# Allergy to cow's milk protein

## Alergia à proteína do leite de vaca

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## ABSTRACT

**Introduction:** allergy to cow's milk protein refers to immunologically mediated reactions that may be IgE mediated or non-IgE mediated. The prevalence of allergy to milk protein revolves around 2.5% in children and 0.3% in adults. **Pathophysiology:** the cow's milk protein allergy can be mediated by the four basic types of reactions of Gell and Coombs: type I (IgE-mediated), type II (cytotoxic reaction), type III (by immune complexes), and type IV (cell mediated). **History and Clinical Manifestations:** the manifestations of allergy to cow's milk protein may be immediate or late. The reactions may be cutaneous, gastrointestinal, respiratory, cardiovascular, or anaphylaxis. Approximately 80% of patients with allergy to cow's milk protein in the first year of life will develop tolerance until the age of five. **Diagnosis:** with well-elaborated medical history combined to the immediate hypersensitivity skin test by puncture (prick test), and proper interpretation of serum specific IgE dosage it is possible to reach a diagnosis in most episodes of IgE-mediated allergy. In some situations, a further oral provocation test may be necessary. In cases of non-IgE mediated, the diagnosis is essentially clinical. **Treatment:** at the moment, the only effective treatment for patients with allergy to cow's milk protein is the exclusion diet. In recent years, the administration of specific antigens, orally or sublingually, has gained increasing attention. **Prevention:** the use of hydrolyzed or partially hydrolyzed formulas can be considered as a strategy to prevent the development of food allergies in children at risk of developing them and who are not exclusively breast-fed in the breast.

**Key words:** Food Hypersensitivity; Milk Hypersensitivity; Milk Proteins.

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## RESUMO

*Introdução: alergia à proteína do leite de vaca refere-se a reações imunologicamente mediadas, podendo ser IgE mediada ou não IgE mediada. A prevalência de alergia à proteína do leite gira em torno de 2,5% em crianças e 0,3% em adultos. **Fisiopatologia:** a alergia à proteína leite de vaca pode ser mediada pelos quatro tipos básicos de reações de Gell e Coombs: tipo I (IgE mediada), tipo II (reação citotoxica), tipo III (por imunocomplexos) e tipo IV (mediada por células). **História e Manifestações Clínicas:** as manifestações da alergia à proteína do leite de vaca podem ser imediatas ou tardias. As reações podem ser cutâneas, gastrintestinais, respiratórias, cardiovasculares ou anafilaxia. Aproximadamente 80% dos pacientes com alergia à proteína do leite de vaca no primeiro ano de vida desenvolverão tolerância até os cinco anos de idade. **Diagnóstico:** com história clínica bem elaborada combinada ao teste cutâneo de hipersensibilidade imediata por punctura (prick test) e interpretação adequada da dosagem sérica da IgE específica é possível chegar a um diagnóstico na maioria dos episódios de alergia mediada por IgE. Em algumas situações pode ser necessário, ainda, o teste de provocação oral. Nos casos não IgE mediados, o diagnóstico é basicamente clínico. **Tratamento:** até o presente momento o único tratamento eficaz para pacientes portadores de alergia*

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*à proteína do leite de vaca é a dieta de exclusão. Nos últimos anos, a administração de antígenos específicos por via oral ou sublingual tem ganhado cada vez mais atenção.* **Prevenção:** *o uso de fórmulas hidrolisadas ou parcialmente hidrolisadas pode ser considerado uma estratégia para prevenir o desenvolvimento de alergia alimentar em crianças com risco de desenvolvê-la e que não são amamentadas exclusivamente ao seio.*

*Palavras-chave: Hipersensibilidade Alimentar; Hipersensibilidade a Leite; Proteínas do Leite.*

## INTRODUCTION

Adverse reactions to food are classified as food intolerance or hypersensitivity. In food intolerance, adverse reactions are caused by metabolic disorders such as lactase deficiency. The term food hypersensitivity or food allergy refers to immunologically mediated reactions that can be IgE mediated or not.

The prevalence of food allergy in the pediatric population is around 5% and increasing in the last decade.[1] The prevalence is less in adults, between 1% and 2%. However, prospective studies reported that 12.4% to 25% of parents believe their children have already experienced at least one adverse reaction to food. After careful evaluation, only 1.5% to 3.5% of these children had a confirmed diagnosis of food allergy[2] indicating that there is a significant difference between the perception of symptoms related to food allergy and the correct diagnosis of food allergies.

Although food allergies can be triggered by any kind of food, the most commonly involved are milk, egg, peanuts, soy, wheat, and fish. The prevalence of allergy to milk protein (APLV) is around 2.5% in children and 0.3% in adults according to studies conducted in North America.[1]

## PHYSIOPATHOLOGY

The gastrointestinal mucosa barrier includes one physiological and one immunological component. The physiological component includes a layer of epithelial cells with tightly jointed cells. They are covered with a thick layer of mucus, which affects the action of antigens, virus and bacteria. Enzymes, bile salts, and gastric pH help to destroy less immunogenic pathogens and antigens. In addition, substances that are secreted by mucus-producing cells in the stomach and intestine help strengthening and restoring the mucosal barrier.[1]

The immune components include the innate immune system (neutrophils, macrophages, and natural killer lymphocytes) and the adaptive immune system (intraepithelial lymphocytes and from the lamina propria, Peyer's patches, secretory IgA, and cytokines).

The immaturity of these components in neonates and young infants results in increased occurrences of intestinal infections and food allergies in this age group. Despite the evolution of the complex mucous barrier, around 2% of ingested food antigens are absorbed, even in mature mucosal barriers.[3]

Most absorbed allergens do not cause symptoms due to the phenomenon of immune tolerance. Food allergies are triggered by the aberrant immune response to oral administration of dietary antigens that occurs when immunological barriers are broken.

The antigenic presentation in the gastrointestinal mucosa is initiated by antigen uptake by M cells, which are specialized in transferring the antigen from the intestinal light to the submucosa, exposing it to dendritic cells. These are responsible for presenting the food antigen to T lymphocytes (Th0) and activating regulatory T cells (Treg), responsible for the phenomenon of oral tolerance.

Therefore, APLV can be mediated by antibodies or cells, and occasionally both mechanisms may be involved with the participation of the four basic types of immunological reactions of Gell and Coombs: type I (IgE-mediated), type II (cytotoxic reaction), type III (by immune complexes), and type IV (cell mediated).

## HISTORY AND CLINICAL MANIFESTATIONS

In the investigation of APLV patients, the clinical history is essential by detailing the age when the symptoms began, time between ingestion of suspect food and clinical manifestations, quantity of ingested food, clinical manifestation type, and duration and reproducibility of symptoms. In the differential diagnosis the following should be considered: lactose intolerance, inflammatory bowel disease, and irritable bowel syndrome.

APLV manifestations can be immediate (IgE mediated) or late (IgE non-mediated). Immediate reactions occur minutes after the exposure to cow's milk protein and, typically, develop with cutaneous, gastrointestinal, respiratory, cardiovascular, or anaphylactic manifestations. Immediate gastrointestinal manifestations are characterized by oral itching, sensation of suffocation and tongue edema, nausea,

vomiting, abdominal pain, cramps, diarrhea, and, occasionally, blood in feces.

Immediate skin manifestations are the most common and predominantly characterized by skin rashes, associated or not to angioedema. Some patients may also develop skin contact rashes after a direct contact between the food and skin.

Immediate respiratory manifestations rarely occur as isolated and are important in patients with more severe clinical manifestations. They are characterized by nasal itching, congestion, rhinorrhea, dyspnea, and wheezing.

Anaphylaxis happens minutes or up to two hours after the ingestion of cow's milk protein, involving the skin or mucosa, or both, and at least one respiratory symptom such as dyspnea, wheezing, and stridor and/or hypoxemia, and drop in blood pressure, hypotension, syncope, gastrointestinal symptoms, and shock. The frequency of anaphylaxis related to cow's milk protein in children is around 10%.[2] Prior asthma has been an indicator of greater severity in cases of anaphylactic reaction.

Late reactions can take hours or days to become evident after the exposure to cow's milk protein. Most of the reactions are gastrointestinal and may include respiratory and skin symptoms. Late gastrointestinal manifestations are gastroesophageal reflux disease, esophagitis or eosinophilic gastritis, enterocolitis, protein-losing enteropathy, proctocolitis or proctitis, and constipation in addition to other manifestations such as nausea, vomiting, abdominal pain, diarrhea, malabsorption, and weight loss. Patients with esophagitis and/or eosinophilic gastritis often show positive IgE for some foods and inhalant allergens, however, they also present IgE non-mediated inflammatory components.

Eosinophilic esophagitis is clinically manifested by symptoms such as dysphagia, intermittent vomiting, food refusal, abdominal pain, irritability, growth deficit, and lack of response to treatment for gastroesophageal reflux, and histologically, by inflammation with predominance of eosinophils (above 15 per field).[4] Peripheral eosinophilia can be present in 50% of the cases. Infants show good response to the removal of the causative protein and use of amino acid-based formulas. In older children and adolescents, the initial exclusion of cow's milk should be tried after treating with omeprazole for at least six months without clinical histological response; however, other foods such as egg, wheat, soy, peanuts, and fish/sea food may be involved in the pathogenesis of eosinophilic esophagitis. Topical corticosteroid, swallowed, is an alternative treatment, such as fluticasone or budesonide, regarded by some authors as the treatment of choice.[4,6] The use of an oral corticosteroid, prednisone, at the dose of 1-2 mg/kg may be necessary in the most serious cases.[4]

Enterocolitis induced by cow's milk protein is IgE non-mediated and usually occurs one to three hours after the ingestion of milk protein.[5] It manifests through uncontrollable vomiting, hypotonia, diarrhea, metabolic acidosis, and hypotension. In the most serious cases, the clinical presentation can be indistinguishable from septic shock.

Protein-losing enteropathy is usually shown in the first few months of life with diarrhea, mild to moderate steatorrhea, low weight gain and, occasionally, hypoproteinemia and blood in feces[6]. They involve IgE non-mediated mechanisms. The biopsy reveals intestinal villus atrophy and inflammatory infiltrate with predominance of mononuclears.[3] The remission of symptoms usually occurs three to 21 days after the exclusion of cow's milk from the child's diet.

Proctocolite or proctitis is a benign disease characterized by mucus and blood in the feces and occasionally, mild diarrhea.[5] Most of these children are exclusively breastfeeding and present symptoms improvement after discontinuation of cow's milk in the maternal diet for up to 72 hours.

Cutaneous manifestations such as atopic dermatitis involve IgE mediated and non-mediated mechanisms. A third of all children with moderate to severe atopic dermatitis presents food associated allergy. Generally, there is a significant improvement after diagnosis and removal of milk from the child's diet.

Approximately 80% of APLV patients will develop tolerance until five years of age in the first year of life.[3,6] The decline in IgE, in serial measurements, is useful for predict the development of tolerance to cow's milk protein in children.

## DIAGNOSIS

It is very important to pay attention to the clinical history and physical examination in order to determine whether the suspicion of APLV is correct. Lactose intolerance is the most important differential diagnosis to consider. Other differential diagnoses include celiac disease, acute gastroenteritis, and nonspecific ulcerative rectocolitis. When APLV is the

main suspect, it is important to characterize if the reaction to cow's milk is IgE mediated or non-mediated. In recent years, there have been important advances in IgE mediated food allergy tests. The detailed clinical history, complemented by immediate hypersensitivity skin test by puncture (prick test), and the proper interpretation of specific serum IgE allow reaching a diagnosis in most cases. In selected cases, the oral provocation test might be needed.

When the reaction is IgE mediated, the prick test needs to be the first to be performed. Using adequate extracts (FDA Allergenic, IPI ASAC, or others), the prick test has a high negative predictive value.[6] However, a positive prick test does not confirm the APLV diagnosis due to its low positive predictive value, generally less than 50%. In other words, usually a negative prick test result excludes APLV IgE mediated. whereas a positive result only suggests the possibility of APLV, which must be confirmed. Those tests presenting papules with at least 3 mm in average diameter, above the negative control, are considered positive. However, in situations where there is severe systemic reaction, anaphylactic, a positive prick test can be considered as a diagnosis if the cause-and-effect relationship is well determined. Similarly, a prick test strongly positive result (papule >8 mm) may be sufficient to confirm the diagnosis.[6] There is no age restriction for the test, however, cutaneous reactivity can be reduced at extreme ages and require care in its interpretation.

The serum dosing of IgE antibodies specific for cow's milk protein (ImmunoCap) can also aid in the diagnosis.[6] This test must be requested only when the prick test did not allow confirming or dismissing the diagnosis. It is important to remember the need for an adequate interpretation of specific IgE. Weakly positive tests (class 1 or 2) have little value for the diagnosis of APLV and are often equivalent to a negative prick test with very low positive predictive value, making diagnosis confirmation impossible. The dosing of IgE specific for cow's milk protein can be very helpful to confirm the diagnosis of food allergy, reaching high positive predictive value and improving considerably diagnostic accuracy. In other words, IgE specific for cow's milk protein above 15 KU/L in children older than two years old, and above 5 KU/L in children under two years old, confirms the diagnosis in 95% of cases.[3]

Although IgE specific for cow's milk protein and the prick test have good clinical correlation, they do not correlate or predict the severity of the allergic reaction.[7]

In recent years, the contact skin test (patch test) has been used to aid in the diagnosis of food allergies. However, many doubts persist regarding the standardization and interpretation of the test; it has been used in some centers, in research studies, however, currently, the patch test should not be used routinely in the assessment of APLV patients.[8]

The diet excluding cow's milk can also be useful in APLV diagnosis. If the exclusion for at least two weeks leads to the disappearance of symptoms, the diagnosis is almost confirmed. This procedure is more important in cases of IgE non-mediated reactions or partially mediated.[7]

The double-blind placebo controlled provocation test (TPDCPC) is the gold standard in the diagnosis of food allergies.[8] The TPDCPC consists in the administration of cow's milk protein and/or placebo at increasing doses, at regular intervals, with the monitoring of possible clinical reactions. The TPDCPC requires professional teams including nurses, nutritionists, and doctors specially trained to assist during possible anaphylaxis in the outpatient or hospital environment, provided with the necessary resources: venous access, resurrecting unit, epinephrine, etc. Patients should be tested with the TPDCPC after the withdrawal of cow's milk for at least two weeks.

Gastrointestinal symptoms induced by cow's milk protein generally requires endoscopy (high and/or low, depending on the symptoms), including biopsy to establish a sure diagnosis. Preferably, the test should be performed while the patient is exposed to cow's milk. In esophagitis and/or eosinophilic gastritis, at least 15 eosinophils per field should be detected for diagnostic confirmation.[4] Histopathological alterations may be localized, intercalated with normal areas. Consequently, multiple biopsies in different regions are needed to confirm the diagnosis.

## TREATMENT

Up to the present moment, the only effective treatment for APLV patients is the diet of exclusion. The prescription of a diet of exclusion must have the same consideration and concern as any medication prescription because it can result in serious side effects. Exclusion diets can lead to malnutrition and poor eating habits. The food antigen can be hidden in a wide variety of foods. Patients and their families should be instructed to read the labels of the different pro-

cessed foods. A recent study revealed that only 7% of parents of children allergic to cow's milk protein and 22% of parents of children allergic to soy protein were able to identify products containing these foods.[7] Despite all care, accidental ingestion frequently occurs .

It is considered that an antigen has a great potential to develop cross-reaction with another one if it has at least eight contiguous amino acids or presents 30% similarity in a window of 80 amino acids.[1] In Brazil, until recently, the adopted convention was to treat children allergic to cow's milk protein with goat's milk based on the lack of awareness of their high rate of cross-reaction. There is no publication of clinical trials demonstrating that goat's milk is a substitute for cow's milk in APLV cases. In addition, studies show that IgE specific for cow's milk protein, produced by allergic patients, also reacts to goat's milk.[9]

The prescription of formulas taken as hypoallergenic is an alternative to replacing cow's milk. The Food and Drug Administration (FDA) along with the American Academy of Pediatrics recommends that the main proteins must be modified in order to reduce its antigenicity in a formula considered hypoallergenic so that 90% of allergic patients to protein can tolerate the formulas without symptoms.[5] The only available formulas that fit this criterion are those that contain extensively hydrolyzed proteins. The use of partially hydrolyzed formulas in the treatment or prevention of allergy to cow's milk protein is not indicated.[5] It is worth noting that all those formulas are expensive and with low palatability, reserved for patients under 6 months of age, when soy formula is contraindicated, or to patients who for some reason do not tolerate diet based on soy isolated protein.

For many years, it was believed that the use of conventional immunotherapy was ineffective in treating food allergy patients. Since early 1990, well-controlled studies started to demonstrate that this form of treatment could be useful in cases of food allergies.[10,11] However, in spite of satisfactory clinical improvement, these clinical trials were marked by high rates of systemic and anaphylactic reactions, including death.[11] These reactions were more frequent when compared with conventional immunotherapy reactions to dust mite and pollen. In fact, only a small percentage of patients could tolerate suitable doses of food antigens for extended time.[11]

Alternative strategies for treating patients with food allergy are beginning to be explored. One of them involves changes in the epitopes of antigenic proteins. The epitope is the fraction of the food protein where IgE links. The simple changing of one amino acid in this region drastically decreases the ability of the protein to be linked to IgE.[10] Therefore, this modified recombinant protein may be able to desensitize the patient without the risk of inducing severe systemic reactions.[10]

In recent years, the administration of specific antigens, orally or sublingually, has drawn more and more attention. Several studies have shown that the oral immunotherapy brings benefits to a substantial number of patients with food allergies.[11,12] The results of this treatment range from protection against accidental ingestion of small amounts of the food allergen, perhaps avoiding an anaphylactic reaction, to the ability to tolerate full doses of the allergen. However, many doubts still persist as to the maintenance dose, procedure safety, and which patient would most benefit from this treatment. For these reasons, its routine use is not recommended by the American Academy of Allergy.[8] Conversely, when all these questions are clarified, the use of the oral immunotherapy can characterize a significant paradigm change in the treatment of IgE mediated food allergies.

Studies have demonstrated that patients with food allergies can tolerate increasing doses of known allergens, including milk, eggs, and peanuts.[11-14] However, most of these studies show results from limited and small samples, with little characterization of the sick population, protocol, and doses used. Longo et al. evaluated 60 children over five years of age with severe allergy history to cow's milk protein; 30 received specific oral immunotherapy (Group A) and 30 received a milk free diet (Group B). After 12 months of follow-up, 36% of the experimental children (Group A) became tolerant to cow's milk, 54% became partially tolerant (tolerance of 5 to 150 mL of cow's milk intake), and 10% remained intolerant. All patients in Group B maintained APLV.[15] A project financed by FAPEMIG (case No. APQ-CDS-02463-09) is being developed in collaboration with the Pediatrics Allergy and Pneumology Service from the João Paulo II Children's Hospital (HIJPII) from the Hospital Foundation of Minas Gerais (FHEMIG) and Allergy and Immunology Service at the Pediatrics Department of the Medical School at UFMG to evaluate the desensitization to cow's milk protein. The objective of this study is to determine whether children who are allergic to cow's milk protein can be desensitized and if this desensitization allows the development of tolerance earlier than expected.

The development of immunological tolerance to cow's milk protein occurs in 80% of cases up to five years of age.[6] Because the milk protein is part of many processed foods, it is very difficult to avoid it entirely. Therefore, it would be very useful if a specific treatment could induce immune tolerance quickly. The decrease in the induction time for immune tolerance would have a significant impact on the quality of life of patients and their families.

## PREVENTION

The recommendations to prevent the development of allergy to cow's milk protein in children have undergone considerable changes over the last five years. Recent studies indicate that restricting maternal diets during pregnancy or lactation does not change the development or clinical course of food allergies.[7] All babies should be breastfed exclusively until six months of age. The use of formulas based on isolated soy protein for infants as a strategy to prevent the development of food allergy or modify its clinical course are not supported by the literature.[7] On the other hand, the use of hydrolyzed formulas or partially hydrolyzed can be considered a strategy to prevent the development of food allergies in children at risk for developing it and who are not exclusively breastfed.[1] Patients with risk of developing food allergies are defined as those in which one or both parents and/or biological brothers presents history of allergic rhinitis, asthma, atopic dermatitis, or food allergies.[7] These children should use hydrolyzed formulas. Nevertheless, the cost and availability of extensively hydrolyzed infant formulas should be considered as limiting factors in certain situations.

The introduction of solid foods should not be postponed after 4-6 months of age.[7] Foods considered as a potential allergen may be introduced at this time, taking advantage of what is called "immunological window." Studies indicate that the introduction of potentially allergenic foods during this period can reduce the incidence of food allergies.[7] Conversely, this very early or very late introduction may contribute to increased incidences of food allergies.[7]

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