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REVIEW PAPER

Cow's Milk Protein Allergy and primary health care: a narrative review of current guidelines

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Abstract

Objectives: To perform a narrative review of the literature about current guidelines for food allergy and present the main recommendations for Cow's Milk Protein Allergy (CMPA) management in children at primary health care by algorithms. **Methods:** We searched for relevant publications on the Cochrane Library, MEDLINE, PubMed, Guidelines International Network, National Guidelines Clearinghouse and National Institute for Health and Clinical Excellence (NICE) using the keywords on this topic. We made a comprehensive review of these publications as well as the recommendations of the Brazilian guide and consensus for food allergy. **Final remarks:** Adequate diagnosis and treatment for CMPA in children is essential, considering its nutritional, emotional and socioeconomic burden. Clinical practice guidelines provide recommendations based on scientific evidence improving quality of care; however, their implementation is challenging due to the lack of practical algorithms applicable and accessible for the management of CMPA in primary care. In addition, the lack of algorithms that favor accessibility to information from the extensive scientific content available is a reality that makes relevant a more practical proposal for a management of CMPA, applicable and accessible in order to consolidate a clinical practice based on scientific evidence.

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INTRODUCTION

Cow's milk protein allergy (CMPA) is one of the most commonly found food allergies in early childhood¹ and can be defined as an adverse reaction of an immunological nature, which occurs often whenever the susceptible individual is exposed to different cow's milk proteins.²

Concerns about the early and timely diagnosis of CMPA, as well as its adequate treatment, have been highlighted over the years, not only because of the nutritional impact it causes, but also its emotional and socioeconomic burden.^{3,4} However, the practice of Evidence-Based Medicine (EBM) in this field is a particular challenge with regards to quality, clarity, applicability, among other aspects of the content published in the different guidelines, which can impair compliance between its recommendations and clinical practice.

The compliance of primary care professionals to the guidelines, as well as the reasons for possible non-compliance with their recommendations, are still not fully known. Different studies have shown that knowledge about AA management among Brazilian healthcare professionals may be inadequate.⁵⁻⁸ We carried out a cross-sectional study among Brazilian pediatricians in 2017 and showed low compliance to food allergy guidelines. The lack of resources was the main barrier to compliance in the perception of the interviewees, but the lack of knowledge was highlighted by the authors as a relevant barrier with an impact on the observed results.⁸

Knowledge and applicability of recommendations are critical points to be considered, especially in primary care. In recent years, we have experienced a huge flow of information about recommendations related to the diagnosis and treatment of CMPA, many of which are widely available, but not exactly accessible, since many are extensive and impractical for a general practitioner. Based on a review of the main current recommendations, published in international guidelines and, in accordance with the Brazilian consensus, this article outlines the different clinical presentations and points out in a simplified way the diagnosis and treatment of CMPA for primary care professionals.

METHODS

This is a narrative review of the main guidelines for the diagnosis and treatment of CMPA. Relevant publications were searched in the Cochrane Library, MEDLINE, PubMed, Guidelines International Network, National Guidelines Clearinghouse and National Institute for Health and Clinical Excellence (NICE) databases using the keywords on the topic and the papers found were selected and reviewed, along with recommendations from the national food allergy guide and consensus.

The selection was based on the publication by Ruszczyński et al., who systematically reviewed the quality of 15 guidelines published for CMPA and demonstrated that the quality scores for each evaluated domain varied between the different documents.⁹ Among the guidelines analyzed in this study, the ten with the highest score and best quality were used as the basis for this review.⁹

The MAP (Milk Allergy in Primary Care guideline)¹⁰ and iMAP (International Milk Allergy in Primary Care)¹¹ guidelines were included because they provide simple and accessible algorithms for physicians in primary care. These documents were not the result of analysis of new evidence, but the presentation of recommendations from current guidelines through easy-to-use algorithms to assist healthcare professionals in the care of children with symptoms suggestive of CMPA.¹¹ In Brazil, recommendations for the treatment of allergy and, in particular, CMPA, are available in guides and consensus that do not meet the methodological criteria necessary to be classified as guidelines, but even so, they were used due to their relevance in clinical practice in our country.¹²⁻¹⁴

CMPA diagnosis

Children are exposed early to cow's milk (CM) proteins by the mother's diet (if breastfed), by ingestion of infant formula or during the introduction of solid foods.¹ Therefore, it is not surprising that CM is considered the main responsible for food allergies in childhood, with an estimated prevalence between 0.5% and 3% in the first year of life.¹ In Brazil, Gonçalves and colleagues (2016) found that 23.5% of parents reported food allergies in their infants, but only 1.9% were confirmed by oral challenge tests, with CM being the main cause of food allergy.¹⁵

CMPA can be classified according to its immune response as: mediated by class-E immunoglobulin (IgE), non-IgE-mediated or mixed (when there is a response with both IgE-mediated and non-IgE-mediated components).¹⁶ The categorization of symptoms according to the immunological mechanism involved is important to aid in the diagnosis (Table 1).

In the IgE-mediated reaction, signs and symptoms are of rapid onset, minutes to two hours after exposure to the allergen.¹⁶ In non-IgE-mediated reactions, they are typically chronic and occur hours and even days after ingestion of CM proteins, such as result of repeated exposures.¹⁷

As seen in Table 1, the signs and symptoms of patients suspected of having CMPA are diverse and affect various body systems.¹⁸ In IgE-mediated reactions, dermatological symptoms stand out (urticaria being the most prevalent representative)¹⁹ and in non-IgE-mediated reactions mediated by IgE, gastrointestinal symptoms (colic, constipation and vomiting).¹⁷ Although each disease has unique signs and symptoms, they can overlap and vary in severity.¹⁷ It is not uncommon for more than one organ to be involved.²⁰

Table 1. Signs and symptoms of suspected cow's milk allergy.

IgE-mediated allergy	Non-IgE mediated
Skin	
• Pruritus • Erythema • Localized or generalized acute urticaria • Acute angioedema around the eyes, lips and face • Moderate or severe atopic dermatitis	• Pruritus • Erythema • Moderate or severe atopic dermatitis
Gastrointestinal tract	
• Angioedema of lips, tongue or palate • Mouth pruritus • Abdominal pain/colic • Vomit • Diarrhea	• GER (if conventional treatment does not improve the symptoms) • Nausea • Vomit • Blood and mucus in the feces • Colic in infants (especially if associated with vomits, food refusal, diarrhea, constipation or atopic dermatitis) • Food refusal or aversion • Abdominal pain • Constipation (if treatment fails, especially in infants fed with formulas) • Perianal hyperemia • <i>Faltering growth</i> associated with one or more of the above-mentioned gastrointestinal symptoms (with or without atopic dermatitis)
Respiratory tract (frequently combined with one or more of the symptoms mentioned above)	
• Nasal pruritus, obstruction, sneezes, rhinorrhea with or without conjunctivitis, stridor, cough, chest pain, and/or wheezing, dyspnea and cyanosis	
Systemic reaction	
• Anaphylaxis	• Acute FPIES

Source: Adapted from the NICE Clinical Guideline, 2011¹⁸

Note: This list does not include all possible symptoms. Absence of the above symptoms does not exclude cow's milk allergy.

Most of the symptoms appear at an early age, often when the child is breastfeeding, which further complicates the diagnosis, since there is a temporal coincidence with functional gastrointestinal disorders that may present similar signs and symptoms (alteration of the habit bowel, reflux, constipation and colic) and occur in up to 31% of infants.²¹

Clinical history and physical examination in CMPA

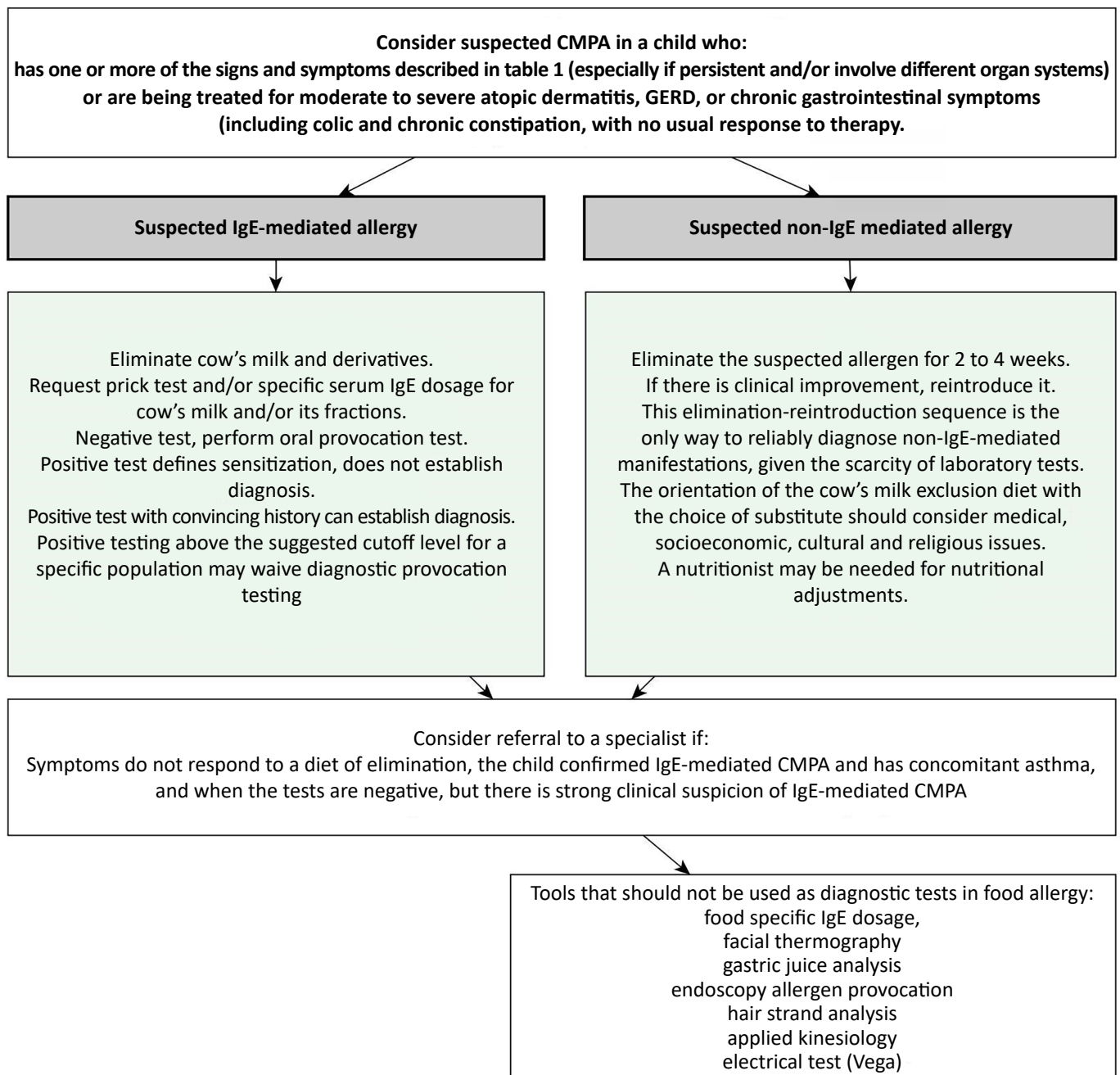
Clinical history remains unanimously the “cornerstone” of the diagnosis of CMPA among the different international guidelines and national recommendations.¹⁴ Information on age of onset and nature of symptoms, frequency of manifestation, time between ingestion and onset of symptoms, amount needed, method of preparation, reproducibility, influence of external factors on the manifestation (e.g. exercise, hormonal changes, emotional factors), food diary, previous records of weight and length, details of previous feeding

(duration of breastfeeding, age of introduction of infant formula and solids and type of formula introduced), responses to restriction diets, and instituted therapeutic interventions must be reported.¹⁹ Personal and/or family history (parents or siblings) of atopic disease, such as atopic dermatitis, asthma, allergic rhinitis, or food allergy, should also be referred.

A detailed anamnesis will help the pediatrician distinguish which symptoms may be related to CMPA and which mechanism is involved, as demonstrated in the previous topic. In flowchart 1, we describe that CMPA should be particularly considered if there is:

- 1) family history of allergic disease;¹⁴
- 2) persistent symptoms affecting different organ systems in infants (one or more symptoms described in Table 1);¹⁴
- 3) moderate to severe atopic dermatitis, gastroesophageal reflux disease (GERD) or other persistent gastrointestinal symptoms (including colic and constipation) in infants unresponsive to therapeutic interventions.^{10,17}

Suspected allergy to cow's milk proteins - immune mechanism involved



Flowchart 1. Suspected allergy to cow's milk proteins - immunological mechanism involved.

Modified and adapted from VENTER et al., 2013.¹²

CMPA: Allergy to cow's milk proteins

GERD: Gastroesophageal reflux disease

Complementary exams in CMPA

The indication of complementary exams varies according to the immunological mechanism involved, the severity and the evolution of the disease. According to the guidelines, they should not be requested before a detailed medical history has been obtained, focusing on the symptoms and signs of CMPA.

If the clinical history is suggestive of IgE-mediated allergy, the physician may order specific *in vitro* serum IgE measurements. The detection of milk specific IgE or its protein fractions in a child indicates sensitization; therefore, the interpretation of the test must be supported by the clinical history. These tests, if well indicated and performed using the ImmunoCap® method, have high rates of sensitivity and specificity.¹³

Cut-off values for CM-specific serum IgE levels and fractions, which would minimize the chance of performing oral provocation tests, were identified in different populations, with divergent results, and it was not possible to establish universal values.²² In Brazil, due to heterogeneity of the populations studied, different cut-off points were established. For children between 1 and 18 years of age, the cut-off point was 11 kU/L.²³ In anaphylactic patients, 3.06 kU/L, (Specificity: 98% and PPV: 95%).²⁴ In children under 3 years of age, with symptoms of IgE-mediated CMPA, the cut-off point was 5.17 kU/L (Specificity: 90% and PPV: 88%).²⁵

In non-IgE-mediated CMPA, there is no evidence that any biomarker, including milk-specific IgE and fractions, has clinical validity in the diagnosis, and although some biomarkers have been studied in research, guidelines are unanimous in not recommending researching them in the clinical practice to date.¹⁷ The mother's exclusion diet with subsequent reintroduction of the CM, after clinical improvement is the best diagnostic tool.²⁶ According to the guidelines, tests to detect abnormal elements in the feces (hidden blood, leukocytes) and other fecal markers such as alpha 1-antitrypsin and calprotectin, when used alone, have no defined value both for diagnosing and ruling out CMPA in patients with nonspecific manifestations.²⁷

Endoscopies and biopsies of the gastrointestinal tract may be indicated to diagnose CMPA and make a differential diagnosis. However, in clinical practice, endoscopy should only be performed when there is strong suspicion of an alternative diagnosis or persistent symptoms (e.g., vomiting and/or diarrhea).²⁷ Patients with eosinophilic esophagitis are potential candidates for performing several endoscopies, not only for diagnosis but also for follow-up (Table 2).

After the evaluations highlighted above, refer to the specialist so that, when necessary, follow-up in the investigation and diagnostic elucidation can be given (Flowchart 1). The review of the guidelines highlighted some relevant aspects in diagnosis:

- The Prick test is a method of detection of specific IgE *in vivo*, performed by a specialist. It can be performed with extracts of total CM and/or its proteins (α -lactalbumin, β -lactoglobulin and casein), in addition to fresh CM28 and is considered positive when the mean diameter of the papule is greater than or equal to 3 mm in relation to the negative control.¹⁹ Its positivity is related to food sensitization, without indicating food allergy.²⁵ *In vivo* tests are contraindicated in situations such as a history of previous anaphylaxis or conditions that may alter the skin response.²⁹
- The Oral Provocation Test (OPT) is considered the gold standard test in the diagnosis of CMPA and consists of administering cow's milk gradually and progressively, by a trained team and in a controlled environment to deal with potentially fatal reactions.³⁰

Differential diagnosis

When the digestive tract is affected, it is essential to rule out malformations; metabolic disorders; infectious, neurological or parasitic causes, and the latter should be given greater emphasis due to its high prevalence in our country.

Table 2. Different clinical presentations and differential diagnosis of non-IgE-mediated CMPA.

Non-IgE mediated CMPA	Clinical findings	Differential diagnosis
Food Protein-Induced Allergic Proctocolitis (FPIAP)	Occasional blood in the stool, with or no mucus, flatulence, anal bruises.	Gastrointestinal infections, anal fissures, Intestinal polyps, necrotizing enterocolitis, Meckel's diverticulum, intestinal intussusception, inflammatory bowel disease)
Food Protein-Induced Enterocolitis Syndrome (FPIES)	Acute FPIES: Vomiting 1-4 h after ingestion, pallor, lethargy, hypovolemia, hypotension, collapse and diarrhea following protein reintroduction after elimination diet Chronic FPIES: intermittent, progressive vomiting, followed by diarrhea.	GERD, sepsis, inborn errors of metabolism, hypertrophic pyloric stenosis, malrotation, intestinal intussusception, gastroenteritis with vomiting.
Food Protein-Induced Enteropathy (FPE)	Abdominal pain, diarrhea, mucus and blood in stool, hypoalbuminemia, faltering growth.	Sepsis, congenital disaccharide deficiency, metabolic diseases, chronic kidney disease, FPIES, autoimmune enteropathy, cystic fibrosis epithelial dysplasia syndrome, immunodeficiency and/or chronic infection, celiac disease
eosinophilic esophagitis (EoE)	Regurgitation, intermittent vomiting, arching of the back, feeding difficulties, and faltering growth	GERD, inflammatory bowel disease
Food protein-induced gastroesophageal reflux disease	Intermittent painful vomiting, regurgitation, arching of the back, feeding difficulties and faltering growth	GERD, Acute gastroenteritis, poisoning
Constipation induced by food protein	Fecal impaction, abdominal pain	Idiopathic constipation, Hirschsprung's disease

Source: Adapted from MEYER et al., 2019.¹⁷

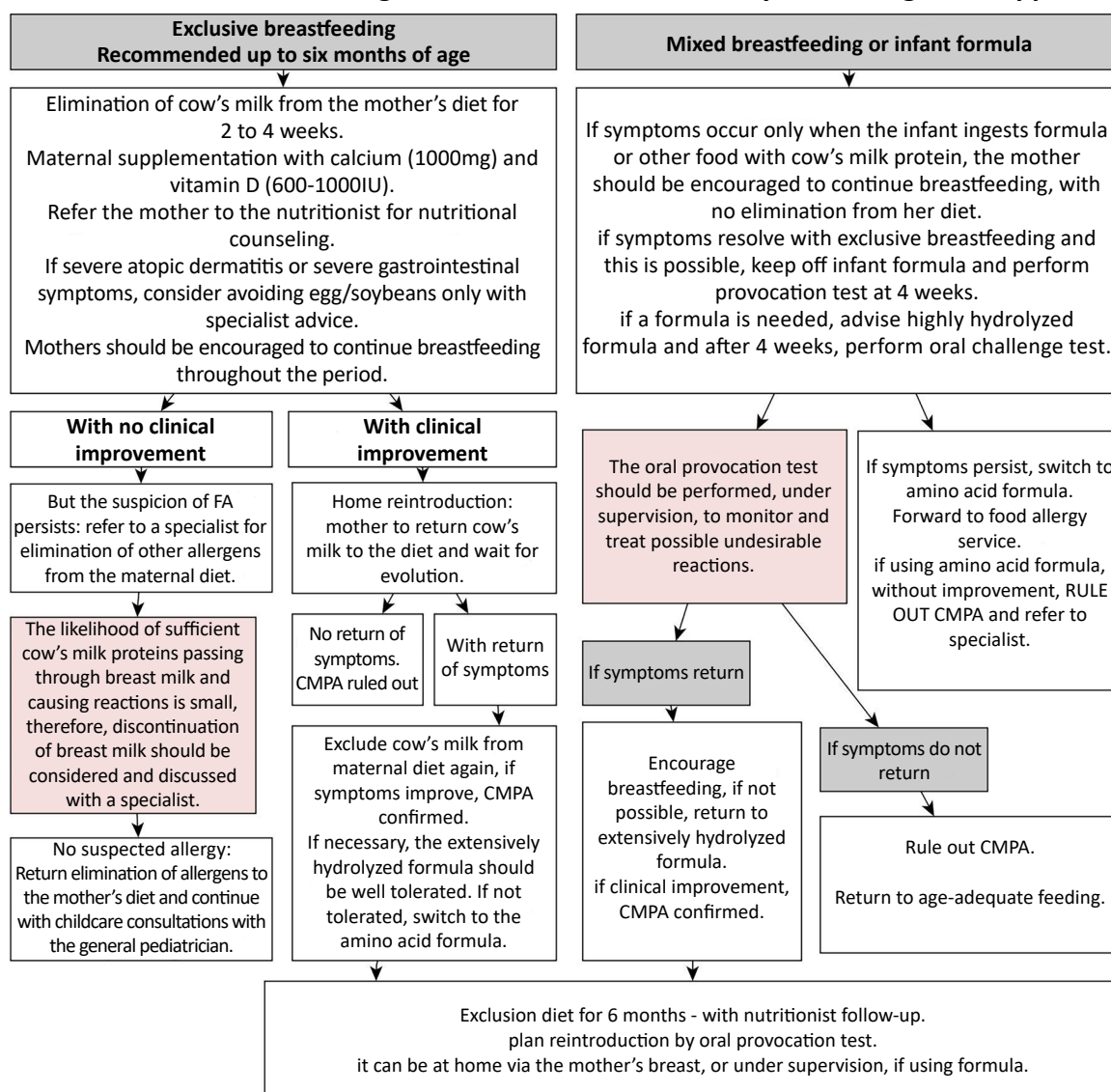
Usually, among patients and doctors, there is a confusion between lactose intolerance and CMPA, which can result in unnecessary food restriction or avoidable reactions.³¹ Lactose intolerance is a non-immunological reaction caused by lactase enzyme deficiency, unlike CMPA that it is an immune reaction to cow's milk proteins. Lactose, the predominant carbohydrate in milk, is a disaccharide made up of the monosaccharides glucose and galactose. Intestinal absorption of lactose requires hydrolysis into its monosaccharides by the enzyme lactase, present in the brush border of the small intestine.³² When lactase is lacking, symptoms including abdominal pain, distention, flatulence and diarrhea can occur and be confused with CMPA.³³

Its occurrence is uncommon, in the primary form, in children under 2-3 years of age, when other etiologies should be investigated.³²

CMPA Treatment

Current recommendations are presented in flowcharts 2 and 3. It is noteworthy that the exclusion of the allergen is still the best treatment option for CMPA. However, the elimination of foods that contribute essential nutrients, especially in childhood, can lead to the development of nutritional problems and predispose to eating difficulties.³ Therefore, good nutritional management, whether in the judicious indication of food(s) to being excluded, whether in choosing a substitute formula, or in micronutrient supplementation, is fundamental.

Management of non-IgE-mediated cow's milk protein allergy Neither skin test nor serum IgE measurement are necessary in the diagnostic approach



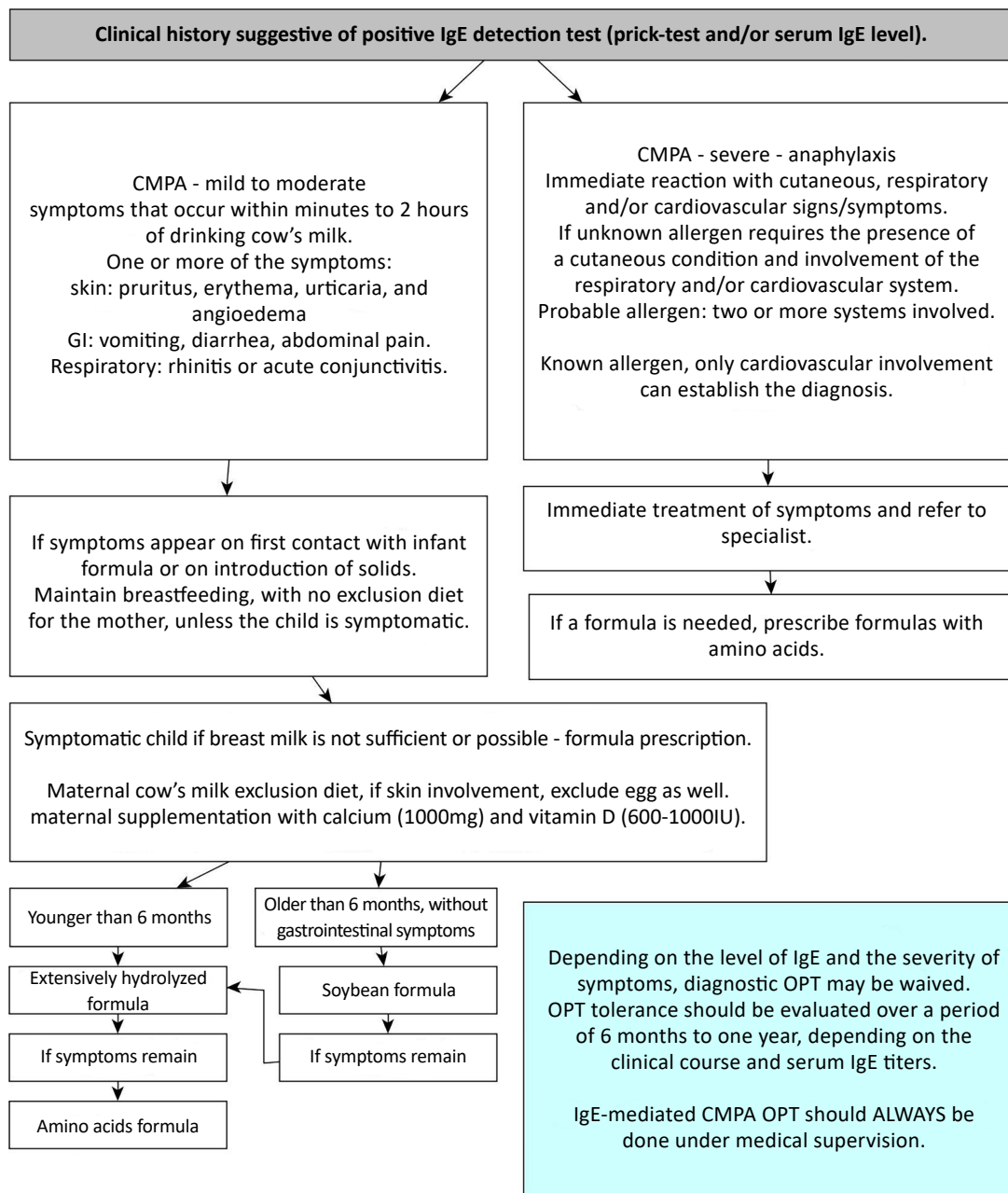
Flowchart 2. Management of non-IgE-mediated cow's milk protein allergy
Modified and adapted from FOX et al., 2019.
CMPA: Allergy to cow's milk proteins.

In CMPA, it is essential to maintain breastfeeding, especially in the first semester of life.³⁴ Mothers should be encouraged to continue breastfeeding and avoid dairy restrictions in their diets, unless the child has symptoms that indicate this need.²² If the child, who is exclusively breastfed, presents symptoms that suggest CMPA, it is recommended that the mother start an elimination diet of CM and derivatives, for an established period (2 to 4 weeks), and take calcium supplementation (1000mg/day)²² associated with vitamin D (600-1000UI/day).³

With an adequate maternal restriction diet, an average improvement of symptoms is observed in infants in the IgE forms between 3 and 6 days, and in the non-IgE mediated forms in up to 14 days. After clinical improvement, cow's milk should be reintroduced into the mother's diet to confirm or rule out the diagnosis (Flowcharts 2 and 3).²⁶

In the impossibility of maintaining breastfeeding, either due to lack of response to the maternal elimination diet, or due to other factors, we recommend using infant formulas.

Management of IgE-mediated cow's milk protein allergy



Flowchart 3. Management of IgE-mediated cow's milk protein allergy
Modified and adapted from FOX et al., 2019.²⁵
CMPA: Allergy to cow's milk proteins; OPT: Oral provocation test.

Choosing the ideal formula for treatment is a decision that must be based on the child's age, clinical presentation, nutritional composition and residual allergenicity of the proposed hypoallergenic formula (Flowchart 2).

Most children with CMPA improve with the use of extensively hydrolyzed formula (EHF). In general, guidelines suggest using formula amino acids (FAA) as a first-line treatment only for more severe presentations of CMPA, such as: (1) symptoms not fully resolved with EhF; (2) Faltering growth (decline of the weight/age or weight/height curve tracing after three successive verifications); (3) multiple dietary eliminations; (4) severe gastrointestinal diseases; (5) eosinophilic esophagitis; (6) FPIES; (7) severe atopic dermatitis, as an exclusively breastfed child; (8) history of anaphylaxis.^{14,17,22,34-38}

Soy formula contains phytates, which can affect nutrient absorption, and isoflavonoids in amounts that make this formula unsuitable for use in children under six months of age.²² It is not recommended as a first choice by international societies.³⁴⁻³⁸ Nonetheless, in Brazil it is indicated as a first treatment option in children older than 6 months with IgE-mediated allergy.¹⁴ It can also be indicated if EhF are not accepted/tolerated or if the higher cost of EhF is a factor that prevents accessibility or if there are strong parental preferences (e.g., vegan diet).²² Soy-based beverages should not be used to treat CMPA in children.^{14,38}

Hydrolyzed rice formulas emerged as a possibility for allergology safety, since they are made from rice - a low-allergenic protein.³⁹ However, their nutritional safety has been studied, which limits, for the time being, their use in clinical practice.¹⁴

Partially hydrolyzed formulas are not considered hypoallergenic, therefore, they should not be used for the treatment of CMPA.²² Lactose-free formulas contain intact cow's milk proteins/ therefore, they should not be used in the treatment of CMPA.²² In addition to the soy-based drink, the use of other vegetable drinks (rice, nuts, oats or similar) as substitutes for formulas in the treatment of children is not recommended, given the nutritional inadequacies for the age group and the high risk of severe malnutrition when using them.¹⁴

Milk from other mammals (goat, sheep, buffalo) should not be used as a substitute for cow's milk due to the similarity in terms of protein structure and chance of cross-reactivity.¹⁴ The possibility of cross-reaction between CM and beef is less than 10%⁶ and it is related to the presence of bovine serum albumin; therefore, beef should not be excluded from the child's diet unless it is certain that its consumption is related to a worsening of symptoms.¹⁴

The introduction of complementary feeding in children with CMPA should follow the same principles recommended for healthy children. There is no restriction on the introduction of foods containing potentially allergenic proteins (eggs, fish, nuts, peanuts) from the sixth month onwards, whether the infants are breastfeeding or using infant formula.

The delay in introducing some allergenic foods may even impair the development of oral tolerance.⁴⁰ Only the simultaneous introduction of two or more protein sources should be avoided.³⁸

FINAL REMARKS

CMPA is an evolving disease with a great impact on children's health, which makes its proper diagnosis and treatment essential. Different clinical practice guidelines have been published to improve the approach in children with suspected or diagnosed CMPA, providing recommendations based on scientific evidence. Restricting CM in the diet is still considered the best way to treat and prevent potentially serious reactions, so its recommendation is unanimous among the guidelines. Attention should be paid to inadequate replacement of the CM, which can lead to nutritional deficiencies or a negative influence on feeding practices with immediate and/or late damages for infants. High quality guidelines, combined with clear and applicable algorithms, as well as effective educational interventions, may be able to consolidate a clinical practice based on scientific evidence by primary care professionals, minimizing negative repercussions of the disease in the short and medium term.

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