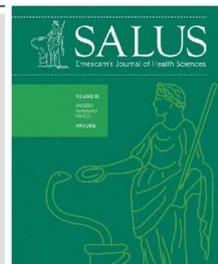




# REVISTA SALUS

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## REVIEW

### Cow's milk allergy: state of the art

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#### Abstract

Objective: To check the state of the art in the steps taken in pediatric practice in cow 's milk allergy . Method: review in the PubMed database 2005 to 2015. Cow 's milk allergy is the main food allergy in childhood. The diagnosis is still difficult to achieve in clinical practice and the lack of standardization of laboratory research a challenge. The importance of correct driving in suspected or confirmed diagnosis is seen in the large potential impact on growth and development of children subjected to food restriction.

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#### Introduction

Food allergy and the so-called food intolerance have caused perplexity in the medical practice. Food allergy or hypersensitivity involves the immunological response of the body to heterologous proteins, whereas food intolerance, for example, lactose intolerance – involving

lactase deficiency –, is not related with hypersensitivity <sup>1</sup>.

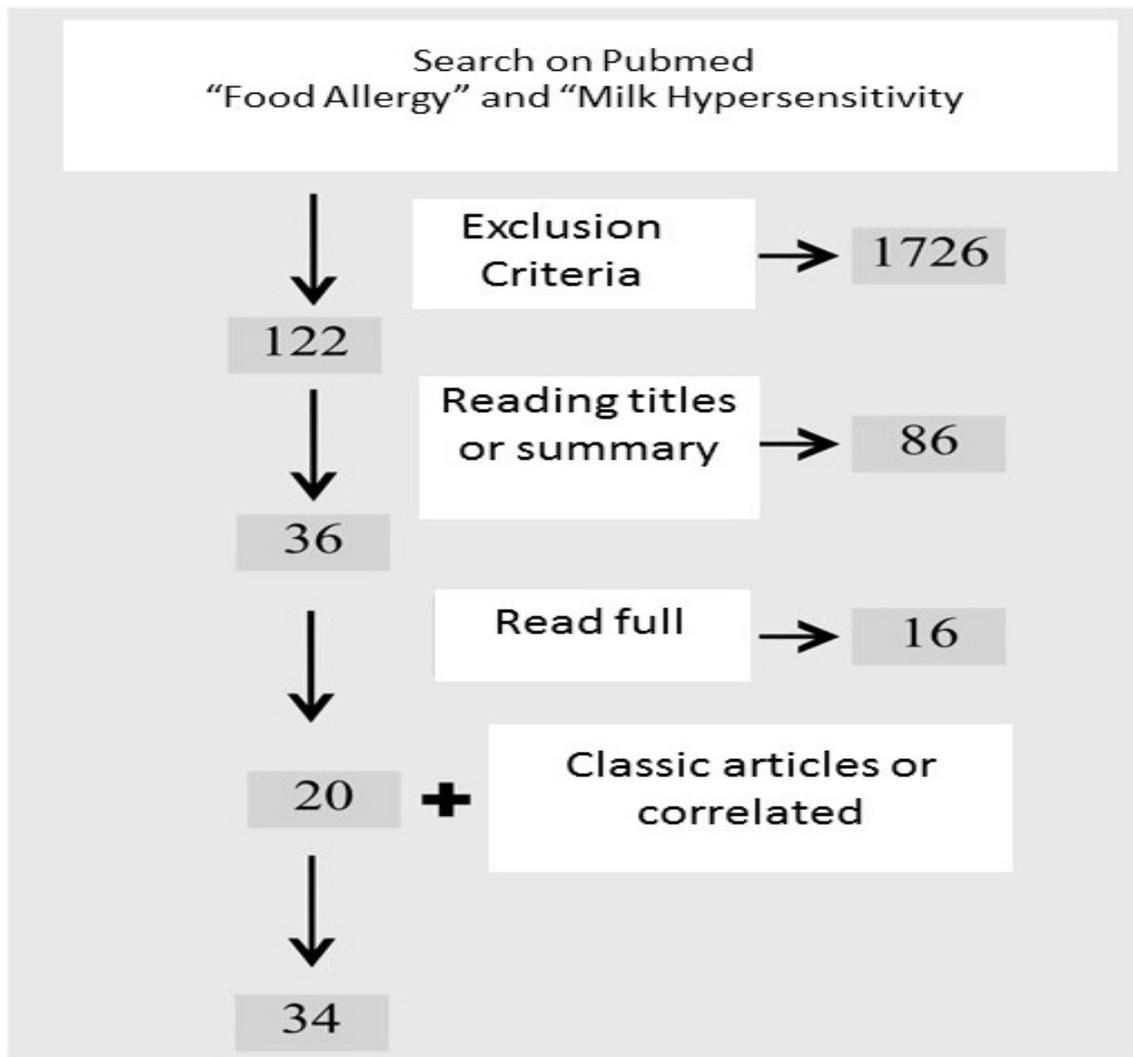
Food allergy prevalence in children ranges from 6% to 10%<sup>2,3,4</sup> and it most frequently involves food such as cow milk, egg, wheat, corn, soybeans, seafood and peanuts<sup>5,6</sup>. Cow's milk protein allergy (ALV) is the most common in children (prevalence between 2% - 3%), among all food allergies <sup>7,8,9,10,11,12,13</sup>.

Fifty percent of allergy cases are diagnosed in the first month of life. Cow’s milk protein desensitization often takes places as age advances, thus, allergy reduces approximately 75% in the first three years of life and 90% at the 6<sup>th</sup> year<sup>11</sup>. Correct ALV diagnosis is important to prevent the inappropriate use of restrictive diets that can bring harm to child development<sup>11,13,14,15,16,17</sup>, or the special and expensive formulas unaffordable by most families. The present research aims to verify the state of art on the steps taken in pediatric practice regarding cow milk protein allergy.

**Research Strategy**

The revision was made in PubMed / Medline database and were considered papers published between 2005 and 2015. Publications were selected according to the terms: "Milk hypersensitivity" and "Food Allergy", which were defined by the Medical Subject Headings (MESH). The texts were filtered by publication date, language (English, Portuguese and Spanish), age (birth to 18 years old) and other inclusion and exclusion criteria. All steps are shown in Figure 1.

**Method**



**Figure 1** - flowchart showing the search strategy , from April 2005 to March 2015

### **Inclusion and Exclusion Criteria**

Original articles, related classic articles and meta-analyses and guidelines involving clinical studies with humans were considered to be the objects of study. Fast communications, letters to the editor, incomplete texts and experimental animal studies were excluded.

### **Selection Strategy**

Unrelated articles were selected by title reading. Works not related with the topic were deleted after abstract reading. The remaining articles were completely read and selected by relevant association with the subject. Classical and correlated articles that did not appear in the search were included due to the direct search done for renowned and specialized group of authors. The two researchers analyzed the articles and agreed on the inclusion of the selected ones.

### **Immunology And Clinical Manifestations**

After cow's milk ingestion, its protein is phagocytosed by antigen-presenting cells (APCs) located in the intestinal mucosal or in the lungs. APCs process the antigen and present their epitopes to the T helper lymphocyte<sup>3</sup>. Tolerance will possibly result from the regulatory action of interleukin (IL) - 10 on the Th2 response. The increased levels of the specific cow milk protein IgG4 will be found in response to IL-10 and it reduces IgE levels, fact that result in the development of tolerance mechanisms<sup>18</sup>.

Cow's milk protein (CMA) may due to the immune reaction of IgE (immunoglobulin) mediated, the mixed reaction (IgE-mediated and cell) or a non-mediated IgE reaction.<sup>11,19</sup> The IgE-mediated reaction is the most common immune response.<sup>17</sup> The

sensitization phase begins after the first contact with the antigen: T lymphocytes secrete Th2 cytokines IL-4, IL-5 and IL-13 and it stimulates IgE by the B lymphocytes. IgE binds to the surface of the mast cell, thus stimulating histamine release. After a new contact with the allergen, the sensitized body triggers the immediate hypersensitivity reaction effector phase (type I) within the first 12 - 24 Hours<sup>3</sup>. Immediate reactions typically occur a few minutes or up to 2 hours after exposure.<sup>11,20</sup> It is characterized by acute inflammatory immune response at the site exposed to the allergen. Such response is also regulated by Th2 T lymphocytes that stimulate effector cells' - neutrophils and eosinophils - maturation and recruitment in the antigen exposed site.<sup>3</sup>

There is the involvement of immunoglobulin E, T lymphocytes and pro inflammatory cytokines in mixed reactions. Eosinophilic esophagitis, eosinophilic gastroenteritis, atopic dermatitis and asthma are examples of this group.<sup>1,11</sup>

Non-IgE-mediated manifestations include cell mediated hypersensitivity reactions that possibly involve cytotoxic and immunocomplex reactions. This group presents late submission manifestations with chronicity tendency<sup>1</sup>. Such manifestations usually occur 48 hours after exposure to the allergen and they may have onset delay up to 1 week.<sup>11</sup>

Most children present symptoms on the following systems: gastrointestinal (50% - 60%), skin (50% - 60%) and respiratory (20% - 30%),<sup>16</sup> when there are two or more affected systems there is greater chance of CMA.<sup>11</sup> Neurological and cardiovascular symptoms may also be found, but they are more often related to anaphylaxis.<sup>1</sup> The most common clinical manifestations are shown in Table 1.

**Table 1** - Key Signs and Symptoms in Allergy to Cow's Milk Protein

<b>Affected Systems</b>	<b>Infants and children</b>	<b>Older children</b>	<b>IgE-Mediated</b>	<b>Non-IgE-mediated</b>	<b>Immediate reaction (within minutes up to 2 hours)</b>
<b>Gastrointestinal</b>	dysphagia	dysphagia	Allergy oral	gastroesophageal reflux	vomit
	gastroesophageal reflux	gastroesophageal reflux	manifestations	enteropathy transient	
	Colic, abdominal pain	dyspepsia	Nausea, vomiting	Enteropathy protein-losing	
	vomiting	Nausea, vomiting	colic	colitis	
	Anorexy, refusal to feed	Anorexy, early satiety	diarrhea	constipation	Failure to Thrive
	Diarrhea with or without loss of protein or blood	Diarrhea with or without loss of protein or blood			
	constipation with or without perianal hyperemia	constipation of abdominal pain			
	Reduction in motility	Fecal occult blood			
	Fecal occult blood				

<b>Respiratory Tract</b>	runny nose  wheezing  Chronic cough (noninfectious cause)	runny nose  wheezing  Chronic cough (noninfectious cause)	rhinoconjunctivitis  Wheezing  Chronic cough (noninfectious cause)  Laryngeal edema  Suppurative otitis media	pulmonary hemosiderosis  (Heiner syndrome)	Cough stridor  Difficulty breathing	or
<b>Skin</b>	Urticaria (without other defined causes)  Atopic eczema  Angioedema (swelling of the lips or eyelids)	Urticaria (without other defined causes)  Atopic eczema  Angioedema	atopic dermatitis  hives  angioedema	skin rash  atopic dermatitis	hives  angioedema	
<b>General</b>	Symptoms of shock with severe metabolic acidosis, vomiting and diarrhea (food protein-induced enterocolitis)	Anafilaxia	anaphylaxis		anaphylaxis  Food protein induced enterocolitis	

Source: Brill, 2008; Koletzko,2012.

## Diagnosis

Clinical and epidemiologic evaluation play a key role in diagnosing adverse reactions to food.<sup>11,16,17,19,20</sup> Family history of allergy among first-degree relatives increases CMA risk. Allergy risk, in general, increases in approximately 20-40% in case of any history of atopy among first-degree relatives and it can raise up to 70% if both parents are atopic.<sup>16,21</sup>

According to a systematic Cochrane review (2006), children exposed to cow's milk or soy-based formulas before 6 months of age are at higher risk of developing allergy or food intolerance.<sup>22</sup> The incidence of CMA is lower in children fed only with breast milk in comparison to those who were formula-fed before 6 months of age.<sup>16,23</sup>

Some diagnostic tests can be performed after the clinical suspicion. The determination of specific IgE has been widely used in cases of type I hypersensitivity. IgE serum levels are indicative of the protein presence in a food, but they do not define if a particular food is causing the symptoms. One should always associate the clinical history and the test results.<sup>5,11,17</sup> The tests can help indicating the

food to be assessed in oral challenge tests. However, there can also be cross-reactions with epitopes from other proteins.

The skin immediate hypersensitivity (skin prick test) is another usual test to assess allergen sensitization.<sup>11</sup> This test shows 95% negative predictive value and is easy to perform. However, it can only evaluate IgE-mediated reactions. Therefore, it is not useful in cell-mediated reactions<sup>1</sup>. The patch test – in which adhesives with specific antigens are adhered to the patient's skin – assesses the cellular hypersensitivity reaction.<sup>7,18</sup> Nevertheless, it still plays limited role in CMA diagnosis due to lack of standardized preparation and to the implementation of the antigen. There is no superiority between total IgE determination and intradermal test.<sup>11</sup>

Oral food challenge tests are considered the main way to establish CMA diagnosis. Double-blind and placebo-controlled oral food challenges are the gold standard for this diagnosis.<sup>11,13,17</sup> However, an open oral challenge test (patient and physician aware) is used due to embodiment difficulties.<sup>1,11</sup>

Table 2

**Table 2** - carrying out instructions from Oral Food Challenge

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Establishing cow milk protein allergy diagnosis after excluding it from the child's diet
Many suspect foods
Previous anaphylactic type reaction
Attempt to establish the cause and effect relationship between allergen and symptoms
Suspected allergic reactions not mediated by IgE or its mixed form

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Source: Cocco, 2007.

Possible allergenic food is excluded from the patient's diet as a means of examination. After 2-4 weeks of exclusion the food is offered to the patient again and it is done in an environment where support can be offered if any adverse event takes place.<sup>5,9,16</sup> The procedure begins with the patients physical examination to compare possible changes that may appear during the test.<sup>16</sup>

The doctor humidifies the child's lips with a formula containing whole cow's milk protein or *in natural* cow's milk; after 30 minutes, 10 ml is administered via a progressive swelling scheme every 20-30 minutes until a 150 minutes round is completed<sup>25</sup>. The patient should be observed for 2 hours after the last administration and examined again before being cleared. The doctor must focuses on

responses from the respiratory and the skin systems.

The oral challenge should be avoided in cases of clear history of immediate reaction to cow's milk protein added to the specific positive IgE due to increased anaphylaxis risk.<sup>11</sup>

### **Treatment**

As soon as the CMA diagnosis or its strong suspicion is established, the total exclusion of the heterologous protein from child's diet must be indicated.<sup>4,11,13</sup>

Only 0.5% of exclusively breastfed children have clinical manifestations associated with cow's milk protein allergy sensitized via human milk supplied by the mother who consumes cow's milk<sup>7</sup>. Most of these symptoms are mild or moderate.<sup>16</sup> A strict cow's milk protein free diet from the mother can be indicated in this case only.<sup>23,26,27</sup>

The European Society of Gastroenterology, Hepatology and Nutrition Pediatric (ESPGHAN)<sup>11</sup> recommended the introduction, of extensively hydrolysed formula based on cow's milk or soya protein or amino acids based formulas after six months of age as treatment, but it does not recommend the use of isolated soy protein-based formulas.<sup>11,28</sup> The two formulas are also effective in reducing symptoms. The amino acids formula is more commonly applied in cases of reaction to extensively hydrolysed protein formulas.<sup>4,11,28,29</sup> However, the American Academy of Pediatrics suggests isolated soy protein formulas to IgE-mediated allergies; however only after 6 months of life.<sup>30</sup>

The Brazilian's Society of Pediatrics considers the two possibilities as treatment options and recommends, in children under 6 months old, in suspected non IgE mediated ALV or in IgE mediated CMA: exclusively breastfed for the first 6 months of life. If it is not possible, exclusively hydrolyzed formula is recommended. As for IgE-mediated CMA suspicion in 6 months old children or older, soy protein-based or extensively hydrolyzed formulas can be introduced.<sup>1</sup>

Infants should be away from cow's milk for at least six months during the treatment. Such

period may be extended to 9 or 12 months and, in case of severe immediate reaction, it must be extended to 18 months before a new oral challenge is done.<sup>11</sup>

### **Nutritional Guidelines**

The nutritional treatment aims to prevent disease progression, the worsening of signs and symptoms and to enable child growth and development. Therefore, nutritional guidance in cow's milk protein allergy is an important step in the treatment.

The child's nutritional, socio-cultural and economic status should be assessed. A food recall of at least four days - including the weekend - should be performed. This is the way to have an idea about the child's diet to avoid an insufficient caloric intake for the age.<sup>1</sup>

Micronutrients intake should be adequate to avoid specific nutritional deficiencies and enable proper metabolism<sup>31</sup>. In a recent study Seppo et al have demonstrated adequate zinc, iron, riboflavin and vitamin E intake by children who were introduced to protein based formula and soybean hydrolysate protein. There was no correct daily calcium intake, fact that requires oral supplementation.<sup>32</sup>

Nutritional assessment and the correct feeding should be performed in sequence in order to avoid too restrictive diets or exclusion diet transgressions. Families should receive proper guidance on the acquired processed foods; they should be informed on how to read labels and understand the terms found in the nutritional information that may indicate milk traces or any milk component such as caseinate, whey, lactoglobulin, casein and lactoferrin. These guidelines can avoid unintentional diet exclusion transgression.<sup>13</sup>

### **Prophylaxis**

The World Health Organization (WHO) recommends exclusive breastfeeding until 6 months of life and it takes into account not just the food allergy prevention aspects, but also other nutritional aspects such as prevention of respiratory and intestinal infections. The introduction of

supplementary feeding is not recommended before 6 months of age by the WHO<sup>33</sup>, but in recent statements the American Academy of Pediatrics discussed the possibility of starting it between the 4 and 6 months of age.<sup>6</sup> During this period there would be a "window period" when contact with food would promote T cell immune modulation response and it would lead to food tolerance however cow's milk introduction is just recommended from the 1st year of age on.<sup>27</sup>

Studies have shown decreased incidence of peanut, egg and fish allergy in populations where these foods were introduced after six months and before one year old. The American, European and Canadian Academies of Pediatrics suggest solid food introduction after 4 to 6 months of life.<sup>6,11,34</sup> Cow's milk protein exclusion from the mother's diet during lactation as CMA primary prevention measure is not recommended. Recent findings suggest that restrictions on maternal diet during pregnancy and lactation do not alter the possibility of developing sensitization processes and food allergy in childhood.<sup>23,26,27,34</sup>

Differently from what is observed in the clinical practice, isolate soy protein formulas are not hypoallergenic,<sup>16</sup> as well as goat, sheep and other mammal's milk,<sup>1</sup> and they should not be used in food allergy prophylaxis.<sup>11,22,27,29,31</sup> Soy protein allergic reactions have been reported in 30% to 50% of infants with CMA.<sup>31</sup>

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