Cow's milk protein allergy: A comprehensive review of epidemiology, pathogenesis, clinical manifestations and diagnostics and management strategies

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ABSTRACT

Cow's milk protein allergy is an adverse immune reaction to proteins found in cow's milk, primarily casein and whey, affecting artificially fed, breastfed and mixed-fed infants. The immunological mechanisms involved lead to diverse clinical presentations, most commonly impacting the digestive and respiratory systems, as well as the skin. Diagnosis relies primarily on clinical evaluation due to the absence of specific diagnostic tests, making accurate identification crucial to prevent misdiagnosis or underdiagnosis. Treatment requires strict avoidance of cow's milk proteins in both children's and breastfeeding mothers' diets, with close monitoring of nutritional status during long-term management. Recent advancements in treatment, including the use of probiotics, provide new options for improving clinical outcomes. This narrative review aims to provide clinicians with evidence to standardise diagnosis and treatment, improve food allergy management by non-allergy specialists and develop accurate feeding recommendations

Key Words: cow's milk protein allergy, clinical manifestations, diagnosis, treatment, prognosis and prevention

INTRODUCTION

Food allergies are becoming increasingly prevalent in children, significantly impacting their health and placing a burden on the public health service sector.[1] Following changes in feeding practices, cow's milk protein is considered a primary cause of food allergies in infants and young children. Cow's milk protein allergy (CMPA) affects the quality of life of patients and their families, causing stress, disruptions in routines and social isolation. It also burdens the healthcare system, requiring frequent visits, specialised guidance and increased costs.[2, 3] Epidemiological studies indicate that CMPA primarily occurs in infants, with a global incidence range of 2.0%–7.5%. According to the World Allergy Organisation 2022 guidelines, in children under 6 years old, the incidence ranges from 0.6%–3.0%. Regional variations exist, with higher rates reported in Western countries. Recent trends suggest a rise in CMPA prevalence, influenced by factors such as changes in diet and gut microbiota. Early onset typically occurs within the first year of life, and although CMPA often resolves by age 3–5 years, it may persist in some cases, especially in children with other atopic conditions. In fact, CMPA in infancy is often linked to the development of other allergic conditions, such as atopic dermatitis (AD), allergic rhinitis (AR) and asthma, a progression known as the 'atopic march'. Studies indicate that children with CMPA have a higher risk of developing these

conditions as they grow, emphasising the importance of early diagnosis and management to potentially mitigate the progression of these allergic diseases.[4-6] According to prospective studies, CMPA can sometimes persist beyond school age.[2] Although it often naturally resolves with age, cow's milk protein remains the most common and significant food allergen. If left untreated, CMPA, as an upstream disease in the allergic process, can have long-lasting adverse effects on the respiratory system in children, impacting their growth and development and increasing the occurrence of other allergic diseases later in life.[7–9] This substantially increases the explicit and implicit burdens on the distribution of healthcare resources. Detecting and identifying CMPA promptly, adjusting the patient's diet and achieving early prevention and intervention can alleviate allergic symptoms and reduce the incidence of this disease. This article presents a review of the literature pertaining to CMPA.

DEFINITION AND PATHOGENESIS

Definition

Cow's milk protein allergy refers to an adverse reaction mediated by the immune system against one or more proteins in cow's milk, primarily casein (α1, α2, β and κ-casein) and whey proteins (α-lactalbumin and β-lactoglobulin).[10]

Pathogenesis

The allergy can occur in exclusively breastfed infants or those who received mixed feeding (with the introduction of milk protein). Three types of inflammatory mechanisms can mediate cow's milk allergy (CMA): 'acute-onset' immunoglobulin (Ig) E-mediated allergies, 'delayed-onset' non-IgE cell-mediated allergies and mixed-type-mediated allergies (Figure 1).[11] Cow's milk protein allergy is characterised by an imbalance in the Th1/Th2 immune response, with a shift towards Th2 dominance. The interaction between milk allergens and the immune system influences this shift. Specifically, milk proteins such as β-lactoglobulin and casein can act as antigens, stimulating antigen-presenting cells to process and present these proteins to naïve T-helper (Th0) cells. In individuals predisposed to allergies, this interaction favours the differentiation of Th0 cells into Th2 cells. Furthermore, Th2 cells secrete cytokines such as interleukin (IL)-4 and IL-5, which promote B-cell class switching to produce IgE antibodies specific to cow's milk proteins. The binding of these IgE antibodies to mast cells and basophils sensitises these cells, leading to allergic reactions upon subsequent exposure to the allergen.[12-17] This Th2-skewed response is central to the pathogenesis of CMPA,Th1/Th2 balance is influenced by maternal transmission and environmental factors,

such as delivery mode and microbial exposure.[18] Food intolerance is commonly caused by a lack of digestive enzymes, leading to the formation of immune complexes and systemic symptoms, with infants and young children being especially vulnerable.[19] In addition, the non-IgE-mediated mechanism of CMPA involves complex immunological processes, including the role of T cells. These reactions are typically delayed and can involve T cell-mediated immune responses, leading to conditions such as food protein-induced enterocolitis syndrome (FPIES) and allergic proctocolitis. Unlike IgE-mediated reactions, which are immediate, non-IgE-mediated reactions can manifest several hours to days after the ingestion of the allergen. In this context, food intolerance is associated with immune reactions mediated by IgG and T cells (Figure 2). The latest meta-analysis found that the rs1800896 variant in the IL-10 gene is associated with CMA in Chinese children. Additionally, the genetic risk for CMA is heightened in those with a parental history of allergy.[3]

Structural, functional and allergenic features of milk

Cow's milk contains several proteins, primarily casein and whey proteins, which can act as allergens. Caseins account for approximately 80% of the total protein content, and whey proteins (e.g. β-lactoglobulin and α-lactalbumin) make up the remaining 20%.[6] These proteins have specific structural and functional characteristics that influence their allergenicity. Heat treatment and food processing can alter the allergenic properties of these proteins. For instance, pasteurisation can denature whey proteins, potentially reducing their allergenic potential. However, caseins are more heat-stable and may retain their allergenic properties even after extensive heat treatment. Understanding these structural and functional characteristics is crucial for developing effective management strategies for CMPA.

EPIDEMIOLOGY

Incidence and age predilection

A recent study by Venter et al.[20] reported a global incidence of CMPA ranging from 2.0% to 7.5%, with an incidence of 0.6%–3.0% in children under 6 years old.[21] This allergy primarily affects infants, with the latest data from a survey in South China indicating an incidence of 2.69% in infants under the age of 1 year.4 Furthermore, this rate tends to increase annually.[22, 23] Infants are particularly susceptible to foreign antigens due to the immature development of their intestinal barrier. Contributing factors include the sparse arrangement of intestinal mucosal cells, high permeability of the intestinal wall, inadequate secretion of digestive fluids and the immaturity of the infant's intestinal immune function, including oral tolerance.

Together, these elements help explain infants' heightened vulnerability to CMPA.[4–6] Studies have shown that CMPA is most likely to occur in infants aged 1–6 months, indicating a higher incidence in younger infants compared with older children.[24] Additionally, the peak age range for CMPA is reported to be 4–6 months, followed by the 2–4-month age group, This increased susceptibility in the 4-6 month age range is largely due to the immaturity of the intestinal barrier and immune system. Factors such as sparse arrangement of intestinal mucosal cells, high permeability of the intestinal wall, and underdeveloped digestive and immune functions contribute to this vulnerability.[25]

Onset - related factors

Types of delivery

Previous research has identified caesarean section (C-section) as a risk factor for the development of CMPA in infants.[26] It is suggested that infants delivered vaginally are more likely to acquire maternal intestinal microbiota, which establishes a healthy intestinal microbiome. This process activates Th1 cell function, shifting the immune system of the foetus from its initial Th2 dominance towards enhanced Th1 function. This shift to Th1 dominance can, to some extent, inhibit allergic reactions and autoimmune responses in infancy.[27, 28] In contrast, infants delivered through C-sections do not undergo this process of exposure to the maternal intestinal microbiota during delivery. More recent publications have reinforced these findings, emphasising the importance of microbial exposure in the early days of life and its impact on immune development and allergy risk.[29] These findings highlight the need for careful consideration of delivery methods and postnatal microbial interventions, such as the use of probiotics, to potentially mitigate the risk of CMPA in infants born via C-section. Further research is needed to develop targeted strategies for reducing allergy risk based on delivery methods and early microbial exposure.[30, 31]

Feeding practices

Cow's milk protein allergy can affect both infants fed with cow's milk formula and those who are breastfed. The primary allergens in cow's milk – whey and casein proteins – maintain their antigenic activity even after processes such as boiling, pasteurisation or dehydration into powdered form.[32] When these proteins enter the human body, they can provoke an exaggerated immune response, potentially harming the infant. In contrast, human milk contains either none or extremely low levels of these antigenic proteins, making it a naturally

hypoallergenic fluid. Furthermore, human milk provides secretory IgA and various soluble factors that enhance the body's tolerance to foreign antigens, thereby helping to minimise the risk of developing allergic diseases. Research has shown that artificially fed infants have a higher risk of CMPA compared with those who are exclusively breastfed.[33, 34] Offering exclusive breastfeeding from birth to 4–6 months may reduce and delay the onset of CMPA and other allergic conditions. However, it is important to note that CMPA can still occur in exclusively breastfed infants, albeit at a lower rate.[35, 36] Research indicates that CMPA occurs in approximately 5% of the exclusively breastfed group, which may be associated with the transmission of a small amount of cow's milk protein through human milk, leading to allergies in the child.[37]

Genetic and environmental factors

Children with CMPA often have a genetic predisposition, frequently accompanied by a family history of food allergies, especially if a first-degree relative – particularly the mother – has experienced such allergies.[38] However, changes in environmental factors and social structures have led to a rapid increase in allergic diseases, indicating that every individual has an immunological basis for allergies. Current evidence suggests that the development of CMPA is likely influenced by a combination of genetic, environmental and other related factors, contributing to the onset of allergic diseases.[39]

The relationship between cow's milk protein allergy and clinical conditions

The clinical presentation of CMPA can involve a range of symptoms affecting multiple systems, including digestive symptoms such as diarrhoea, vomiting and colic; respiratory symptoms such as wheezing and coughing; and skin manifestations such as eczema and urticaria.[16] Symptoms can vary significantly depending on the child's age, with infants more commonly experiencing gastrointestinal issues, whereas older children may present with respiratory or skin symptoms.[25]

Cow's milk protein allergy can lead to various clinical manifestations involving multiple organs and tissues, which increases the risk of misdiagnosis or underdiagnosis. Additionally, CMPA is often associated with other atopic conditions, such as eczema, AR and asthma. The presence of CMPA can exacerbate these conditions, making the comprehensive management of atopic comorbidities essential for affected patients. Non-IgE-mediated food allergies due to CMPA (e.g. FPIES,[40] food protein-induced allergic proctocolitis,[41] enteropathy and gastrointestinal motility disorders) should also be considered.[42] When the skin is involved,

CMPA can lead to conditions such as eczema, urticaria and specific dermatitis, with incidence peaking in the first year after birth and gradually decreasing with age. Eczema, particularly AD, is a common manifestation of CMPA. Moreover, CMPA can occur alongside eczema and act as a significant trigger and exacerbator of AD, influencing its onset, progression and management. Early-onset persistent AD is strongly associated with food allergies, with approximately 40% of paediatric cases experiencing both conditions simultaneously.[43] The involvement of the respiratory system is mainly characterised by rhinitis, wheezing and chronic coughing. As the allergic process progresses, AR can be triggered by food allergies, including CMPA. Several studies have retrospectively analysed serum allergen test results in children with AR and identified cow's milk protein as a predominant allergen.[44-47] Children with early‐onset food allergies may subsequently develop respiratory allergies, leading to recurrent wheezing episodes and chronic coughing.[10] Multiple retrospective studies on blood allergen test results in children with wheezing have revealed that cow ' s milk protein is a significant food allergen.[48–50] Food allergy is strongly associated with bronchial asthma, which is a risk factor for this condition.[51] Cheng et al.[52] investigated risk factors for the occurrence and continuous development of asthma in children under 5 years old in Guangzhou between 2010 and 2014. The study results showed that cow's milk protein was the most common food allergen in children with asthma. Among children under 10 years old, 41% of the CMPA cases were accompanied by asthma, and 31% of the cases involved AR or conjunctivitis.[53] Infants with CMPA also show a higher frequency of itchy eyes and noses. In terms of the digestive system, CMPA can trigger symptoms such as vomiting, diarrhoea, abdominal distension and pain, poor feeding, swallowing difficulties and changes in stool characteristics, which can vary from normal to watery stools or the presence of mucus or blood. Cao et al.[54] conducted faecal examinations on 70 children with CMPA‐associated enterocolitis. The stool samples were mostly loose and sticky, and the detection rate of red blood cells under the microscope was significantly higher than that in the non‐allergic and healthy control groups. In addition to the aforementioned systems, CMPA manifests through diverse effects on other systems. For example, CMPA can trigger allergic reactions in the body, leading to the secretion of significant amounts of IL-6.[15] It can also induce an excessive production of platelet-derived growth factor through liver stimulation, causing an elevation in platelet levels.[55] Cow's milk protein allergy‐induced enteropathy or gastroenteritis may lead to a reduction or loss of Dcytb and DMT1, resulting in iron absorption disorders.[56] Antigenic fragments of CMPA entering the liver through the portal vein may induce immune damage to

liver tissues.[57] Children with CMPA are prone to vitamin D deficiency,[58] and it may increase the occurrence of night sweats and dark circles under the eyes.[59,60] This disease also has adverse effects on the development of the nervous system, producing harmful compounds and inflammatory factors detrimental to it.[61] Prolonged exposure to CMPA in children may result in delayed growth and development.[10]

DIAGNOSIS OF COW'S MILK PROTEIN ALLERGY

The clinical diagnosis of CMPA primarily relies on the patient's clinical manifestations and allergen screening. For example, IgE antibody testing includes the skin prick test (SPT), specific serum IgE (sIgE) determination, the atopy patch test (APT) and detection of food-specific sIgG antibodies (where IgG antibodies indicate exposure and IgG4 antibodies may indicate tolerance). Additionally, the elimination diet and food challenge test are considered gold standard methods for diagnosing CMPA. The basophil activation test (BAT) is a novel diagnostic tool that shows promise in identifying the condition. It measures the activation of basophils in response to allergens and can provide additional information beyond traditional IgE tests. Eosinophils (EOS) are sensitive indicators of allergic diseases, and an increase in the EOS count (EOS#) and percentage (EOS%) can serve as auxiliary diagnostic indicators for CMPA.[62] The BAT and other cellular tests have emerged as valuable tools, revealing specific immune cell populations associated with allergies.

Recent advancements in allergy diagnostics have focused on improving the accuracy and reliability of tests to better predict clinical allergies. The oral food challenge (OFC) test remains a cornerstone for diagnosing food allergies, particularly in distinguishing between sensitisation and actual allergic reactions. Studies have highlighted that traditional allergy tests often fall short in predicting clinical allergies for certain foods, such as tree nuts. More advanced antigen-based tests, including component-resolved diagnostics and epitope reactivity, offer promising improvements.[63] Starting with minimal doses in OFCs, especially in high-risk populations, ensures safety and accuracy in diagnosis.[64]

Cow's milk avoidance and provocation test

Clinically, dietary avoidance of cow's milk is recommended for suspected cases of CMPA before considering any other treatment. The duration of avoidance varies among patients, depending on the type of reactions and feeding methods. For immediate CMPA, children consuming cow's milk should avoid it for 3–5 days, whereas breastfeeding mothers should refrain from cow's milk and dairy products for 3–6 days before resuming breastfeeding. In

cases of delayed CMPA, children fed with cow's milk should avoid it for 1–2 weeks. For those with chronic diarrhoea or delayed growth and development, dietary avoidance may need to be extended to 2–4 weeks.[65, 66] Mothers of breastfed infants should also abstain from consuming cow's milk for 14 days. If clinical symptoms improve with the elimination diet, an OFC test should be conducted.[67] This food challenge test necessitates cooperation between parents and their children, which may involve certain risks. Due to the absence of an internationally recognised standardised protocol for its execution and interpretation, this test has limited applicability in clinical practice.[68] During the test, if the child exhibits allergic symptoms consistent with their medical history, the test is deemed positive, enabling a definitive diagnosis of CMPA. In this case, the test should be terminated immediately, and appropriate measures should be taken for any allergic symptoms that appear. A negative result is obtained if no allergic symptoms occur throughout the test. However, to prevent the underdiagnosis of delayed CMPA, the child should be closely monitored for at least 72 hours after the test.

Cow's milk protein allergy screening tests

The SPT, sIgE determination and the APT are collectively referred to as IgE‐mediated screening tests for CMPA. This type of test, with a positive predictive value lower than 50% and a relatively high negative predictive value (>95% in children over 1 year old), is preferred for food allergy screening. It is an *in vivo* test, and emergency medications (e.g. 1% adrenaline and glucocorticoids) should be prepared in advance. Compared with the SPT, sIgE testing for CMPA shows relatively high positive and negative predictive values.[69, 70] In clinical practice, a value of >0.35 kIU/L is typically considered the positive threshold for sIgE. However, CMPA may not be detected with an sIgE value of <0.35 kIU/L, suggesting a risk of generating false-negative results (i.e. the patient tests negative for sIgE but exhibits CMPA-related allergic reactions), Chinese Evidence-Based Guidelines for Food Allergy in Children: These guidelines highlight that while 0.35 kIU/L has traditionally been used as the cutoff due to technical limitations, advancements in technology have lowered the quantifiable threshold to 0.1 kIU/L. The findings suggest that sIgE levels between 0.1 and 0.35 kIU/L may still carry clinical significance, particularly in young children.15,69,70 The APT is rarely used due to its low sensitivity and weak objectivity in result interpretation.[68,71] Children with CMPA tend to develop immunotolerance as they grow up, and the levels of IgE in the body gradually decrease.[72] Non‐IgE‐mediated CMPA involves delayed allergic reactions,

typically IgG - and cell - mediated immune responses. Food intolerance screening (specific IgG measurement for food allergens) is frequently used as a potent complement to allergen - specific IgE tests,[19, 73, 74] offering a new direction for determining the causes of many conditions.[72]

Eosinophil count and percentage

Eosinophils serve as sensitive indicators of allergic diseases and demonstrate predictive value in the development of such conditions.[75–77] Peripheral blood EOS tests (EOS# and EOS%) can assist in diagnosing CMPA and monitoring the clinical efficacy of treatment regimens. However, careful clinical consideration is required for differentiation, as EOS levels can be easily affected by factors such as infections, premature birth, haematological disorders and systemic autoimmune rheumatic diseases.[78]

TREATMENT OF COW'S MILK PROTEIN ALLERGY

Dietary avoidance is the cornerstone of treatment for patients with CMPA. These individuals must eliminate foods containing cow's milk-derived allergens from their diets. Recent advancements in extensively hydrolysed formulas and elemental formulas have enhanced their efficacy and safety profiles. According to the latest guidelines, the choice of formula should be based on the severity and type of CMPA. For children following a cow's milk-based diet, an elimination diet involves substituting cow's milk and dairy products with an amino acid formula or an extensively hydrolysed formula. Amino acid formulas, composed of free amino acids derived from fully degraded proteins, are allergen-free and serve as an ideal alternative.[79–81] The formula is created by artificially breaking down proteins into amino acids to eliminate peptide chains.[79–81] An extensively hydrolysed formula involves a process in which proteins in cow's milk powder are broken down into amino acids and peptide chains, which may still retain allergenicity due to the presence of peptide chains. Children with CMPA should undergo re-evaluations every 3–6 months to prevent nutritional deficiencies resulting from the long-term avoidance of cow's milk.[82-84] For those who have experienced severe allergic symptoms, dietary avoidance should be extended as necessary. Soybean milk, deficient in nutritional components and prone to cross-sensitisation with cow's milk, is generally not recommended as a substitute. Similarly, goat's milk or milk from other animals is also not advised.[85]

For breastfed infants, a clear distinction must be made between diagnostic elimination diets and therapeutic diets. Diagnostic elimination involves the short-term exclusion of cow's milk protein to confirm CMPA, whereas therapeutic diets involve long-term management to avoid allergens and ensure nutritional adequacy (ESPGHAN 2023).[86]

In cases where children with CMPA exhibit severe allergic reactions, medications such as antihistamines (e.g. loratadine) and corticosteroids (e.g. prednisone) can be considered to help alleviate allergic symptoms. In the event of an anaphylactic shock, the immediate administration of intramuscular adrenaline is crucial to manage the reaction and save the patient's life. Additional supportive measures (e.g. antihistamines and corticosteroids) may also be required to stabilise the patient. Children with CMPA often experience gut microbiota imbalance with a significant decrease in faecal bacterial diversity, a reduction in bifidobacteria and streptococcal species and an increase in *Bacteroides, Lachnospira* and *Ruminococcaceae*.[87–89] Therefore, the prevention and treatment of CMPA should focus on the colonisation and reconstruction of healthy gut microbiota, as recent studies have highlighted the significant role of gut microbiota in modulating immune responses and allergic reactions. Probiotics and prebiotics, as well as synbiotics (a combination of probiotics and prebiotics), have been shown to offer beneficial support in managing CMPA by enhancing gut barrier function, promoting immune tolerance and reducing inflammation. Recent evidence suggests that certain strains of probiotics, such as *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis*, are particularly effective in promoting immune tolerance and reducing allergic symptoms in infants with CMPA. Some infant formulas now incorporate these probiotics to promote gut health, whereas additional biotics may be recommended to further enhance immune function and alleviate allergic manifestations.[90] Desensitisation treatment and immunotherapy represent promising future strategies for managing CMPA. Desensitisation aims to gradually increase tolerance to cow's milk protein, whereas immunotherapy seeks to modulate the immune system's response to allergens. Both approaches require further research, but they have the potential to reduce the severity of CMPA and improve long-term outcomes.[91]

Recent advances in the treatment of CMPA include the development of immunotherapy approaches.[92] Oral immunotherapy (OIT) involves the gradual introduction of small amounts of cow's milk protein to build tolerance. Studies have shown promising results, indicating that OIT can increase the threshold of reactivity and potentially induce long-term tolerance. Additionally, sublingual immunotherapy and epicutaneous immunotherapy are being explored as less invasive alternatives to OIT. These treatments aim to modify the immune response to

allergens and offer hope for the long-term management of CMPA. However, further research is needed to fully understand the safety, efficacy and long-term outcomes of these approaches.

PROGNOSIS AND PREVENTION OF COW'S MILK PROTEIN ALLERGY

In CMPA, the Th1/Th2 immune balance represents a primary immune mechanisms that has been compromised and is shifting towards Th2 immunity. This imbalance persists until around the age of 3 years and is reported to gradually improve thereafter.[93] Prospective studies indicate that 56% of children with CMPA no longer exhibit allergy to cow's milk at the age of 1 year, 70% at the age of 2 years and 87% at the age of 3 years.[94, 95] Notably, children with severe allergic reactions, more than two types of food allergies or a significant family history of allergies tend to have a poorer prognosis. Exclusive breastfeeding for 4–6 months is recognised as the cornerstone for preventing CMPA.[12,96] Considering the inconclusive findings of dietary avoidance of cow's milk during pregnancy and lactation, it is not recommended for pregnant or breastfeeding women to avoid cow's milk.[60,97]

Cow's milk protein has emerged as a significant sensitiser for early childhood food allergies, contributing to the rising incidence of CMPA. This not only adversely affects the skin, respiratory and digestive systems of children in both the short and long term but also impacts their healthy growth and development, thereby increasing the risk of other allergic diseases later in life.[7, 8, 10] Therefore, it is crucial to prioritise close monitoring of the condition and ensure the early identification, diagnosis and treatment of CMPA. This proactive approach helps reduce the risks of misdiagnosis and underdiagnosis and effectively prevents the progression of the allergic process.

CONCLUSION

In conclusion, CMPA remains a prevalent concern in paediatric health, with its management requiring accurate and early diagnosis to prevent complications and progression to other allergic conditions. This review highlights the importance of recognising the diverse clinical manifestations of CMPA and the need for personalised treatment strategies, including dietary management and emerging therapies. Recent advancements, particularly the use of probiotics such as *L. rhamnosus* GG, offer promising potential in restoring gut microbiota balance and improving patient outcomes. Early intervention and ongoing research into novel treatments are critical in refining CMPA management and improving long-term health outcomes for affected children

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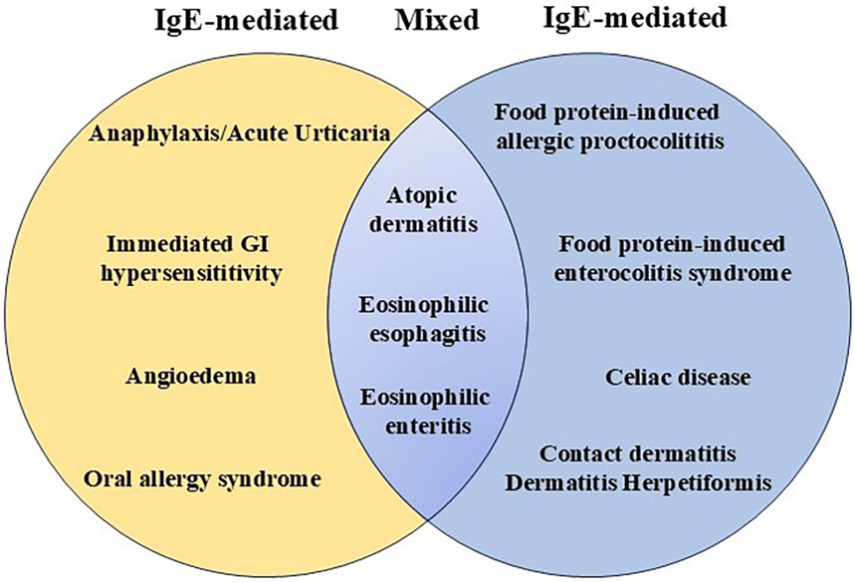

Figure 1. The types of cow's milk protein allergy

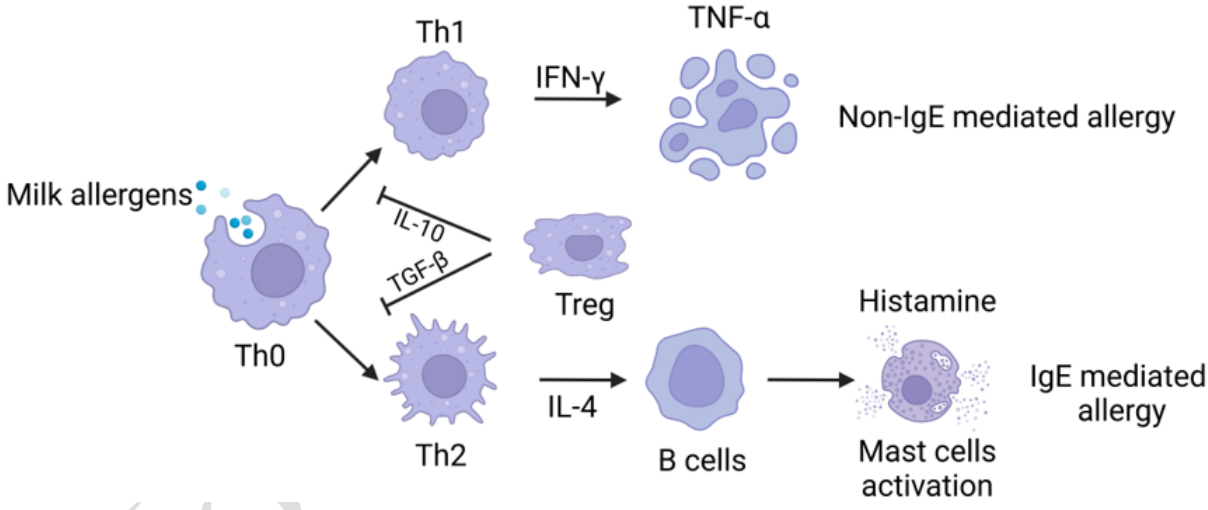

Figure 2. The molecular mechanisms of cow's milk protein allergy. IL: Interleukin, TNF-α: Tumor Necrosis Factor-alpha, IFN-γ: Interferon-gamma, Th: T helper

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