

Cow's Milk Protein Allergy

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Abstract

Cow's milk protein allergy (CMPA) is a common condition encountered in children with incidence estimated as 2% to 7.5% in the first year of life. Formula and breast-fed babies can present with symptoms of CMPA. It is important to accurately diagnose CMPA to avoid the consequences of either under- or overdiagnosis. CMPA is classically categorized into immunoglobulin E (IgE)- or non-IgE-mediated reaction that vary in clinical manifestations, diagnostic evaluation, and prognosis. The most commonly involved systems in patients with CMPA are gastrointestinal, skin, and respiratory. Evaluation of CMPA starts with good data gathering followed by testing if indicated. Treatment is simply by avoidance of cow's milk protein (CMP) in the child's or mother's diet, if exclusively breast-feeding. This article reviews the definition, epidemiology, risk factors, pathogenesis, clinical presentation, evaluation, management, and prognosis of CMPA and provides an overview of different options for formulas and their indication in the treatment of CMPA.

Keywords

cow's milk, protein, allergy, breast-feeding, formula feeding, Allergic colitis, elimination diet, oral challenge, extensively hydrolyzed formula, amino-acid based formula

Introduction

Cow's milk protein allergy (CMPA) is common in infants. The symptoms suggestive of CMPA may be found in 5% to 15% of infants.¹ However, CMPA is a clinical diagnosis and there is no laboratory test that is diagnostic. Infants who are fed cow's milk-based formula as well as those who are exclusively breast-fed can develop CMPA.² CMPA in exclusively breast-fed babies is thought to be due to β -lactoglobulin of cow's milk that is found in human milk 4 to 6 hours after maternal consumption of cow's milk.³

Definition

Cows' milk allergy or cow's milk protein allergy is an immune reaction to proteins found in cow's milk.⁴ Milk proteins can either be directly ingested by drinking cow's milk-based formula or passed through breast milk. Casein and whey proteins are usually the culprits. CMPA can be immunoglobulin E (IgE) mediated or non-IgE mediated. The World Allergy Organization definition for CMPA is "hypersensitivity reaction brought on by specific immunologic mechanisms to cow's milk."⁴ CMPA should be differentiated from cow's milk intolerance where the former is an immune mediated reaction while the latter is usually due to lactase deficiency which is rare in infants except following

gastrointestinal infections.⁵ Table 1 summarizes diagnostic criteria for CMPA according to Host and Halken¹ and for allergic colitis per Fiocchi et al.⁶

Epidemiology

The incidence of CMPA during first year of life is estimated to be 2% to 7.5%.^{7–9} while the prevalence of CMPA in breast-fed infants is 0.5%,^{10,11} and it is the most common food allergy in children younger than 3 years.^{12,13} Prevalence of CMPA decreases to less than 1% in children 6 years or older.¹⁴ According to a Danish cohort study, 54% of CMPA is due to IgE-mediated and 46% is due to non-IgE-mediated immune response.¹⁵ A large prospective study from Israel showed that only 0.16% of the general population develops isolated rectal bleeding due to CMPA.¹⁶

Misdiagnosis of CMPA

It is important to recognize the importance of diagnosing CMPA correctly in infants because misdiagnosis

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Table 1. Summary of diagnostic criteria for CMPA according to Host and Halken¹ and for allergic colitis per Fiocchi et al.⁶

Diagnostic Criteria for CMPA	Diagnostic Criteria for Allergic Proctocolitis
1. Elimination diet should result in resolution of symptoms	1. Presence of rectal bleeding in an infant with adequate weight and height parameters
2. Recurrence of the exact same symptoms with the oral challenge	2. Exclusion of infectious causes of colitis
3. Other causes of symptoms like lactose intolerance or gastrointestinal infections are ruled out	3. Disappearance of symptoms after elimination of cow's milk and dairy products from the child's and/or mother's diet

leads to unnecessary elimination diet in infants and breast-feeding mothers. Prevalence of a real food allergy in general is less than what is perceived by parents.^{17,18} In a study from Norway, 35% of children younger than 2 years were labeled by their parents with having a reaction to food (most commonly milk).¹⁹ Majority of infants who get misdiagnosed with CMPA present within the first 3 months of life with nonspecific manifestations typically involving a single system most commonly gastrointestinal or skin. Factors that were found to be associated with mislabeling as infant having CMPA are atopic dermatitis in the infant and higher maternal academic education.²⁰

Risk Factors

Atopic dermatitis is a risk factor for IgE-mediated common food allergies and the suspicion for CMPA should be stronger in moderate to severe atopic dermatitis that starts in the first 6 months of life.^{21,22} Asthma, especially when poorly controlled, is associated with frequent and severe reactions to milk.²³ It is controversial if paternal history of atopy is associated with higher incidence of CMPA in infants. A study published in 2013 showed that parental history of atopy alone does not predict which infants are at greatest risk for developing IgE-mediated CMPA.²⁴ While another study²⁵ found that there is increased occurrence of atopy in families of children with eosinophilic proctocolitis (allergic proctocolitis).

Pathogenesis

The immunologic mechanism behind the development of CMPA is not yet clear. However, it is clear that CMPA is caused by IgE- as well as non-IgE-mediated immune reactions. IgE-mediated CMPA is better described and it is typically immediate, type 1 hypersensitivity (minutes to 2 hours after consumption of cow's milk) while non-IgE-mediated CMPA is delayed, type 4 hypersensitivity. In patients with non-IgE-mediated reactions presence of both CD 8 and CD4 lymphocytes as well as eosinophils in all 3 layers of the colonic mucosa were demonstrated.²⁶

Lymphocytic transformation assays in these infants revealed evidence of circulating memory cells, which suggests involvement of T cells in the pathogenesis of CMPA.²⁷

The mechanism for rectal bleeding in allergic colitis is believed to be due to thinning of mucosa over the enlarged hyperplastic submucosal lymphatic tissue, with subsequent small mucosal ulcerations. Bleeding is most common when nodules are present in the sigmoid colon and rectum, suggesting friability of the stretched mucosa unmasked by passage of a fecal matter.

Clinical Presentation

Symptoms of CMPA are best divided into early versus delayed onset. Early onset symptoms occur within minutes to 2 hours after consumption of cow's milk. Late or delayed onset symptoms occur 48 hours and up to 1 week after consumption of cow's milk. As stated earlier, early symptoms are more likely to be IgE mediated and late symptoms are more likely to be non-IgE-mediated.²⁸ Non-IgE-mediated CMPA is more difficult to diagnose because (1) symptoms occur hours to days after milk consumption; (2) symptoms usually involve gastrointestinal system and skin, which are very commonly involved in many other conditions; and (3) there is no specific laboratory test to confirm or exclude the diagnosis.²⁹

CMPA usually presents within the first month of life and involves 2 or more symptoms in 2 or more systems¹ and rarely presents beyond 12 months of age.^{30,31} Most common symptoms are skin symptoms followed by gastrointestinal and then respiratory symptoms.¹ If symptoms are severe and response to standard treatment is poor, then CMPA needs to be considered to be the cause of gastroesophageal reflux or eczema.²⁹

In exclusively breast-fed infants, CMPA usually presents with atopic dermatitis and/or allergic proctocolitis.³² Allergic colitis usually presents with fresh blood mixed with the stool. Typically, stool is foamy, mucousy, and non-foul smelling, but it can commonly be blood tinged otherwise normal appearing newborn stool. Eczema is

also a common manifestation of CMPA in exclusively breast-fed babies.¹

In IgE-mediated CMPA, about 85% of symptoms are mild while 15% are severe such as stridor and wheezing and about 9% can develop into anaphylaxis within minutes to few hours after ingestion of cow's milk.^{29,31} Symptoms involve oral pruritus, urticaria, rhinorrhea or rhinoconjunctivitis, angioedema of oropharynx, eczema, vomiting, and diarrhea.

In non-IgE-mediated reactions symptoms are not very specific and include gastrointestinal symptoms (gastroesophageal reflux disease, vomiting, diarrhea, malabsorption, constipation,³³ and bloody stool,^{28,29}) due to gastrointestinal inflammation and dysmotility; skin (atopic dermatitis, urticaria, angioedema); respiratory (wheezing, cough); colic,^{28,34,35} and food aversion.³⁶ These symptoms are usually chronic and persist despite traditional standard therapies.²⁹ CMPA can sometimes present with failure to thrive (FTT) or isolated iron deficiency anemia, which is the most common nutritional deficiency in patients with CMPA.³⁷ It is reported that 25% of patients with CMPA have iron deficiency anemia.³⁸ Occasionally, irritability and colic may be the only symptom of food allergy.³⁷

Other presentations of non-IgE-mediated CMPA are allergic proctocolitis or food-induced proctocolitis,²⁸ allergic eosinophilic gastroenteritis (esophagitis, enterocolitis, proctocolitis), transient enteropathy (mimics celiac disease), protein-losing enteropathy,^{1,30,33,39} rectal bleeding,⁴⁰ and rarely, pulmonary hemosiderosis (Heiners syndrome).¹

Evaluation

Appropriate diagnosis and avoiding both under- and overdiagnosis is very important. Missing cases of CMPA can result in continuous blood loss and unnecessary, ineffective treatment of eczema while overdiagnosis can lead to dietary deficiencies and difficulty in reintroducing eliminated food items.⁴¹

As always, history remains very important in diagnosing CMPA as well as to differentiate between IgE- and non-IgE-mediated allergy, although it is sometimes not easy to differentiate between these based on history alone. Questions to ask are the following: What symptoms? How severe? How long after taking cow's milk do they occur? How long do they last? Which treatments have been tried and how effective were they?²⁹ Ask if symptoms are related to switching from breast milk to formula. Past medical history should include asking about atopic dermatitis, allergic rhinitis and asthma in older children. Also ask about any food that was already excluded from the patient's diet, results, and any food challenges.²⁹

If IgE-mediated milk protein allergy is suspected based on history, skin prick test, or specific blood IgE level is the next step in diagnosis. Checking IgE levels are more convenient because the skin prick test should be performed in centers well equipped with managing anaphylaxis and other severe reactions.⁴² However, history of exposure to the allergen remains the key element in making a diagnosis of cow's milk allergy because positive skin prick test or high IgE levels only indicate that there is a higher probability of clinical allergy and it is not enough for diagnosis.⁴³ There is actually a controversy whether or not the diameter of the wheal on the skin prick test and the IgE antibody levels specific to cow's milk protein actually correlate with the probability of developing a reaction to cow's milk, and persistence or severity of symptoms.^{29,44-46} When allergy tests do not help in the diagnosis of suspected CMPA, then elimination diet followed by double blind placebo controlled food challenge is the gold standard for establishing the diagnosis of CMPA.²⁹ Food challenge helps make a diagnosis and differentiate CMPA from other functional gastrointestinal disorders²⁸ and thus decreases the incidence of over-/underdiagnosis.⁴⁷ However, if ingestion of milk causes immediate symptoms or if the patient had serious reaction and the IgE levels specific for CMP are high then oral challenge is not necessary for diagnosis. In this case, the patient should follow CMP-restricted diet for at least 1 year⁶ after which oral challenge can be tried and it should be performed in hospital setting where access to emergency treatment is readily available. Also, if there is clear history of immediate symptoms following CMP ingestion but specific IgE is absent, then hospital based oral challenge is the next step.²⁸

If symptoms are suspected to be non-IgE mediated, allergy testing is not cost-effective^{28,33,40,48,49} and strict elimination diet is the only reliable diagnostic test. Diet restriction either for infant or mother should be tried for 2 to 8 weeks and if there is improvement of symptoms with recurrence with reintroduction of cow's milk, then it strongly supports CMPA. If no improvement of symptoms with diet restriction, then it is unlikely to be CMPA and milk should be reintroduced.²⁹ Exception to this is that some patients require switching to amino acid formulas (AAF) instead of extensively hydrolyzed formulas (eHF) before we can see improvement in symptoms. Also, if elimination and reintroduction test is positive, allergy testing may be performed to assess the possibility of immediate reaction with future exposure to CMP.²⁸ In general, diet restriction should be kept as short as possible and just long enough to detect change in symptoms (improvement vs resolution vs no change).

In infants with blood in stool because of CMPA, gross blood ceases to occur within 3 weeks of avoidance.

Table 2. Summary of indications for amnio-acid based formula in CMPA.

Anaphylaxis or severe reactions ²⁹
Rectal bleeding leading to hemodynamic instability ²⁹
Growth failure with or without hypoproteinemia/severe anemia ²⁹
Baby had symptoms with breast milk and later family wants to switch to formula (controversial) ^{29,37}
Persistence of symptoms with extensively hydrolyzed formula ^a

^aThose are estimated <10% of infants with cow's milk protein allergy but may be higher in case of severe enteropathy or multiple food allergies,^{55,56} especially severe symptoms in the IgE-mediated type, which is associated with severe atopic dermatitis or failure to thrive.^{34,55,59}

However, occult blood can be detected till 6 to 12 weeks after avoidance of CMP. If gross blood is still seen beyond 3 weeks or occult blood is still detected beyond 12 weeks, sigmoidoscopy is the indicated next for diagnosis. The most common cause of persistence of bloody stool in infants with allergic colitis is nodular lymphoid hyperplasia.

Management

Breast-feeding should always be the first choice. Second choice is hypoallergenic formula, which can be whey or casein based.

IgE mediated: remove cow's milk protein from the diet.

Non-IgE mediated: remove cow's milk protein as well as soy protein due to cross reactivity with CMP.²⁸

Breast-feeding: In breast-fed infants, the mother should follow CMP-free diet for 3 to 5 days if immediate reaction and for about 2 to 3 weeks if delayed symptoms. If no improvement in the symptoms, then it is unlikely to be CMPA and mother can resume her regular diet and the child should be further investigated for other causes of his/her symptoms. If symptoms improve or completely resolve with modifying maternal diet, reintroduction of dairy products into the mother's diet can be done gradually as long as the baby is tolerating it.³⁷ If symptoms recur, then the mother should resume CMP-free diet supplemented with calcium 1000 mg per day^{28,50} and 400 IU of vitamin D daily.^{34,51} In case symptoms recur despite mother's strict diet avoiding CMP, the mother has 2 options, either restriction of other allergenic food in her diet or switching to therapeutic (digested cow milk or noncow milk) formula instead of breast milk.^{52,53} If severe symptoms, such as severe eczema or enterocolitis with FTT/hypoproteinemia/severe anemia are present in an exclusively breast fed infant, then the infant may be fed therapeutic formula (typically AAF although there is no good evidence supporting benefit of AAF over other therapeutic formulas in breast fed babies) while his mother is

following strict CMP-free diet and expressing milk until the child's condition is stable.²⁸

If symptoms develop when formula is introduced to a previously breast-fed baby, treatment is ideally exclusive breast milk without any maternal elimination diet since the infant was asymptomatic when the infant was drinking only breast milk.^{28,37}

Formula feeding: Treatment is to replace the formula with extensively hydrolyzed formula (eHF) or amino acid-based formula (AAF). Common practice is to start with eHF and use AAF only if eHF fails, which is in fact a 2008 American Academy of Pediatrics recommendation.⁵⁴ However, duration after which switching from eHF to AAF should be considered varies from 2 to 8 weeks.⁵⁵⁻⁵⁷ Some experts recommend that AAF may be considered first-line treatments in infants with CMPA with severe reactions or severe enteropathy (FTT, hypoalbuminemia, etc)⁵⁸ while others suggest that AAF formula and eHF are both accepted first-line options in cases of anaphylaxis, eosinophilic enteropathy, FTT, and severe colitis.³⁷ The European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines recommend using eHF in most of the patients with CMPA because it is more affordable and well tolerated.²⁸ Table 2 summarizes indications for AAF.

A dietitian should be consulted to optimize nutrition of the child on CMP-restricted diet as both malnutrition and obesity can occur in these patients.^{42,60} It is also important to watch for nutritional deficiencies, especially poor calcium intake. In addition, Epipen is indicated for children with anaphylactic reactions to milk (IgE-mediated allergy).⁴² Parents should also be counseled and educated on reading labels and all dairy products as well as any food that has the following components on the label: casein, whey, lactalbumin, albumin, and so on, should be excluded from the child's diet.³⁷ Table 3 summarizes indications for referral to immunology.

Table 3. Summary of indications for referral to Immunologist in suspected CMPA.**When to Refer to a Specialist²⁹:**

Severe or systemic reactions
Failure to thrive
Atopic comorbidities (eg, IgE-mediated cow's milk allergy with asthma)
Multiple food allergies
Complex symptoms
Diagnostic uncertainty
No response to exclusion diet

In cow's milk-associated rectal bleeding, it is recommended to continue with elimination diet until symptoms resolve and then reintroduce cow's milk shortly after resolution of symptoms, which helps decrease unnecessary prolonged elimination diet.¹⁶

Formula Options

Extensively Hydrolyzed Formula

The European Commission sets the following criteria for the hydrolysate: (1) It should not cause sensitization to the milk protein in animal models when given orally. (2) It should be tolerated by >90% of children with CMPA in the sample studied¹⁰⁴. The commonly used eHF are Alimentum, Nutramigen LIPIL, Nutramigen with Enflora LGG, and Pregestimil LIPIL. These are lactose free and derived from the milk protein casein. There is no proven benefit of one formula versus other although some studies suggest that Nutramigen is tolerated slightly better than other hydrolyzed formulas.⁶¹⁻⁶⁷

Amino Acid–Based Formula

The commonly used AAF are Elecare (also with docosahexaenoic acid [DHA]/arachidonic acid [ARA]), Neocate infant (also with DHA/ARA), and Nutramigen AA Lipil. AAF for 1- to 10-year-old are Elecare, EO28 Splash, Neocate junior, and Vivonex Pediatric.

Other formulas

The common soy protein formulas are, Prosobee, Enfagrow soy next step, Good start soy plus, Isomil, and Similac go and grow. Soy-based formula for older children (1-10 years) available are Bright Beginnings soy pediatric drink, and ESP-GHAB. Soy-based formulas are not recommended due to cross-reactivity between soy and milk protein.⁵⁴ In fact, soy is shown to have 60% cross-reactivity with non-IgE-mediated and 14% with

IgE-mediated CMPA.⁴² Soy formula is also not recommended for infants less than 6 months as it contains isoflavins, which have a weak estrogen effect.^{37,68} In addition, phytate present in soy-based formula decreases the absorption of minerals and trace elements, which makes it less nutritious.⁶⁹

Rice protein hydrosylates formulas contain proteins not derived from cow's milk and Novarice is an example and it has the first two of the three recommended added amino acids tryptophan, lysine, and threonine. However, it is not commercially available in the United States. Rice formula has no clear indication, but still can be an option for vegan families or in infants refusing to take or not tolerating therapeutic cow's milk based formulas,^{4,70,71} provided that the infant is older than 6 months.

Goat, sheep, donkey, horse, and other mammals' milks are not indicated for treatment of CMPA and they are not nutritionally appropriate for infants.^{5,37} In addition, the cross-reactivity with CMP is about 80%.⁵⁷ Juices made of almond, coconut, chestnut, soy, and rice that are called "milks" are not nutritionally adequate for infants and should not be used to treat CMPA.²⁸

There is no evidence that delaying introducing foods that are known to cause allergy like eggs, fish, and wheat to infants with CMPA is effective in preventing food allergy and therefore these food items should not be avoided unless there is clear allergy to a specific food.⁷² Currently, there is no evidence that adding probiotics or even *Lactobacillus rhamnosus* (LGG) to hypoallergenic formula is beneficial,^{73,74} yet many of the commercially available formulas have them.

About 13% to 20% of children with CMPA are allergic to bovine serum albumin and generally to beef and veal meat as well^{1,75} but overall the majority of children with CMPA tolerate these meat well.³⁷ Therefore, the practice of excluding beef and veal is not recommended in the treatment of CMPA. However, some will argue that in the absence of diagnostic tests (skin tests or radioallergosorbent test), it is logical to avoid these meats during the diagnosis by elimination diet and test their tolerance thereafter. In general, cooked beef is better tolerated because heat destroys some of the allergens. Inversely, it was observed that 92% of children with beef allergy had allergy to CMP.⁷⁵

It was suggested in some studies that children with CMPA may develop an allergic reaction to the lactose (depending on the degree of purification) or probiotics (raised on lactose or milk) contaminating cow's milk proteins.⁷⁶⁻⁷⁸ However, excluding lactose from the diet due to concern of contamination of cow milk-derived formulas is not recommended due to lack of evidence in literature.²⁸ Regardless, eHF containing purified lactose is available for infants older than 6 months.⁷⁹ In some

Table 4. Natural history of CMPA in different populations and settings.

Authors/Year of Publication	Country	Number of Subjects	Population/Study Design	Tolerance Rate
Host et al, 2002	Denmark	39 (21 IgE-mediated)	General prospective birth cohort	56% by 1 y, 77% by 2 y, 87% by 3 y, 92% by 5 y, and 97% by age 15 y
Vanto et al, 2004	Finland	162 (95 IgE-mediated)	Referral prospective	44% by 2 y, 69% by 3 y, and 77% by age 4 y
Garcia-Ara et al, 2004	Spain	66 IgE-mediated	Referral prospective	68% by age 4 y
Saarinén et al, 2005	Finland	118 (75 IgE-mediated)	General prospective birth cohort	51% by 2 y, 74% by 5 y, and 85% by age 8.6 y
Skipak et al, 2007	USA	807 IgE-mediated	Referral retrospective	19% by 4 y, 42% by 8 y, 64% by 12 y, and 79% by age 16 y
Fiocchi et al, 2008	Italy	112 IgE-mediated	Referral prospective	52.7% by age 5 y
Martorell et al, 2008	Spain	170 IgE-mediated	Referral prospective	82% by age 4 y
Santos et al, 2010	Portugal	139 (66 IgE-mediated)	Referral retrospective	41% by age 2 y
Ahrens et al, 2012	Germany	52 IgE-mediated	Referral retrospective	61.5% by age 12 y
Elizur et al, 2012	Israel	54 IgE-mediated	General prospective birth cohort	57.4% by 2 y, 65% by age 4 y
Wood et al, 2013	USA	293 IgE-mediated	Referral prospective	53% by age 5.5 y
Yavuz et al, 2013	Turkey	148 IgE-mediated	Referral retrospective	20% by 2 y, 34% by 4 y, and 39% by age 6 y

cases where the child has CMP enteropathy with diarrhea causing secondary lactose intolerance, lactose-free eHF should be used.²⁸

Oral Challenge

In general, once CMPA is confirmed with restriction/reintroduction of cow's milk, diet free in CMP should be continued for at least 6 months or until the patient is 9 to 12 months if non-IgE-mediated CMPA before oral challenge is performed. For IgE-mediated CMPA with severe, immediate symptoms, diet free of CMP should be continued for 12 to 18 months before oral challenge.²⁸ Generally, for non-IgE-mediated CMPA oral challenge can be done at home unless the anticipated symptoms are severe (like enterocolitis causing diarrhea and vomiting leading to dehydration and need for intravenous fluids)⁸⁰ while for IgE-mediated CMPA, oral challenge should be performed in the hospital because of the risk of anaphylaxis. First, tolerance to CMP should be assessed by checking IgE levels or performing skin prick test and when tolerance is established, then only a hospital based oral food challenge is performed. If the oral challenge is positive, elimination diet should be continued for another 6 to 12 months before reevaluation.

Prognosis

Overall, CMPA has a very good prognosis with variations in the rate of CMP tolerance. By age 5 years, 80% to 90% of children develop tolerance to CMP.¹⁴ The

tolerance rate is 30% to 50% at 1 year, 55% to 75% at 2 years, and 70% to 90% at 3 years.^{14,81} It has been observed that IgE-mediated CMPA resolves in 53% to 57% children by 5 years of age and non-IgE-mediated CMPA usually resolves by 2.5 years of age.⁸²⁻⁸⁵ Mild proctocolitis due to CMPA, resolves in the majority of infants by the time they turn 1.^{4,86}

Table 4 summarizes multiple studies from different countries that looked at the natural history of CMPA (Adapted from Nicolaou et al).⁸⁷

A study published in 2008 showed that about 70% of patients with IgE-mediated CMPA tolerated baked milk products like cakes and pastries.⁸⁸ It is thought that proteins in cow's milk that cause allergic reactions get denatured by heat and are no longer allergic. Also, it is suggested now that development of tolerance to heat treated CMP actually helps induce tolerance to native cow's milk protein faster than that with complete avoidance of milk protein containing food items.⁸⁹

Table 5 summarizes several studies that looked into various prognostic factors for the development of tolerance or persistence of CMPA.^{14,82,87,89-100} There were some variations in results between studies that were attributed to differences in settings and populations, inclusion and diagnostic criteria, laboratory methods applied and time points of reassessment, and follow-up duration.

Other factors not mentioned in the table and found to be associated with persistence of CMPA are allergy to casein compared with other milk proteins, and longer duration of time from ingestion of CMP to symptoms onset.¹⁰¹

Table 5. Factors related to tolerance and persistence of CMPA.

Favor Shorter Duration and Tolerance	Favor Longer Duration and Persistence
Clinical Non-IgE-mediated Later age at presentation (eg, >1 month) Milder symptoms (eg, gastrointestinal) Higher eliciting dose (eg, > 10 mL) Tolerance of heated milk Absent or mild comorbidities (eg, asthma, rhinitis, eczema, and other food allergies) No family history of atopy	IgE-mediated Earlier age at presentation (eg, < 1 month) Severe symptoms (eg, respiratory) Lower eliciting dose (eg, <10 mL) Intolerance of heated milk Present and severe comorbidities (eg, asthma, rhinitis, eczema, and other food allergies) Family history of atopy
Laboratory Lower levels of sIgE and/or smaller skin prick test (SPT) wheal size to whole and individual (eg, casein) cow's milk proteins at diagnosis and follow-up measurements Significant reduction in sIgE levels and/or SPT wheal size over time Recognition of specific IgE conformational epitopes, increased binding to IgG ₄ epitopes	Higher levels of sIgE and/or larger SPT wheal size to whole and individual (eg, casein) cow's milk proteins at diagnosis and follow-up measurements Nonsignificant reduction in sIgE levels and/or SPT wheal size over time Recognition of specific IgE linear epitopes, greater sIgE epitope diversity and higher affinity Multiple sensitizations to other foods (eg, egg, soy) and inhalant allergens by sIgE/SPT

It is important to remember that in CMPA recovery does not necessarily mean complete recovery and tolerance, and sometimes the daily dose tolerated by the child may be limited.³⁷

On the Horizon

Oral immunotherapy is a promising field of research in treatment of CMPA. It is based on introducing gradually increasing doses of cow's milk to induce tolerance.¹⁰² Further studies are needed to support it as an effective and safe therapy for CMPA. Another promising treatment is omalizumab, monoclonal antibody against IgE either alone or in conjunction with immunotherapy.¹⁰³

Author Contributions

GM did the data gathering and most of the writing of the article and DK was GM's mentor and helped with editing/correcting/rephrasing.

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