Diagnostic Approach and Management of Cow's-Milk Protein Allergy in Infants and Children: ESPGHAN GI Committee Practical Guidelines

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ABSTRACT

Objectives: This guideline provides recommendations for the diagnosis and management of suspected cow's-milk protein allergy (CMPA) in Europe. It presents a practical approach with a diagnostic algorithm and is based on recently published evidence-based guidelines on CMPA.

Diagnosis: If CMPA is suspected by history and examination, then strict allergen avoidance is initiated. In certain circumstances (eg, a clear history of immediate symptoms, a life-threatening reaction with a positive test for CMP–specific IgE), the diagnosis can be made without a milk challenge. In all other circumstances, a controlled oral food challenge (open or blind) under medical supervision is required to confirm or exclude the diagnosis of CMPA.

Treatment: In breast-fed infants, the mother should start a strict CMP-free diet. Non–breast-fed infants with confirmed CMPA should receive an extensively hydrolyzed protein-based formula with proven efficacy in appropriate clinical trials; amino acids–based formulae are reserved for certain situations. Soy protein formula, if tolerated, is an option beyond 6 months of age. Nutritional counseling and regular monitoring of growth are mandatory in all age groups requiring CMP exclusion.

Reevaluation: Patients should be reevaluated every 6 to 12 months to assess whether they have developed tolerance to CMP. This is achieved in >75% by 3 years of age and >90% by 6 years of age. Inappropriate or overly long dietary eliminations should be avoided. Such restrictions may impair the quality of life of both child and family, induce improper growth, and incur unnecessary health care costs.

Key Words: amino acid formula, cow's-milk protein allergy, elimination diet, hydrolyzed formula, oral challenge, skin prick test, soy formula

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Food allergy is an increasing health care concern. Food allergy is defined as an adverse health effect arising from a specific immune response that occurs reproducibly following exposure to a given food (1). The immune reaction may be immunoglobulin (Ig)E mediated, non-IgE mediated, or mixed. Cow's-milk protein (CMP) is the leading cause of food allergy in infants and young children younger than 3 years (2,3); however, CMP allergy (CMPA) with gastrointestinal tract manifestation alone can be diagnosed in all age groups (4,5). Gastrointestinal manifestations of CMPA are nonspecific. In infants, history and physical examination may not distinguish between gastroesophageal reflux disease (GERD) and CMPA. In a small group of older children, CMPA may present with symptoms of GERD (5) but also with dyspepsia or abdominal pain, and hence may be easily confused with functional gastrointestinal disorders or lactose intolerance. Therefore, the challenge remains to make a correct diagnosis while minimizing the burden to patient and family.

Without an appropriate diagnostic workup, including food challenge procedures, there is a high risk of both over- and underdiagnosis (6) and thus over- and undertreatment. A correct diagnosis allows the appropriate diet to be given to affected infants, thus supporting normal growth and development. In contrast, a diet that is not indicated or continued when the child may have already developed tolerance may impair growth and quality of life of both child and family, while incurring significant unnecessary health care costs. It is, therefore, in everyone's best interest that clear, evidence-based guidance is available when advising parents on the right course of action for their child.

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During the last few years, several national and international consensus articles and evidence-based guidelines have been published for the diagnosis and management of CMPA (7–13). Some give recommendations for mainly suspected IgE-mediated CMPA (9); however, in clinical practice, it is often not possible to distinguish between IgE- and non–IgE-mediated CMPA based on history and physical examination alone. Several studies in unselected group of patients have shown that a high proportion of infants with CMPA, proven by double-blind, placebo-controlled food challenge (DBPCFC), have negative test results for CMP-specific IgE (6,14); however, some of these children do become IgE positive over time (15). Because non–IgE-mediated CMPA more commonly occurs in infants and children with gastrointestinal manifestations, additional guidance is needed.

This position paper provides a practical approach to managing children with predominantly gastrointestinal symptoms. Particular emphasis is placed on gastrointestinal manifestations and the role of diagnostic tools and elimination/challenge procedures in these situations. Because of the nonspecific symptoms of CMPA with manifestation in the gastrointestinal tract, awareness is needed for the recognition of symptoms and signs. The recommendations and algorithm are derived from recently published literature and guidelines (7,9,10), although for most statements and recommendations, the quality of evidence is low and the contribution of expert opinion significant (1). The suggested algorithm attempts to simplify and streamline the diagnostic process.

EPIDEMIOLOGY

The prevalence of CMPA in infants and children was reported in a meta-analysis as part of the EuroPrevall program (16). This article reported marked heterogeneity between published studies regardless of the type of assessment and age stratification (3). CMP, together with hen's egg protein, are the key triggers of food allergy in infants and young children (2,3). Parents perceive CMPA in their children far more often than can be proven by oral food challenge; however, true CMPA does seem to peak in the first year of life, with a prevalence of approximately 2% to 3% in the infant population (2,3,17). This prevalence then falls to $<1\%$ in children 6 years of age and older (18). A few exclusively breast-fed infants may also develop clinically significant CMPA via dairy protein transfer into human breast milk (19).

CLINICAL PRESENTATION

CMPA can induce a diverse range of symptoms of variable intensity in infants. It is helpful to differentiate between the ''immediate'' (early) reactions and ''delayed'' (late) reactions. Immediate reactions occur from minutes up to 2 hours after allergen ingestion and are more likely to be IgE mediated, whereas delayed reactions manifest up to 48 hours or even 1 week following ingestion. The latter may also involve non–IgE-mediated immune mechanisms. Combinations of immediate and delayed reactions to the same allergen may occur in the same patient. It is important to remember that nonallergic reactions (eg, toxic, pharmacologic) may mimic CMPA.

Symptoms and signs related to CMPA may involve many different organ systems, mostly the skin and the gastrointestinal and respiratory tracts (Table 1). The involvement of ≥ 2 systems increases the probability of CMPA, whereas some symptoms are more likely to be present in children with a positive test for CMP-specific IgE (eg, angioedema, atopic eczema); however, there is a large overlap. The same symptoms may appear in CMP IgE-positive and IgE-negative patients, particularly in children with gastrointestinal manifestations (eg, allergic proctitis or proctocolitis) (20).

Clinical symptoms and signs in the digestive tract may be due to inflammation, dysmotility, or a combination of both. The signs of CMPA are rather variable but most of the time are nonspecific and include oral and perioral swelling; dysphagia, and food impaction (eg, impaired esophageal motility) (21); vomiting, regurgitation, dyspepsia, early satiety, anorexia, and food refusal (delayed gastric emptying) (5); and diarrhea (with or without malabsorption or protein loss due to enteropathy), rectal bleeding (22), failure to thrive, abdominal pain, severe colic (23), and persistent constipation often with perianal abnormalities (24). Chronic iron-deficiency anemia may be the sole manifestation of CMPA in infants and children (25). Failure to thrive is nonspecific but can have severe consequences for a growing child. Rare cases of anaphylactic shock leading to death have been reported following CMP ingestion in sensitized children (26). Severe shock-like reactions with metabolic acidosis are characteristic for the ''food protein–induced enterocolitis syndrome,'' which is a non–IgE-mediated manifestation (27).

Studies in unselected infants with CMPA show that approximately half of them have atopic eczema, and 25% to 50% are affected by some gastrointestinal tract involvement (14), whereas other clinical manifestations are less common (17). Sensitization to cow's-milk allergens through breast-feeding manifests primarily as exacerbation of atopic eczema and/or as allergic proctocolitis (28). There are insufficient data on GERD as the sole manifestation of CMPA to confidently diagnose this as CMPA in exclusively breast-fed infants.

DIAGNOSTIC PROCEDURES

The first step is a thorough medical history and physical examination. If any of the features listed in Table 1 occur in an infant or child and cannot be explained by another cause, CMPA may be considered a potential diagnosis. In most cases with suspected CMPA, the diagnosis needs to be confirmed or excluded by an allergen elimination and challenge procedure. This can be performed as open, single-, or double-blind challenge, depending on symptoms, history, and age of the child; however, there are circumstances under which a challenge procedure may be omitted because either the likelihood of CMPA is extremely high or an allergen challenge procedure would be too risky (eg, history of anaphylaxis in a sensitized child) (Fig. 1).

Determination of Specific IgE and Skin Prick Test

For clinical practice, the determination of specific IgE in a blood sample and the skin prick test (SPT) are useful diagnostic tests at any age, but a combination of the 2 tests is not necessary for the diagnostic workup (1). The presence of CMP-specific IgE and/or a positive SPT to cow's milk indicates sensitization to CMP and an ongoing IgE-mediated immunological process; however, these results must be interpreted in the context of medical history and food challenge procedure. Commercial extracts for testing for CMPA are less reliable than cow's milk (29). Quantification of both of these test results allows prediction of the likelihood of a further reaction and hence is useful for prognostic purposes (30). The higher the antibody titer and the larger the diameter of the SPT reaction, the greater is the probability of having a reaction to CMP (31–33) and allergy persistence (30). Nevertheless, an oral challenge test is necessary in most cases to confirm an adverse reaction to CMP. Children with gastrointestinal manifestations of CMPA are more likely to have negative specific IgE test results compared with patients with skin manifestations, but a negative test result does not exclude CMPA (6,14). A positive test for specific

TABLE 1. Some symptoms and signs related to CMPA

	Infants and toddlers	Older children	Immediate reaction (within min–2 h after ingesting CMP)
Digestive	Dysphagia	Dysphagia	Vomiting
	Frequent regurgitation	Food impaction	
	Colic, abdominal pain	Regurgitation	
	Vomiting	Dyspepsia	
	Anorexia, refusal to feed	Nausea, vomiting	
	Diarrhea ± intestinal protein or blood loss	Anorexia, early satiety	
	Constipation ± perianal rash	Diarrhea ± intestinal protein or blood loss	
	Failure to thrive	Constipation	
	Occult blood loss	Abdominal pain	
	Iron-deficiency anemia	Occult blood loss	
		Iron-deficiency anemia	
Respiratory	Runny nose	Runny nose	Wheezing or stridor
	Wheezing	Wheezing	Breathing difficulties
	Chronic coughing (all unrelated to infections)	Chronic coughing (all unrelated to infections)	
Skin	Urticaria (unrelated to infections, drug intake, or other causes)	Urticaria (unrelated to infections, drug intake, or other causes)	Urticaria
	Atopic eczema	Atopic eczema	Angioedema
	Angioedema (swelling of lips or eyelids	Angioedema (swelling of lips or eyelids)	
General	Anaphylaxis	Anaphylaxis	Anaphylaxis
	Shock-like symptoms with severe metatobolic acidosis, vomiting, and diarrhea (FPIES)		FPIES

CMPA = cow's-milk protein allergy; FPIES = food protein–induced enterocolitis syndrome.

IgE at the time of diagnosis predicts a longer period of intolerance as compared with those children who have negative tests (18,34,35).

Atopy Patch Test, Total IgE, and Intradermal Tests

Although there may be a role for the atopy patch test in the future in children with negative CMP-specific IgE (36–38), there is no agreement on standardization on the preparation and application of antigen. In addition, reading the test is difficult and remains subjective. For this reason, the atopy patch test cannot be recommended at the present time (1).

Neither the determination of total IgE nor the ratio of specific IgE to total IgE offers a benefit over specific IgE alone in the diagnostic workup of CPMA (39). Intradermal testing should not be performed because it carries a risk of systemic allergic reaction in highly sensitized individuals (1).

Specific IgG Antibodies and Other Nonstandardized or Unproven Tests and Procedures

Determination of IgG antibodies or IgG subclass antibodies against CMP has no role in diagnosing CMPA (40), and therefore is not recommended (1). Other tests, such as basophil histamine release/activation, lymphocyte stimulation, mediator release assay, and endoscopic allergen provocation, are used in research protocols, but not in clinical practice. In agreement with US guidelines (7), we do not recommend either facial thermography and gastric juice analysis for diagnosing CMPA. In addition, hair analysis, applied kinesiology, provocation neutralization, cytotoxicity assay, and electrodermal testing should not be used for diagnosing CMPA.

Endoscopy and Histology

In patients with otherwise unexplained significant and persistent gastrointestinal symptoms, failure to thrive, or iron-deficiency anemia, upper and/or lower endoscopies with multiple biopsies are appropriate; however, macroscopic lesions and histological findings, such as mucosal atrophy or eosinophilic infiltrates, are neither sensitive nor specific for CMPA (41), and these should be interpreted in the context of medical history and oral challenges. The diagnostic yield of these procedures is higher for finding diagnoses other than CMPA.

Diagnostic Elimination of CMP

If symptoms are relevant and CMPA is likely, a diagnostic elimination of CMP (in the infant's/child's diet or in the mother's diet in case of breast-feeding) should be initiated for a limited period of time, even in cases with negative specific IgE result. The duration of a diagnostic elimination diet depends on

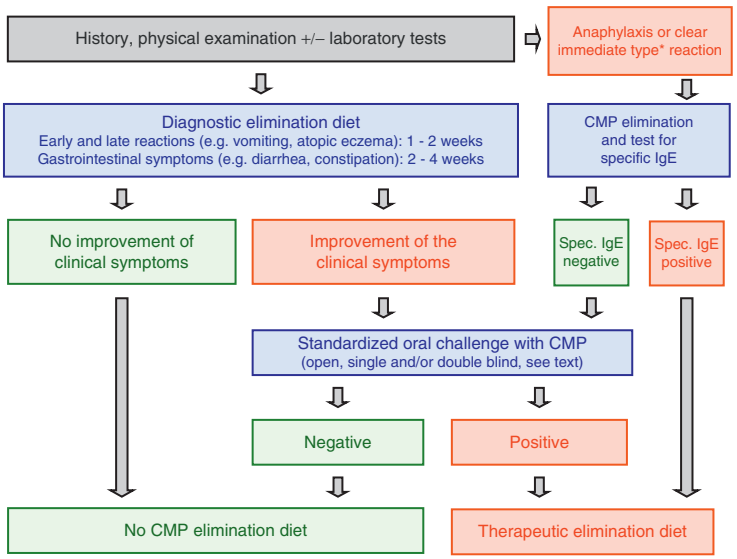

FIGURE 1. Algorithm for infants and children with symptoms suggestive of cow's-milk protein allergy (CMPA). eHF: extensively hydrolyzed formula based on cow's-milk protein, AAF: amino acid–based formula. See text for definition of clear immediate-type reactions.

manifestation and should be kept as short as possible, but long enough to judge whether clinical symptoms resolve or not or become stable. This ranges from 3 to 5 days in children with immediate clinical reactions (eg, angioedema, vomiting, exacerbation of eczema within 2 hours) to 1 to 2 weeks in children with delayed clinical reactions (eg, exacerbation of eczema, rectal bleeding). In patients with gastrointestinal reactions (eg, chronic diarrhea, growth faltering), it may take 2 to 4 weeks on a CMP-free diet to judge the response.

If there is no improvement in symptoms within these timelines, then CMPA is unlikely; however, exceptions may occur. Infants with significant gastrointestinal symptoms with no improvement using a hydrolyzed or a soy formula may benefit from a further period of observation on an amino acid–based formula (AAF) before CMPA is excluded. This is particularly true in patients with multiple sensitizations (42,43). If the clinical symptoms do not improve on a diagnostic elimination diet with AAF, then it is highly unlikely that the symptoms are due to CMP. There is, therefore, no indication for any longer-term use of a therapeutic formula for diagnostic purposes.

Breast-fed Infants

Mothers should be encouraged to continue breast-feeding while avoiding all milk and milk products from their own diet. This usually requires qualified dietary counseling to completely exclude hidden sources of CMP. If the infant receives any complementary feedings or drugs, these must be free of CMP. If the history suggests an immediate reaction, then the maternal elimination diet needs to be maintained for only 3 to 6 days. If delayed reactions are suspected (eg, allergic proctocolitis), then the diet should be continued for up to 14 days. If there is no improvement, then it is likely that diagnoses other than CMPA are the cause of the symptoms and the child should be further evaluated. If symptoms improve, then a reintroduction of CMP into the mother's diet should then be performed. Should this challenge prove positive and the mother wishes to continue breast-feeding while maintaining a CMP-free diet, she should be given calcium supplements (eg, 1000 mg/day spread across the day) and dietetic counseling to ensure her nutritional needs (44). In some breast-fed infants, proteins other than CMP (eg, soy, egg) may cause allergic reactions (45). If there is a valuable benefit of maternal elimination diet on the well-being of the infant, then the mother should be encouraged and supported to continue breast-feeding while eliminating the causative foods from her own diet.

In breast-fed infants with severe symptoms (eg, severe atopic eczema or allergic (entero) colitis complicated by growth faltering and/or hypoproteinemia and/or severe anemia), the infant may be fed with a therapeutic formula for a period of from several days to a maximum of 2 weeks (45). Even if not evidence based, it is common practice in many countries to use AAF for diagnostic elimination in these extremely sick exclusively breast-fed infants. This approach is to stabilize the child's condition while the mother expresses breast milk in transition to her CMP-free diet. In cases in which symptoms recur on breast milk despite a strict CMP-free diet in the mother, further elimination of other highly allergenic foods from the mother's diet or weaning from breast milk to a therapeutic formula is recommended (46,47).

Non–breast-fed Infants

In non–breast-fed infants, cow's-milk–based formula and supplementary foods containing CMP or other unmodified animal milk proteins (eg, goat's milk, sheep's milk) should be strictly avoided (48,49). If the first feeds with cow's-milk–based formula in a breast-fed infant cause symptoms, the infant should return to exclusive breast-feeding without any elimination in the maternal diet. An elimination diet in formula-fed infants usually starts with an extensively hydrolyzed infant formula (eHF) with proven efficacy in infants with CMPA (9,48). In infants with extremely severe or life-threatening symptoms, an AAF may be considered as the first choice. Soy protein–based formula may be an option in infants older than 6 months who do not accept the bitter taste of an eHF, or in cases in which the higher cost of an eHF is a limiting

factor, provided that the tolerance to soy protein has been established. If there is no improvement within 2 weeks, then an allergic reaction to the remaining peptides in the eHF must be considered, particularly in infants with sensitization against multiple foods (43,42). In these cases, an AAF should be tried before CMPA is ruled out as cause of the symptoms.

Previous concerns that infants with CMPA would react to residual protein traces in lactose have often resulted in complete avoidance of both lactose and CMP. Adverse reactions to lactose in CMPA are not supported in the literature, and complete avoidance of lactose in CMPA is no longer warranted. eHFs containing purified lactose are now available and have been found safe and effective in the treatment of CMPA (50). These formulae may also be more palatable for infants older than 6 months. It is, however, possible for secondary lactose intolerance to coexist in infants who have enteropathy with diarrhea, and therefore a lactose-free eHF will be required initially in these cases.

Toddlers and Children

In children older than 2 years, a nutritionally adequate elimination diet can be provided by solid foods and liquids free of CMP unless the child has multiple allergies. Goat's- and sheep's-milk protein should be strictly avoided because of the high cross-reactivity with CMP (49). Counseling by a dietician experienced in pediatric nutrition is highly recommended to avoid hidden allergens. If multiple food allergies are suspected in highly atopic children or in cases of eosinophilic disorders of the digestive tract, then an exclusive feeding with an AAF may be considered to allow symptom improvement before an oral challenge with CMP is performed.

Oral Food Challenge Procedure With CMP

Open and Blind Challenges

After documentation of significant improvement on the diagnostic elimination, the diagnosis of CMPA should be confirmed by a standardized oral challenge test performed under medical supervision. Exceptions are described below. Challenge tests can be performed in inpatient or outpatient settings. This allows documentation of any signs and symptoms and the milk volume that provokes symptoms, and allows symptomatic treatment as needed.

A DBPCFC is the reference standard and the most specific test for diagnosing CMPA; however, the test is time-consuming and expensive. Therefore, an open challenge is usually the first step, particularly if the history indicates a low likelihood of a reaction. If no symptoms are elicited within 2 weeks of regular cow's-milk feeding, CMPA can be excluded. If symptoms occur after an open challenge test, DBPCFC is recommended in cases of uncertain or questionable symptoms, and in cases of moderate to severe eczema. This allows the observer to minimize bias by patient, caregiver, and physician. The DBPCFC can be omitted if the open challenge elicits objective symptoms (eg, recurrent vomiting, bronchial obstruction, urticaria) and those symptoms correlate with the medical history and are supported by a positive specific IgE test.

Type of Milk and Dose

In the first year of life, a challenge test should be performed with an infant formula based on cow's milk. Fresh pasteurized cow's milk can be used above 12 months of age. To rule out a false-positive challenge due to primary lactose intolerance, in children older than about 3 years the challenge procedure may be performed with lactose-free CMP-containing milk.

The starting dose during an oral milk challenge should be lower than a dose that can induce a reaction and then be increased stepwise to 100 mL (eg, in children with a delayed reaction, stepwise doses of 1, 3.0, 10.0, 30.0, and 100 mL may be given at 30-minute intervals (51,52)). If severe reactions are expected, then the challenge should begin with minimal volumes (eg, stepwise dosing of 0.1, 0.3, 1.0, 3.0, 10.0, 30.0, and 100 mL given at 30-minute intervals). If no reaction occurs, then the milk should be continued at home every day with at least 200 mL/day for at least 2 weeks. The parents should be contacted by telephone to document any late reactions.

Test Conditions in In- and Outpatient Settings

The following conditions are mandatory when performing oral challenges:

1. The patient must be under medical supervision.
2. Severe anaphylaxis can be treated effectively at any time.
3. Patients should be observed for at least 2 hours following the maximum dose (if there are any clinical reactions, then medical supervision should be continued as appropriate).
4. Infants should only be tested 2 to 3 hours after their last meal, that is, not on a full stomach and not after overnight fasting, because the latter can cause distress as only small amounts of milk are given in the first titration steps.
5. Intravenous access is only necessary in selected cases, but always if a severe or systemic reaction is likely.

Challenges should be preferably carried out in a hospital setting under the following circumstances:

1. A history of immediate allergic reactions (9)
2. Unpredictable reaction (eg, infants with positive specific IgE who have never been exposed to cow's milk or have not been given cow's milk for a long time)
3. Severe atopic eczema (due to the difficulty in accurately assessing a reaction)

Patients With Atopic Eczema. The condition of the skin should be documented and graded according to severity (eg, by SCORing Atopic Dermatitis [SCORAD]) (53) before and after the challenge and then again 24 and 48 hours later. If the results cannot be clearly interpreted, then a placebo-controlled challenge should be performed as further confirmation, even in infancy.

Patients With Diarrhea. If CMPA manifests clinically with diarrhea, the stool frequency and consistency should be documented (eg, in infants with a stool form scale) (54). If significant diarrhea recurs during the challenge (open and/or DBPC), then the diagnosis of CMPA is confirmed and a therapeutic formula can be recommended. If there are no recurrent symptoms, then the child should continue to receive its previous formula.

HOW TO PROCEED IN CLINICAL PRACTICE

To minimize the burden for patients and their families, and to reduce costs, an oral challenge procedure can be omitted in certain cases without increasing the risk of a false-positive diagnosis. The diagnostic workup therefore depends on taking a careful history and physical examination (Fig. 1)

Patients With a Clear History of Immediate Symptoms and/or Severe Reactions

If acute and objective symptoms of skin (acute urticaria, angioedema), respiratory tract (stridor, wheezing), or systemic reactions (anaphylaxis) occur immediately, or up to 2 hours after

a clear history of ingesting dairy products, then CMP should be strictly excluded. Testing for specific IgE against CMP or an SPT with natural cow's-milk or whole-protein formula should be performed. CMPA can be assumed with a high likelihood if testing for specific IgE is positive. In this situation, the oral challenge test can be omitted (Figure 1). The child should be given a strict CMP-free diet for a period of at least 1 year before an oral food challenge is performed (9). A specialist should assess the patient before an oral challenge is performed in a hospital with adequate emergency facilities. If the immediate symptoms are clear but test for specific IgE against cow's milk is negative, then an oral challenge procedure should be carried out in a hospital under strict medical supervision.

Patients With Neither Clear Nor Severe Reactions

This approach applies to children with gastrointestinal symptoms, to children with exacerbation of atopic eczema after exposure to cow's milk, and to children with low or moderate suspicion of CMPA. Because many children with atopic eczema show clinically nonrelevant IgE sensitization, the diagnosis of CMPA in these children should always be confirmed by an elimination diet followed by an oral challenge (Fig. 1).

In cases of nonspecific symptoms with a low risk of CMPA or a high likelihood for non–IgE-mediated immune response due to CMPA (eg, frequent regurgitation, constipation, bloody stools), allergy tests for CMPA are not cost-effective as part of the primary diagnostic workup (22,24,55,56). If, however, diagnostic allergen elimination is effective and a subsequent CMP challenge is positive, then an allergy test may be carried out to assess the risk of an immediate reaction at later challenges and offer a prognosis for the development of tolerance. If the oral challenge test is positive but the test for specific IgE is negative, then the reaction is likely to be non–IgE-mediated allergy. This is particularly often the case with isolated gastrointestinal symptoms; however, a false-negative specific IgE test or nonimmune-mediated intolerance to cow's milk such as primary or secondary lactase deficiency should also be considered.

TREATMENT

The strict avoidance of CMP is presently the safest strategy for managing CMPA. Whether a substitute formula is needed to fulfill nutritional requirements in an individual child with CMPA and the best choice of such a formula depends mostly on the age of the patient and the presence of other food allergies. Different types of immunotherapy such as oral immunotherapy or sublingual immunotherapy have been tried in older children with transient and persistent CMPA with conflicting results (57–59). Whether introduction of extensively heated (baked) CMP-containing products, which is tolerated by a subset of children older than 2 years (60), accelerates tolerance induction is under investigation in large clinical trials (59).

Infants Up to Age 12 Months

If the diagnosis of CMPA is confirmed, then the infant should be maintained on an elimination diet using a therapeutic formula for at least 6 months or until 9 to 12 months of age. Infants/children with severe immediate IgE-mediated reactions may remain on the elimination diet for 12 or even 18 months before they are rechallenged after repeated testing for specific IgE. The factors that determine the choice of formula used in an individual infant include residual allergenic potential, formula composition, costs, availability, infant's acceptance, and presence of clinical data showing the efficacy of the formula. Infants should grow and thrive normally when treated with either eHF or AAF formula with proven efficacy. Unfortunately, only a few studies have been performed with eHF presently available in Europe in scientifically sound clinical trials with a sufficient number of children (61). In addition, well-performed randomized controlled trials with sufficient power are needed to determine whether the development of tolerance is influenced by the choice of formula, eHF versus AAF.

eHF Based on CMP

The majority of infants and children with CMPA tolerate an extensively hydrolyzed formula with whey or casein as a nitrogen source. Although the American Academy of Pediatrics (AAP) defines an extensively hydrolyzed formula as a formula containing only peptides that have a molecular weight of <3000 Da (62), there is no clear evidence that such a threshold would ensure the prevention of allergic reactions in infants and young children with CMPA. In addition to appropriate preclinical testing, therapeutic formulae must demonstrate in clinical studies that with 95% confidence they do not provoke allergic reactions in 90% of infants or children with confirmed cow's-milk protein allergy (63); however, this has been shown for only some eHF (61).

AAF

Formulae containing free amino acids as the only nitrogen source are the best option in infants reacting to eHF. This risk is estimated to be $<10\%$ of all infants with CMPA, but it may be higher in the presence of severe enteropathy or with multiple food allergies (42,43). For that reason, AAF may be considered a first-line treatment despite limited evidence in infants with severe anaphylactic reactions and infants with severe enteropathy indicated by hypoproteinemia and faltering growth (64).

Partially or extensively hydrolyzed formulae based on rice protein are also an option provided that they have been proven safe and efficient in infants with CMPA (15,65). Because of the limited short- and long-term data on allergic reactions (not sensitization) to rice-based formulae, we support the present guidelines that recommend that a hydrolyzed rice formula may be considered in selected infants, which are either refusing or not tolerating an eHF based on CMP, or in vegan families (9).

Soy protein–based formulae are tolerated by the majority of infants with CMPA, but between 10% and 14% of affected infants react to soy protein, with higher proportions in infants younger than 6 months (14,66). The European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) (67) and the AAP (68) recommend that cow's-milk–based formulae should be preferred over soy formula in healthy infants, and soy protein–based formulae should not usually be used during the first 6 months of life. Soy formulae have nutritional disadvantages because their absorption of minerals and trace elements may be lower because of their phytate content (69), and they contain appreciable amounts of isoflavones with a weak estrogenic action that can lead to high serum concentrations in infants (70,71). As a result, both ESPGHAN and AAP consider eHF based on CMP or AAF if eHF is not tolerated preferable over soy protein–based formulae for the dietary treatment of infants with CMPA (67,68); however, a soy formula may be considered in an infant with CMPA older than 6 months if eHF is not accepted or tolerated by the child, if these formulae are too expensive for the parents, or if there are strong parental preferences (eg, vegan diet).

Substitute Formulae That Are Considered to Be Unsafe or Not Nutritionally Adequate in Infants With CMPA

Partially hydrolyzed formulae based on CMP or other mammalian protein are not recommended for infants with CMPA (48,49). There is no evidence that probiotics and prebiotics have a role in the treatment of CMPA (72). Although there may be a role in the primary prevention of allergy, this is not the focus of this article.

Industrial juices made of soy, rice, almond, coconut, or chestnut are improperly called ''milks.'' They are totally unsuitable to meet infant nutritional needs and should therefore not be used.

Weaning Food. In exclusively breast-fed and formula-fed infants with proven CMPA, weaning food should be free of CMP until a supervised successful oral challenge indicates the development of tolerance. Other supplementary foods should be introduced one by one in small amounts, preferably while the mother is still breast-feeding but not before the infant is 17 weeks of age (73,74). Delaying introducing weaning foods with a higher allergenic potential such as egg, fish, or wheat has no proven beneficial effect for allergy prevention and should be avoided unless there is a proven allergy to any of them (73).

Children Beyond the Age of 12 Months

Children with CMPA that continues beyond the first 12 months of age need individualized nutritional advice. Dietetic assessment is required to ensure whether the supply of nutrients, especially proteins, calcium, vitamin D, and vitamin A, is sufficient on the elimination diet and whether a therapeutic formula or supplements is required to support normal growth for age (75). Supervision of the diet by a specialist dietician/pediatrician trained in pediatric nutrition is strongly recommended in such cases.

First-line therapy for CMPA is substitution of CMP by therapeutic formulae (eHF, a formula based on a nonrelated protein with no cross-reactivity, eg, soy protein–based infant formula, or AAF if neither options are tolerated). If the child does not consume sufficient formula, then calcium supplements should be considered; however, many patients regardless of age with multiple food allergies, including CMP and soy protein, require a therapeutic formula to fulfill their nutritional needs.

REEVALUATION

There is insufficient evidence to recommend an optimal interval before reevaluation. The duration of exclusion will depend on the age, severity of a child's symptoms, and positivity of specific IgE for CMP. Convention is that a challenge with cow's milk may be performed after maintaining a therapeutic diet for at least 3 months (eg, specific IgE negative, mild symptoms) up to at least 12 months (eg, high-positive IgE test or severe reaction) to avoid continuing a restrictive diet for an unnecessarily long time (1). Such restrictions may result in improper growth. If a challenge is positive, then the elimination diet is usually continued for between 6 and 12 months. If the challenge is negative, then cow's milk is fully reintroduced into the child's diet. The prognosis for CMPA in infancy and young childhood is good. Approximately 50% of affected children develop tolerance by the age of 1 year, >75% by the age of 3 years, and >90% are tolerant at 6 years of age (18).

CONCLUDING REMARKS

CMPA is common and often not properly diagnosed. Strict diagnostic criteria should be applied to minimize misdiagnosis. In the absence of reliable objective diagnostic tools, clinical assessment with CMP elimination and challenge within 4 weeks remains a fundamental for the accurate diagnosis of CMP. So as not to prolong unnecessary dietary restrictions, supervised CMP challenges are required, although the optimal interval for reevaluation depends on the clinical scenario. Further research is required to better understand the mechanism of tolerance induction. This knowledge may influence the choice of formula and potential intervention in a subgroup of children with CMPA.

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