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Management of CMPA in infancy: current approaches and future perspective

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ABSTRACT

Cow's milk protein allergy (CMPA) is a common food allergy among infants, with increasing incidence and severity in recent years. The objective of this study is to review the methods of CMPA diagnosis and treatment, assess the impact of probiotic supplementation on tolerance development, examine the role of butyrate in immune modulation, and investigate preventive measures against the "Atopic March." A comprehensive review of existing guidelines for CMPA diagnosis and treatment was conducted, with a focus on allergen avoidance and nutritional optimization through hypoallergenic formulas. The effectiveness of probiotic supplementation, particularly Lactobacillus casei CRL431 and Bifidobacterium lactis Bb-12, in expediting tolerance development was explored. Additionally, the potential of butyrate in modulating immune responses was examined and the impact of hypoallergenic formulas with probiotics, such as LGG was studied, in reducing other allergic manifestations and FGIDs. Studies assessing the preventive measures to curb the progression of FGIDs in CMPA children were also reviewed. This study signifies the achievement of immune tolerance in CMPA management. While some studies suggest a positive impact of probiotics on tolerance development, controversies exist, thus necessitating further research. Nutritional optimization is crucial in preventing growth deficits and micronutrient deficiencies. The potential of butyrate in modulating immune responses and mitigating food allergies is promising. Additionally, hypoallergenic formulas with probiotics may reduce the incidence of other allergic manifestations and FGIDs, while improving oral tolerance acquisition. Preventive measures hold the potential to curb the progression of FGIDs in CMPA children.

KEYWORDS

Cow's milk protein allergy (CMPA); Immune tolerance; Probiotic supplementation; Butyrate; Allergic manifestations

ARTICLE HISTORY

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Introduction

Food allergy (FA) describes adverse reactions to foods with an immunological mechanism and comprises two basic types: IgE-mediated and non-IgE-mediated. Symptoms of IgE-mediated FA appear shortly after exposure to the allergen, usually in the first 1-2 hours. In non-IgE mediated FA symptoms usually appear some hours and days after allergen exposure. Cow's milk proteins are among the first proteins that newborns and infants are exposed to, making Cow's Milk Protein Allergy (CMPA) the most common food allergy during infancy. Its prevalence varies between 1.9% and 4.9% according to different authors and countries [1]. Therefore, CMPA is a common allergy during childhood with an increase in the last 20 years in incidence and prevalence with subsequent clinical manifestations and therefore risk of persistence of allergy in its different manifestations [2].

At diagnosis, most CMPA children aged less than 6 months may require hypoallergenic formulas if breast milk is unavailable. These hypoallergenic formulas constitute extensively hydrolyzed formulas (eHF) and free amino acid-based elemental formulas (AAF). Hypoallergenic formulas do not serve to treat CMPA, they only meet the main objectives of CMPA: avoidance of the allergen and ensure a state of nutrition with optimal growth following a restricted diet. To be able to talk about the treatment of CMPA, it is necessary to think about achieving tolerance as soon as possible and avoiding subsequent manifestations.

Methods

Guidelines cow´s milk protein allergy

CMPA Guidelines for the Diagnosis and Treatment of food allergy and other guidelines are published periodically by different societies and official bodies, the most updated documents being those presented in Table 1 [3-12]. CMPA is the most common food allergy in young children, and it has been possible to observe a change in the frequency and presentation of the disease with an increase and severity, need for hospitalization, risk of persistence in later ages, risk of inflammatory processes, risk of atopic disease and risk of functional gastrointestinal disorders [13].

Among the clinical aspects that differentiate IgE-mediated and IgE-non-mediated CMPA, it is worth mentioning in Table 2. The current objectives in the Pediatric Guidelines for the diagnosis and treatment of CMPA are the avoidance of the allergen and the maintenance of an optimal nutritional status although in recent years there have been publications that suggest new medium and long-term objectives that should be included in the new CMPA Update Guidelines that we will describe below in Table 3.

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Table 1. Main consensus and guidelines in the diagnosis and treatment of CMPA.

Italy/Europe	Italian Society of Pediatric Allergy/WAO	DRACMA	Focus on CMPA IgE medand non-IgE med	[3]
Europe	ESPGHAN	Guidelines ESPGHAN CMPA	Focus on CMPA IgE medand non-IgE med	[4]
Europe	EAACI	Guidelines Food Allergy	Not limited to CMPA	[5]
Spain	SEICAP	GUIDELINES CMPA	Focus on CMPA IgE medand non-IgE med	[6]
Italy/Europe	Italian Society of Pediatric Allergy/WAO	Update DRACMA	CMPA Diagnosis anttreatment	[7]
UK	NICE-derived	MAP (Milk allergy in primary care)	Focus on non-IgE CMPA inprimary care	[8]
UK	NICE-derived	Update i-MAP (International MAP)	Focus on non-IgE CMPA inprimary care	[9]
Spain	SEGHNP/AEPAP/SEPEAP/SEICAP	Guidelines CMPA	Focus on non-IgE CMPA	[10]
Europe	EAACI	Diagnosis and management of Non- IgE gastrointestinal allergies in breastfed infants	Focus on non-IgE CMPA	[11]
Italy/Europe	Italian Society of Pediatric Allergy/WAO	DRACMA	Update guidelines CMPA	[12]

Table 2. Clinical aspects that differentiate IgE mediated and IgE non-mediated CMPA.

	Clinical Presentation and Diagnosis	Treatment	Prognosis
CMPA IgE mediated	Cutaneous, respiratory, anaphylaxis (<2 hours of allergen intake) Diagnosis: RAST and/or PRICK positive test and positive oral food challenge (OFC)) if it is possible.	Allergen avoidance with Human milk (mother diet without cow´s milk protein) or extensively hydrolyzed formula (eHF) as the 1st choice and in severe cases or anaphylaxis elemental formula (AAFree).	Tolerance 70% around 2-3 years
CMPA non-IgE mediated	Gastrointestinal (vomiting, diarrhea, anorexia, irritability, poor growth, etc.), usually within 3-4 days of allergen intake). Diagnosis: RAST and/or PRICK negative test and positive oral food challenge (OFC) if it´s posible.	Allergen avoidance with Human milk (mother diet without cow´s milk proteins) or extensively hydrolyzed formula (eHF) as the 1st choice and in severe cases or anaphylaxis with an elemental formula (AAFree).	Tolerance 80-85% around 1-2 years

Table 3. New targets in the treatment of CMPA.

Current objectives (International Guidelines)	New objectives (not included in the current Guidelines)
Strict avoidance of cow´s milk protein	Acquisition of tolerance (as soon as possible)
Maintenance of the optimal state of nutrition	Reduction in the appearance of other allergic manifestations (asthma, czema, urticaria and rhinoconjunctivitis)
	Prevention of Functional Gastrointestinal Disorders (FGIDs)

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Results and Discussion

Strict avoidance of cow´s milk protein

Strict avoidance of the allergen (in this case, cow´s milk protein), is the main objective in the CMPA and the formula chosen will depend on the age of the patient, the composition and residual allergenic potential of the formula, its cost and availability and acceptance by the baby and the presence of other allergies. The requirements of the chosen formula (with data that support its efficacy, tolerance and growth with a clinical trial), will basically be good palatability, its nutritional adequacy and low economic cost. A new concept of functionality has recently been added, which is to facilitate the acquisition of tolerance that we will discuss later.

Extensively hydrolyzed formulas (eHF) with 100% of the peptides <3,000 Daltons are the first option, and only in case of failure and/or anaphylaxis, or in multi-allergic or highly sensitized children, an elemental formula based on free amino acids (AAF) will be chosen.

The current criteria on the degree of hydrolysis for eHF, or hypoallergenic formula, is that all peptides in the formula are below 3,000 Daltons, although the presence of peptides between 3,000 and 5,000 Daltons in small amounts is present in some formulas, the effectiveness of which will depend on the sensitivity of the child affected by CMPA. Therefore, it is advisable in very sensitive children to test the tolerance to the chosen formula with an open provocation test, under the supervision of the specialist, and avoid subsequent formula changes, due to the different degrees of hydrolysis between them.

Hydrolyzed rice protein (RHF) formulas are a valid and equally effective alternative to eHF, which taste better and are generally well accepted by the baby, although they are not available in all countries. They are also an excellent choice for vegan or vegetarian families. Soy formulas (SF) are recommended for children >6 months, due to the presence of phytoestrogens and isoflavones. They are less and less used in CMPA, because most babies are diagnosed in the first half year of life when their use is restricted. Partially hydrolyzed formulas (pHF) whose degree of hydrolysis is >5,000 Daltons, drinks or smoothies of soy, rice, oats, almonds, etc. (misnamed "milks") are not recommended, due to the danger of malnutrition in young children [14,15]. The ideal formula for CMPA must have the following characteristics: avoid the allergen (in this case cow´s milk protein), complete absence of intact cow´s milk proteins, degree of hydrolysis of 100%<3,000 Daltons, proven efficacy, nutritionally adequate, pleasant taste and low economic cost [3,4,6,7].

Maintenance of the optimal state of nutrition

In FA, specifically in CMPA, the elimination of food allergens that provide essential nutrients for growth can produce irreversible nutritional disorders in the short and medium term such as growth deficit, micronutrient deficit (vitamins and minerals) and even feeding difficulties due to the palatability of hypoallergenic formulas. This does not necessarily translate into a deficit demonstrated by nutritional or anthropometric biomarkers. Calcium and vitamin D have been extensively studied and it has been seen that there is a lasting impact beyond childhood and adolescence on bone mineral density and consequently on your future bone health.

The avoidance of allergens that in the case of CMPA are cow´s milk proteins that provides macro and micronutrients essential and indispensable for the infant's diet, if breastfeeding is not available. Individualized nutritional advice to avoid elimination of unnecessary nutrients and choice of the most appropriate hypoallergenic formula is part of a comprehensive treatment of FA. All the Allergy Guidelines provide nutritional advice to ensure nutritional optimization and avoid growth delays or nutritional deficiencies, despite this, publications appear every year on growth deficits in allergic children with low intake of vitamins and minerals and even cases of severe malnutrition [16,17].

Acquisition of immune tolerance

Several recent studies have shown that CMPA is linked to an underdeveloped immune system response, both locally and systemically, and is associated with changes in the gut microbiome composition. Over the past two decades, food allergies have been on the rise in developed nations, and the variations in the gut microbiome composition, including the levels of bifidobacteria and lactobacillus, as well as overall microbial diversity, might be crucial in understanding the increased prevalence of allergies. From this point of view, it seems that probiotics could restore dysbiosis and be effective against FA.

The immune response within the gastrointestinal mucosa is influenced by signals from the intestinal microbiota. These signals interact with Toll-like immune receptors of various types, which are pivotal in shaping tolerance development. However, these effects can be specific to particular microbial strains. Certain studies indicate that combining probiotic supplementation with the administration of low doses of antigens containing eHF can potentially facilitate the development of tolerance [18]. However, there are controversies whether such eHF supplementation with certain probiotics can accelerate the acquisition of tolerance.

Clinical studies have examined the effectiveness of specific probiotic strains in managing food allergies, particularly in promoting the development of tolerance. This effect seems to vary depending on the particular probiotic strain used and is more pronounced in pediatric populations. Hol et al. conducted a double-blind randomized study with the primary aim of investigating whether supplementing an eHF with a combination of two probiotics, namely Lactobacillus casei CRL431 and Bifidobacterium lactis Bb-12, would impact the acquisition of tolerance in children diagnosed with CMPA. Included in the study were 193 infants under 6 months of whom 119 met the inclusion criteria (mean age, 4.2 months; age range, 1.4-6.0 months; 55% children).

The authors' findings indicated that the use of the tested probiotics in an extensively hydrolyzed formula did not hasten the development of tolerance in infants diagnosed with CMPA. As a result, the results did not provide support for supplementing with these specific probiotics (*L. casei* CRL431 and *B. lactis* Bb-12) for the tertiary prevention of CMPA in childhood. The effectiveness of other probiotics in this regard remains uncertain [19].

Using a similar design, Berni Canani et al., in an initial, open-label, randomized controlled trial with a small number of patients (n=55) demonstrated that an eHF formula

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containing *L. rhamnosus* (LGG) was able to accelerate the acquisition of immune tolerance in children with CMPA. Children (1 to 12 months), consecutively referred for suspected CMPA (IgE mediated or non-IgE mediated), but still receiving cow's milk proteins, were evaluated in the study.

Participants in the study were randomly allocated to one of two groups for dietary interventions: EHCF (control group); and EHCF-LGG containing LGG (at least 1.4 × 107 CFU/100 ml; intervention group). After 12 months, placebo-controlled double-blind food provocation was negative in 15 of 28 control infants (53.6%) and in 22 of 27 infants receiving EHCF with LGG (81.5%, p=0.027). No adverse effects were observed [20]. Given the results of the previous study, Berni Canani, et al. conducted a new prospective comparative open-label study with a larger number of patients and assessed the development of tolerance in a group of 260 children who had been diagnosed with CMPA. The study examined the impact of five distinct dietary approaches: eHF-Casein (eHF- C), eHF-Casein with LGG (eHF-C+ LGG), hydrolyzed rice formula (RHF), soy formula (SF), and free amino acid-based elemental formula (AAF) in children affected by IgE- or non-IgE mediated CMPA.

After 12 months of treatment, the percentage of children who developed immune tolerance was notably higher ($p<0.05$) in the groups that received either eHF-C (43.6%) or eHF-C+LGG (78.9%) in comparison to the other groups: RHF (32.6%), SF (23.6%) and AAF (18.2%). Binary regression analysis identified that the likelihood of patients developing tolerance at the end of the study was influenced by two specific factors, the IgE-mediated mechanism (B-2.05, OR 0.12, 95% CI 0.06-0.26; $p < 0.001$) and the chosen formula, i.e., those receiving eHF-C (B 1.48, OR 4.41, 95% CI 1.44-13.48; p=0.009) or, even better, eHF-C+LGG (B 3.35, OR 28.62, 95% CI 8.72-93.93; $p<0.005$). This study has been widely commented on in the world literature on the tolerance acquisition in CMPA, but more studies are required to validate these results since the initial study was NOT- RANDOMIZED [21].

Qamer et al. systematically review the effect of probiotics on CMPA and conclude that there is limited low-quality evidence that probiotic supplementation may be associated with earlier acquisition of tolerance in children with CMP. Well-designed, large patient-conferred trials are essential to confirm these findings [22].

However, LGG is among the most extensively researched and studied probiotics in the field of allergy with multiple actions in the gastrointestinal tract highlighting:

1. Effect at the level of the intestinal lumen with the ability to modulate the intestinal microbiota [23].
2. Increase in the production of local IgA [24].
3. Ability of hydrolyzing casein antigenic peptides [25].
4. Effect at the level of the intestinal mucosa with the ability to modulate intestinal permeability [26].
5. Cell growth stimulation and differentiation [27].
6. Effect beyond the intestinal mucosa with modulation capacity of the innate immune system of infant to adaptive of older child and adult and also capacity of induction to oral tolerance (Figure 1) [28].

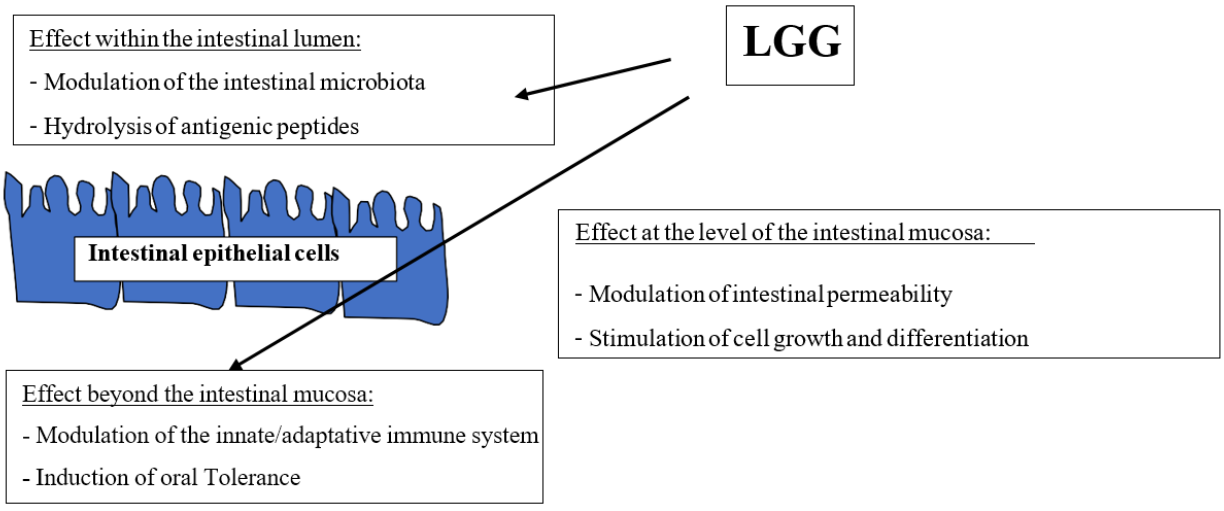

Figure 1. Effects of *Lactobacillus rhamnosus* GG on the Gastrointestinal Tract.

A formula extensively hydrolyzed with casein (eHF-C) that includes the probiotic LGG has the potential to influence the immune tolerance network. This influence is achieved through two main mechanisms: the action of peptides resulting from the breakdown of specific casein components and the impact of LGG on the structure and function of the intestinal microbiota. This, in turn, leads to an increased production of short-chain fatty acids (SCFAs), primarily dominated by butyrate. Various factors, both related to the immune system (such as cytokines and immune cells) and non-immune aspects (like the integrity of the intestinal barrier), play a role in this modulatory process. These effects are regulated by epigenetic mechanisms and may have the ability to prevent the progression of Atopic March [29].

It seems that after the 12-month treatment period with LGG improves the development of tolerance to cow's milk in allergic children so that LGG can modulate immune functions through different pathways of maturation and tolerance of the immune system including enterocytes, monocytes, mast cells, DCs and Tregs.

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The mechanisms of action are complex, LGG acts through intestinal fermentation with production of butyric acid and elevation of cytokines such as IL-10 and IFN-gamma with epigenetic effects on DNA methylation. These epigenetic findings suggest a novel approach as DNA methylation would play significant role in the development of tolerance in food allergy [30].

Recent research highlights the significance of modifying the gut microbiota in pediatric patients with food allergies through various dietary interventions. In CMPA, those who were treated with soy and rice-based formulas displayed reduced levels of Coriobacteriaceae and Bifidobacteriaceae in their fecal microbiota. Conversely, children with CMPA who consumed extensively hydrolyzed formula showed an increase in Coriobacteriaceae and bacteria belonging to the genus Collinsella, which is a key bacterium involved in lactose metabolism in the gut. Furthermore, the study revealed a positive correlation between fecal butyrate levels and the abundance of Coriobacteriaceae. Treatment with an eHF-C containing the probiotic LGG in children with CMPA significantly increased fecal levels of butyrate and SCFAs-producing bacteria. These effects were associated with immune tolerance acquisition [31].

There is evidence of butyrate deficiency in children with allergies. Short-chain fatty acids (SCFAs), produced by gut bacteria, have been linked to the regulation of the proportions and functional abilities of regulatory T cells (Tregs). Some studies have specifically associated this regulatory effect with the production of butyrate.

In addition, SCFAs can increase the number of CD4 cells but not the number of Th1 or Th17 cells. Collectively, the evidence from these findings points to the possibility of adopting a "postbiotic" strategy, which involves using SCFAs, especially butyrate, as a potential approach in managing food allergies. Butyrate has demonstrated its ability to inhibit acute allergic responses on the skin, reduce anaphylactic symptom severity, lower body temperature, enhance intestinal barrier function, decrease IgE production, and reduce IL-4 and IL-10 responses to β-lactoglobulin in a mouse model of CMPA. These results suggest that butyrate may play a protective role against food allergies [32,33].

Reduction of the appearance of other allergic manifestations

Food allergies, particularly CMPA, may be associated with the development of various allergic conditions, including rhinitis, atopic dermatitis, asthma, and urticaria, a phenomenon known as the "Atopic March." Additionally, they can be linked to functional gastrointestinal disorders (FGIDs), inflammatory bowel diseases (IBD), and psychiatric disorders such as autism spectrum disorders (ASD), attention deficit hyperactivity disorder (ADHD), and obsessive-compulsive disorder. While the exact mechanisms underlying these connections are not yet fully understood, there is evidence to support the hypothesis that disruptions in the gut microbiome (dysbiosis) may play a pivotal role. This dysbiosis can lead to alterations in the immune system and the gut-brain axis, potentially influencing the onset of food allergies and related conditions later in life.

Numerous genetic and epigenetic factors have been associated with the development of these conditions. However, recent evidence underscores the central role of gut microbiota dysbiosis, which can be influenced by environmental factors, in their pathogenesis. The emergence of changes in both the function of the intestinal barrier and the immune system, leading to the development of food allergies and the Atopic March, as well as the disruption of the brain-endocrine-immune gut axis, contributing to the onset of FGIDs, IBD, and neuropsychiatric disorders, is driven by the activation of epigenetic mechanisms. The Atopic March, characterized by initial symptoms such as gastrointestinal issues and atopic dermatitis in confirmed allergies, is followed by the development of atopic comorbidities, including asthma and allergic rhinitis.

Recent observations also demonstrate a link between food allergy in early childhood and functional gastrointestinal disorders and extraintestinal manifestations in adulthood. Hence, with proper immunological and nutritional management, it is possible to shorten the duration of CMPA and atopic dermatitis, while also offering protection against the development of other atopic conditions in children with CMPA. [34-37].

Berni Canani et al. in a randomized controlled trial studied whether the administration of an eHF with LGG in children with CMPA could reduce the occurrence at later ages of other allergic manifestations.

A total of 220 children were randomized: 110 children in the eHF-C group and 110 children in the eHF-C group with LGG. The occurrence of at least 1 allergic manifestation for 36 months and the acquisition of tolerance to cow's milk at 12, 24 and 36 months were evaluated. The authors conclude that children in the eHF-C group with LGG reduced the incidence of other allergic manifestations (asthma, eczema, urticaria and rhinoconjunctivitis) and accelerated the development of oral tolerance in children with CMPA.

These effects may result, to some extent, from the immune function modulation triggered by specific components of LGG on various pathways, including enterocytes, monocytes, mast cells, dendritic cells, and Tregs. Consequently, research involving children with eczema and/or CMPA who were administered extensively hydrolyzed formula with LGG demonstrated advantages in reducing inflammation and alleviating gastrointestinal symptoms [13].

Prevention of functional gastrointestinal disorders

Functional gastrointestinal disorders (FGIDs) are very common in childhood, According to the Rome IV criteria [38,39], they are a variable combination of chronic intestinal or gastrointestinal symptoms chronic or recurrent without an organic cause that justifies it and are a consequence of several factors:

a) alterations in motility, b) hypersensitivity visceral, c) alteration of the mucosa, d) alteration of immune function in the form of dysregulation and, e) alteration of the intestinal microbiota in the form of intestinal dysbiosis. Several mechanisms are causing the clinical effects on CMPA that could be responsible for intestinal inflammation and dysbiosis.

Nocerino et al. in a cohort study investigated whether adding LGG to an eHF-C formula for the treatment of CMPA diagnosed during the first year of life could reduce the

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occurrence of FGIDs at later ages.

FGIDs were diagnosed based on the diagnostic criteria of Rome III, and the diagnosis was made by researchers who were unaware of the participants' prior treatments. A cohort of consecutive healthy children was assessed as a control group for comparison. We included 330 subjects, 110 per cohort (eHF-C, eHF-C+LGG and healthy controls). The rate of subjects with at least 1 FGIDs was significantly lower in the eHF-C+LGG cohort compared to the eHF-C cohort (40% vs. 16.4%; P<0.05). The prevalence of FGIDs in the healthy cohort was lower than that of the eHF-C cohort and similar to that of the eHF-C+LGG cohort. These results confirm the increased risk of developing FGIDs in children with CMPA and suggest that eHF-C+LGG might reduce this risk [40].

Conclusions

The current objectives in the Pediatric Guidelines for the diagnosis and treatment of CMPA are the avoidance of the allergen and the maintenance of an optimal nutritional status. In recent years there have been publications that suggest new medium and long-term objectives that should be included in the new CMPA Update Guidelines. New objectives in the treatment of CMPA must be considered aimed at the acquisition of tolerance as soon as possible. Avoid the progression of Atopic March with the prevention of other allergic manifestations and functional gastrointestinal disorders at later ages. Addition of functional ingredients of proven efficacy in extensively hydrolyzed formulas and other special formulas indicated in the treatment of CMPA will help improve treatment of CMPA.

Disclosure statement

No potential conflict of interest was reported by the author.

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