

# DRACMA

**D**iagnosis and **R**ationale for **A**ction against **C**ow's **M**ilk **A**llergy



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

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**Keywords:** Cow milk allergy; oral food challenge; epidemiology; DBPCFC; amino acid formula; hydrolyzed milk formula; hydrolyzed rice formula; hydrolyzed soy formula; skin prick test; specific IgE; OIT; SOTI; GRADE

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# DRACMA

## Diagnosis and Rationale for Action against Cow's Milk Allergy

WAO Journal, April 2010

Pediatr Allergy Immunol 2010;21:S21:1-125

# Cow's Milk Allergy (CMA)

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

# CMA

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- Newborns with early introduction of milk formulas have increased risk of more severe cow's milk allergy

# Outcome

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- 85% children with CMA develop clinical tolerance at 5 years old
- Direct relationship with decrease of specific IgE.

# Outcome

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

# Outcome (tolerance)

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- CMP:



62% → 12 years

- Egg:



37% → 10 years

- Wheat:



65% → 12 years

- peanut:



20% → 10 years

- Nut:



9% → 10 years

# Diagnosis

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- Time of elimination diet:
- acute reactions: 2 weeks.
- Gastrointestinal late reactions: 4 weeks



# Diagnosis (Skin Prick Test)

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- Diagnostic elimination diet is suggested before allergy skin tests in patients with atopic dermatitis to improve skin inflammation.

# Diagnosis

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

# Oral Food Challenge

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- 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

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

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- In Vitro Test : (Phadiatop)

✓ + Test= specific IgE > 2.5 KU/L

• peanut	→	14 KU/L	} 95%
• milk	→	15 KU/L	
• egg	→	7 KU/L	

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- Not validated tests:
    - Provocation / Neutralization
    - Cytotoxic tests
    - Capillary analysis
    - IgG<sub>4</sub> / IgG
    - Endoscopic provocation test

# Patch tests

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

# Cow's Milk Allergy Treatment

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



# Milk free diet

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- 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

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- 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

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- Strict adherence to the diet affects quality of life for the patient and their family members

# Cow's Milk Allergy

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- 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

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- Safe and balanced diet
  - Provide protein, energy, calcium, vitamin D and micronutrients
  - Nutritionist assistance

# Cow's Milk Allergy Treatment

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- Frequent medical visits
- Annual oral challenges to prevent prolonged elimination diets

# Cow's Milk Allergy Treatment

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- 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

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- 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

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- 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

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- 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

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- Onset of signs and symptoms with accidental intake → (+) oral challenge



- Oral challenge next year

# Cow's Milk Allergy Treatment

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- Severe Cow's milk allergy with accidental intake:

Consider tolerance induction



Oral immunotherapy

Anti IgE

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# Cow's Milk Allergy Treatment

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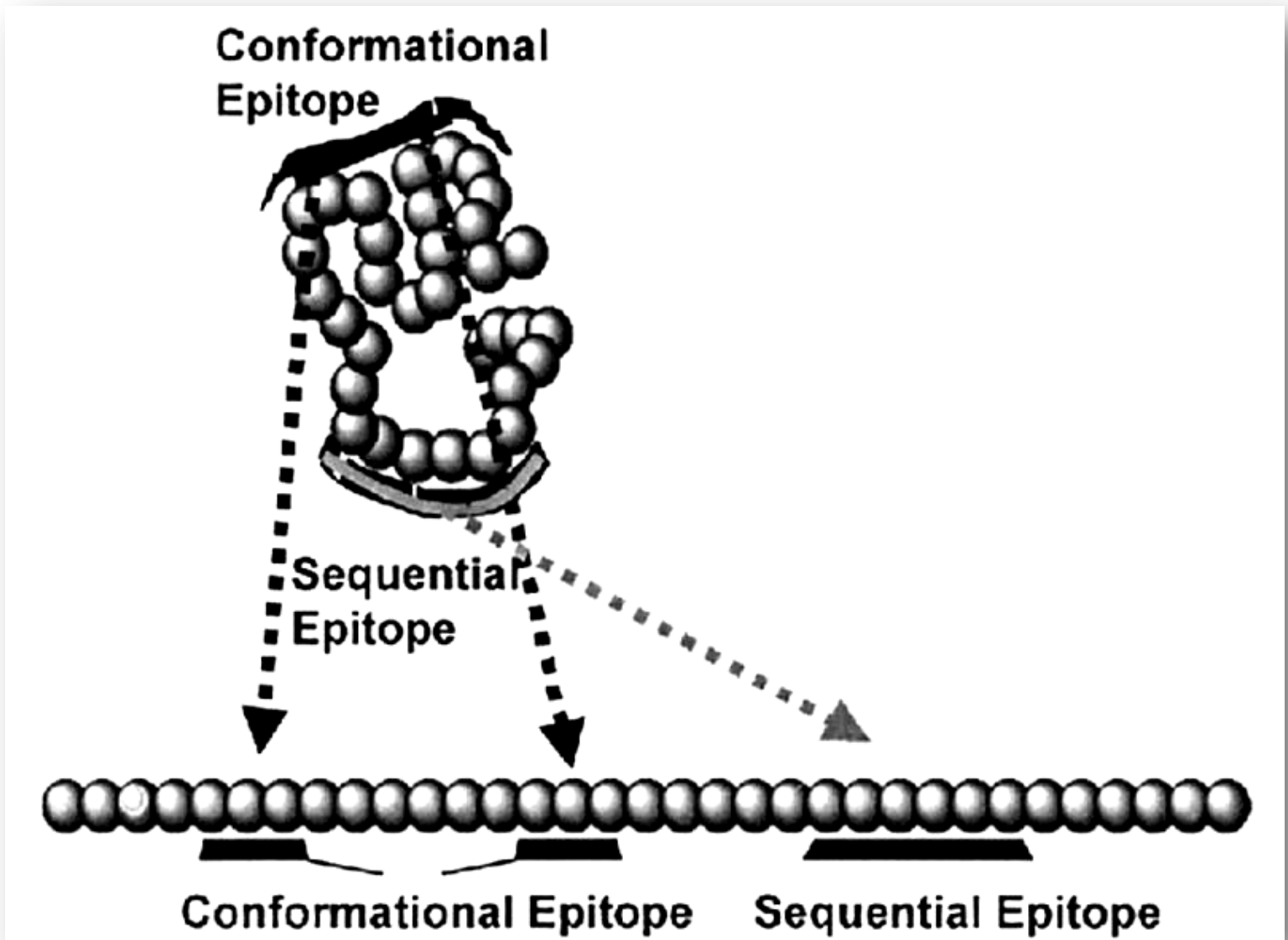
- Special formulas (GRADE):
  - Extensively hydrolyzed (eHF)
    - Casein (eHcF)
    - Whey (eHwF)
  - Soy (SF)
  - Hydrolyzed rice (HRF)
  - Amino acids (AAF)

# Cow's Milk Allergy Treatment

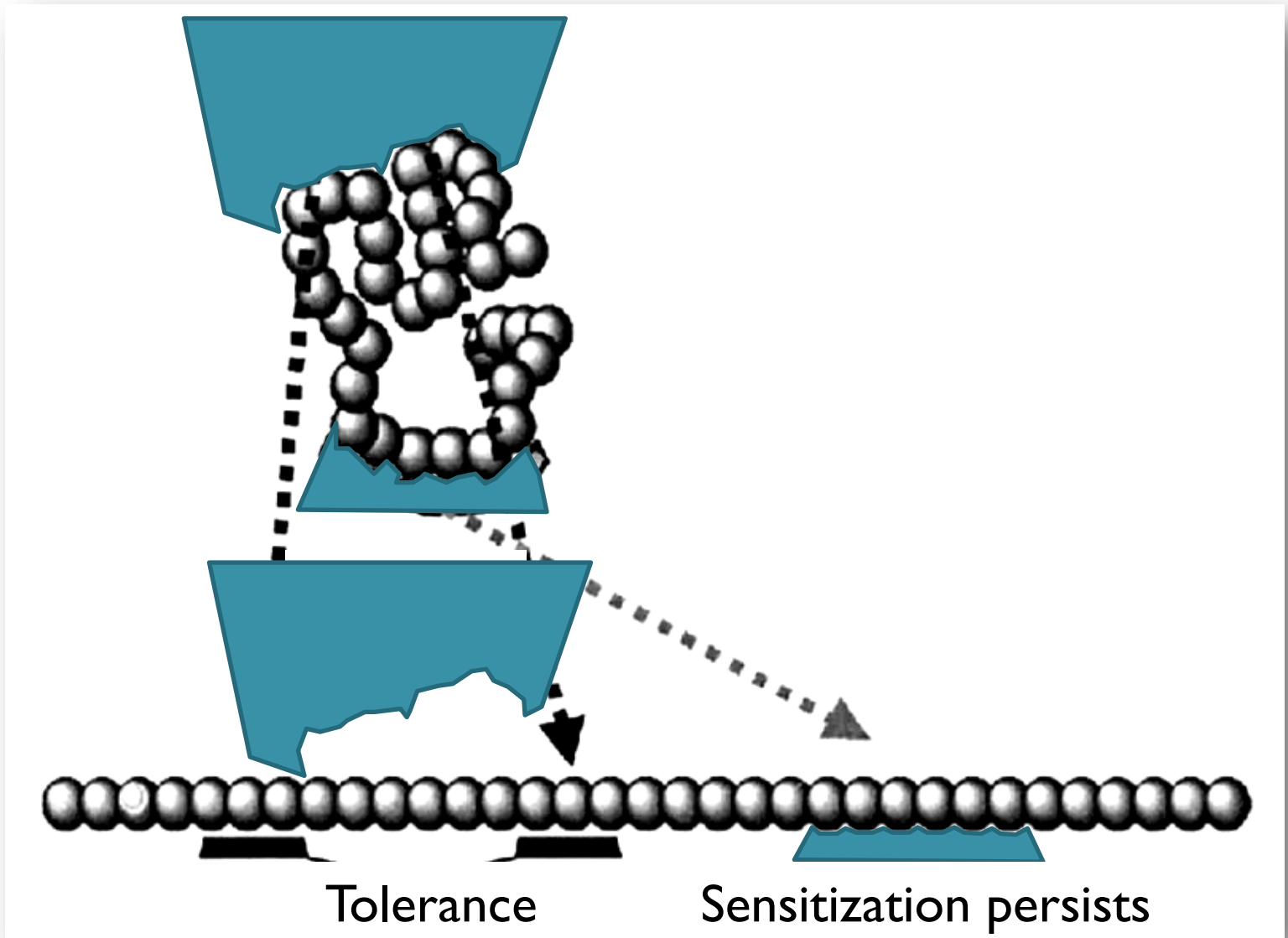
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- 90% Of children with cow's milk allergy tolerate eHF
- 10% that cannot tolerate:
  - Amino acid formula
  - Hydrolyzed rice formula

# Conformational epitopes vs sequential epitopes



## Conformational epitopes vs sequential epitopes





# Cow's Milk Allergy Treatment

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

# Reference Guide: WAO 2010

Clinical presentation	1 <sup>st</sup> Choice	2 <sup>nd</sup> Choice	3 <sup>rd</sup> Choice	Observations
Anaphylaxis	AAF	eHF HRF	SF	SPT (-) to eHF
Acute urticaria angioedema	eHF HRF	AAF SF	-----	
Atopic dermatitis	eHF HRF	AAF SF	-----	
Immediate gastrointestinal allergy	eHF HRF	AAF SF	-----	

# Reference Guide: WAO 2010

Clinical presentation	1 <sup>st</sup> Choice	2 <sup>nd</sup> Choice	3 <sup>rd</sup> Choice	Observations
Allergic eosinophilic oesophagitis	AAF	-----	-----	
GERD	eHF	AAF	-----	
CMP induced enteropathy	eHF HRF	AAF	-----	
Food protein induced enterocolitis Sx (FPIES)	eHF	AAF	-----	

# Reference Guide: WAO 2010

Clinical presentation	1 <sup>st</sup> Choice	2 <sup>nd</sup> Choice	3 <sup>rd</sup> Choice	Observations
CMP-induced gastroenteritis & proctocolitis	eHF	AAF		
Severe irritability (colic)	eHF	AAF		
Constipation	eHF	AAF	Donkey milk	Based on reports from one case series
Milk-induced chronic pulmonary disease (Heiner's Syndrome)	AAF	eHF	SF	

# Cow's milk allergy treatment

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- With each new formula,  
  
check adverse effects after the  
  
first administration

# Cow's milk allergy treatment

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- 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

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- 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

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- **Whey:**
  - Alfaré
  - Althéra
  - Friso Intensive HA
  - Pepti Junior





# Extensively Hydrolyzed Formulas

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- **Casein:**
  - Alimentum
  - Friso Allergy Care
  - Pregestemil
  - Nutramigen



# Amino acid Formulas

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- Under 12 months old:
  - Neocate LCP
  - Elecare
- Older than 12 months old:
  - Neocate advance
  - Pepti Jr
  - Vivonex



# Soy Formulas

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- Isomil Advance
- Nan Soya
- Nursoy
- Prosobee

## Proteins:

- Conglycine (180 000 D)
- Glycine (320 000 D)



# Partially Hydrolyzed Rice Formula

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- Blemil plus arroz
- Alternative treatment
- Molecular weight: 2000 to 5000 Daltons

# Milks from different animals

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- Goat
- Sheep
- Mare
- Donkey
- Camel
- Lamb formula



# Milks from different animals

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- 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

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- 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

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- 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

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- 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

**TABLE 15-1. Mammalian Taxonomy: Milk Protein Composition and Homology<sup>5</sup>**

	Dromedary	Horse	Donkey	Human
Genus	<i>Camelus</i>	<i>Equus</i>	<i>Equus</i>	<i>Homo</i>
Species	<i>C. dromedarius</i>	<i>E.f. caballus</i>	<i>E. asinus</i>	<i>H. sapiens</i>
Protein (g percent)	3.6	2.14	2.2	1.25
Casein (percent)	74	56	58	40
Whey proteins (percent)	26	44	42	60
Homology				
$\alpha_{s1}$ -Casein	44.2	43.3	—	31.9
$\alpha_{s2}$ -Casein	58..3	—	60.0	—
$\beta$ -Casein	69.2	60.5	—	56.5
$\kappa$ -Casein	58.4	57.4	—	53.2
$\alpha$ -Lactalbumin	69.7	72.4 (A), 69.1(B/C)	71.5	73.9
$\beta$ -Lactoglobulin	Absent	59.4 (1)	56.9 (1), 51.6 (2)	Absent
Serum albumin	—	74.5	74.1	76.6
Average	60.0	62.4	62.8	58.4

# Milks from different animals

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- 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

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



