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Middle East Consensus Statement on the Prevention, Diagnosis, and Management of Cow's Milk Protein Allergy

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Presented are guidelines for the prevention, diagnosis, and treatment of cow's milk protein allergy (CMPA) which is the most common food allergy in infants. It manifests through a variety of symptoms that place a burden on both the infant and their caregivers. The guidelines were formulated by evaluation of existing evidence-based guidelines, literature evidence and expert clinical experience. The guidelines set out practical recommendations and include algorithms for the prevention and treatment of CMPA. For infants at risk of allergy, appropriate prevention diets are suggested. Breastfeeding is the best method for prevention; however, a partially hydrolyzed formula should be used in infants unable to be breastfed. In infants with suspected CMPA, guidelines are presented for the appropriate diagnostic workup and subsequent appropriate elimination diet for treatment. Exclusive breastfeeding and maternal dietary allergen avoidance are the best treatment. In infants not exclusively breastfed, an extensively hydrolyzed formula should be used with amino acid formula recommended if the symptoms are life-threatening or do not resolve after extensively hydrolyzed formula. Adherence to these guidelines should assist healthcare practitioners in optimizing their approach to the management of CMPA and decrease the burden on infants and their caregivers.

Key Words: Allergy and immunology, Breast feeding, Hypersensitivity, Infant formula, Milk hypersensitivity

INTRODUCTION

An allergy is a hypersensitivity reaction initiated by specific immunologic mechanisms [1]. Food allergies affect both adults and children and can be defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food [2].

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Cow's milk protein allergy (CMPA) is the most common food allergy in infants [3]. An important differentiation in the management of milk hypersensitivities is between allergy and intolerance [1]. CMPA is a reproducible clinically abnormal reaction to cow's milk protein (CMP) due to the interaction between one or more milk proteins and one or more immune mechanisms, while intolerance is a non-allergic food sensitivity as the result of lactase deficiency, the dietary enzyme required to digest lactose which is the predominant sugar in milk [2].

Epidemiology

The prevalence of allergic diseases worldwide is rising dramatically in both developed and developing countries [4]. These diseases include asthma, rhinitis, anaphylaxis, eczema, urticaria, angioedema, and drug, food, and insect allergy. This increase is especially problematic in children, who are bearing the greatest burden of the rising trend which has occurred over the past two decades.

Comparable international epidemiological evidence on CMPA prevalence is lacking, predominantly due to methodological and geographical differences in clinical evaluation [1]. European prospective cohort studies from the past 15 years suggest that the prevalence of CMPA is between 1.9% and 4.9% [5]. This is consistent with a meta-analysis which found that CMPA is the most common food allergy in early childhood with an incidence of 2-3% in the first year of life [6]. While there are indirect data favoring an increase in CMPA prevalence, knowledge of the time trend of CMPA prevalence is very limited and there are no unequivocal data to suggest an increase.

Etiology and pathophysiology

Food allergens are the components of food recognized by allergen-specific immune cells which then elicit immunologic reactions resulting in characteristic symptoms [2]. Allergy can be immunoglobulin E (IgE)-mediated or non-IgE-mediated. IgE-mediated allergy is associated with atopic manifestations such as urticaria, angioedema, vomiting, diarrhea, eczema, rhinitis, and anaphylaxis [7]. Non-IgE-mediated allergy is associated with symptoms including gastro-esophageal reflux, vomiting, constipation, hemosiderosis, malabsorption, villous atrophy, eosinophilic proctocolitis, enterocolitis, and eosinophilic esophagitis. However, in some infants, irritability and colic may be the only symptoms of food allergy [8].

The risk of developing allergic sensitization, atopy, and asthma is increased in children with a positive family history for atopy in first-degree relatives [7]; however, it has not been demonstrated that there is an increased risk for CMPA if there is a positive family history. A genetic basis for atopic disease is supported by twin studies which show that allergies such as asthma, eczema, and hay fever correlate more highly in monozygotic than dizygotic twins irrespective of whether the monozygotic twins were raised together or apart [9].

Allergic symptoms often develop in a common sequence and pattern in what is termed the allergic march, with progression of atopic disease from eczema to asthma, and then to allergic rhinoconjunctivitis [7]. This is thought to be the result of regional allergic response leading to systemic allergic inflammation.

Although CMPA is common, affecting 2-4% of the population, it is often not properly recognized. As the development of allergy can be influenced, preventing CMPA may prevent further manifestations of allergy. The symptomatic manifestations of CMPA place a considerable burden on both the infant and their parents; therefore, it is important that there is sufficient awareness of the possibility for preventing CMPA as well as guidelines for diagnosis and management of the condition.

A number of guidelines have been published on both the prevention [7,10,11] and management [1,2,7] of CMPA. Regionally within the Middle East there is a lack of focus on infant allergy, with limited studies on epidemiology, prevention, diagnosis, and treatment. There are no regional publications of guideline recommendations. There is, therefore, a need for region-specific recommendations for the prevention, diagnosis, and treatment of allergy which assess the latest available literature and tailor

it to the region with due consideration of local experiences and challenges. These guidelines are created to reflect the issues that are specific to the region, such as cultural differences, epidemiological differences, lack of healthcare practitioner and parental awareness, and product availability and affordability. The objective of this manuscript is to provide clinical guidelines on the prevention, diagnosis, and treatment of CMPA for the region.

METHODS

A panel of experts met on 14 September 2013 in Dubai to develop consensus recommendations to aid the prevention, diagnosis, and management of CMPA in the Middle East. The panel included experts from across the Middle East with expertise in allergology, gastroenterology, nutrition, and pulmonology. The six experts represented four countries from the region. The panel was led by an international chair with extensive experience on the subject of CMPA.

Recommendations from recent international guidelines for infant and childhood allergy and other relevant literature identified by a PubMed search were reviewed prior to the expert panel meeting. The panel critically analyzed recommendations from these guidelines as well as available published literature, including randomized control trials and review articles on infant and childhood allergy.

The validity, clinical relevance, and applicability of the evidence for infant and childhood allergy in the Middle East were discussed. After considering the evidence, the panel achieved a consensus on a number of recommendations that are supported by best scientific evidence and expert clinical opinion.

PREVENTION OF COW'S MILK PROTEIN ALLERGY

The risk of allergy has a genetic component and can be classified based on family history (Table 1). Historical data show that the incidence of atopic disease is around 15%; however, this is increased in infants with a family history of atopic disease. Risk is increased to 20-40% if one parent has a history of atopy, to 40-50% if both parents have a history of atopy, and to 70-80% if both parents have a history of the same atopic disease [12,13]. There are no recent data on the familial risk of atopic disease. Furthermore, if a child within a family has an allergy, the risk of allergy in subsequent siblings is 10 times higher than that within the general population [14]. There is no available evidence that risk of CMPA is higher in those with a family history of CMPA versus a family history of atopic disease as these studies have not been performed.

Breastfeeding is universally acknowledged to be the best way of providing ideal food for the healthy growth and development of infants. The World Health Organization recommends that infants should be exclusively breastfed for the first 6 months of life in order to achieve optimal growth, development, and health. After this, infants should receive nutritionally adequate and safe complementary foods while breastfeeding continues for up to 2 years of age or beyond.

Exclusive breastfeeding has been shown to be the best method to prevent allergy. Data from the German Infant Nutrition Intervention (GINI) study

Table 1. The Familial Basis of Atopic Disease [12,13]

Category	Low risk	Medium risk	High risk	
Family history	No family history of atopic disease	One parent atopic	Two parents atopic	Two parents atopic for same allergies
Percentage of newborns born into category (%)	70	25	5	
Percentage of babies within category that develop atopic disease (%)	15	20-40	40-50	70-80

showed that exclusive breastfeeding had a significant protective effect against atopic dermatitis when compared with conventional cow's milk formula (CMF) [15]. This finding is supported by meta-analyses which show that breastfeeding is associated with a decreased risk of atopic dermatitis compared with conventional formula feeding [16].

Recent guidelines are consistent in their recommendation that maternal diet should not be modified during pregnancy or lactation as a strategy for preventing the development or clinical course of food allergy [2,10,11]. Studies have failed to demonstrate that modulation of maternal diet decreases incidence of allergy [17,18]. Furthermore, a systematic review of studies of maternal diet restriction found that restriction was associated with a statistically significantly lower mean gestational weight gain and therefore a maternal restriction in diet may risk an unbalanced diet that affects one or both of fetal and maternal nutrition [19].

In infants who are not exclusively breastfed, guidelines routinely recommend the use of hydrolyzed formulae for the prevention of CMPA [2,10,11]. A number of studies have demonstrated the efficacy of using both partially hydrolyzed formula (pHF) and extensively hydrolyzed formula (eHF) for the prevention of allergy in infants at high risk of allergy [20,21]. Some of the most compelling data come from the GINI study. In infants with a hereditary risk for allergy randomly assigned to standard CMF, a partial hydrolysate, or one of two extensive hydrolysates, the incidence of atopic dermatitis was significantly reduced in those receiving the pHF or one of the eHF formulae [15]. Follow-up studies at both 6 years and 10 years have shown that this effect is without rebound [15].

It is important to acknowledge that some studies have failed to demonstrate a preventative effect of hydrolyzed formulae on prevention of allergy, with some reviews claiming that there is limited evidence that prolonged feeding with a hydrolyzed formula compared to a CMF reduces infant and childhood allergy [22-24]. Despite this, most guidelines acknowledge that there is modest evidence for hydrolyzed formulae in the prevention of atopic dermatitis and support their recommendation in infants at risk of allergy [2,10,11].

Hydrolyzed formulae are those where the proteins have been hydrolyzed in order to remove allergenic epitopes. Partially hydrolyzed formulae have been developed to minimize sensitizing epitopes while retaining peptides of sufficient size and immunogenicity to stimulate the induction of oral tolerance [25]. Extensively hydrolyzed formulae are further hydrolyzed for greater hypoallergenicity, but key considerations in their use are the increased cost over pHF [26] and their reduced palatability [27]. Furthermore, it has been suggested that the reduced immunogenicity of eHF may prevent the immune system from developing tolerance to milk proteins [25]; however, a recent study has shown that eHF does induce tolerance in symptomatic sensitized infants when used in the treatment of CMPA [28]. Amino acid formulae (AAF) have been developed to overcome the hypersensitivity that can arise from the residual proteins in eHF [29]; however, these are more expensive, have no evidence to support their efficacy in prevention of CMPA, and are therefore not recommended for prevention of CMPA.

All studies on the prevention of allergy have been performed in infants with an increased risk of allergy based on family history of atopic disease, and therefore this is the only group of infants in which routine prevention of allergy should be recommended. The reality, however, is that identification of infants who are at risk is challenging and they are frequently not appropriately identified within primary care, with some receiving normal infant formula before they can be accurately identified as at risk and moved onto an appropriate prevention formula. At-risk infants who have been fed standard CMF before their risk has been identified but have not yet developed any symptoms can be safely moved onto a hydrolyzed formula; however, there is no strong evidence to demonstrate the clinical efficacy of a preventative effect on allergy in this instance. The expert panel are aware that common practice in some centers is for all infants not exclusively breastfed to receive pHF until

their risk for developing allergy based on family history can be assessed by a healthcare provider. This ensures that all infants at risk of allergy receive the necessary prevention diet and are not inadvertently exposed to CMP.

With regard to infant diet, there is conflicting evidence on the preventative effect of delaying the introduction of solid food on the incidence of allergy. While some studies suggest that restricting type and delaying timing of introduction of food may prevent allergy [30,31], other studies suggest that early introduction has no adverse effect and may even protect against allergy [32-36]. Furthermore, it is suggested that restricting developmentally appropriate solid food variety beyond age 6 months can lead to inadequate nutrient intake, growth deficits, and feeding problems [2]. On balance, the evidence suggests that there is not a strong benefit in delaying introduction or imposing specific restriction of potentially allergenic food beyond 4-6 months (17-27 weeks).

Prebiotics and probiotics are commonly marketed with claims that they may help in prevention of allergy [37]. There are studies to suggest that probiotic supplementation of mothers during pregnancy and lactation may prevent early atopic disease in infants [38]. There is also evidence to suggest that supplementation of eHF with prebiotics may decrease incidence allergic manifestations, including of atopic dermatitis, recurrent wheezing, and allergic urticaria in infancy [39]. There are no studies published that demonstrate whether this is also true of pHF supplemented with prebiotics. These data suggest that prebiotics and probiotics are safe and, while there is some evidence that they may reduce incidence of allergy, further evidence is required before they can become routine recommendation [37].

Consensus recommendations

The experts agreed that exclusive breastfeeding for 4-6 months (17-27 weeks) is the best method of preventing infant allergy. There is no evidence that modification of maternal diet during pregnancy or lactation has a protective effect against allergy in at-risk infants, and furthermore a modified diet may cause nutritional deficiencies in the lactating mother and infant.

Infants who are not exclusively breastfed and are at risk of allergy should receive a prevention diet. At-risk infants should be identified on the basis of a family history of one or more immediate family members (father, mother, brother, or sister) with a history of atopic disease (CMPA, food allergy, atopic dermatitis, asthma, eczema). Due to the difficulties in assessing allergy in neonates, where exclusive breastfeeding is impossible all infants should receive a pHF for prevention of allergy until their risk has been assessed by a healthcare provider. In hospitals where ready-to-feed formulae are used, a ready-to-feed pHF should be used instead of ready-to-feed standard CMF where available.

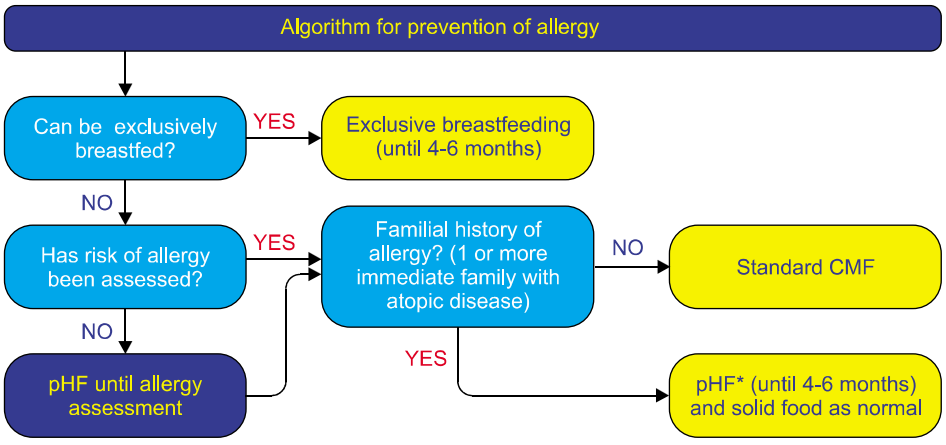

Fig. 1. An algorithm for the prevention of infant allergy. *eHF also has proven efficacy in prevention of allergy and can be used; however, pHF is recommended due to cost and palatability considerations. CMF: cow's milk formula, pHF: partially hydrolyzed formula, eHF: extensively hydrolyzed formula.

There is no evidence to suggest that delaying introduction of solid foods, or even potentially allergenic foods, beyond age 4-6 months offers any protective effect against allergy. The consensus recommendations for the prevention of CMPA are shown in Fig. 1.

DIAGNOSIS OF COW'S MILK PROTEIN ALLERGY

While symptoms suggestive of CMPA are encountered in 5-15% of infants, the true prevalence of CMPA in infancy is about 2-3% [3,6]. This suggests a need for appropriate diagnostic elimination and challenge procedures in the diagnosis of CMPA.

CMPA typically develops within first few weeks of exposure to CMP [40]. For diagnosis of CMPA there is a need for an appropriate diagnostic work-up, including family history and a physical examination. There is no one symptom pathognomonic of CMPA; it can present with an array of symptoms affecting different organ systems - typically the skin, respiratory, and gastrointestinal tracts-with many infants developing symptoms in more than one organ system. Anaphylaxis in CMPA is rare, and infants with life-threatening symptoms or anaphylaxis should be immediately referred to the nearest emergency department [2,41]. Diagnosis of CMPA should be made on the basis of symptoms [2,7,40].

There are a number of confirmatory tests which can add value when diagnosing CMPA; however, diagnosis is difficult to prove and an oral challenge test is the gold standard in confirming an adverse reaction to CMP [42]. Specific IgE testing helps to confirm diagnosis in IgE-mediated allergy, and prick tests can be used to add value to the diagnosis, but positive results are not necessarily predictive for food challenge outcome [43,44]. Other tests marketed for diagnosis of CMPA include atopy patch tests and food prints; however, scientific evidence and consensus on their specificity, application, and interpretation is currently limited and they are therefore not recommended.

Table 2. Symptomatic Diagnosis of Cow's Milk Protein Allergy

Organ system	Symptom
Systemic	· Anaphylaxis (flaccidity/floppiness; pallor/cyanosis)
	· Shock-like symptoms with severe metabolic acidosis, vomiting & diarrhea (FPIES)
	· Infantile colic
Gastrointestinal (50-60%)	· Oral allergy syndrome
	· Vomiting, regurgitation, reflux
	· Dysphagia; food impaction
	· Delayed gastric emptying
	· Abdominal pain
	· Diarrhea (bloody stools, protein loosing enteropathy)
	· Proctocolitis
	· Constipation +/- perianal rash
	· Anorexia, failure to thrive, early satiety
	· FPIES
	· Eosinophil infiltration (eosinophilic esophagitis, gastritis, enterocolitis)
Dermatological (5-60%)	· Urticaria (unrelated to infections, drug intake, or other causes)
	· Atopic dermatitis
	· Angioedema
Respiratory (20-30%)	· Runny nose (rhinitis)
	· Wheezing, stridor
	· Chronic coughing (all unrelated to infections)

The common manifestations of cow's milk protein allergy (CMPA) ordered by organ system. Adapted with permission from Lippincott Williams and Wilkins/Wolters Kluwer Health: Koletzko et al., J Pediatr Gastroenterol Nutr, 2012;55:221-9 [7]. Adapted by permission from BMJ Publishing Group Limited: Vandenplas et al., Arch Dis Child, 2007;92:902-8 [40].
FPIES, food protein-induced enterocolitis syndrome.

Consensus recommendations

The experts agreed that when CMPA is suspected there is a need for a diagnostic work-up which includes an assessment of family history and a physical examination. Diagnosis should be made on the basis of symptoms (Table 2). CMPA should be suspected if:

1. Symptoms develop within 2 months after the introduction of cow's milk
2. Symptoms develop within 2 hours after ingestion (IgE-mediated)
3. More than one organ system is involved
4. Family history of atopy
5. Symptoms are not responding to "classic" treatment in monosymptomatic infants

Specific IgE or prick testing may then be used to confirm the diagnosis of CMPA.

TREATMENT OF COW'S MILK PROTEIN ALLERGY

If CMPA is suspected then a diagnostic elimination diet should be initiated. For infants that are breastfed, this involves elimination of the cow's milk-containing products from the maternal diet. In this case dietary counselling on sources of CMP may be necessary. Breastfeeding mothers undergoing prolonged elimination of cow's milk products from their diet should be advised to take calcium supplements and given appropriate dietary advice in order to avoid nutritional deficiencies.

For infants that are not exclusively breastfed, cow's milk-based formula and any complementary food containing CMP should be avoided. Infants on formulae should be given a therapeutic formula that is clinically proven to have reduced allergenicity, in that with 95% confidence it is tolerated by ≥90% of infants with CMPA [8,45]; this criterion is met by some eHF and by AAF. Both eHF and AAF have proven efficacy in treating CMPA, with studies demonstrating their ability to reduce CMPA symptoms in confirmed or suspected cases [46]. An eHF should be considered as the first choice in all but the most severe cases of CMPA, predominantly due to the fact it is cheaper than AAF milk [47] and has been shown to be better at inducing tolerance [28]. The use of AAF is warranted in severe cases such as anaphylaxis and also in infants who do not tolerate eHF [46,48].

Historically, it has been common practice to feed infants with CMPA milk from other mammalian species; this should be avoided due to the risk of cross-reactivity between these milks. In particular, sheep and goat's milk have a high degree of homology and cross-reactivity to cow's milk [49]. While mare, donkey and camel milk appear to be better tolerated, there is still a risk of cross-reactivity [49,50]. Furthermore, these mammalian milks are not nutritionally adapted to the needs of the infant.

Other modified formulae are commercially available. The use of soy-based formulae is deeply rooted in the treatment of allergy in some countries [8] and they have been shown to induce fewer allergies than cow's milk-based formulae [51,52]. Soy formula is well tolerated by most individuals with CMPA, with 10-14% of infants with CMPA shown to be sensitized to soy and reports of anaphylaxis very rare [53]. There have been concerns raised about the isoflavone (phytoestrogen) content of soy formulae and its potential adverse effect on sexual development and reproduction; however, a recent meta-analysis has shown that the patterns of growth, bone health, and metabolic, reproductive, endocrine, immune, and neurologic functions seen in infants fed soy-based formulae are similar to those observed in children fed CMF or human milk [54].

The higher tolerance of infants with CMPA to eHF supports the recommendation of eHF over soy-based formulae in the treatment of allergy; however, the use of soy formulae can be considered where eHF may be considered unaffordable, or where eHF is rejected by the infant due to its decreased palatability [27]. Most guidelines recommend against the use of soy before the age of 6 months [7,52,55] on the basis that adverse reactions to soy are more common in infants under 6 months [53]. It is the expert opinion of this panel that this recommendation is not strong as it is made on the basis of one study in which the group aged less than 6 months that was fed soy formula contained only 20 infants.

Rice-based formulae are another alternative. While they are not currently widely available within the Middle-East region, the expert panel are aware that their popularity is growing in other parts of the world and they may be more widely available in the future. These are CMP-free, well tolerated, palatable, nutritionally adapted to the needs of infants, and are cheaper than extensive hydrolysates [27,56,57]. However, rice formulae have not been extensively studied to establish their 90% efficacy and there are also concerns about the levels of arsenic that may be present [58]. At this point there are no firm recommendations on rice-based formulae.

Following an elimination diet, a challenge test should be used to confirm allergy. It should be noted that parents may refuse a challenge test if symptoms have resolved and they are concerned about a reaction. It is recommended that the existing guidelines for conducting oral challenges are followed [7]. It is important that the following points are strictly observed for an oral challenge:

1. There should be medical supervision present
2. There should be effective treatment calculated and available prior to the challenge for patients who may experience severe anaphylaxis
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 not be tested on a full stomach or after an overnight fast (2-3 hours after their last meal is advisable)
5. Intravenous access is necessary if a severe or systemic reaction is likely

Furthermore, challenges should be carried out in a hospital setting if any of the following conditions are met:

1. There is a history of moderate-severe immediate allergic reactions

2. The reaction is unpredictable (e.g., infants with positive specific IgE who have never or not recently been exposed to cow's milk)

3. There is severe atopic eczema (due to the difficulty in accurately assessing a reaction)

While it is recommended that challenges are performed under clinical supervision, the experts acknowledge that challenges are frequently conducted at home by family members, but this is not supported by recommendations. If there is no response to a CMP challenge test, it is safe to move the infant to a standard CMF. If there is no response to eHF challenge test for infants on an AAF, it is safe to move the infant to an eHF. If there is a response to either a CMP or eHF challenge test, the infant should remain on the therapeutic formula which has been shown to resolve their CMPA symptomatic manifestations. Where symptoms do not resolve, infants should be referred to the appropriate specialist based on their symptoms: a gastroenterologist for gastrointestinal symptoms, a dermatologist for dermatological symptoms, or a pulmonologist for respiratory symptoms [59]. The prognosis of CMPA is good, with resolution of symptoms in 45-50% of infants by 1 year, 60-75% by 2 years, 85-90% by 3 years, and persistence in only 10% of infants [6]. High IgE levels correlate with persistence of allergy, and are therefore a useful predictor of patient outcome [60].

Consensus recommendations

The experts agreed that continued breastfeeding is the best treatment for infants with CMPA. The diet of breastfeeding mothers with infants with CMPA should be restricted to avoid all dairy products. If there is dairy exclusion, calcium supplements for the mother should be advised. In infants that are not exclusively breastfed, treatment should be with eHF, with AAF used as first choice only in anaphylaxis, or where eHF treatment fails. If there is no response to AAF, allergy is not likely and a further diagnostic workup for other potential causes of the symptoms should be performed. The use of a therapeutic formula should continue to age 1 year and/or at least for 6 months. However a challenge with standard CMF should be performed after 4 weeks if the diagnosis was not confirmed to avoid an incorrect diagnosis and unnecessary prolonged use of expensive eHF. If eHF is unavailable or unpalatable, then soy infant formula may be considered, although it may be associated with

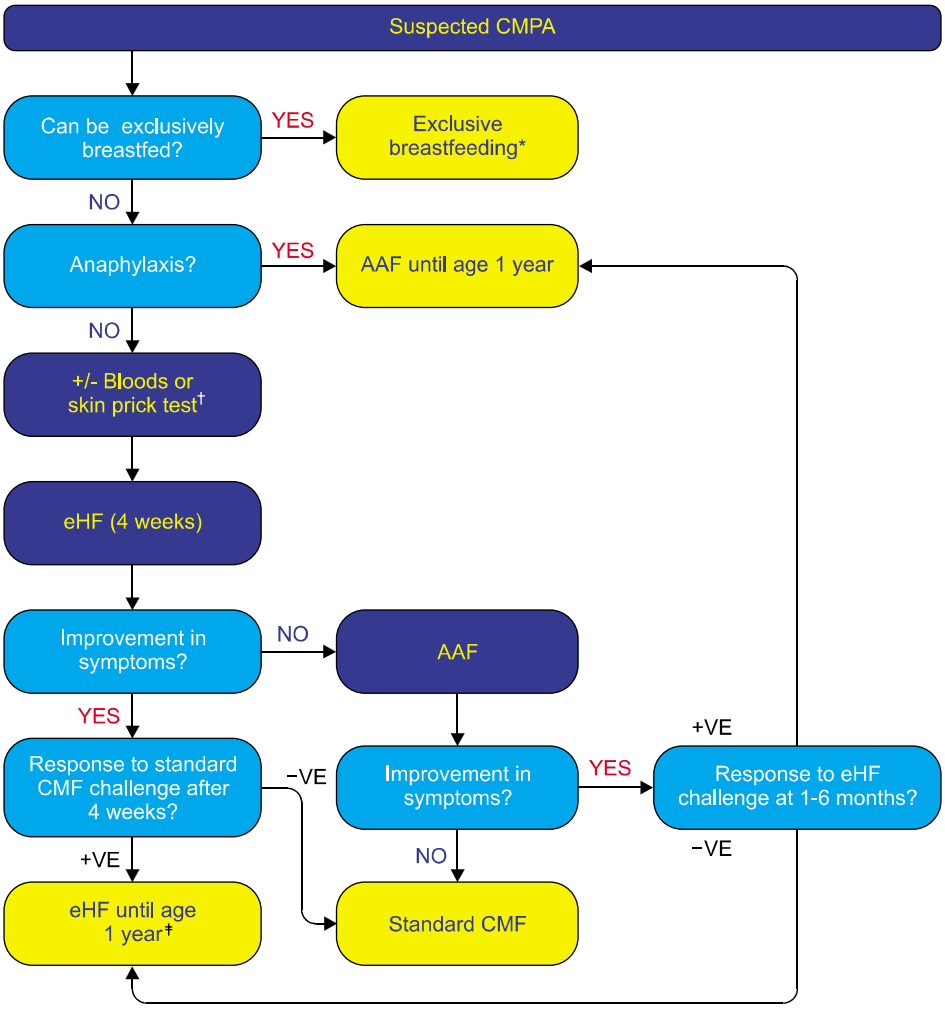

Fig. 2. An algorithm for the treatment of CMPA. *Breastfeeding mothers should exclude all products containing CMP from their diet and take calcium supplements. †IgE-specific test or skin prick test can be performed if laboratory facilities are available. ‡Soy formula can be used if eHF is unavailable or unpalatable. CMPA: cow's milk protein allergy, AAF: amino acid formula, CMF: cow's milk formula, eHF: extensively hydrolyzed formula, +VE: positive, -VE: negative.

cross-allergy and theoretical potential side effects especially in the first 6 months of life. Other animal milks should not be used (due to high cross-reactivity which is up to 80%). Infants with CMPA should not be given milk or supplementary foods containing CMP for at least 6 months and up to the age of 1 year. Diversification of introduction of food should be no different in children with allergy versus children without allergy. The consensus recommendations for the treatment of CMPA are shown in Fig. 2.

CONCLUSION

This consensus manuscript is the first to provide region-specific guidelines for the Middle East on the prevention and management of CMPA. The guidelines take into account the challenges that are unique to the region; namely cultural and epidemiological differences, lack of healthcare practitioner and parental awareness, and product availability and affordability.

The main limitation of these guidelines centers on the fact that there are limited local and regional studies on the prevalence of CMPA or the efficacy of treatment strategies for CMPA. The guideline recommendations are therefore dependent on the expert clinical opinion of the panel members.

One of the main differences in these guidelines is the recommendation that all infants that are not exclusively breastfed should be fed a pHF formula until

their risk for allergy has been assessed. This recommendation is made on the basis that there is a lack of parental and healthcare practitioner awareness, and that assessment of allergy in the region is frequently performed after a standard CMF has been given to an infant when the window for a proven preventative effect of pHF on CMPA has passed. Furthermore, the experts are aware that this is routine practice in some pediatric centers around the world.

Another difference in these guidelines is the recommendation that soy formula can be used as a substitute for eHF if eHF is unavailable or unpalatable. This recommendation is made with two main considerations. The first is a re-evaluation of the evidence that precludes the use of soy formulae before the age of 6 months in previous guidelines [53,54]. The second is the consideration that affordability of formulae is recognized by the panel of experts as a key challenge in the region, and therefore there is a need for an alternative recommendation that reflects this challenge.

The expert panel also identified that awareness of CMPA among both parents and healthcare practitioners is a challenge within the region. Education of healthcare practitioners on the clinical significance of CMPA is therefore of paramount importance. It is important for them understand that the failure to adequately identify infants at risk results in a missed opportunity for prevention. Furthermore, it is important to educate on the clinical manifestations and the best practice treatment strategies. In parallel to this, it is important that there is a concerted effort to educate parents about the familial risk for allergy, the possibility for prevention, the key symptoms to look for in their child, and the importance of maintaining a therapeutic diet where indicated.

In summary, these guidelines have been written by the panel to provide best practice for the region on the prevention, diagnosis, and treatment of CMPA with the hope the burden of this condition can be reduced and optimally managed.

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REFERENCES

1. Fiocchi A, Brozek J, Schünemann H, Bahna SL, von Berg A, Beyer K, et al. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines. World Allergy Organ J 2010;3:57-161.
2. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al; NIAID-Sponsored Expert Panel. Guidelines for the Diagnosis and Management of Food Allergy in the United States: Summary of the NIAID-Sponsored Expert Panel Report. J Allergy Clin Immunol 2010;126:1105-18.
3. Sicherer SH. Epidemiology of food allergy. J Allergy Clin Immunol 2011;127:594-602.
4. Pawankar R, Canonica GW, Holgate ST, Lockey RF. WAO white book on allergy 2011-2012: executive summary. Milwaukee: World Allergy Organization, 2011.
5. Venter C, Pereira B, Grundy J, Clayton CB, Roberts G, Higgins B, et al. Incidence of parentally reported and clinically diagnosed food hypersensitivity in the first year of life. J Allergy Clin Immunol 2006;117:1118-24.
6. Høst A. Frequency of cow's milk allergy in childhood. Ann Allergy Asthma Immunol 2002;89(6 Suppl 1):33-7.
7. Koletzko S, Niggemann B, Arato A, Dias JA, Heuschkel R, Husby S, et al; European Society of Pediatric Gastroenterology, Hepatology, and Nutrition. Diagnostic approach and management of cow's-milk protein allergy in infants and children: ESPGHAN GI Committee practical guidelines. J Pediatr Gastroenterol Nutr 2012;55:221-9.

8. American Academy of Pediatrics. Committee on Nutrition. Hypoallergenic infant formulas. Pediatrics 2000;106:346-9.
9. Feijen M, Gerritsen J, Postma DS. Genetics of allergic disease. Br Med Bull 2000;56:894-907.
10. Greer FR, Sicherer SH, Burks AW; American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Section on Allergy and Immunology. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. Pediatrics 2008;121:183-91.
11. Høst A, Halken S, Muraro A, Dreborg S, Niggemann B, Aalberse R, et al. Dietary prevention of allergic diseases in infants and small children. Pediatr Allergy Immunol 2008;19:1-4.
12. Aberg N, Engström I, Lindberg U. Allergic diseases in Swedish school children. Acta Paediatr Scand 1989;78: 46-52.
13. Kjellman NI. Atopic disease in seven-year-old children. Incidence in relation to family history. Acta Paediatr Scand 1977;66:465-71.
14. American College of Allergy, Asthma, & Immunology. Food allergy: a practice parameter. Ann Allergy Asthma Immunol 2006;96(3 Suppl 2):S1-68.
15. von Berg A, Filipiak-Pittroff B, Krämer U, Hoffmann B, Link E, Beckmann C, et al; GINIplus study group. Allergies in high-risk schoolchildren after early intervention with cow's milk protein hydrolysates: 10-year results from the German Infant Nutritional Intervention (GINI) study. J Allergy Clin Immunol 2013;131: 1565-73.
16. Yang YW, Tsai CL, Lu CY. Exclusive breastfeeding and incident atopic dermatitis in childhood: a systematic review and meta-analysis of prospective cohort studies. Br J Dermatol 2009;161:373-83.
17. Fälth-Magnusson K, Kjellman NI. Allergy prevention by maternal elimination diet during late pregnancy--a 5-year follow-up of a randomized study. J Allergy Clin Immunol 1992;89:709-13.
18. Lilja G, Dannaeus A, Foucard T, Graff-Lonnevig V, Johansson SG, Oman H. Effects of maternal diet during late pregnancy and lactation on the development of IgE and egg- and milk-specific IgE and IgG antibodies in infants. Clin Exp Allergy 1991;21:195-202.
19. Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. Cochrane Database Syst Rev 2006;(3):CD000133.
20. Marini A, Agosti M, Motta G, Mosca F. Effects of a dietary and environmental prevention programme on the incidence of allergic symptoms in high atopic risk infants: three years' follow-up. Acta Paediatr Suppl 1996;414:1-21.
21. Vandenplas Y, Hauser B, Van den Borre C, Clybouw C, Mahler T, Hachimi-Idrissi S, et al. The long-term effect of a partial whey hydrolysate formula on the prophylaxis of atopic disease. Eur J Pediatr 1995;154:488-94.
22. Halken S, Hansen KS, Jacobsen HP, Estmann A, Faelling AE, Hansen LG, et al. Comparison of a partially hydrolyzed infant formula with two extensively hydrolyzed formulas for allergy prevention: a prospective, randomized study. Pediatr Allergy Immunol 2000;11:1 49-61.
23. de Seta L, Siani P, Cirillo G, Di Gruttola M, Cimaduomo L, Coletta S. The prevention of allergic diseases with a hypoallergenic formula: a follow-up at 24 months. The preliminary results. Pediatr Med Chir 1994;16:251-4.
24. Osborn DA, Sinn J. Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. Cochrane Database Syst Rev 2006;(4): CD003664.
25. Crittenden RG, Bennett LE. Cow's milk allergy: a complex disorder. J Am Coll Nutr 2005;24(6 Suppl): 582S-91S.
26. Su J, Prescott S, Sinn J, Tang M, Smith P, Heine RG, et al. Cost-effectiveness of partially-hydrolyzed formula for prevention of atopic dermatitis in Australia. J Med Econ 2012;15:1064-77.
27. Pedrosa M, Pascual CY, Larco JI, Esteban MM. Palatability of hydrolysates and Other substitution formulas for cow's milk-allergic children: a comparative study of taste, smell, and texture evaluated by healthy volunteers. J Investig Allergol Clin Immunol 2006;16:351-6.
28. Berni Canani R, Nocerino R, Terrin G, Frediani T, Lucarelli S, Cosenza L, et al. Formula selection for management of children with cow's milk allergy influences the rate of acquisition of tolerance: a prospective multicenter study. J Pediatr 2013;163:771-7. e1.
29. Berni Canani R, Nocerino R, Leone L, Di Costanzo M, Terrin G, Passariello A, et al. Tolerance to a new free amino acid-based formula in children with IgE or non-IgE-mediated cow's milk allergy: a randomized controlled clinical trial. BMC Pediatr 2013;13:24.
30. Fergusson DM, Horwood LJ, Shannon FT. Early solid feeding and recurrent childhood eczema: a 10-year longitudinal study. Pediatrics 1990;86:541-6.
31. Morgan J, Williams P, Norris F, Williams CM, Larkin M, Hampton S. Eczema and early solid feeding in preterm infants. Arch Dis Child 2004;89:309-14.

32. Zutavern A, Brockow I, Schaaf B, Bolte G, von Berg A, Diez U, et al; LISA Study Group. Timing of solid food introduction in relation to atopic dermatitis and atopic sensitization: results from a prospective birth cohort study. Pediatrics 2006;117:401-11.
33. Poole JA, Barriga K, Leung DY, Hoffman M, Eisenbarth GS, Rewers M, et al. Timing of initial exposure to cereal grains and the risk of wheat allergy. Pediatrics 2006;117:2175-82.
34. Du Toit G, Katz Y, Sasieni P, Mesher D, Maleki SJ, Fisher HR, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. J Allergy Clin Immunol 2008;122:984-91.
35. Snijders BE, Thijs C, van Ree R, van den Brandt PA. Age at first introduction of cow milk products and other food products in relation to infant atopic manifestations in the first 2 years of life: the KOALA Birth Cohort Study. Pediatrics 2008;122:e115-22.
36. Koplin JJ, Osborne NJ, Wake M, Martin PE, Gurrin LC, Robinson MN, et al. Can early introduction of egg prevent egg allergy in infants? A population-based study. J Allergy Clin Immunol 2010;126:807-13.
37. Osborn DA, Sinn JK. Prebiotics in infants for prevention of allergy. Cochrane Database Syst Rev 2013;3: CD006474.
38. Kalliomäki M, Salminen S, Poussa T, Arvilommi H, Isolauri E. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. Lancet 2003;361:1869-71.
39. Arslanoglu S, Moro GE, Schmitt J, Tandoi L, Rizzardi S, Boehm G. Early dietary intervention with a mixture of prebiotic oligosaccharides reduces the incidence of allergic manifestations and infections during the first two years of life. J Nutr 2008;138:1091-5.
40. Vandenplas Y, Koletzko S, Isolauri E, Hill D, Oranje AP, Brueton M, et al. Guidelines for the diagnosis and management of cow's milk protein allergy in infants. Arch Dis Child 2007;92:902-8.
41. De Greef E, Hauser B, Devreker T, Veereman-Wauters G, Vandenplas Y. Diagnosis and management of cow's milk protein allergy in infants. World J Pediatr 2012;8:19-24.
42. Costa AJ, Sarinho ES, Motta ME, Gomes PN, de Oliveira de Melo SM, da Silva GA. Allergy to cow's milk proteins: what contribution does hypersensitivity in skin tests have to this diagnosis? Pediatr Allergy Immunol 2011;22:e133-8.
43. Celik-Bilgili S, Mehl A, Verstege A, Staden U, Nocon M, Beyer K, et al. The predictive value of specific immunoglobulin E levels in serum for the outcome of oral food challenges. Clin Exp Allergy 2005;35:268-73.
44. Verstege A, Mehl A, Rolinck-Werninghaus C, Staden U, Nocon M, Beyer K, et al. The predictive value of the skin prick test weal size for the outcome of oral food challenges. Clin Exp Allergy 2005;35:1220-6.
45. Giampietro PG, Kjellman NI, Oldaeus G, Wouters-Wesseling W, Businco L. Hypoallergenicity of an extensively hydrolyzed whey formula. Pediatr Allergy Immunol 2001;12:83-6.
46. Hill DJ, Murch SH, Rafferty K, Wallis P, Green CJ. The efficacy of amino acid-based formulas in relieving the symptoms of cow's milk allergy: a systematic review. Clin Exp Allergy 2007;37:808-22.
47. Taylor RR, Sladkevicius E, Panca M, Lack G, Guest JF. Cost-effectiveness of using an extensively hydrolysed formula compared to an amino acid formula as first-line treatment for cow milk allergy in the UK. Pediatr Allergy Immunol 2012;23:240-9.
48. de Boissieu D, Dupont C. Allergy to extensively hydrolyzed cow's milk proteins in infants: safety and duration of amino acid-based formula. J Pediatr 2002;141:271-3.
49. Järvinen KM, Chatchatee P. Mammalian milk allergy: clinical suspicion, cross-reactivities and diagnosis. Curr Opin Allergy Clin Immunol 2009;9:251-8.
50. Ehlayel M, Bener A, Abu Hazeima K, Al-Mesaifri F. Camel milk is a safer choice than goat milk for feeding children with cow milk allergy. ISRN Allergy 2011; 2011:391641.
51. Halpern SR, Sellars WA, Johnson RB, Anderson DW, Saperstein S, Reisch JS. Development of childhood allergy in infants fed breast, soy, or cow milk. J Allergy Clin Immunol 1973;51:139-51.
52. Bhatia J, Greer F; American Academy of Pediatrics Committee on Nutrition. Use of soy protein-based formulas in infant feeding. Pediatrics 2008;121:1062-8.
53. Katz Y, Gutierrez-Castrellon P, González MG, Rivas R, Lee BW, Alarcon P. A comprehensive review of sensitization and allergy to soy-based products. Clin Rev Allergy Immunol 2014;46:272-81.
54. Vandenplas Y, Castrellon PG, Rivas R, Gutiérrez CJ, Garcia LD, Jimenez JE, et al. Safety of soya-based infant formulas in children. Br J Nutr 2014;111:1340-60.
55. ESPGHAN Committee on Nutrition, Agostoni C, Axelsson I, Goulet O, Koletzko B, Michaelsen KF, et al. Soy protein infant formulae and follow-on formulae: a commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr 2006;42: 352-61.
56. D'Auria E, Sala M, Lodi F, Radaelli G, Riva E, Giovannini M. Nutritional value of a rice-hydrolysate formula in infants with cows' milk protein allergy: a randomized pilot study. J Int Med Res 2003;31:215-22.

57. Vandenplas Y, De Greef E, Hauser B, Paradice Study Group. Faltering weight gain normalizes with an extensively hydrolyzed rice protein formula in the treatment of cow's milk protein allergic infants. European Journal of Pediatrics 2014. [Epub ahead of print]
58. Jackson BP, Taylor VF, Punshon T, Cottingham KL. Arsenic concentration and speciation in infant formulas and first foods. Pure Appl Chem 2012;84:215-23.
59. Ludman S, Shah N, Fox AT. Managing cows' milk allergy in children. BMJ 2013;347:f5424.
60. Skripak JM, Matsui EC, Mudd K, Wood RA. The natural history of IgE-mediated cow's milk allergy. J Allergy Clin Immunol 2007;120:1172-7.