

# The challenge of cow milk protein allergy<sup>☆</sup>

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## Abstract

Hypersensitivity to cow milk proteins is one of the main food allergies and affects mostly but not exclusively infants, while it may also persist through adulthood and can be very severe. Different clinical symptoms of milk allergy have been established. The diagnosis of milk allergy differs widely due to the multiplicity and degrees of symptoms, and can be achieved by skin or blood tests. Cow milk contains more than 20 proteins (allergens), that can cause allergic reactions. Casein fractions and  $\beta$ -lactoglobulin are the most common cow milk allergens. Human milk is free of  $\beta$ -lg, similar to camel milk. On the contrary,  $\beta$ -lg is a major whey protein in cow, buffalo, sheep, goat, mare and donkey milk. Caseins in milk of the different species differ in fraction number, amino acid composition, and their peptide mappings.  $\beta$ -Casein is the major fraction in goat casein, which is similar to human casein and different from cow casein. The peptide mappings of goat  $\alpha$ -1a and  $\beta$ -lg are completely different from those of cow milk. Different procedures can reduce the allergenicity of cow milk proteins by heat or enzymatic treatment to some degree. Allergies to milk proteins of non-bovine mammals have also been documented due to cross-reactivity between cow milk proteins and their counterpart in other species, and even between goat and sheep caseins. Genetic polymorphisms of milk proteins play an important role in eliciting different degrees of allergic reactions. Goat milk lacking  $\alpha$ -s1-casein, which is the main casein in cow milk, is less allergenic than goat milk with  $\alpha$ -s2-casein, which is more typical for many goat breeds. Several studies have reported real and dramatic benefits from using goat, camel, mare or even soy milk as alternatives in cases of cow milk allergy and they can be considered hypoallergenic. However, therapeutic benefits vary with the degree of severity of the allergy and may be only around 60% of all cases, since other studies revealed allergenicity to occur also for any of those other milks.

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## 1. Introduction

Milk is a biological fluid designed to contain all nutritional requirements of a specific mammalian newborn; therefore, the composition of milk differs by the needs of the neonate of different species. For example, human milk is the most fit food for human infants, but when breast-feeding is not available, cow milk is usually used

as a substitute for human milk. This substitution can lead to nutritional and immunological problems, such as allergy to cow milk proteins.

## 2. Definition of cow milk allergy (CMA)

The word allergy means an altered or abnormal reaction. Such a reaction may occur when there is contact between a foreign protein “an allergen” and body tissues, that are sensitive to it. The allergy may reach the tissues by direct contact with the skin or mucous membranes or through the blood stream after absorption. Allergic reactions have been classified into two types:

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- (1) The immediate reaction type in which the allergic manifestations occur within hours of the patient coming in contact with the allergen and often within seconds or minutes; in this form of allergy skin tests are nearly always positive.
- (2) The delayed reaction type in which manifestations may not appear for many hours or even for 2 or 3 days; in this type skin tests are usually negative.

Cow milk allergy is clinically an abnormal immunological reaction to cow milk proteins, which may be due to the interaction between one or more milk proteins and one or more immune mechanisms, and resulting in immediate IgE-mediated reactions. On the other side, reactions not involving the immune system are defined as cow milk protein intolerance.

CMA occurs in some infants after ingestion of an amount of cow milk. In some cases allergy to goat and sheep milk or cheeses made from them has also been recognized (Dean et al., 1993; Wuthrich and Johansson, 1995; Umpierrez et al., 1999; Pessler and Nejeat, 2004). CMA is generally more serious in early infancy (Hill and Hosking, 1996; Jarvinen et al., 2002).

### 3. Incidence of cow milk allergy

Cow milk is one of the most common food allergies in children. Although most children out-grow CMA by the age of 4 years, some retain the allergy for life. CMA may occur in adults usually involving immediate allergic reactions or eczema. The incidence of CMA ranges from 0.3 to 7.5% in population-based studies in different countries (Goldman et al., 1963; Gerrard et al., 1973; Ghosh et al., 1989; Dean, 1995; Motrich et al., 2003). The wide range in these estimates may be due mainly to different diagnostic criteria in addition to other factors such as race, age of the tested patients, type of infant feeding, as well as the duration of observations (Taylor, 1986).

### 4. Clinical manifestation of CMA

Symptoms of CMA can appear immediately or start several hours or even days after the intake of moderate to large amounts of cow milk or its infant formula. A wide spectrum of clinical manifestations has been recorded with CMA including gastrointestinal, respiratory, cutaneous as well as systemic anaphylactic symptoms (Fig. 1). Clinical symptoms involve immediate or delayed reactions operating separately or together (Bahna and Gandhi, 1983a; Amon et al., 1999; Drouet et al., 1999). Immediate reactions are mainly IgE-dependent, leading to cutaneous, intestinal or respiratory

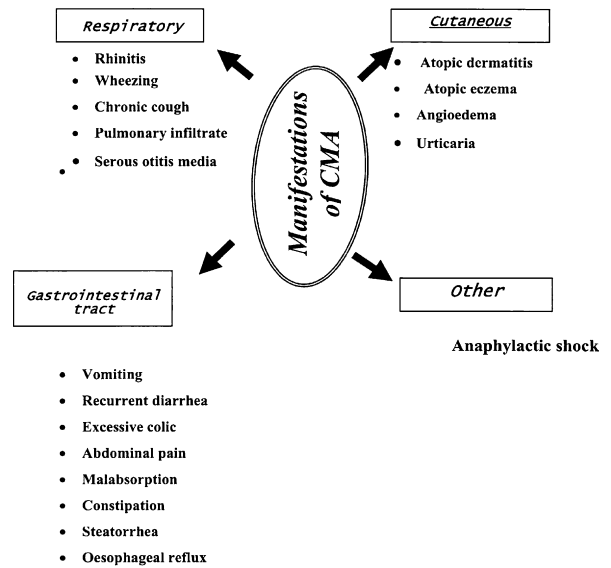


Fig. 1. Manifestations of CMA (Taylor, 1986; Host, 1994; Amon et al., 1999; Drouet et al., 1999; Majamaa et al., 1999; Heine et al., 2002; Hidvegi et al., 2002).

symptoms and in some cases to anaphylactic reaction (Sicherer, 2000). Delayed reactions happen after T-cell dependent mechanisms and can be operative both at the skin and the intestinal level (Taylor, 1986). The most frequent symptoms among the common manifestations of CMA are gastrointestinal, which have been encountered in 50–75% of patients with CMA (Ghosh et al., 1989). Respiratory and the skin symptoms are also commonly involved in CMA. These symptoms were recorded in 10–30 and 50% of patients with CMA, respectively (Ghosh et al., 1989). Rhinitis is the most common respiratory manifestation of CMA in some infants. Anaphylactic shock is a particularly serious symptom of CMA. In some cases, death can result. Anaphylaxis was noted in 12% of patients with CMA, but it was less commonly observed than most other symptoms (Lebenthal, 1975; Host, 1994).

### 5. Milk protein allergy diagnosis

The clinical diagnosis of milk allergy differs widely due to the multiplicity of symptoms. Diagnosis can be achieved by skin or blood tests. The positive blood or skin test is accomplished only with the immediate milk allergy reactions, that develop after a few minutes because these detect IgE that are involved in the immediate type reaction. In the young child about 60% of milk allergy reactions are not of the immediate type but are the delayed type “intolerant”, consequently unlikely to give positive results with blood and skin tests. Different

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