different animals

- Goat
- Sheep
- Mare
- Donkey
- Camel
- Lamb formula
Milks from different animals

- More studies are required to respond: ?
  - Nutritional value mainly in children under 2 years of age
  - Tolerance
    - How many children react to them
    - How many children have late reactions
    - Multiple allergies
  - Cost/ taste
Milks from different animals

- Considered in undeveloped countries if there are no hydrolyzed, soy, rice, or amino acids formulas available
- Identify according to nutritional and clinical status
Goat’s Milk

- 95% of children with CMA have more reactions to goat milk
- > protein concentration than human milk
- > solute renal load
- It has no vitamin B12 and B9
- Great similarity with sheep’s milk
Milks from different animals

- Camel’s milk in 2 years older:
  - North-East Africa, the Middle East, the Arabic Peninsula and China
  - Human and Camel’s milk do not contain beta lactoglobulin
Camelus dromedarius
# Protein Homology

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<th>TABLE 15-1. Mammalian Taxonomy: Milk Protein Composition and Homology$^5$</th>
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<tr>
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<tr>
<td>Genus</td>
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<tr>
<td>Species</td>
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<tr>
<td>Protein (g percent)</td>
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<tr>
<td>Casein (percent)</td>
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<tr>
<td>Whey proteins (percent)</td>
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<tr>
<td>Homology</td>
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<tr>
<td>$\alpha_\text{s1}$-Casein</td>
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<tr>
<td>$\alpha_\text{s2}$-Casein</td>
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<tr>
<td>$\beta$-Casein</td>
</tr>
<tr>
<td>$\kappa$-Casein</td>
</tr>
<tr>
<td>$\alpha$-Lactalbumin</td>
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<tr>
<td>$\beta$-Lactoglobulin</td>
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<tr>
<td>Serum albumin</td>
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<tr>
<td>Average</td>
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Milks from different animals

- Mare and donkey’s milks have a composition closer to human milk than cow's milk
- More serum proteins
- Mare’s Milk:
  - Adequate amounts of linoleic acid
  - Different sequence of amino acids between the bovine and the equine
  - Low cross reactivity with cow’s milk
Treatment

- Herbal Chinese Medicine
- Anti IgE monoclonal antibodies
- Anti IL-5 monoclonal antibodies
- Recombinant peptides and proteins
- Oral/sublingual immunotherapy