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Prevention and management of cow's milk allergy in infants

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This review explores current strategies for the prevention and management of cow's milk allergy (CMA) in infants, emphasizing the role of breastfeeding, hydrolyzed formulas, and early allergen exposure. Exclusive breastfeeding is the preferred approach to reduce allergy risk, offering various protective immune mechanisms. The use of partially hydrolyzed formulas (pHF) has been investigated for CMA prevention, with mixed results; while some studies suggest benefits in reducing atopic dermatitis and respiratory symptoms, recent evidence questions its efficacy. Extensively hydrolyzed formulas (eHF) are recommended as the first-line treatment for infants with CMA, but variations in peptide profiles necessitate stricter standards and better testing. Amino acid-based formulas (AAF) are utilized in severe CMA cases where eHF are ineffective, though their long-term use poses risks such as hypophosphatemic bone disease. The potential of early exposure to cow's milk proteins (CMP) to promote tolerance highlights that timing and individual factors might significantly influence outcomes. Emerging evidence points to the importance of personalized approaches in CMA management, recognizing that dietary and environmental factors play critical roles in allergy development.

Keywords: cow's milk allergy, breastfeeding, extensively hydrolyzed formulas, partially hydrolyzed formulas, amino

INTRODUCTION

Food allergies (FAs) have become a significant health issue over the past decades since they have been increasing in prevalence worldwide, particularly among infants and young children. [1] The allergic reaction occurs due to pathological immune reaction of hypersensitivity, triggered by specific food protein allergens. Cow's milk allergy (CMA) is one of the most prevalent FAs in infants, affecting up to 3.8% of young children in developed countries [2]. The allergy usually occurs in the first two years of life and is frequently one of the earliest food allergies identified in infants. CMP are commonly among the first food proteins they encounter, as it is the primary source of nutrition either through breastfeeding (with CMP passed through maternal diet) or formula feeding [3]. CMA is a multifactorial condition that can be presented with both IgE-mediated and non-IgE-mediated mechanisms. It is characterized by a consistent immune reaction to one or more CMP, typically casein or serum β-lactoglobulin [4].

It's crucial to differentiate CMA from other adverse reactions to CM, lactose intolerance in particular, as they involve distinct underlying mechanisms and require different management approaches. CMA is an immune-mediated response to proteins found in milk, leading to allergic reactions, whereas lactose intolerance is not immune-mediated and results from the body's inability to digest lactose, due to a deficiency of the enzyme lactase [5].

Our aim is to identify, elucidate and analyze the mechanism laying behind CMA and the contemporary strategies for its prevention and management.

PATHOGENESIS OF COW'S MILK ALLERGY

Cow's milk proteins

Cow's milk contains about 32 g of protein per liter, which is divided into two main fractions: caseins (~80%) and whey proteins (~20%). [6, 7] (Table 1). Cow's milk allergens are labeled "Bos d," based on the genus and species name (*Bos domesticus*), followed by an identification number [9]. For instance, Bos d 8 refers to all caseins, which are further categorized: Bos d 9 for αs1-casein (~32% of total casein), Bos d 10 for αs2-casein (~10%), Bos d 11 for β-casein (~28%), and Bos d 12 for κ-casein (~10%) [10]. These caseins are classified as secreted calcium-binding phosphoproteins with a loose structure, forming quaternary structures known as casein micelles. These micelles have a hydrophobic core of αs1, αs2, and β-caseins interacting with calcium phosphate, and a hydrophilic surface layer of κ-casein [11]. The

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structure of casein micelles is dynamic, changing with pH, temperature, and pressure. For example, rennet treatment causes micelles to lose solubility and form aggregates. Caseins are major allergens, implicated in over 50% of IgE-mediated cow's milk allergy (CMA) cases [12].

In the whey protein fraction, the most abundant protein is β-lactoglobulin (Bos d 5, ~10% of total proteins), followed by α-lactalbumin (Bos d 4, ~5%), immunoglobulins (Bos d 7, ~3%), bovine serum albumin (Bos d 6, ~1%), and lactoferrin (<1%). β-lactoglobulin and α-lactalbumin are major allergens, characterized by globular structures stabilized by disulfide bridges [13-15]. Although bovine serum albumin is present in small amounts, it is a common allergen, with up to 50% of CMA patients producing IgE against it. [16, 17] Along with lactoferrin, bovine serum albumin has a high number of disulphide bridges, making its structure very stable even under denaturing conditions. [18] While lactoferrin is not registered as an allergen, studies indicate its potential to trigger allergic reactions. [9, 19-21]

CMA usually involves reactivity to multiple CMP, both caseins and whey proteins [22]. IgE antibodies target specific regions within these proteins, known as epitopes, which can be linear (continuous amino acid sequences) or conformational (discontinuous sequences formed by protein folding). Both types of epitopes are present in cow's milk allergens [23-25].

Pathophysiologic mechanisms of cow's milk allergy

Food allergies can be classified into IgE-mediated and non-IgE-mediated types based on their underlying mechanisms [26]. IgE-mediated food allergies are the most well-known and studied type, consisting of two phases: sensitization and elicitation [27-29]. During the initial exposure to food proteins, sensitization may occur when the immune system first encounters the antigens. Antigen-presenting cells (APCs), primarily dendritic cells (DCs), process the food proteins into smaller peptides and present them on their surface main histocompatibility complex (MHC) II molecules to T-cell receptors (TCRs) on naïve T cells specific to the peptide. This triggers T cell activation, facilitated by the interaction of CD28 on T cells with CD80 and CD86 on DCs, along with co-stimulatory signals from pro-inflammatory cytokines like IL-4, IL-25, IL-33, and TSLP [30, 31] . These signals cause naïve T cells to differentiate into CD4+ Th2 cells [32, 33].

The activated Th2 cells then engage with naïve B cells through their TCRs and MHC II-bound allergens on the B cells, alongside signals from IL-4 and IL-13 secreted by Th2 cells. This interaction promotes the maturation of B cells into plasma cells that secrete IgE specific to the food allergen. These IgE molecules bind to high-affinity FcεRI receptors on the surface of tissue mast cells or blood basophils, completing the sensitization phase [27, 34].

The elicitation phase occurs with subsequent exposure to the same or cross-reactive food allergens, where these allergens cross-link FcεRI-bound IgEs on mast cells and basophils, leading to their degranulation and the release of mediators such as histamine. These mediators cause the symptoms of a food allergic reaction, which can affect multiple organs, leading to gastrointestinal issues, respiratory inflammation, skin and eye itching and swelling, and in severe cases, life-threatening anaphylaxis [27].

Non-IgE-mediated cow's milk allergy engages distinct immunological pathways, predominantly involving T cell-mediated mechanisms rather than the classical IgE antibody-driven responses. The strongest evidence points to the involvement of food allergen-specific suppressor CD8 T cells in patients with food protein-induced enteropathy (FPE). The presence of food-specific IgE antibodies locally in the gut, despite their absence in the bloodstream, suggests a role for local mucosal IgE in these conditions [33]. Food protein-induced enterocolitis syndrome (FPIES) is often thought to be mediated by T cells, although research on T cells in FPIES patients is limited. Some studies have shown T-cell proliferation in response to food antigens, but the stimulation index is not consistently different from that of nonallergic controls [31]. Increased levels of intestinal interferon-gamma (IFN-g) have been associated with villous damage, and in FPIES patients, an imbalance between intestinal tumor necrosis factor-alpha (TNF-a) levels and reduced transforming growth factor-beta (TGF-b) expression has been observed [35]. It is suggested that T-cell activation by food allergens might trigger local intestinal inflammation by releasing proinflammatory cytokines, such as TNF-a and IFN-g, leading to increased intestinal permeability and fluid shift [35, 36]. The clinical manifestation of symptoms usually appears several hours to days following the ingestion of cow's milk. Unlike IgE-mediated allergies, non-IgE-mediated food hypersensitivities predominantly target the gastrointestinal system, with minimal involvement of the cutaneous or respiratory systems [37]. The symptoms include diarrhea, constipation, vomiting, abdominal pain, gastroesophageal reflux disease (GERD).

PROPHYLAXIS AND MANAGEMENT OF COW'S MILK ALLERGY

The literature reveals diverse strategies aimed at reducing the incidence and managing CMA in infants. Primary prevention strategies should be implemented in infants considered at high risk for developing CMA. This group includes infants reported with first-degree relatives with a history of FAs, history of atopic dermatitis or other allergic conditions and delayed introduction of common allergenic food during infancy [38].

The role of maternal diet in cow's milk allergy prophylaxis

There is limited evidence to support altering the maternal diet during pregnancy or lactation to prevent CMA [39]. Kramer and Kakuma analyzed five trials and concluded that avoiding allergens during pregnancy and lactation is unlikely to reduce the risk of atopy in children [40]. Studies have shown that avoiding specific foods, like cow's milk or eggs, during pregnancy and lactation does not decrease the incidence of CMA or egg allergy in infants [41, 42]. This is because the relationship between allergen exposure and allergy risk follows a bell-shaped curve: high exposure fosters tolerance, very low exposure fails to elicit a response, and mid-range exposure increases the risk of sensitization. Avoidance merely shifts this curve, leading to no significant change in the overall population, with some individuals moving from high-dose tolerance to mid-range sensitization, and others from mid-range to low-dose without sensitization.

High-dose allergen exposure during pregnancy is an emerging approach in CMA prophylaxis. Animal studies suggest potential benefits, for instance, administering oral ovalbumin during pregnancy induced tolerance in infant BALBc mice, a protective effect disrupted by inhibiting placental IgG transfer or infant memory T-cell IFN-γ production [43]. Additionally, a study of 1.277 mother-child pairs in the USA found that high peanut consumption in the first trimester reduced the risk of peanut allergy, while high milk intake in the first trimester lowered the odds of developing asthma and rhinitis. High wheat intake in the second trimester was also associated with a reduced risk of eczema [44].

Breastfeeding as a primary option in cow's milk allergy prophylaxis

The composition of breastmilk is complex and consists of many biologically active substances, immunomodulating proteins, growth factors and antioxidants. (Figure 1). These mechanisms include the anti-allergic properties found in breast milk, the possibility that extended breastfeeding might delay allergen introduction, and the presence of antibodies in the milk that may bind with food antigens to promote tolerance [45]. In animal studies, it has been shown that antigen-immunoglobulin G immune complexes from sensitized mothers can be transferred to their newborns *via* the neonatal Fc receptor, leading to the development of antigen-specific FoxP3(+) CD25(+) regulatory T cells [46]. This transfer may induce tolerance and support the primary prevention of CMA [47].

Recent research has highlighted the role of short-chain fatty acids (SCFAs), particularly butyrate, in enhancing oral tolerance in offspring. [48, 49] Additionally, human milk oligosaccharides (HMOs) in breast milk, as well as prebiotics like galactooligosaccharides or specific HMOs such as 2-fucosyllactose included in infant nutrition, can stimulate SCFA production, suggesting a potential role in preventing CMA [50]. Breast milk also contains a variety of bioactive components, including immune-active peptides (cytokines), fatty acids, HMOs, microbial content, and micronutrients, all of which have been shown to modulate the immune system [51].

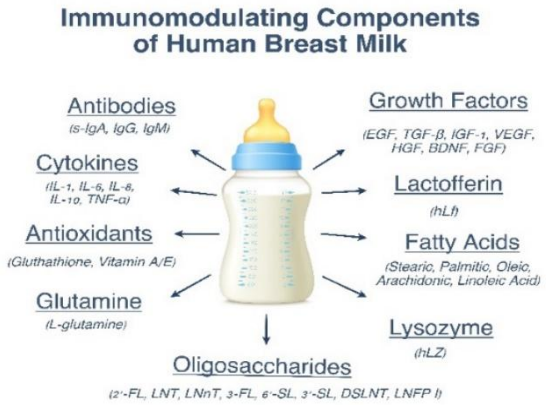

Figure 1. Molecules in the human milk with potential immune-modulating role. Abbreviations: s-IgA - soluble Immunoglobulin A; IgG - Immunoglobulin G; IgM - Immunoglobulin M; IL-1 - Interleukin 1; IL-6 - Interleukin 6; IL-8 - Interleukin 8; IL-10 - Interleukin 10; TNF-α - Tumor Necrosis Factor-Alpha; EGF - Epidermal Growth Factor; TGF-β - Transforming Growth Factor-beta; IGF-1 - Insulin-like Growth Factor 1;VEGF - Vascular Endothelial Growth Factor; HGF - Hepatocyte Growth Factor ; BDNF - Brain-Derived Neurotrophic Factor; FGF - Fibroblast Growth Factor; hLf - Human Lactoferrin; hLz - Human Lysozyme; 2'-FL - 2'-Fucosyllactose; LNT - Lacto-N-tetraose; LNnT - Lacto-N-neotetraose; 3-FL - 3-Fucosyllactose; 6'-SL - 6'-Sialyllactose; 3'-SL - 3'-Sialyllactose; DSLNT - Disialyllacto-N-tetraose; LNFP I - Lacto-N-fucopentaose I.

In a study of non-high-risk newborns followed up to 17 years of age, breastfeeding was associated with lower rates of food allergy at 1 and 3 years, as well as a lower "score of respiratory allergies" up to 17 years of age compared with cows' milk formula fed individuals [52, 53]. Exclusive breastfeeding is recommended by the World Health Organization (WHO) as the optimal feeding practice for the first 6 months of the infant's life [54]. Breast milk promotes the development of oral tolerance to allergens as it contains various immunologically active components. A multidisciplinary systematic review concluded that exclusive breastfeeding has a protective effect against CMA in early childhood, particularly in infants considered to be at high risk [55]. However exclusive breastfeeding does not totally eliminate the risk as statistics show that approximately 0,5% of exclusively breastfed infants still develop CMA [56].

The PROBIT trial, one of the longest cohort studies, recently reported that infants who were breastfed had a lower risk of developing flexural dermatitis when 18 years old. However, the study found no significant impact on lung function or the incidence of CMA and asthma [57].

Secondary alternatives in cow's milk allergy prophylaxis and management

If breastfeeding is insufficient or not possible, infants at high-risk can be recommended a hypoallergenic formula as a primary prevention strategy [58]. The most common hypoallergenic alternatives include infant formulas based on CMP. Enzymatic hydrolysis is a key biochemical process in reducing the allergenicity of CMP and providing a safe nutritional option for high-risk infants or those already diagnosed with CMA. By breaking down proteins into smaller fragments with low immunogenic characteristics, the immune system is less likely to trigger an allergic response but at the same time the exposure to small protein fragments helps in inducing oral tolerance to CMP. A social-metric study conducted among infants with atopy signs shows that hydrolyzed formulas can minimize the clinical signs and prevent severe allergic reactions [59]. Other less common alternatives include plant-based formulas or formulas based on mammalian milk proteins (goat, sheep, camel, horse, donkey).

✓ *Partially hydrolyzed formulae for non-exclusively breastfed infants.* Partially hydrolyzed formulae (pHF) typically contain peptides with molecular weights under 5,000 Da, reducing allergenicity by removing some sensitizing epitopes while retaining peptide sizes that promote oral tolerance. [60-62] The role of pHF in preventing CMA has been debated [63]. The GINI study, a long-term, large-scale research project, found that whey pHF significantly reduced atopic dermatitis (AD) and respiratory symptoms up to age 15. However, more recent studies, including those with prebiotic-enriched pHF, have shown no preventive effect [64-68]. There is no consensus on the impact of early exposure to intact CMP on CMA risk later in life. Some studies suggest that early introduction of CMP within the first 14 days of life may lower IgE-mediated CMA rates, while delayed introduction is associated with higher atopy risk by age of 2 [69].

✓ *Continuous early CMP exposure* might reduce CMA risk, while intermittent exposure followed by avoidance could increase it, with family history possibly influencing outcomes [70].

✓ *Extensively hydrolyzed formulae* Whey- or casein-based extensively hydrolyzed formulas (eHF) are considered the primary treatment for formula-fed infants with CMA [71]. These formulas contain short peptides derived from cow's milk, created through enzymatic breakdown and ultrafiltration of intact proteins. There are notable differences in the peptide molecular weights and profiles within eHF products [72, 73]. Due to this variation, the European Academy of Allergy and Clinical Immunology (EAACI) has advocated for stricter standards for eHF in Europe, including preclinical testing, quality assurance, and specific labeling requirements [74]. In 2016, DRACMA expanded their recommendations to include rice hydrolysate as a first-line option in regions where it is available [75]. According to ESPGHAN, eHF should be recommended as a first choice for CMA management for infants when breastfeeding is insufficient or not possible [76].

✓ *Amino acid-based formulae* Amino acid-based formula (AAF) is a synthetic, nutritionally complete formula free of cow's milk antigens, used to treat infants with severe CMA. Its cost-effectiveness varies depending on the healthcare system and formula costs in different countries [77, 78]. AAF is not a first-line treatment but is recommended for infants who do not respond to eHF or have very severe symptoms like cow's milk anaphylaxis or multiple food intolerances [79, 80]. Since tolerance development is believed to be driven by exposure to antigens, AAF is unlikely to promote tolerance, although a recent study found that adding synbiotics to AAF improved gut microbiota in non-IgE-mediated allergic infants [81, 82]. However, prolonged use of AAF for more than six months has been linked to hypophosphatemic bone disease, particularly in children with complex

gastrointestinal conditions, with calcium and phosphorus levels normalizing after switching to eHF [83, 84]. Studies on healthy volunteers showed no differences in calcium and phosphorus bioavailability from various types of AAF, even when used with acid-suppressant medication [85].

CONCLUSION

CMA is the most common and most studied FA in early childhood particularly in infants considered as high-risk. Despite recent advances in the understanding of CMA, it still represents a challenging condition with many uncertainties regarding its prophylaxis and treatment. A significant body of evidence highlights the important role of exclusive breastfeeding as a gold standard for infant nutrition and a primary preventive measure against CMA. For non-breastfed infants at risk of developing CMA, pHF or eHF are considered a safe and successful alternative for both prevention and management among high-risk infants with a family history of allergy. Additionally, infants with confirmed CMA who show severe allergic reactions, such as anaphylaxis, are recommended the use of a non-allergenic infant formula, where AAF is considered an alternative. The allergenicity of proteins in AAF is completely reduced in order to avoid elicitation of allergic reactions, and is thus suitable for the management of CMA. Overall, CMA management requires a personalized approach, ongoing research, and refinement of dietary and formula-based interventions to better prevent and treat food allergies in infants.

List of abbreviations

CMA	Cow's milk allergy
pHF	Partially hydrolyzed formulas
eHF	Extensively hydrolyzed formulas
AAF	Amino acid-based formulas
FAs	Food allergies
IgE-mediated	Immunoglobulin E-mediated
non-IgE-mediated	Non-immunoglobulin E-mediated
CM	Cow's milk
CMP	Cow's milk proteins
APCs	Antigen-presenting cells
DCs	Dendritic cells
MHC	Major histocompatibility complex
TCRs	T-cell receptors
TSLP	Thymic stromal lymphopoietin
IL	Interleukin
FPE	Food protein-induced enteropathy
FPIES	Food protein-induced enterocolitis syndrome
IFN-g	Interferon-gamma
TNF-α	Tumor Necrosis Factor-alpha
TGF-β	Transforming Growth Factor-beta
GERD	Gastroesophageal reflux disease
Ig	Immunoglobulin
EGF	Epidermal Growth Factor
IGF-1	Insulin-like Growth Factor 1
VEGF	Vascular Endothelial Growth Factor
HGF	Hepatocyte Growth Factor
BDNF	Brain-Derived Neurotrophic Factor
FGF	Fibroblast Growth Factor
hLf	Human Lactoferrin
hLz	Human Lysozyme
2'-FL	2'-Fucosyllactose
LNT	Lacto-N-tetraose
LNnT	Lacto-N-neotetraose
3-FL	3-Fucosyllactose
6'-SL	6'-Sialyllactose
3'-SL	3'-Sialyllactose
DSLNT	Disialyllacto-N-tetraose
LNFP I	Lacto-N-fucopentaose I
WHO	World Health Organization
AAP	American Academy of Pediatrics
AD	Atopic dermatitis
EACCI	European Academy of Allergy and Clinical Immunology

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