An ESPGHAN Position Paper on the Diagnosis, Management, and Prevention of Cow's Milk Allergy

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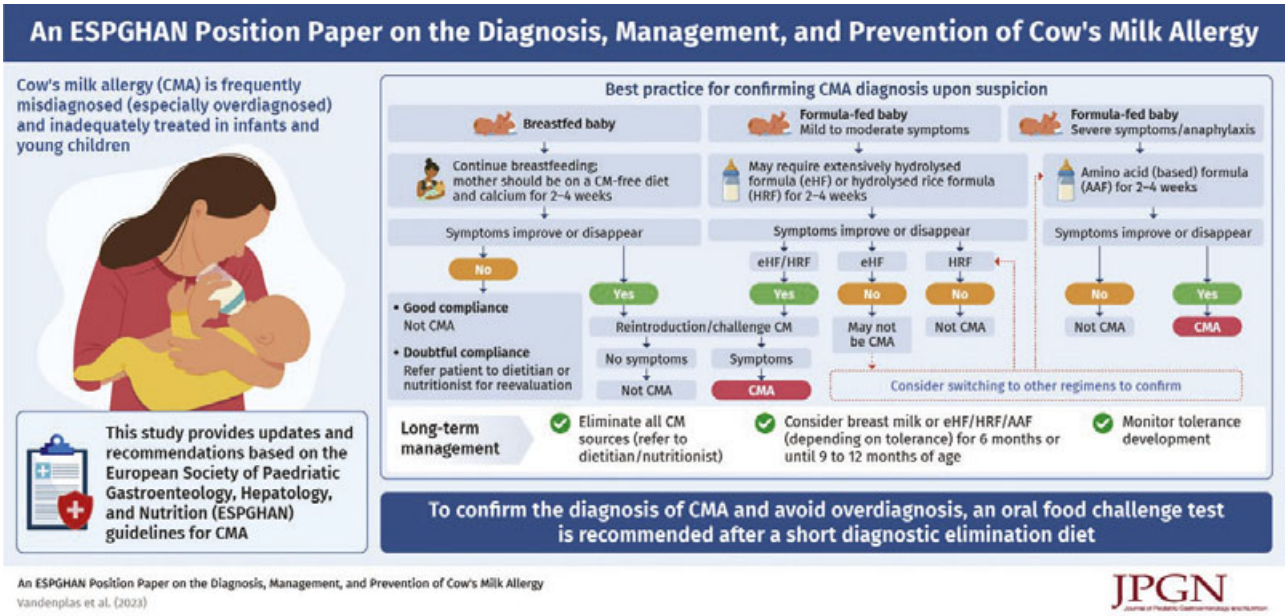

ABSTRACT

A previous guideline on cow's milk allergy (CMA) developed by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) was published in 2012. This position paper provides an update on the diagnosis, treatment, and prevention of CMA with focus on gastrointestinal manifestations. All systematic reviews and meta-analyses regarding prevalence, pathophysiology, symptoms, and diagnosis of CMA published after the previous ESPGHAN document were considered. Medline was searched from inception until May 2022 for topics that were not covered in the previous document. After reaching consensus on the manuscript, statements were formulated and voted on each of them with a score between

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Prof Vandenplas has participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for Abbott Nutrition, Alba, Arla Foods, Ausnutria, Biogaia, By Heart, CHR Hansen, Danone, ELSE Nutrition, Friesland Campina, Nestlé Health Science, Nestlé Nutrition Institute, Nutricia, Mead Johnson Nutrition, Phathom Pharmaceuticals, Pileje, United Pharmaceuticals (Novalac), Yakult, and

0 and 9. A score of ≥6 was arbitrarily considered as agreement. Available evidence on the role of dietary practice in the prevention, diagnosis, and management of CMA was updated and recommendations formulated. CMA in exclusively breastfed infants exists, but is uncommon and suffers from over-diagnosis. CMA is also over-diagnosed in formula and mixed fed infants. Changes in stool characteristics, feeding aversion, or occasional spots of blood in stool are common and in general should not be considered as diagnostic of CMA, irrespective of preceding consumption of cow's milk. Over-diagnosis of CMA occurs much more frequently than under-diagnosis; both have potentially harmful consequences. Therefore, the necessity of a challenge test after a short diagnostic elimination diet of 2–4 weeks is recommended as the cornerstone of the diagnosis. This position paper contains sections on nutrition, growth, cost, and quality of life.

Key Words: amino acid formula, breastfeeding, CMA, diagnosis; disorder of gut-brain interaction

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What Is Known

- Cow's milk allergy (CMA) is mostly a disease of infancy and early childhood.
- Although both over- and under-diagnosis do occur, over-diagnosis is more frequent; both are associated with potentially long-term negative health consequences.
- A previous guideline on CMA developed by European Society of Paediatric Gastroenterology, Hepatology and Nutrition was published in 2012.

What Is New

- Available evidence on the role of dietary practice in the prevention, diagnosis, and management of CMA was updated and recommendations formulated.
- The impact of CMA on nutrition, growth, cost, and quality of life is discussed.
- The roles of hydrolysed rice formula, soy, and vegetable infant feeds in the diagnostic and therapeutic approaches to CMA are discussed.

A hypersensitivity reaction to cow's milk (CM) can be defined as cow's milk allergy (CMA) if it involves immunological mechanisms, which can be divided into 3 categories: IgE-mediated, non-IgE-mediated and mixed. The diagnosis of CMA in infants and young children remains a clinical challenge because many of the presenting symptoms are common in healthy infants, do not necessarily indicate pathology and can be similar to those experienced in other conditions. The presenting symptoms of CMA are, therefore, non-specific. The absence of a sensitive and specific diagnostic tool and the non-specific clinical presentation complicate a correct diagnosis. Both over- and under-diagnosis do occur, but over-diagnosis is likely to occur more frequently, especially in non-IgE mediated allergy. Misdiagnoses carry allergic and nutritional risks, including acute reactions, growth faltering, micronutrient deficiencies and a diminished quality of life for infants and caregivers. An inappropriate diagnosis may also add a financial burden on families and on the health care system (1).

Although the role of breast milk in preventing food allergy remains uncertain, promoting, protecting and supporting exclusive breastfeeding for as many infants as possible up to the age of 6 months, followed by continued partial breastfeeding, should be encouraged. Furthermore, inappropriate marketing of breastmilk substitutes should be banned (2,3).

In many countries, England, Norway and Australia as an example, specialized formula prescriptions increased significantly in the early 21st century and exceeded expected levels (4). In 2020, total volumes were 9.7- to 12.6-fold greater than expected in England, 8.3- to 15.6-fold greater than expected in Norway and 3.3- to 4.5-fold greater than expected in Australia, where prescribing restrictions were introduced in 2012 (4). Also, unnecessary specialized formula use may make a significant contribution to free sugars consumption in young children (4).

Although less frequent than egg (9%) and peanut allergy (3%) (5), CMA was reported in the previous 2012 European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guideline to have a prevalence of 2%–3% (6). Since then, new data on prevention, diagnosis and management of CMA became available making it necessary to update the ESPGHAN recommendations.

The contents of the paper are listed in Appendix 1 (Supplemental Digital Content 1, *http://links.lww.com/MPG/D245*).

METHODS

We evaluated evidence from systematic reviews and meta-analyses regarding prevalence, pathophysiology, symptoms and diagnosis of CMA published after the 2012 ESPGHAN guideline (6). Medline was searched from inception until May 2022 for topics that were not covered in the previous ESPGHAN document (6).

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For this position paper, a detailed search strategy as required for systematic reviews and guidelines was not used.

After finalization of the manuscript, the most important conclusions and recommendations were summarized in "statements" and circulated among all co-authors. When consensus on the formulation of the statements was reached, all authors voted on each of them with a score between 1 and 9; a score of ≥6 was arbitrarily considered as agreement. The higher the score, the stronger the agreement. If 4 or more panel members voted <6, there was <75% consensus, and the statement was rejected.

The paper has been open for public consultation received from both ESPGHAN members (main contributors) and non-members (n: 20) between September 30 and October 12, 2022. Comments were discussed within the group, resulting in adaptations and reformulation and re-voting of some statements (the statements can be found in Appendix 2, Supplemental Digital Content 2, *http://links.lww.com/MPG/D246*, and the rejected statements in Appendix 3, Supplemental Digital Content 3, *http://links.lww.com/MPG/D247*).

Information on the pathophysiology of CMA can be found as Appendix 4 (Supplemental Digital Content 4, *http://links.lww.com/MPG/D248*).

PREVALENCE OF CMA

The true prevalence of CMA remains controversial due to the different methods used for assessment. Determining the exact prevalence of CMA is confounded by the lack of precise criteria for its diagnosis. Epidemiological studies have shown an increase in the incidence and prevalence of allergic diseases over the last decades likely due to complex environmental, lifestyle and dietary changes (7), as well as changes in perception.

The most reliable epidemiologic data are from birth cohorts that are free from selection bias (8). The EuroPrevall study reported on oral food challenge (OFC) proven CMA across Europe on a total of 9336 (77.5%) from an initial cohort of 12,049 children that were followed up to the age of 2 years (9). CMA was suspected in 358 children and confirmed in 55 leading to an overall incidence of 0.54% [95% confidence interval (CI): 0.41–0.70] (9). National incidences varied and ranged from <0.3% (in Lithuania, Germany and Greece) to 1% [in the Netherlands and United Kingdom (UK)] (9). Of all children with CMA, 23.6% had no CM-specific serum IgE (9). Importantly, 69% (22/32) of the CM-allergic children that were re-evaluated 1 year after the diagnosis tolerated CM, ranging from 57% of those with IgE-mediated CMA to 100% of those with non-IgE mediated CMA (9). Munblit et al reported that CMA proven by food challenge affects approximately 1% of infants, while troublesome crying, vomiting or rashes are each reported in 15%–20% of infants (3). According to the EuroPrevall data, non-IgE-mediated CMA has a prevalence of less than 1% in children (10).

According to old data, the prevalence of CMA during infancy was 1.9% in a Finnish study, 2.16% in the Isle of Wight (UK), 2.22% in a study from Denmark, 2.24% in the Netherlands, and up to 4.9% according to data from Norway (8). The British Society for Allergy and Clinical Immunology reported an estimated population prevalence of CMA between 2% and 3% during the first year of life (11). However, more recent data confirm a lower prevalence of CMA in about 1% of formula-fed infants, as shown in the EuroPrevall study (9). Recent data showed a prevalence of 0.5% (3/569) in exclusively breastfed infants who were 3 months of age and randomly assigned to the early introduction of 6 allergenic foods (peanut, cooked egg, CM, sesame, whitefish and wheat; early-introduction group) or of 0.7% (4/597) in infants who were advised to follow the current practice recommended in the UK of exclusive breastfeeding until approximately 6 months of age (12).

The incidence of CMA in exclusively breastfed infants is almost always reported to be low in the range of 0.4%–0.5% (13,14). The probability of an IgE-mediated allergic reaction in an infant breastfed by a woman consuming the relevant food can be estimated as ≤1:1000 for CM, egg, peanut and wheat (15). But figures as high as 2.1% are reported as well, suggesting an over-diagnosis of CMA in breastfed infants (15). It remains unanswered whether these differences reflect a different genetic background, a difference in selection of patients or both. Other interfering factors may be confounding variables such as differences in the composition of the GI microbiome because of the mode of delivery (natural delivery vs. caesarean section), feeding, pollution and the administration of medication such as antibiotics and proton pump inhibitors early in life (16).

CMA also occurs in older children. Patient reports of presumed CMA range between 1% and 17.5%, 1% and 13.5% and 1 and 4% in pre-schoolers, in children 5–16 years of age and adults, respectively (6). CM-specific IgE (sIgE) sensitization point prevalence progressively decreased from about 4% at 2 years to less than 1% at 10 years of age in the German Multi-Centre Allergy Study (6). At the age of 12 years, CMA was diagnosed in 3% of children, although 14.5% in a Swedish population-based cohort study reported CM hypersensitivity (17). A double-blind placebo-controlled food challenge (DBPCFC) confirmed the diagnosis in <1% (18). A narrative review reported an overall pooled estimate of self-reported CMA of 6.0% (95% CI: 5.7–6.4) (19). However, the prevalence of food challenge defined CMA was 10 times lower: 0.6% (0.5–0.8) (19).

In summary: there is evidence for the over-diagnosis of CMA. In all studies, the prevalence according to the outcome of a DBPCFC is below 1%, while the prevalence based on the perception of parents is often reported to be around 10%.

Statement 1	Mean/ median	Votes
Over-diagnosis of CMA is common. The prevalence of authenticated cow's milk allergy (CMA) in infants and children is <1%.	9/9	9 (13x)

CLINICAL GASTRO-INTESTINAL PRESENTATION OF CMA

Because of the impact on long-term health, the diagnosis of CMA should only be suspected on the basis of a complete history and physical examination (20). In the majority of infants, CMA symptoms can be clinically recognized as either IgE-, non-IgE mediated and mixed onset. In IgE-mediated allergy, the onset of symptoms is usually within minutes following ingestion. In non-IgE mediated allergy, the onset of symptoms is delayed and develops usually after ≥2 hours, usually between 6 and 72 hours (21,22). Venter et al (21,22) categorized CMA symptoms as mild, moderate and severe. The severity of IgE-mediated allergy may be difficult to categorize as external factors often determine the severity of reaction, with anaphylaxis being the most severe presentation (22). The spectrum of non-IgE-mediated CMA is broad encompassing symptoms that range in severity from mild rectal bleeding in milk protein induced proctocolitis to severe vomiting and a sepsis-like presentation that can be seen in food protein-induced enterocolitis syndrome (FPIES) (22). Evidence from the UK shows that the majority of infants presenting with suspected CMA have a "mild-to-moderate" presentation of non-IgE-mediated allergy (22). With the exception of anaphylaxis (occurring in 1%–4%), there are no specific symptoms of allergy (Table 1). Clinical manifestations are predominantly cutaneous (70%–75%), and less frequently,

TABLE 1. Signs and symptoms associated with cow's milk allergy*

	IgE†	Non-IgE†
General	Anaphylaxis	Colic, irritability Failure to thrive Iron deficiency anaemia
Gastro-intestinal‡	Regurgitation, vomiting Diarrhoea	Food refusal Dysphagia Regurgitation, vomiting‡ Diarrhoea‡ Constipation Anal fissures Perianal rash Blood loss
Respiratory‡	Rhinitis and/or conjunctivitis Asthma Mild dysphonia	Rhinitis Wheezing Chronic cough
Skin	Eczema (atopic dermatitis) Acute urticaria‡ Angio-oedema Oral allergy syndrome	Eczema (atopic dermatitis)

IgE = immunoglobulin E. * None of the symptoms is specific. † Patients may also present with mixed IgE and non-IgE symptoms. ‡ Unrelated to infection.

gastrointestinal (GI) (13%–34%) and respiratory (1%–8%) (6). Up to 1 infant in 4 presents with a combination of symptoms involving more than 1 organ or system (6).

GI symptoms may be driven by an interplay of factors such as oesophagitis and GI inflammation, dysmotility, visceral hyperalgesia, dysbiosis and others (23).

The existence of a family history of allergy, the involvement of several organ systems (digestive, cutaneous, respiratory) and lack of improvement to usual therapeutic measures increases the likelihood of non-IgE mediated CMA in these cases, although is not diagnostic (16,20,21,24–36). According to epidemiological data, the expected overlap between CMA and gastro-oesophageal reflux disease (GORD) can be observed in less than 1% of breastfed or formula-fed infants (27). The prevalence of CMA in infants with functional gastrointestinal disorders (FGIDs), for example, colic and regurgitation, now referred to as disorders of gut-brain interaction (DGBI) by the Rome IV criteria, is controversial with a natural resolution in the majority of cases around the 5th month of life for colic and 1 year of life for regurgitation (28–30). In some infants, however, food allergens appear to play a role as triggers for FGIDs that occur in association with other GI, respiratory or skin manifestations as well as poor growth (31,32). Regarding GI symptoms, food protein-induced allergic proctocolitis (FPIAP) and FPIES are conditions that need special mention.

Statement 2	Mean/ median	Votes
Within the GI tract, non-IgE CMA can manifest with entities such as FPIAP, FPIES and eosinophilic GI disorders (EGIDs).	8.7/9	7 (2x); 9 (11x)

FPIAP

FPIAP (formerly known as allergic or eosinophilic proctocolitis) often presents with haematochezia associated with persistent mucus-streaked diarrhoea in otherwise healthy young infants (33). Green or mucous stools should not be considered as symptoms of CMA in otherwise presumed healthy infants. Reports on the prevalence of FPIAP range widely and has been reported as low as 0.16% in healthy children and as high as 64% in patients with haematochezia (34–36). FPIAP usually begins within the first weeks of life and resolves in late infancy in most cases. FPIAP is characterized by inflammation of the distal colon in response to 1 or more food proteins through a mechanism that does not involve IgE. Whether treatment of FPIAP is needed or not is debated (33,37–39). The management of mild FPIAP in the absence of other atopic symptoms in exclusively breastfed infants should be limited to observation of the symptoms without dietary intervention during the first month of haematochezia (1) as it is generally a benign and a self-limiting disorder despite marked mucosal abnormality on endoscopy. Maternal dietary restriction is not usually necessary to manage CMA, and for exclusively breastfed infants with chronic symptoms, CMA diagnosis should only be considered in rare circumstances (40). Whether a diagnostic elimination diet should be started in formula-fed infants is debated since a large cohort study reported that CM FPIAP was associated with increased risk of developing IgE-CMA [with adjusted odds ratio (OR) 5.4 (95% CI: 1.4–20.8)] and raised concerns about the potential role of delayed introduction in IgE-CMA development in this vulnerable population (41,42). If a 2–4 weeks diagnostic elimination diet was started, reintroduction of CM is recommended.

The exclusion of CM from the maternal or infant diet to manage common symptoms in infants without demonstrated CMA is not consistently supported by clinical trials. Breastfeeding should be encouraged. In selected cases with long-lasting and severe haematochezia (35,36), CM elimination in the maternal diet can be considered. Although it seems logical to eliminate all animal milk (e.g. goat, sheep, etc.) from the mother's diet, given the high cross-allergenicity (43), this specific aspect has not been studied.

Statement 3	Mean/ median	Votes
FPIAP occurs mostly in breastfed infants, and is in most cases a benign, easily recognized condition that may not need treatment in some breastfed infants, depending on the severity and frequency of blood in the stools.	8.4/9	2; 8, 9 (11x)

FPIES

FPIES is a non-IgE-mediated food allergy with CM being one of the most commonly reported triggers (44). The estimated cumulative incidence rates in the United States, Israel, Australia and Spain range from 0.015% to 0.7% (45). FPIES subtypes and criteria for mild to moderate and severe FPIES have been discussed elsewhere in a Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology (44). FPIES is still underdiagnosed despite being considered a potential medical emergency. Acute FPIES typically presents in infancy with repetitive protracted emesis approximately 1–4 hours after food ingestion. If the vomiting occurs soon after ingestion, determination of sIgE might contribute to separate IgE mediated vomiting from FPIES. Emesis is often accompanied by lethargy and pallor and can be followed by diarrhoea. Watery diarrhoea (occasionally with blood and mucous) develops in some cases within 5–10 hours of ingestion and can be present for up to 24 hours (46–50). The delayed onset and absence of cutaneous and respiratory symptoms suggest a systemic reaction different from anaphylaxis. Severe cases can progress to hypothermia, methaemoglobinemia, metabolic acidosis and arterial hypotension, mimicking sepsis and potentially making the diagnosis of FPIES difficult. The manifestations and severity of FPIES depend on the frequency

and dose of the triggering food, as well as on the age of the patient (46,47,51–53). Symptoms of acute FPIES usually appear within 24 hours after food ingestion. Most children with acute FPIES are well between episodes and show normal growth. Interestingly, FPIES may not develop each time the patient ingests the responsible food, which may be due to its delayed onset and atypical presentation leading to difficult or even misdiagnosis (44).

Chronic FPIES is less well characterized than acute FPIES and is almost exclusively reported in infants younger than 4 months of age fed with CM or soy infant formula (44). Chronic FPIES is uncommon and reported more frequently in Japan and Korea (48,50). It develops after repeated ingestion of the triggering food, and presents as chronic/intermittent emesis, watery diarrhoea and faltering growth, potentially leading to dehydration and shock (44,53,54). Hypoalbuminemia and poor weight gain can hint to the presence of chronic CM-induced FPIES in young infants with persistent GI symptoms (55). With the elimination of the food trigger(s), symptoms resolve, but accidental feeding can induce an acute FPIES reaction within 1 to 4 hours of food ingestion (44). The diagnosis of FPIES is primarily based on a clinical history of typical characteristic signs and improvement of symptoms after withdrawal of the suspected trigger food. The exclusion of other potential causes and use of OFCs to help confirm the diagnosis should be considered if the history is unclear and there is a favourable risk/benefit ratio (44). Therefore, if only a single FPIES episode has occurred, a diagnostic OFC under medical supervision should be considered to confirm the diagnosis. OFC is helpful to establish whether the child is still allergic to the food trigger and may be performed 12–18 months after the most recent reaction, although, there is no consensus on the exact timing (44).

Statement 4	Mean/ median	Votes
Acute FPIES is a potential medical emergency whose accurate diagnosis remains a challenge and is based on symptoms and their timing.	8.8/9	8 (2); 9 (11x)
Statement 5		
The diagnosis of FPIES is based on a clinical history of typical characteristic signs and improvement of symptoms after withdrawal of the suspected trigger food.	8.8/9	8 (2x); 9 (11x)
Statement 6		
In case the history is unclear, but FPIES is suspected, other potential causes not related to CMA should be excluded and, if there is a favourable risk/benefit ratio, an OFC can be considered in order to help confirm the diagnosis.	8.8/9	7; 9 (12x)

EGIDs

EGIDs are characterized by increased eosinophil counts on tissue biopsies associated with clinical findings such as abdominal pain, nausea, vomiting and diarrhoea (56). Data regarding CMA in EGIDs are minimal and likely to reflect the lack of clarity regarding the diagnostic criteria largely resulting from a paucity of normative reference values for eosinophil counts in the GI tract. There are reports about the improvement of EGIDs by elimination of CM (see specific comorbidities and (57–63)). It is outside the remit of this paper to describe EGIDs in any more detail and their diagnosis and management is well reviewed in other articles (64,65).

Statement 7	Mean/ median	Votes
CMA is considered a possible factor in the pathogenesis of EGIDs.	8.9/9	7; 8 (3x); 9 (9x)

Eosinophilic oesophagitis

Eosinophilic oesophagitis (EoE) is the most frequent eosinophilic GI disorder, and is characterized by (i) oesophageal symptoms including feeding intolerance, GORD, dysphagia and food impaction, and (ii) an eosinophil predominant inflammation of ≥15 eosinophils per high power field (HPF; standard size of ~0.3 mm^2) in the oesophageal tissue after exclusion of other disorders associated with similar clinical, histologic or endoscopic features (66). There is a similar increase in incidence and prevalence as in other allergic conditions (67). Multiple studies support the central role of allergy in the aetiopathogenesis of EoE based on 3 pieces of evidence: (i) the association of an allergic history and/or correlation with other allergic manifestations in children with EoE; (ii) the fact that the majority of children with EoE respond to dietary exclusion (68); (iii) the existence of animal models of allergy with sensitization and allergen exposure associated with the development of oesophageal mucosal eosinophilia (69). In a Danish study, the incidence rate of EoE increased from 3.9 per 100,000 person-years in 2011 to 11.7 per 100,000 person-years in 2018 (70). The question was raised if a plateau was reached (71). Across a number of studies, especially in children, culprit foods are identified by assessing the impact of elimination diets and individual reintroduction. CMA is implicated in 43%–90% of cases and in almost all studies CM is the most common food trigger (72–78). Diets specifically eliminating CM have been reported with encouraging histologic remission rates (~60%), but additional prospective studies are needed to better assess the effect of this intervention (79,80). After a diagnostic elimination diet, normalization of histology has to be ascertained. Up to now, guidelines recommend amino acid-based formula (AAF), although it has to be acknowledged that trials with extensively hydrolysed formula (eHF) have not been performed in infants. One trial in 17 adults showed tolerance of an eHF in 15 of 17 (81).

Statement 8	Mean/ median	Votes
CMA is considered a possible factor in the pathogenesis of EoE, and where the index of suspicion is high oesophageal biopsies should be taken whilst on a CM containing diet.	8.3/9	6; 7 (3x); 9 (9x)

CMA and DGBI

The array of symptoms that could be suggestive of a non-IgE-CMA is broad and non-specific and there is likely to be significant over-diagnosis of non-IgE-CMA given the lack of practical gold standards (82). The prevalence of FGIDs in infants is estimated to be around 25% (1). The prevalence of FGIDs is significantly higher than that of CMA. Regurgitation, constipation, dyschezia and colic or distress are normal phenomena in healthy infants. Therefore, algorithms on the management of FGIDs in infants consequently start by recommending "reassurance and anticipatory guidance" as an approach (82).

CM elimination often results in improvement of symptoms, although this may partially be ascribed to inherent non-immune effects of feed constituents on GI physiology (e.g. on gastric emptying), the natural course or a placebo effect and, therefore, needs to be interpreted with caution. The elimination of lactose may be

another interfering factor. It may, therefore, be difficult to separate allergic reactions from FGIDs, because (i) some symptoms and signs of functional disorders and allergy are similar, (ii) there is no sensitive and specific diagnostic tests to distinguish FGIDs from (non IgE-mediated) allergy and (iii) in both conditions, symptoms can improve on an elimination diet.

The exclusion of CM from the diet of infants with common GI symptoms such as infant colic, regurgitation or constipation, without established CMA, based on a period of exclusion followed by the re-introduction of CM at home, has the risk to establish a false diagnosis of CMA in many infants (83). The prevalence of CMA in infants with FGIDs is controversial. In infants presenting with GI symptoms associated with CM intake, the prevalence is estimated to be approximately 20%–25% of all infants (84–86). Whether these symptoms are considered as an FGID or a non-IgE mediated allergy, is related to the background of the consulted health care professional (HCP) (e.g. primary health care, paediatric gastroenterology, allergy). A family history of allergies, the involvement of several organ systems (digestive, cutaneous, respiratory), younger age and the lack of improvement despite optimization of the usual therapeutic measures for FGIDs increase the likelihood of non-IgE mediated CMA, but this is not diagnostic (6,20,21,24–36). GI symptoms may be driven by an interplay of factors such as oesophagitis and GI inflammation, dysmotility, visceral hyperalgesia and dysbiosis (23). In some infants, food allergens play a role as triggers for FGIDs that occur in association with other GI, respiratory or skin manifestations as well as poor growth (31,32).

Statement 9		
Some patients with suspected FGIDs can improve with CM elimination regardless of CMA, but there are no specific tests to allow clarification of the diagnosis by discriminating between CMA and FGIDs.	7.8/9	4 (2x); 7 (2x); 8;9 (9x)
Statement 10		
In patients not responding to conventional therapies for FGIDs, CMA can be considered, and patients trialled on a time limited elimination diet for 2–4 weeks which should be followed by an OFC.	8.4/9	6; 7; 8 (3x); 9 (8x)

GOR(D)

Regurgitation is a common condition in all infants. GORD occurs in infancy, but is much less common than regurgitation. CMA is unlikely to be responsible for regurgitation. To confirm the diagnosis of CMA in infants presenting with GORD, it is recommended to eliminate CM for 2–4 weeks, especially before treatment with acid suppressors for GORD (11,20,87). Breastfeeding should be encouraged while the mother may be advised to exclude CM in her diet for 2–4 weeks and reintroduce CM thereafter. A maternal exclusion diet can potentially lead to early cessation of breastfeeding (88). Therefore, careful consideration of the mother's commitment to breastfeed should be given full attention before advising on an exclusion diet and support provided by a nutritionist is encouraged where possible. In formula-fed infants, an eHF can be beneficial regarding regurgitation and colic probably due to enhanced gastric emptying and due to the fact that most hydrolysates are lactose free (33,89,90), indicating that the improvement may not be related to CMA.

Statement 11	Mean/ median	Votes
In patients not responding to conventional therapies for GOR(D), CMA can be considered, and patients trialled on a time limited elimination diet for 2–4 weeks which should be followed by an OFC.	8.8/9	8 (3x); 9 (10x)

Irritability, Crying and Infant Colic

Crying and irritability occur in approximately 20% of infants and CMA is rarely the culprit. Many of these parents consult a HCP because their infants present with excessive crying and irritability, which are described as infant colic. Infant colic is a common distressing condition characterized by excessive crying in the first few months of life. The aetiopathogenesis of infant colic is unclear but most likely multifactorial. A number of psychological, behavioural and organic factors (food hypersensitivity, allergy; gut dysbiosis and dysmotility) may contribute to infant colic. Probiotics, fennel extract and spinal manipulation show promise to alleviate symptoms of colic, although some concerns regarding their efficacy remain (91). Acupuncture and the use of soy infant formula are currently not recommended (91). The role of diet remains controversial. A Cochrane review of dietary modifications for the treatment of colic found that data are insufficient and at significant risk of bias (92). The few available studies had small sample sizes, and most had serious limitations. In many studies, the dietary changes are not limited to hydrolysed protein but include also elimination of lactose. There are insufficient studies, thus limiting the use of meta-analysis (92). Benefits reported for hydrolysed formulas are inconsistent (92). However, in this Cochrane review, infant colic was still defined as "full-force crying for at least three hours per day, on at least three days per week, for at least three weeks" (92). According to Rome IV, the definition of infant colic, for clinical purposes, must include all of the following: (i) an infant who is <5 months of age when the symptoms start and stop; (ii) recurrent and prolonged periods of infant crying, fussing or irritability reported by caregivers that occur without obvious cause and cannot be prevented or resolved by caregivers; (iii) no evidence of faltering growth, fever or illness (28). However, for research purposes, the definition is stricter: (i) caregiver reports infant has cried or fussed for 3 or more hours per day during 3 or more days in 7 days in a telephone or face-to-face screening interview with a researcher or clinician; (ii) total 24-hour crying plus fussing in the selected group of infants is confirmed to be 3 hours or more when measured by at least one prospectively kept 24-hour behaviour diary (28).

Statement 12	Mean/ median	Votes
In infants who present with crying and irritability, there is insufficient data to recommend a time-limited CM elimination diet for 2–4 weeks followed by an OFC.	8.4/9	6; 7; 8 (3x); 9 (8x)
Statement 13		
There is insufficient data to support infant colic occurring as a single manifestation of CMA.	8.4/9	6; 7; 8 (2x); 9 (8x)
Statement 14		
When treatment for infant colic, fulfilling Rome IV clinical research criteria, is considered, and where CMA is suspected based on additional symptoms, a time limited elimination diet for 2–4 weeks can be trialled which should be followed by an OFC.	7.9/9	4; 7 (3x); 8 (4x); 9 (5x)

Constipation

Constipation is highly prevalent in childhood with the vast majority deemed to have functional constipation, which has a reported worldwide prevalence of 9.5% (93). CMA is only rarely the cause of constipation. A number of studies have reported an association between CM consumption and constipation (94–108). A number of these deal with constipation refractory to standard medical therapy. In a systematic review and meta-analysis of non-pharmacologic treatment for functional constipation, 2 randomized

controlled trials (RCTs), albeit with a high risk of bias, suggested the effectiveness of a CM exclusion diet in children not responsive to conventional treatment (95,102,109).

The pathophysiology of CMA-related constipation is still being debated, with proposed mechanisms including pain-related withholding from proctitis, anal fissures and visceral hypersensitivity, increased resting anal sphincter pressure, and incomplete anal sphincter relaxation related to the presence of allergic inflammation (increased eosinophil and mast cells) of the rectal mucosa (100). These factors (e.g. pain, proctitis, fissures, increased anal sphincter tone, etc.) resolve after a CM elimination diet (100). The joint guideline for functional constipation from the European and North American Societies for Paediatric Gastroenterology, Hepatology, and Nutrition published in 2014 suggests, based on expert opinion, to consider a 2- to 4-week trial of avoidance of CM in the child with intractable constipation (109).

Statement 15	Mean/ median	Votes
In patients not responding to conventional therapies for constipation, including laxatives in optimal dosage, CMA can be considered, and a time limited elimination diet for 2–4 weeks can be started which should be followed by an OFC.	7.9/8	6; 7 (4x); 8 (3x); 9 (5x)

Functional Abdominal Pain Disorders (FAPDs)

Recurrent or chronic abdominal pain is a frequent condition and CMA is only unusually involved. In a case-control study, Saps et al (110) found that 10 of 52 children (19.2%) with a history of CMA within the first year of life went on to fulfil Rome III criteria for a FGID [7 with irritable bowel syndrome (IBS) and 2 with functional dyschezia] compared to none of an age-matched control group without history of CMA. Pre-schoolers with a history of allergic disease (including food allergy) also have an increased risk for IBS in school age (111). This is also supported by a questionnaire-based birth cohort study of 4089 children in Sweden that found that allergy-related diseases (asthma, allergic rhinitis, eczema and food hypersensitivity) were associated with abdominal pain at 12 years. Specifically, food hypersensitivity at 8 years was significantly associated with abdominal pain at 12 years. Of 653 cases of food hypersensitivity at 12 years, 29 also fulfilled Rome III criteria for an FGID with a significant OR of an abdominal pain-related FGID (AP-FGID) in children with food hypersensitivity at 12 years (OR 1.86; 95% CI: 1.33–2.60) (112). More recent data from the same study showed that food hypersensitivity at 12 and 16 years were associated with an increased risk for any AP-FGID (notably IBS) at 16 years (113).

Schäppi et al (114) performed a small open label study of gastric mucosal CM challenge and gastroscopy in 10 atopic and 6 healthy children (ages 2–12 years) with functional dyspepsia. Eosinophils and mast cells within the lamina propria were increased in the children with atopy and were shown to degranulate rapidly after CM challenge. No differences were seen in non-atopic control patients. Mast cells were closely associated with mucosal nerve fibres and released tryptase, which colocalized with proteinase-activated receptors on mucosal nerve fibres. On surface electrogastrography, patterns of abnormal gastric motility were apparent within 2 minutes of CM challenge in atopic children (114).

Overall, there is very limited data to support the role of food allergies in the pathogenesis of FAPDs in children and data are largely limited to case reports and small studies (115).There is no indication for a time limited CM elimination diet in the routine management of FAPDs. More evidence is needed to clarify the role of allergy and immune activation in the pathogenesis of FAPDs in children.

Risk for Infectious Disease

The high rate of respiratory infections in early life has a major impact on health care resources and antibiotic use with the associated risk of increasing antibiotic resistance, changes in intestinal microbiota and, consequently, on the future health of children. Infants with CMA may have an increased susceptibility to infections (116). According to expert opinion in a review paper, secondary outcomes of trials suggest a trend in decreasing frequency and severity of respiratory tract (mainly) and GI infections as well as in reducing antibiotic intake in infants with CMA on an elimination diet supplemented with prebiotics, probiotics and synbiotics (116). In a retrospective study, with non-standardized definition of CMA, GI, skin, respiratory and ear infections were reported to affect significantly more children with CMA than those without, increasing by 74% ($P < 0.001$), 20% ($P < 0.001$), 9% ($P < 0.001$) and 30% ($P < 0.001$), respectively (117). These infections also recurred more often among children with CMA, increasing by 62% for GI infections, 37% for skin and respiratory infections and 44% for ear infections ($P < 0.001$) (117).

Statement 16	Mean/ median	Votes
There is insufficient evidence regarding a higher risk of infectious disease in infants with CMA.	8.3/9	5; 7; 8 (3x); 9 (8x)

RISK FACTORS

Family History and Other Risk Factors

History of allergic disease in first degree family members, diagnosed by an HCP, has long been recognized as a risk factor for allergic disease (118). Having a sibling with allergic disease was reported to almost double the risk for food allergy in the child compared with having no family history of allergy, even in the absence of a parental history of allergy (9.6% vs. 5.6% in children with siblings, $P = 0.025$) (119). There is always a query regarding the correct diagnosis in the index case. However, infants without family history can also develop allergies (119), and overall allergy without a family history outnumber those with allergy. Moreover, reliable reporting of a family history for allergy would require education of parents and a confirmed diagnosis. Noteworthy, both the Australian and the UK guidelines on allergy prevention no longer consider family history a risk factor (119). Confounding variables are among others pollution and the administration of medication such as antibiotics and proton pump inhibitors early in life (120,121). Living in an industrial versus a rural, farming environment has been known for many years to be a risk factor for allergic disease. This may be related to a difference in GI microbiome development (122).

Statement 17	Mean/ median	Votes
Absence of family history does not exclude the possibility of CMA.	8.8/9	8 (2x); 9 (11x)
Statement 18		
Environmental factors [e.g. pollution, antibiotic (over-)use] are possible risk factors for CMA.	7.8/8	4; 6 (2x); 7; 8 (3x); 9(7x)

Awareness and Management Tools

The acronym CoMiSS stands for Cow's Milk-related Symptom Score. CoMiSS should not be considered as a "screening tool", because it is not intended to test or investigate a large number of children for disease, more specifically CMA. An "awareness tool"

is a tool to make aware that something (CMA) might exist, and that the knowledge of this possibility is important. CoMiSS was initially developed to monitor the evolution of symptoms during an elimination diet in infants with CMA (123). Thereafter, it has been proposed as an "awareness tool" to alert HCPs that in infants presenting with combinations of multiple symptoms such as excessive crying, regurgitation, stool pattern changes as well as skin and respiratory symptoms, these might be related to CM, especially if an infant present with a combination of different symptoms. CoMiSS indicates the possibility of CM-related symptoms, but the diagnosis of CMA necessitates a positive OFC. A low score of an awareness tool offers the HCP the ability to highlight normality to the parents that are consulting. The specificity, sensitivity, positive and negative predictive values (PPV and NPV) regarding the outcome of an OFC were reported in 25 original studies, making CoMiSS the most documented awareness tool (124). However, the design and inclusion criteria of the studies were quite different, making it difficult to draw a conclusion. The broad range of sensitivity, specificity, PPV and NPV is explained by the heterogeneity of study designs. Nevertheless, many studies report a sensitivity and specificity of more than 70% (124). CoMiSS was reported to be a simple and operable method to screen for CMA (125,126).The impact of genetic or regional difference on CMA symptoms needs to be further studied (125). According to a recent meta-analysis, CoMiSS may be a promising symptom score in CMA awareness and a useful tool in monitoring the response to a CM-free diet (126), although it cannot be regarded as a stand-alone CMA diagnostic test (127). However, there is a lack of agreement on which cut-off to use (128). CoMiSS reduction following CM elimination was predictive for a reaction in the OFC to diagnose CMA as well as for monitoring symptom improvement (127).

A multi-disciplinary task force of the European Academy of Allergy and Clinical Immunology developed a paediatric diet history tool with the goal to develop a structured approach to connect symptoms, suspected foods and dietary intake (129). Another awareness tool based on 25 questions has been tested in 43 infants aged up to 2 years (130). The authors described a sensitivity of 88% and a specificity of 71% for a cut-off of 6, improving to 79% and 93% if some items were excluded (130). A questionnaire based on 16 questions tested in children up to 5 years of age reached a sensitivity of 94.4% and a specificity of 96.9% for a cut-off of 7 (131). The latter 2 scores were, however, not further evaluated.

The international Milk Allergy in Primary Care (iMAP) guideline is a management algorithm. iMAP and CoMiSS screening tool clearly require a challenge test for confirmation of diagnosis (84,132). A major limitation is that the iMAP and CoMiSS tools are non-specific, as shown in the secondary analysis of the EAT cohort (10). The post hoc analysis of the EAT cohort found that 74% of participants reported ≥2 mild-moderate symptoms and 9% ≥2 severe symptoms in at least 1 month after enrolment at 3 months of age through 1 year of age (133). Guidelines do not discriminate sufficiently between normality and disease (133).

Statement 19	Mean/ median	Votes
The baseline CoMiSS and its reduction during an elimination diet may be indicative for CMA, but is not diagnostic.	8.4/9	6; 7; 8 (2x); 9 (9x)

DIAGNOSIS OF CMA

The diagnosis of CMA is a challenge because of the absence of specific symptoms and diagnostic tests with sufficient specificity and sensitivity, especially in non-IgE mediated allergy. Whilst under-diagnosing CMA does occur in a minority and has potential consequences, there is a major issue with CMA over-diagnosis in multiple countries (134). Concern has been expressed that previous position papers and guidelines are contributing to the latter (10,135). The impact of infant feeding guidelines on CMA prescribing in UK primary care was evaluated in a prospective study (135) and showed that the total quantity of hypoallergenic formulas increased by 63.2% but also that alternative prescriptions decreased by 44.6% ($P < 0.001$) (135). The total amount of all prescribed products decreased by 41.0% ($P < 0.001$) (135). Guideline-defined symptoms of non-IgE-mediated CMA are very common in infants. Guidelines may promote CMA over-diagnosis by labelling normal infant symptoms as possibly being due to milk allergy (10), although they have, at the same time, reduced the prescription of inappropriate medication, mainly proton pump inhibitors (135). However, the prevalence of non-IgE mediated allergy might be underdiagnosed given that 5 countries in the EuroPrevall study reported no cases of non-IgE mediated allergy (9,136).

Diagnostic CM Elimination Diet

Symptoms and signs of CMA involve skin (urticaria, angioedema, atopic eczema/dermatitis), the GI tract (i.e. vomiting, colic, abdominal pain, diarrhoea, constipation), and respiratory tract (rhinorrhoea, sneezing, cough, dyspnoea) and CMA can lead to systemic reactions (cardiovascular collapse) (137). Reactions are mostly triggered by milk ingestion but can also be triggered by inhalation of and skin contact with milk (137). A proper diagnosis of CMA should always start with an "allergy-focused clinical history" and a complete physical examination (21). Attention should be given to the presenting symptoms and signs that may indicate possible CMA. Information regarding the infant's feeding history and the personal and familial history of allergic disease should be obtained.

In non-IgE mediated CMA, the diagnostic elimination diet typically requires 2–4 weeks before reintroduction, while for IgE-mediated allergy the time window may be shorter (1–2 weeks) (1). Improvement will be faster in IgE-mediated than in non-IgE mediated allergy. According to 1 study (138), it may take 6 up to 8 weeks before improvement occurs in infants with severe atopic dermatitis, although this may as well be the natural evolution. There is only evidence for the use of CM-based eHFs for diagnostic elimination diet; hydrolysed rice formulas (HRFs) and soy formula are possibly as well efficacious, but they cannot be recommended because of lack of evidence.

Over-diagnosis regards children considered to have CMA, and treated as such, but who present the symptoms because of a different condition, and are thus being exposed to the harms of an unnecessary elimination diet (1). Non-IgE-mediated CMA presents with a multitude of symptoms, which are very common in infants and shared with other health conditions (1). Therefore, HCPs are to be encouraged to properly follow dedicated guidance and apply a short-term diagnostic elimination diet followed by reintroduction/OFC, before embarking on a long-term therapeutic elimination diet (1).

Although CMA in exclusively breastfed infants is a rare condition, many breastfeeding mothers are put on unwarranted elimination diets contributing to maternal nutritional deficits and premature and unnecessary discontinuation of breastfeeding, which might also have negative effects (3,138). In formula-fed infants, the economic aspect is of utmost importance, because all therapeutic formulas suitable for CMA are much more expensive than standard infant formulas (1). From the nutritional point of view, it is safe to assume that if the volume of formula intake is adequate based on the infant's age and weight, there is no safety concern as the formulas contain all required nutrients (1), except for the overconsumption of free sugars which are potential risk factors for obesity and non-communicable diseases. Excessive intake of sugars is

associated with less healthy dietary intake. An important consideration in the unwarranted use of therapeutic formulas is that they have a different taste, due to the hydrolysis of protein and amino acids, which has been shown to have a potential long-term impact on taste preferences (139,140).

An OFC can be performed in an open or blinded manner, the latter being single- or double-blinded. In the majority of cases in the first year of life, when there is a low risk of bias due to for, example, psychological factors, an OFC with an objective unequivocal reaction is sufficient for the diagnosis of CMA (6,141,142). However, a number of patients with a positive CM OFC may have a negative result in the DBPCFC as the OFC tends to overestimate CMA (142–144). A blinded challenge of half a day may underestimate the number of allergic children as this procedure will miss non-IgE mediated delayed reactions.

Statement 20	Mean/ Median	Votes
The response to a diagnostic elimination diet followed by an OFC is the corner stone for the diagnosis of CMA.	8.9/9	8; 9 (12x)

Diagnostic Elimination Diet in Breastfed Infants

Exclusively breastfed infants with non-IgE mediated CMA may react to protein from the maternal diet (145,146). It is well-established that food proteins, such as egg, soya, CM and wheat, are detectable in breast milk for many hours or days after ingestion (147).

CMA in exclusively breastfed infants is a rare condition. Munblit et al (3) estimated that for more than 99% of infants with proven CMA, the breast milk of a CM-consuming woman contains insufficient milk allergen to trigger an allergic reaction. Dietary restrictions in a breastfeeding mother are usually not necessary (40). Therefore, in exclusively breastfed infants with chronic symptoms, CMA should only be considered in specific, rare circumstances (40).

The exclusion of CM from the maternal or infant diet to manage common symptoms in infants without demonstrated CMA is not consistently supported by clinical trials (3). Up to 20% of breastfed infants have spontaneous resolution of symptoms such as rectal bleeding without any changes in the maternal diet (146).

Breastfeeding with maternal elimination diet for CM may be considered for 2–4 weeks (148). Recommendations to manage symptoms as CMA are not evidence based, especially in breastfed infants who are not directly consuming CM and may cause harm by undermining confidence in breastfeeding (3). Professional dietary counselling is recommended to ensure good quality of the mother's diet, and follow-up is important to ensure that the exclusion of CM does not continue if not effective (149). In case of a prolonged maternal elimination diet, supplementation of mothers with calcium and vitamin D is recommended, while supplementation with iodine and vitamin B12 can be considered (150–152). When symptoms improve the mother should reintroduce CM in her diet.

Exceptionally, in very severe cases, a temporal introduction of AAF may be warranted. However because of the limited evidence other options, such as eHF, could be considered based on the specific needs and circumstances of each patient. The decision regarding which option to choose should be individualized and based on the specific needs and circumstances of each patient. Mothers should be encouraged to express breast milk during this period to avoid unnecessary cessation of breastfeeding. After symptom improvement, an OFC with mother's milk must be performed for definitive diagnosis.

Statement 21	Mean/ median	Votes
In rare cases when CMA is suspected in an exclusively breastfed infant, a diagnostic maternal CM-free diet for 2–4 weeks whilst continuing to breastfeed may be considered. In order to confirm the diagnosis, CM should then be reintroduced in the maternal diet with monitoring of symptoms.	8.8/9	8 (3x); 9 (10x)

Diagnostic Elimination Diet in Non-Breastfed Infants

For the non-breastfed infant, eHF are the first choice for CMA management, whereas AAFs are reserved for more severe cases and/or those with an impaired nutritional status (6,153) (Table 2). It is preferable to use CM-based eHFs that have been tested in RCTs. There are insufficient comparative trials to make a recommendation whether to use whey versus casein hydrolysates (154). In the presence of severe diarrhoea lasting longer than a week, lactase deficiency may be suspected and a temporary lactose-free eHF may be preferred. The presence of lactose in the diagnostic elimination diet was a topic of debate; while 4 of our group considered that there was evidence to prefer lactose as carbohydrate source in the eHF during a diagnostic elimination diet, 9 considered there was no evidence favouring lactose. As this is a diagnostic elimination diet, the duration should be 2–4 weeks. We refer to an international consensus that discussed the severity and

TABLE 2. Properties of different hydrolyzed formulae, amino acid formula and soy infant formula (146)

	Protein	Carbohydrate	Lipids	Additional information
Partially hydrolyzed formula	Oligopeptides from hydrolyzed cow's milk proteins [whey and/or casein with MW < 5000 Dalton (Da) (range 3000–10,000 Da)]	Glucose polymers		
Extensively cow's milk hydrolyzed formula	Peptides from hydrolyzed cow's milk proteins [whey and/or casein with MW < 3000 Da (mostly <1500 Da) and free amino acids]	Glucose polymers Some contain lactose	5%–50% MCT	
Amino acid-based formula	Mixture of free synthetic essential and non-essential amino acids.	Glucose polymers Lactose free	10%–50% MCT	
Soy-based formula	Isolated soy protein, native or enzymatically hydrolyzed, supplemented with amino acids (methionine, taurine, and carnitine)	Glucose polymers Lactose free		Phytate and isoflavones
Rice-based formula	Hydrolyzed rice proteins supplemented with essential AA (threonine, lysine, tryptophan, taurine) and carnitine	Glucose polymers Lactose free		Check arsenic content

MCT = medium chain triglycerides.

management of diarrhoea (155). We could not find studies related to the usage of medium chain triglycerides (MCT) in the event of CMA-related diarrhoea.

The American Academy of Pediatrics (AAP) defines partially hydrolysed formulas (pHFs) as those containing oligopeptides with a molecular weight of <5000 Da and eHF as those containing peptides with a molecular weight <3000 Da (156). The AAP and European Academy of Allergy and Clinical Immunology (EAACI) require for a formula to be called "hypoallergenic" that at least 90% of infants with documented CMA with a 95% confidence interval do not manifest any clinical symptoms under double-blind, placebo-controlled conditions. Thus, according to these groups of experts, the term "hypoallergenic" is applied only to products for treatment.

The decision which formula to use is based on symptoms and on the nutritional composition, and the residual allergenicity of the hypoallergenic formula (21). CM hydrolysates are obtained by chemical and/or enzymatic cleavage of peptide bonds and are composed of free amino acids, peptides and residual intact protein in different proportions (157). These products differ by the protein source (whey and/or casein) and the size of the peptides. Efficacy and safety should be established for each hydrolysed formula as the protein source, hydrolysis method and degree of hydrolysis, which often depends on the manufacturer, may be different. Each company has its own technique to disrupt the vast majority of allergenic epitopes by enzymatic hydrolysis and heat treatment (158). Significant residual beta-lactoglobulin or casein-derived immunogenic peptides or proteins found in some eHF products suggests incomplete hydrolysis and/or contamination during manufacturing (158). However, it has been poorly studied if these differences in hydrolyzation process and peptide size also result in a different clinical outcome. A comparative trial did not show a difference in efficacy between a whey (with probiotics – this product was never commercialized) and a casein eHF with probiotics (122). The eHFs evaluated to date appear to be well-tolerated by most children with CMA (159). However, published studies do not allow for any conclusion regarding one formula to be superior to another formula for CMA management (159).

For most children with CMA, an eHF will be sufficient for symptom resolution, although some papers report that up to half of the children with proven CMA have incomplete resolution of symptoms upon treatment with a particular eHF (160). Data from the UK report a 29% failure rate of some eHFs (161). Conversely, the efficacy of some other eHFs was reported to be equal to that of AAF (162). Therefore, only eHFs that have been studied in the setting of a diagnostic elimination diet can be recommended.

Resolution of GI symptoms in non-IgE mediated forms of CMA is variable: a few hours in FPIES and several weeks in food protein-induced enteropathy (146). There is no consensus on minimal and maximal duration of a diagnostic elimination diet, but we recommend to consider a 2–4 weeks elimination diet for most infants. If symptoms persist, the diet needs to be carefully re-evaluated as potential food allergens may have been missed or another diagnosis is considered (137).

Because of severity of symptoms at the one hand, and because of failure of the CM-based eHF at the other hand, there is a subset of children where an AAF may be indicated: (i) anaphylaxis; (ii) faltering growth; (iii) multiple and severe complex GI food allergies; (iv) acute and chronic severe FPIES; (v) eosinophilic esophagitis not responding to an extended exclusion diet; (vi) to avoid any risk of sensitization; (vii) symptom persistence on eHF (even partially) (137,163,164).

Although some guidelines recommend a step-down approach using AAF as diagnostic elimination diet, this approach is mainly for economic reasons not broadly applied. Modelling the resource implications and budget impact of managing CMA in Australia was reported to potentially release limited hospital resources for alternative use within the paediatric health care system (165). In Brazil, the use of AAF as elimination diagnostic diet followed by an OFC is a dominant pharmaco-economic approach that has a lower cost and results in an increased number of symptom-free days (166). In the "step-down" concept an AAF is used as a diagnostic elimination diet, and when the OFC is positive, an eHF is used for the therapeutic elimination diet (166). A Turkish guideline also recommends the step-down approach (167). Finally, there are Chinese consensus papers of gastroenterologists and dermatologists recommending AAF as diagnostic elimination diet (168,169).

HRFs have become more available and are an alternative option for the treatment of CMA as they do not contain any CM (87,170–173), although there are only limited data on their use for diagnostic elimination diet in suspected CMA. Regarding arsenic, it is important to take the arsenic content of water into account when mixing formulas, which may affect arsenic levels (174). Although native rice has a high arsenic content, that of HRF is reported to be 10-times below the WHO limit, and is thus within the recommended limits (174). Therefore, HRFs were evaluated as safe by the ESPGHAN Nutrition Committee (175). However, the arsenic content is not mentioned for all commercialized HRFs (175). Therefore, only HRFs of which the arsenic content is known (and low) should be used. To date, no data exist on the efficacy of HRFs in infants not tolerating eHF as an alternative to AAF (155). The European Food Safety Authority (EFSA) approved HRFs as a "food for special medical purposes" (FSMPs), indicated for the management of infants with CMA. As a consequence, HRFs were considered to be used in a limited number of infants for limited time. HRFs have not been evaluated for safety and nutrition in the same way as CM-based eHFs. Because of the growing popularity of plants-based diets for infants, and because of their increasing availability, HRFs will be used more frequently, possibly also in healthy infants. Obviously, arsenic content should be determined in every produced batch of HRF. More data on nutrition and safety on HRFs will be welcomed. Also, manufacturers of infant formulas could allay concerns by making data on milk consumption and adverse events (if any) available.

Soy protein-based infant formulas contain enzymatically hydrolysed soy protein isolate. The reason to use soy isolate is for technical and protein quality reasons. Soy formula also contains phytate, aluminium, and phytoestrogenic isoflavone at levels not present in milk-based formulas, although in the last few decades there has been a significant reduction in these components. Aluminium and estrogens are present in breast milk, and the latter are increased in mothers who consume large amounts of soy (176). Global evaluation of the impact of modern soy formulas on human development suggests that their use is not harmful (177,178).

A commentary by the ESPGHAN Committee on Nutrition (179) and a clinical report by the AAP (180) based on the study by Klemola et al (181) and Zieger et al (182) recommended against the use of soy infant formula especially below the age of 6 months because of the risk of co-allergy. The age limit was proposed based on data from a small subgroup of 20 infants (181). Klemola et al (183) reported later that all children with co-allergy between CM and soy had non-IgE mediated allergy. Zieger et al (182) concluded that 14% of infants with IgE-CMA were also allergic to soy. However, this study included 99 children from 5 centres, of which not all had a positive skin prick test (SPT) or detectable or very low soy sIgE (182). So, co-allergy between CM and soy is rare in IgE-mediated CMA, and soy infant formula can also be considered as an alternative treatment option (182,183). However, in non-IgE mediated CMA co-allergy might be more frequent, although there are discrepancies in study outcomes. In an Italian study in 21 infants with atopic dermatitis due to CM hypersensitivity, 20 of 21 cleared

symptoms with soy formula (one refused to drink soy) (184). A possible secondary sensitization to soy was found in one infant in whom dietary therapy alone was not effective (184). In another Italian study in 66 children with FPIES, none had coexisting CM and soy allergies (185). In a Korean study, patients with positive soy-sIgE accounted for 18.3% of 224 children sensitized to CM (186). The prevalence of sensitization to soy decreased with age (36.8% in the first year, 16.4% in the second year and 13.7% in the third year of life) (172). Of 21 CMA patients, 42.9% (n = 9) had soy allergy (mean age 10.3 months) (186). However, US studies report that about 30%–50% of infants with FPIES react to both CM and soy, whereas most non-US studies report a far smaller percentage (187). Soy infant formula is less commonly used in non-IgE mediated allergy. Of note, in many European countries, the availability of soy formula has decreased in recent years. Therefore, soy infant formula may be considered in CMA if other elimination diets are not possible due to economic or cultural reasons, especially in IgE-mediated allergy because of the low co-allergy with CM. The palatability of soy formula is perceived to be better than that of the eHFs.

Statement 22	Mean/ median	Votes
In formula-fed infants, a CM-derived eHF is the first choice for a diagnostic elimination diet.	7.2/9	0 (2x); 7; 8 (3x); 9 (7x)
Statement 23		
Only CM-derived eHFs tested in randomized clinical trials should be used.	8.6/9	7 (2x); 8; 9 (10x)
Statement 24		
There are insufficient comparative trials to make a recommendation whether to use whey versus casein hydrolysates.	8.8/9	8 (3x); 9 (10x)
Statement 25		
In patients with CMA and severe diarrhoea and/ or with severe malnutrition, the transient use of a formula without lactose for 2–4 weeks may be preferred.	7.0/8	0; 5 (2x); 7 (3x); 8 (3x); 9 (4x)
Statement 26		
In formula-fed infants, AAF for a diagnostic elimination diet should be reserved for severe cases or patients with severe malnutrition.	8.5/9	7; 8 (4x); 9 (8x)
Statement 27		
Although some consensus papers recommend a step-down approach using AAF as diagnostic elimination diet in every infant suspected of CMA, there is insufficient evidence for this recommendation.	8.6/9	6; 8 (2x); 9 (10x)
Statement 28		
Although less studied than CM-based eHFs, HRFs can be considered as an alternative for a diagnostic elimination diet.	7.4/8	1; 5; 6; 7 (2x); 8 (2x); 9 (6x)
Statement 29		
Soy infant formula should not be used as the first choice for the diagnostic elimination diet but can be considered in some cases for economic, cultural and palatability reasons.	7.6/9	0; 6; 7 (2x); 8 (2x); 9 (7x)

Oral Food Challenge

An OFC is mandatory in the work-up of infants with CMA, except for those presenting with life-threatening symptoms such as anaphylaxis and with high levels of sIgE.

However, OFC are often refused by parents and HCPs. An audit of patients prescribed hydrolysed formula in 43 South East London General Practices found that only 21% had undergone a home challenge to confirm the diagnosis of a non-IgE mediated CMA (10). In a RCT comparing two hydrolysates, only 85 of 116 (73%) of the parents accepted to perform the OFC to which they had agreed in during informed consent (122). The OFC is refused because the suggestion to re-challenge completely ignores the huge placebo effect of a doctor confidently stating that this special formula milk will solve their infant's problems. When 11 infants with symptoms clinically suggestive of GOR were prescribed an AAF, 10 of 11 infant's parents reported a significant decrease in the reflux score despite no change in multiple different objective measures of reflux status (188).

The milk OFC should start with a very small dose (e.g. 1 mL) and increase stepwise to a significant volume of at least 100 mL (1,118). If severe immediate reactions are expected, the OFC should start with a drop on the lips followed by a stepwise increasing dosing of small volumes at 30-minute intervals to end up with 100 mL. Patients should be observed for at least 2 hours following the maximum dose. If no reaction occurs during the OFC, CM should be continued at home every day with at least 200 mL/day for at least 2 weeks (6). The parents should be prepared to document any late reactions. In IgE-mediated allergy, an OFC should always be performed under direct supervision of an HCP. An OFC should preferably be carried out in a hospital setting when: (i) there is a history of immediate allergic reactions; (ii) the reaction is unpredictable; (iii) in case of severe atopic eczema with the difficulty in accurately assessing a reaction (6). Intravenous access is only necessary in selected cases, but always if a severe or systemic reaction is likely. In non-IgE CMA, the challenge can be done at home, but the interpretation of the OFC remains under the responsibility of a HCP.

The DBPCFC is the gold standard for the diagnosis of food allergy (6,142). The food should be blinded for taste, smell, texture and appearance (consistency, colour and shape). The placebo and the active food should be sensorially indistinguishable from each other. The sequence of sessions administering either the test food or the placebo is random. However, due to its time-consuming and resource-intensive implementation, the use of the DBPCFC is restricted to clinical practice. A DBPCFC is preferred when evaluating subjective symptoms with possible psychological interference (e.g. abdominal pain), late reactions or chronic symptoms (e.g. moderate to severe atopic dermatitis, isolated GI reactions or chronic urticaria), when an open or single-blind challenge result is ambiguous, or in research settings (6). The DBPCFC also has its limitations, as the food is not taken by the patient in its natural form, with issues regarding quantities and especially duration. It is also difficult to continue a daily intake of at least 200 mL during 1 week in a double-blind way in order to detect late reactions to CM (189). A negative DBPCFC should be followed by a negative open OFC with a regular age-appropriate serving (6,141) to conclude that there is tolerance (Table 3). While a DBPCFC may underestimate the prevalence of non-IgE-mediated CMA and miss delayed reactions, a placebo response to an elimination diet and/or open food challenge may result in an overestimation of the diagnosis of CMA. A longer observation period of at least 48–72 hours is recommended for non-IgE-mediated CMA.

Statement 30	Mean/ median	Votes
In IgE-mediated allergy, the response to the diagnostic elimination diet is to be expected within 1– 2 weeks.	8.8/9	8 (2x); 9 (11x)

Statement 31		
In non-IgE mediated allergy, the response to the diagnostic elimination diet is to be expected within 2–4 weeks.	8.7/9	7; 8; 9 (11x)
Statement 32		
A DBPCFC is the gold standard for confirming a diagnosis of CMA.	8.9/9	8; 9 (12x)
Statement 33		
In clinical practice, the open OFC is clinically more feasible and practical than DBPCFC and is sufficient to confirm the diagnosis of CMA and the development of oral tolerance.	8.7/9	7; 8 (2x); 9 (10x)
Statement 34		
In IgE-mediated CMA, the OFC test should be supervised by trained medical health care professionals	8.8/9	7; 8; 9 (11x)
Statement 35		
The DBPCFC is recommended for unclear cases and research purposes.	8.8/9	8 (2x); 9 (11x)
Statement 36		
The result of a negative DBPCFC should be followed by an OFC of a regular age-appropriate serving to exclude delayed reactions.	8.4/9	6; 7; 8 (3x); 9 (8x)
Statement 37		
If an elimination diet was not effective in reducing symptoms and/or the OFC unable to reproduce symptoms, the diagnosis of CMA cannot be made.	8.8/9	7; 9 (12x)

Determination of sIgE and Skin Prick Test

Total IgE levels do not contribute to the diagnosis of CMA, but may be useful in infants with severe eczema as a very high total IgE level suggests that positive sIgE results should be interpreted with care as they may represent asymptomatic sensitization (137).

In a systematic review and meta-analysis by the EAACI (190), atopy patch test (APT), SPT and sIgE were compared with DBPCFCs. When the analysis was restricted to CMA, pooled sensitivities were lower [53% (95% CI: 33–72)] for APT, and higher [88% (95% CI: 76–94)] for SPT and sIgE [87% (95% CI: 75–94)]. The specificities decreased from 88% (95% CI: 76–95) for APT, to 68% (95% CI: 56–77) and 48% (95% CI: 36–59) for SPT and sIgE, respectively. Therefore, if the history and clinical presentation are suggestive of IgE-mediated CMA, sIgE to CM or a SPT with CM are useful in the diagnostic workup, although these tests have a low specificity leading to over-diagnosis (191). The 95% PPV for the SPT was >6 mm in children <2 years and ≥8 mm in older children (192). The 95% PPV for sIgE in children <2 years old was 5 kU/L and >15 in older children (191); the 50% NPV was 2 kU/L in all children (191).

The concordance between SPT and sIgE in CMA is variable, but never high (192–194). The choice of test is guided by local availability and relative and absolute contraindications for the SPT (137,195), which include severe eczema/dermatographism, recent anaphylaxis, significant co-morbidities such as cardiovascular disease or arrhythmias, use of antihistamines or other medications that cannot be discontinued and may interfere with its proper interpretation (196,197). Although the risk of systemic reactions is low, the SPT should always be performed under medical supervision, with access to emergency equipment for the treatment of anaphylaxis. It may be performed in patients of any age, but the reactivity may be lower in infants (137,198).

A positive SPT or elevated sIgE demonstrates sensitization to CM, but does not prove CMA. The NPV of both is >90% for IgE-mediated CMA (193). With an increasing size of the wheal on SPT and an increasing level of CM-specific serum IgE, the PPV of the test increases although this is dependent on the population studied, the severity of the allergic reaction and age (195). Young infants may initially have a negative SPT and absence of CM-specific serum IgE. To verify a diagnosis of CMA, the test results must be interpreted according to the history and clinical presentation and in most cases, the diagnosis should be confirmed by CM elimination and a supervised OFC (137,187,195). A 3 mm cut-off for the SPT results in a high sensitivity and NPV, but yields a low specificity and PPV, and thus may lead to over-diagnosis (191).

TABLE 3. Algorithm for oral food challenge [adapted from ref (180)]

0	Drop on lips
+ 15 min	0.5 mL
+ 30 min	1 mL
+ 30 min	3 mL
+ 30 min	10 mL
+ 30 min	30 mL
+ 30 min	50 mL
+ 30 min	100 mL
2 hours observation	
Each day for 2 weeks	200 mL/day

Statement 38	Mean/ median	Votes
Elevation of total IgE does not generally contribute to the diagnosis of CMA.	8.8/9	8 (2x); 9 (11x)
Statement 39		
Elevated sIgE and SPT show sensitization to CM, but do not confirm CMA, whose diagnosis is based on the presence of symptoms.	8.8/9	8 (2x); 9 (11x)
Statement 40		
The NPVs of sIgE and SPT are high when evaluating IgE mediated allergy.	8.5/9	7; 8 (4x); 9 (8x)

APT

At present, there are insufficient studies demonstrating advantages of the APT over SPT or sIgE (137,189,195,199) in part due to the lack of standardized test substances. Therefore, APTs are not recommended for routine diagnosis of food allergy (137).

Statement 41	Mean/ median	Votes
The APT is not recommended for the routine diagnosis of non-IgE mediated CMA mainly due to insufficient evidence for reproducibility and efficacy.	8.6/9	6; 8 (2x); 9 (10x)

Component Resolved Diagnostics and Basophil Activation Test (BAT)

Component resolved diagnostics is an emerging diagnostic tool that detects sIgE to allergenic molecules or the epitope of the allergen (195,200). In a systematic review of selected components,

including components of CM, the reported sensitivity-specificity were: Bos d 4 (α-lactalbumin), 62.0% and 87.5% (with a cut-off value defining a positive test of >0.01 kUa/L) and 50.0% and 93.0% [at >0.1 fluorescent intensity (FI)]; Bos d 5 (β-lactoglobulin), 82.0% and 62.5% (at >0.35 kUa/L) and 23.8 and 95.3% (at >0.1 FI); Bos d 8 (caseins), 88.0% and 56.3% (at >0.35 kUa/L). Among the α-, β- and κ-caseins, κ-casein had the highest accuracy with a sensitivity and specificity of 38.1% and 88.4% (at >0.1 FI), respectively (201). Since there are only few conducted studies to date, it remains challenging to draw firm conclusions, and further research to establish clinically relevant cut-off values, risk assessment and cost-effectiveness of component resolved diagnostics is needed (201).

The BAT uses flow cytometry to measure the expression of activation markers that are present on basophils following stimulation with an allergen and has been assessed in the diagnosis of CMA (202,203). The PPV for the threshold of CD203c expression was 85.7% for milk and 75.0% for casein (202). The BAT demonstrated higher specificity and NPV than the SPT and sIgE, while retaining sensitivity and PPV (137). Current limitations are the lack of large clinical trials evaluating its diagnostic performance and the availability of a specialized laboratory setting for the performance of the BAT (137).

Statement 42	Mean/ median	Votes
Currently, component resolved diagnostics and the BAT are not recommended for the routine diagnosis of CMA due to insufficient evidence for reproducibility and efficacy.	8.8/9	8 (2x); 9 (11x)

Endoscopic Evaluation

In CMA, endoscopy may reveal esophagitis, gastritis and lymphoid nodular hyperplasia in the duodenum. Quantification and distribution of eosinophils along the oesophagus is one of the features that help to differentiate GORD from eosinophilic oesophagitis. Villous atrophy, an increased number of intraepithelial lymphocytes and eosinophils in the lamina propria, eosinophilic cryptitis on antral and/or duodenal biopsies may be found in children with CMA (27,204–206), but are not diagnostic as these findings can be found in other upper GI pathologies. Lower GI endoscopy findings are as well non-specific, including focal mucosal erythema, loss of vascular patterns, erosions, ecchymosis and lymphoid nodular hyperplasia (34,205–207). Lymphoid nodular hyperplasia is a common finding in infants with CMA and may be found in the colon and/or terminal ileum (208).

Lozinsky et al (63,148) showed that 89.3% (236/264) of infants had eosinophils (between 5 and 25 per high-power field) in their colonic biopsies. Mennini et al (34) emphasize the importance of eosinophil quantification in different colonic segments. In neonatal transient eosinophilic colitis, endoscopy and histology findings are the same as in CMA, but bleeding observed in this condition is self-limiting and ceases without CM elimination diet (209,210).

To date, there are no specific recommendations on the timing and necessity of colonoscopy in children suspected to have CMA (34). In a cohort of 730 children aged 1–18 years undergoing colonoscopy because of rectal bleeding, allergic colitis was found in 3.3% of cases (211).

Statement 43	Mean/ median	Votes
There is insufficient evidence to recommend routine upper or lower GI endoscopy for diagnosing CMA because of lack of specificity of histological findings.	9/9	9 (13x)

Biological Markers

A number of alternative diagnostic approaches are popular among complementary and alternative medicine practitioners, for example, bioresonance, kinesiology, iridology, hair analysis, cytotoxic test and IgG and IgG4 levels (137). These tests are currently not validated and cannot be recommended for the diagnosis of food allergy (137). Food-specific IgG4 indicates that the atopic individual has been repeatedly exposed to high doses of food components, which are recognized as foreign proteins by the immune system (137).

Faecal biomarkers such as calprotectin, alpha-1-antitrypsin, beta defensin, tests such as the allergen-specific lymphocyte stimulation test and determination of thymus and activation-regulated chemokines are not useful in the diagnosis of CMA (191,212). In a recent paper including 30 infants aged 0–9 months with CMA, levels of faecal calprotectin were higher in CM allergic than in healthy infants at diagnosis but differences did not reach statistical significance ($P = 0.119$) (212). After 1 month of elimination diet, faecal calprotectin levels decreased in the CMA group, but no statistically significant differences with basal levels were found ($P = 0.184$) (212). Prospective studies with larger populations are needed to establish the value of faecal calprotectin as a biomarker of CMA.

Statement 44	Mean/ median	votes
IgG-antibodies against CM and biomarkers such as calprotectin, alpha-1-antitrypsin, beta defensin and tests such as the allergen-specific lymphocyte stimulation test, and determination of thymus and activation-regulated chemokines are not indicated in the routine diagnosis of CMA.	8.8/9	8 (1x); 9 (12x)

NUTRITIONAL ASPECTS OF ELIMINATION DIETS WITH CMA

Professional dietary counselling should be offered to mothers on a CM elimination diet. Mothers should receive supplements of calcium (1 g/day) and vitamin D (600 IU/day) (213). There are no clinical indicators that suggest the need to exclude other proteins from the diet of the breastfeeding mother, with the exception of other animal milk such as goat and sheep milk.

In formula-fed infants, long lasting elimination diets, especially over the age of 1 year, can be associated with nutritional deficiencies, eating disorders and changes in taste preferences (140,214). Elimination diets have also a negative impact on taste development and preferences (215,216). In infants, it is possible to propose an alternative formula, while in older children suggesting suitable substitutes is challenging. Extensively hydrolysed or CM-free infant formulas improve the quality of the CM protein free diet, particularly regarding intake of vitamin D, vitamin E, energy, protein, calcium, iron and zinc (217,218). Between the age of 6 and 12 months, when the intake of eHF decreases below 500 mL/day, calcium supplementation is required. In children with CMA who do not reach tolerance, supplementation with calcium is recommended after the first year for the entire duration of the exclusion diet.

Avoidance of a key food group such as milk compromises the intake of several nutrients including energy, protein, B vitamins, vitamin D and A, minerals (especially calcium) and trace elements (e.g. iron, zinc and iodine) (219,220). Since the absorption of calcium decreases from 30%–40% to 10%–15% when there is also vitamin D deficiency, both calcium and vitamin D should be supplemented (214,221). Particular attention must be paid to protein-energy intake (213), as Meyer et al (222) found that only

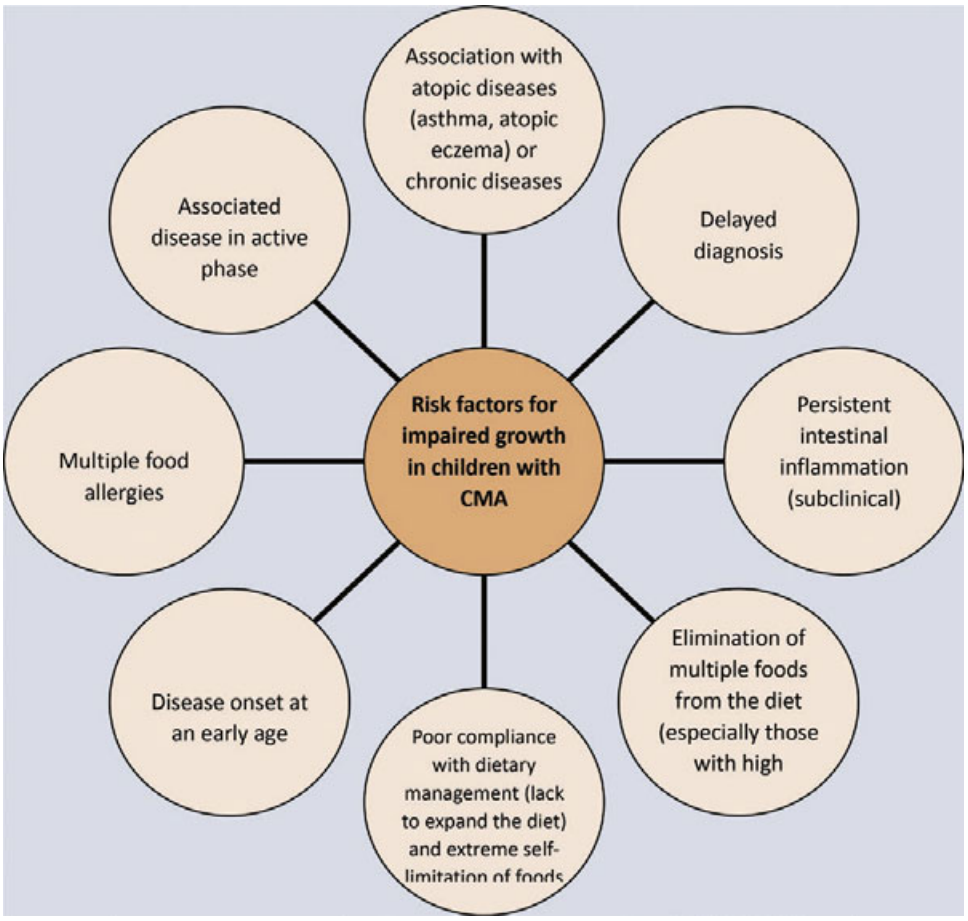

FIGURE 1. Risk factors for impaired growth in children with cow's milk allergy (CMA).

68.2% and 50.0% out of 130 children with a median age of 23.3 months and multiple allergies (mainly CM, soy and egg) met the requirements for energy and protein, respectively. However, with appropriate nutrition counselling, children with food allergies reach the recommended levels of nutrients intake without an impact on nutrient intakes matching the recommended levels similarly to non-allergic children without an impact on growth and nutritional status (140,223–225).

Also, lipid and carbohydrate intakes may be inadequate during an exclusion diet, and alternative sources should be used in older children (219,223,226). In a cohort of 91 children with a mean age of 18.9 months (SD 16.5–21.3), the plasma levels of linoleic, docosahexaenoic and arachidonic acid warrant particular attention being lower compared to controls (223). High levels of free sugars in amino acid and most EHFs and some plant-based milk alternatives are of potential concern, since they are associated with obesity and an increased risk of non-communicable diseases (227,228).

The supplementary dose of elemental calcium can vary from 500 mg/day in infancy and toddlerhood to 1000 mg/day or more during adolescence, remaining below the maximum tolerable dose according to the recommended intake per age (140). Regarding vitamin D supplementation, patients at risk for vitamin D deficiency had a daily requirement of 400–1000 IU in the first years of life and 600–1000 IU from 1 to 18 years (229).

Several studies have found improved nutrient intake in CMA children who receive dietary advice from a dietitian (217,224).

Statement 45	Mean/ median	Votes
Professional dietary counselling should be offered to mothers on CM elimination diets. Supplements of calcium and vitamin D are recommended for lactating mothers.	8.8/9	8 (2x); 9 (11x)
Statement 46		
Complementary feeding should be introduced at the same age as in children without CMA. The introduction of foods should follow the same recommendations as for those without CMA, except for dairy.	8.8/9	7; 8; 9 (11x)
Statement 47		
Dietary monitoring of an adequate intake of macro- and micro-nutrients, particularly vitamin D and calcium, is required in children on a CM elimination diet especially in those older than 1 year of age.	9/9	9 (13x)
Statement 48		
As CM exclusion diets could be associated with micronutrient and growth deficiencies close dietary monitoring is essential, especially after the introduction of complementary feeding.	8.8/9	8 (2x); 9 (11x)
Statement 49		
Professional dietary counselling by a dietitian should be offered to children on CM elimination diets to prevent malnutrition and promote a varied diet leading to normal feeding behaviour.	8.8/9	7; 8; 9 (11x)

GROWTH OF INFANTS WITH CMA

Different factors, such as therapeutic elimination diets, feeding difficulties, use of corticosteroids, coexisting asthma, sleep disturbances, impaired growth hormone release and a poor use or loss of nutrients caused by sustained allergic inflammation might negatively influence growth of allergic children though evidence exists only for children with CMA and atopic dermatitis (230) (Fig. 1). Final adult height (n = 87) was shown to be lower in those with CMA compared to healthy controls (225).

Children with CMA and eczema show impaired linear growth compared to healthy controls and this was mostly associated with the severity of eczema (231,232). The younger the infant was at initial diagnosis, the greater the risk for growth retardation, as no catch-up growth was detected by 24 months of age and the relative weight in patients continued to decrease compared to that in the control group despite the CM-free diet (230,233).

Clinical trials have investigated the effect of different formulas on growth. In one prospective randomized trial in infants with CMA, 84 soy fed infants and 84 extensively hydrolysed whey formula (eHF-W) fed infants showed growth within reference values (234). Another study prospectively examined growth in 4 groups (breast milk, soy formula, casein hydrolysate, rice hydrolysate) of infants with CMA between the age of 6 and 12 months (235). No between-group differences in growth were found, but all 4 groups showed negative values for both weight-for-age (WA) and height-for-age (HA) *z* scores at 6 months (235). Infants fed the 2 hydrolysed formulas showed a better weight gain between the age of 6–12 months (235).

An RCT with 65 children aged between 5 and 12 months fed with 2 different types of formulas (AAF, eHF-W) compared to controls showed a difference in WA *z* scores between the 2 CMA groups and the healthy control group at T0 and after 3 months of follow up (236). The authors concluded that long-term use of eHF-W and AAF is safe and lead to normalization of anthropometric parameters without considerable alterations in protein metabolism (236).

A recent systematic review analysed 7 RCTs conducted in infants with confirmed CMA fed both with AAF with and without synbiotics (*Bifidobacterium breve* M16-V and prebiotics) (237). All studies showed adequate growth parameters at baseline and after treatment, however, in only 2 studies growth was a primary outcome. AAF with synbiotics was associated with fewer symptoms (−37%, $P < 0.001$), infections (−35%, $P < 0.001$), medication prescriptions (−19%, $P < 0.001$) and health care contacts (−18%, $P = 0.15$) compared to AAF (238). Infants prescribed AAF with synbiotics had a significantly higher probability of achieving asymptomatic management without elimination diet (adjusted hazard ratio 3.70, 95% CI: 1.97–6.95, $P < 0.001$), with a shorter clinical course of symptoms (1.35 vs. 1.95 years) (238). This systematic review and meta-analysis showed that adequate growth was observed through the study duration; however, in only 2 studies, growth was a primary outcome (238). A prospective study evaluated anthropometric data of 183 children followed for 3 and 5 years after a diagnosis of CMA and fed with either casein eHF with or without *Lacticaseibacillus rhamnosus* GG (LGG) showing no differences in anthropometric parameters (239).

Statement 50	Mean/ median	Votes
Close monitoring of growth is mandatory in children with CMA as they may suffer from growth faltering.	8.8/9	8 (2x); 9 (11x)

NUTRIENT COMPOSITION OF REPLACEMENT FORMULAS FOR CMA

There is a relatively wide choice of nutritionally adequate formulas in infants with CMA: eHF (whey or casein), plant-based formulas (hydrolysed rice and soy-protein formulas) and AAF (240). The EFSA requires for all newly marketed hydrolysates at least 1 RCT demonstrating non-inferiority in growth compared to a standard formula (240).

Protein

According to European Regulation 2016/127, the protein range of hydrolysed formulas must be between 1.86 and 2.80 g/100 kcal. Since soy protein has a lower biological value, the recommended protein content in this case is higher (2.25–2.80 g/100 kcal) (241). In particular, minimum and maximum values for essential amino acids should be similar to breast milk (241) and special considerations for amino acids should be addressed such as, for example, sulphur containing amino acids for soy- and branched chain amino acids (BCAAs) for rice-based formulas (242).

For optimal utilization, the hydrolysed protein source should respond to a precise pattern of essential amino acids with BCAAs and valine representing around 50% of the essential amino acid fraction (243). There may be different rates of digestion, absorption and metabolism of amino acids. In hydrolysed formulas, the concentration of free amino acids is about 100 times higher than in standard formulas (244), mainly represented by BCAAs and glutamate (245). After ingestion of hydrolysed proteins an increase in blood urea levels has been observed (245).

The rate of entry into the circulation of amino acids from hydrolysed protein is faster than that from intact dietary proteins and may even be faster than the rate from free amino acids (246). From a satiety perspective, intact protein suppresses ghrelin levels to a greater extent than hydrolysed protein (247). Considering the use of AAF, it is crucial to achieve a balance between the amino acids ingested (to prevent an excessive increase of nitrogen excretion) and the energy intake (via glucose), to promote protein anabolism. Therefore, a ratio of 3–4.5 g protein (equivalent)/100 kcal corresponding to 12%–18% total energy has been suggested (248).

Lipids

There is no evidence for requirements of essential fatty acids or MCT in formulas for the treatment of CMA, although regarding MCT, beneficial effects have been suggested (249–252). A recent in vitro study investigated the digestion of MCT at different concentrations of 0%, 20%, 30% and 55% and showed no differences (253).

Carbohydrates

Historically, it was technically almost impossible to manufacture lactose that was strictly CM free. In 2010, ~70% of hypoallergenic formulas were lactose-free and contained glucose polymers instead (6). However, lactose is the primary carbohydrate source in human milk and has a prebiotic function. Therefore, in the absence of enteropathy, an eHF with lactose as carbohydrate source may be preferable.

For decades, non-human oligosaccharides have been added to infant formula because of their prebiotic effects. Recent interest has arisen regarding human milk oligosaccharides (HMOs), the third most prevalent component in human milk. HMOs have a complex structure and well-studied effects (234), and some biotechnologically produced structures identical to those present in breast milk (human identical milk oligosaccharides; HiMOs) are added to some therapeutic formulas (254). Further studies are needed to

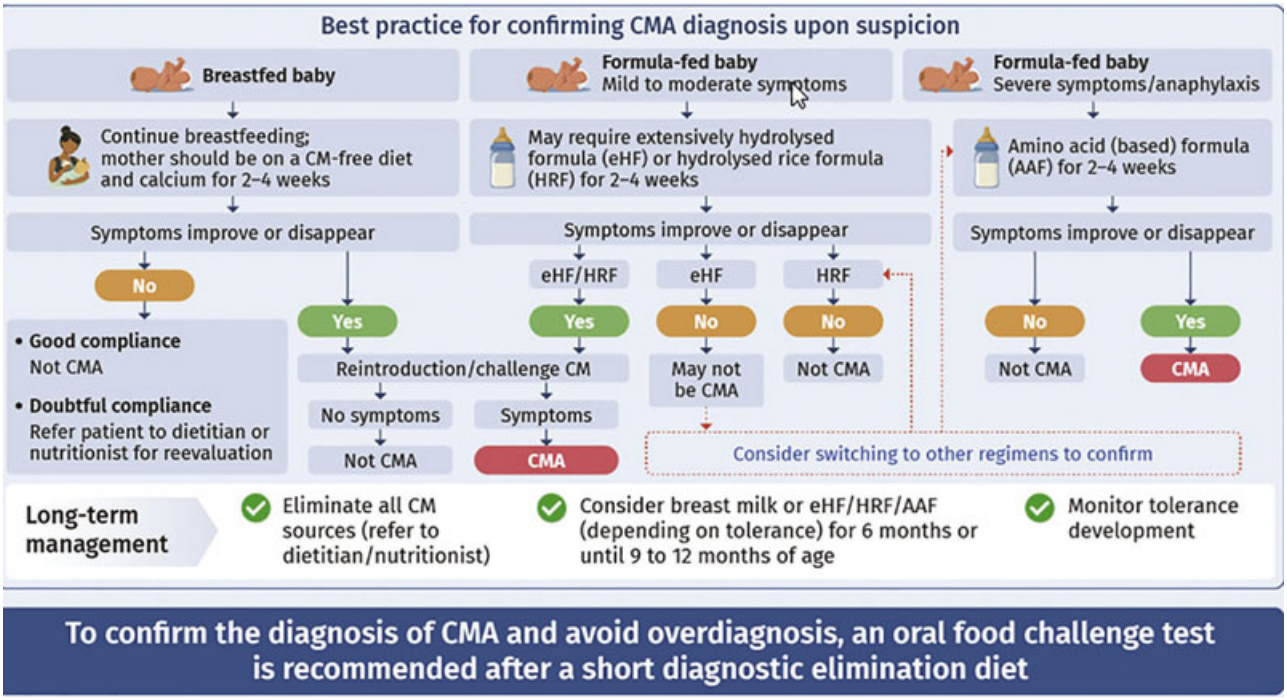

FIGURE 2. Best practice for confirming cow's milk allergy (CMA) diagnosis upon suspicion.

evaluate the efficacy and nutritional value of HMO-supplemented formulas in comparison to those supplemented with non-human prebiotics.

Statement 51	Mean/ median	Votes
We recommend to use only FSMPs, such as eHFs and AAFs, for which appropriate growth and nutritional studies have been published.	8.8/9	7; 8; 9 (11x)

DIETARY TREATMENT OF CMA IN PRACTICE

Dietary treatment depends on if the infant is exclusively or partially breastfed, or exclusively formula fed (Fig. 2). Regarding the duration of the treatment, the ESPGHAN practical guideline of 2012 suggested that it should be at least for 6 months or up to the moment when the infant reaches the age of 9–12 months, whatever is reached first (6). Complementary feeding should be introduced at the same age as in children without CMA (6,189). The introduction of foods should follow the same recommendations as for those without CMA.

In the case of CMA in an exclusively breastfed infant, recommendations for diversification should not differ from healthy infants. When human milk substitutes are needed, general recommendations for formula-fed infants should be followed.

If breast milk is not available, a CM-based eHF is the first option (6,156,180,255,256). Given the specificity of each hydrolysate, the formula for the therapeutic diet should be the same as for the diagnostic elimination diet, but this approach is not supported by evidence. It was discussed before that in the presence of severe diarrhoea lasting longer than a week, a transient lactase deficiency may be suspected, indicating that a lactose-free eHF may be temporary preferred for the diagnostic elimination diet. After the 2–4 weeks diagnostic elimination diet, the mucosa should have recovered. However, a temporary continuation of the lactose free eHF may be considered if diarrhoea had not completely resolved or reappeared during the OFC. Previous concerns that infants with CMA would react to residual protein traces in lactose have often resulted in complete avoidance of both lactose and CM. Adverse reactions to lactose in CMA are not supported in the literature, and complete avoidance of lactose in CMA is no longer warranted. eHFs containing purified lactose are now available and have been found safe and effective in the treatment of CMA (58). These formulas 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 diarrhoea, and therefore a lactose-free eHF will be required initially in these cases. Occasionally, in toddlers with persistent CMA late-onset primary lactose intolerance may develop thus requiring a lactose-free eHF as well. pHFs are not recommended in the treatment of CMA (241). Recent data show that eHFs supplemented with probiotics (LGG, *Bifidum breve* M16-V), prebiotics [fructo-oligosaccharides, galacto-oligosaccharides and HMOs (2′-FL, LNnT)] are well tolerated, although an increased efficacy has not been demonstrated systematically. There are some data suggesting that AAF with synbiotics results in a faster recovery than the same AAF without synbiotics (238). Therefore, we estimate that there is insufficient evidence to recommend the addition of "biotics" to a therapeutic elimination diet for a better efficacy in the management of CMA. However, this opinion might be adapted if new information becomes available.

Introduction of weaning foods should not be delayed, although these foods should be offered one at a time in small amounts after the infant is at least 17 weeks of age, preferably while the mother is still breastfeeding (152). Weaning food is recommended to be CM-free until tolerance is confirmed by an OFC (146). The elimination diet should be thoroughly monitored to exclude hidden milk allergens and results evaluated to establish or exclude the diagnosis and to prevent unnecessary food restrictions.

The indications for AAF during the therapeutic elimination are the same as for the diagnostic elimination diet (163). If children with CMA do not achieve total control of their symptoms or full

nutritional recovery with an eHF mainly due to residual allergenicity or to adverse reactions not mediated by immune responses, an AAF should be used (257).

There is evidence that HRFs are an alternative for eHFs as therapeutic elimination diet (87,171–173), although there are insufficient RCTs with HRFs.

As discussed before, soy protein-based formula is not recommended for infants <6 months (68), but may be used in the treatment of CMA in infants because of economic and cultural reasons (and better palatability). Co-allergy between CM and soy has been reported, but is low in IgE-mediated allergy. Based on data from 40 studies, the established weighted prevalence of soy allergy is 0%–0.5% for the general population, 0.4%–3.1% for the referred population and 0%–12.9% for allergic children (258).

There is no place for any other animal milk with intact protein in CMA (259,260). The significant homology between milk from cow, sheep and goat results in cross-reactivity (261). However, mare's or donkey's milk may be tolerated by some individuals (43,260), but they are expensive and nutritionally not adapted. There is also no place for any other legume milk with intact protein, except soy, because these legume milks have not been tested in infants and children with CMA (259,262).

Statement 52	Mean/ median	Votes
In formula-fed infants, a CM-derived eHF is the first choice for a therapeutic elimination diet.	7.8/9	0; 7 (2x); 8 (3x); 9 (7x)
Statement 53		
There is insufficient evidence demonstrating that the addition of pro-, pre- or synbiotics studied so far to eHFs improves their therapeutic efficacy.	8.9/9	8; 9 (12x)
Statement 54		
Partially hydrolysed CM-based formulas (pHF) are not recommended in the treatment of CMA.	8.8/9	7; 8; 9 (11x)
Statement 55		
62B. Regarding the therapeutic elimination diet, AAF should be reserved for severe cases or infants with an absent or partial response to eHF.	8.3/9	1; 8; 9 (11x)
Statement 56		
HRFs can be considered as an alternative to CM-derived eHF for therapeutic elimination diet.	7.8/8	5 (2x); 7 (3x); 8 (2x); 9 (6x)
Statement 57		
If a diagnostic elimination diet followed by OFC has shown efficacy of a soy infant formula, such a formula can be considered as an alternative for a therapeutic elimination diet for economic, cultural and/or palatability reasons.	7.6/8	0; 7 (3x); 8 (3x); 9 (6x)

After the First Therapeutic Elimination Diet

As discussed above, the duration of the first therapeutic elimination diet should last for 6 months or up to the moment when the infant reaches 12 months, whatever is attained first (6). However, there are no RCTs comparing different durations of therapeutic elimination diets. After 6 months of elimination diet, or when the child is 1 year old, an OFC should be performed. In IgE-mediated CMA, sIgE levels should be measured before the challenge and guide timing of the OFC. The OFC can be the same as after the diagnostic elimination diet, but one may also consider introducing CM according to the "milk ladder" (21) starting with small amounts of baked milk. As heating changes the structure of the peptides, patients may tolerate baked milk (42,263–268). Home introduction protocols are safe in non-IgE mediated food allergy (Table 4) (269). Interestingly, the concept of "baking" milk is questionable. Boiling any liquid at 100°C typically means the entire volume has reached the higher temperature. Conversely, during baking the core temperature of foods containing milk, for example, muffins does not generally exceed 80°C. In that respect boiling milk should change the structure of allergenic components more than baking.

TABLE 4. Patient-specific factors for home challenge using a milk ladder [adapted from ref (269)]

- Non-IgE-mediated allergy (excluding FPIES)
- IgE-mediated with prior mild, non-anaphylactic reactions
- Non-asthmatic is ideal, with stable, treated asthmatics potentially suitable
- Willing and prepared patients and families with no language or comprehension barriers
- Families ideally have ready access to emergency services
- High previous reaction threshold
- Low or decreasing skin prick test wheal or serum specific-IgE levels
- Younger patients (e.g. preschool) are preferred, though not without risk, since older patients may be prone to persistence of allergy and suffer from coexisting allergies

FPIES = food protein-induced enterocolitis syndrome; IgE = immunoglobulin E.

However, standardization of the home challenge is recommended (270). The foods proposed in the milk ladder can be replaced by others according to the regional dietary habits. If this challenge is positive, it is proposed to plan a re-challenge after periods of 6 months, again considering sIgE levels in IgE-mediated allergy. There are, however, no data regarding the optimal timing for re-challenges.

Statement 58	Mean/ median	Votes
The OFC after the first period of therapeutic elimination diet can be done in a similar fashion to that after the diagnostic elimination diet or according to the milk ladder, starting with small amounts of baked milk (e.g. milk containing biscuits).	8.8/9	8 (3x); 10 (9x)
Statement 59		
Standardization of the home challenge applying the milk ladder adapted to local dietary habits is recommended.	8.8/9	8 (3x); 10 (9x)

Oral Immune Therapy (OIT)

OIT consists of daily ingestion of increasing doses of the allergen during the up-dosing phase, and ingestion of a constant dose during the maintenance phase based on specific tailored protocols (271). Indications and safety of OIT in infants and children with CMA are debated. OIT is limited to patients with IgE-mediated CMA and it is the method of choice for preventing anaphylaxis and severe response to accidental exposure. While some authors report almost absence of adverse effects, other report these are frequent, notably aversion to the allergen and oral syndromes as well as systemic allergic symptoms (261,271,272). OIT in children with severe and persistent CMA deserves consideration, but currently this approach should be reserved for selected patients and restricted to specialized centres. Currently there are no standardized and validated protocols or products for CM OIT.

Statement 60	Mean/ median	Votes
The provision of OIT in selected patients with persistent IgE-mediated CMA should be limited to specialized centres.	8.8/9	8 (2x); 9 (11x)

NUTRITIONAL INTERVENTION AS PRIMARY PREVENTION OF CMA

Breastfeeding

There are studies that show a protective effect, no effect, or even a predisposing effect of breastfeeding for developing CMA. A recent systematic review identified 5 large prospective birth cohorts that examined the link between breastfeeding and food allergy in the general population, and 2 studies focused on infants at increased risk (273). Overall, the relative risk (RR) for CMA ranged between 0.38 and 2.08, but evidence was low and diagnostic criteria were mostly lacking. Another systematic review did not find an association of breastfeeding with allergic disorders such as asthma or eczema (274). Despite the controversy, there is a consensus that even if breastfeeding does not provide a strong protective effect, it should be promoted for its multiple other benefits.

Although it is recommended to opt for exclusive breastfeeding for 6 months as a desirable goal (275), this may be challenged in the future. In the Prevent ADALL study, the introduction of tiny amounts of "allergenic" (peanut, milk, wheat and egg) foods from age 3 months reduced the risk of food allergy in the general population (i.e. not infants at high risk of allergy as in the LEAP study and other studies) (276).

An antigen avoidance diet in high-risk women during pregnancy is unlikely to reduce substantially her child's risk of atopic diseases, and such a diet may adversely affect maternal and foetal nutrition (277,278). Prescription of an antigen avoidance diet to a high-risk woman during lactation may reduce her child's risk of developing atopic eczema, but better trials are needed (277). There is no evidence for dietary restriction in a breastfeeding mother to prevent CMA (274).

Statement 61	Mean/ median	Votes
Breastfeeding should be promoted for its multiple benefits, although its preventive effect on CMA has not been consistently documented.	9/9	9 (13x)
Statement 62		
Dietary restrictions, other than those warranted for the pregnant woman herself, are not indicated during pregnancy and lactation to prevent CMA.	9/9	9 (13x)

Avoiding Early Introduction of CM Formula

Several papers suggest that exposure to CM of breastfed infants during the first few days of life in the maternity ward may considerably increase the risk of CMA. The initial observation was made by Høst et al (13) and led to the concept of "dangerous bottle" (of CM formula) given at maternity ward and increasing the risk of CMA.

A recent systematic review found that avoidance of CM-based formula may not reduce CMA in infancy or early childhood when the formula is regularly consumed (273). The absolute effect ranged from a 22% decrease to a 2% increase in the prevalence of food allergy with a low level of evidence (273). There is, however, controversy with regards to the effects of brief early exposure to CM formula. Another systematic review identified 1 RCT (279) documenting that avoiding temporary supplementation with CM formula in the first 3 days of life may result in a large decrease in the risk of CMA in early childhood (273,279). In a multivariate model, only CM given at the maternity hospital (OR = 1.81 [1.27–2.59]), family history of allergy (OR = 2.83 [2.01–3.99]) and avoidance of dairy products during pregnancy or breastfeeding (OR = 5.62 [1.99–15.87]) were independent risk factors of CMA (280). Wide confidence intervals call for caution in interpreting these results. In a subsequent RCT (281), 504 infants were randomized to the ingestion group (at least 10 mL of CM formula daily) or the avoidance group (no CM formula; breastfeeding was supplemented with soy formula if needed). The intervention was performed between 1 and 2 months of age. This trial found that daily ingestion of CM formula between 1 and 2 months of age reduced the risk of CMA confirmed by OFC at 6 months (RR: 0.12; 95% CI: 0.01–0.50; $P < 0.001$) (281).

According to a prospective cohort study involving 6209 exclusively breastfed infants followed from birth for CMA, one of the significant risk factors for presence of CM sIgE was the exposure to CM protein in the maternity ward (14). Breastfed infants receiving CM formula supplementation (45.8% of neonates less than 24 hours old) had a 7.03 times increased risk to develop CMA than those exclusively breastfed (282). In an open clinical trial on breastfeeding supplemented with AAF or CM formula (5 mL/day up to 5 months of age), sensitization to CM (IgE level >0.35 IU/mL) at the infant's second birthday occurred in 16.8% infants in the group supplemented with AAF compared to 32.2% in the breastfeeding-CM group (RR: 0.52; 95% CI: 0.34–0.81) (279). In an observational case-control study, additional bottle feeding in the maternity ward increased the risk for CMA compared to age-matched controls (283). Sakihara et al (281) showed that none of the 31 infants who avoided CM formula in the first 3 days of life developed CMA, irrespective of their subsequent diet. From the same study, in the primary intention-to-treat analysis population, 2 of the 242 ingestion group participants (0.8%) and 17 of the 249 avoidance group participants (6.8%) had OFC-confirmed CMA at 6 months of age (RR: 0.12; 95% CI: 0.01–0.50; $P < 0.001$) (281). The authors concluded that daily ingestion of CM formula between 1 and 2 months of age prevents CMA (281). In a later manuscript, the authors reported that the analysis from the same data suggested that regular soy formula intake between 1 and 2 months of age in infants avoiding CM formula was significantly associated with a reduced risk of food sensitization in infancy (282). Early, consistent CM exposure was reported to be protective against adverse reactions to CM (280,284). Occasional exposure to CM increases the risk for IgE-mediated CMA and should be avoided (284). Overall, the effects of brief early exposure (during the first week of life or between 1 and 2 months of age) are not consistent. It remains unclear whether avoiding regular consumption of CM-based formula during early life reduces the risk of CMA in children (285). There are no publications showing a beneficial effect of the introduction of a CM formula during the first 3 days of life.

Statement 63	Mean/ median	Votes
There is no convincing scientific evidence that the avoidance or delayed introduction of CM-based formula reduces or increases the risk of CMA in infants considered at high risk of allergic diseases.	8.4/9	4; 8 (3x); 9 (9x)
Statement 64		
It remains unclear whether avoiding regular consumption of CM-based formula during early life reduces the risk of CMA in children.	8.5/9	6; 7; 9 (11x)
Statement 65		
Feeding supplementation (i.e. providing any kind of formula beyond breast milk) during the first days of life is not recommended for the prevention of CMA.	8.8/9	5; 9 (12x)

Protein Hydrolysates

A systematic review concluded that partially or eHF-Whey (W) or eHF-Casein (C) may not reduce the risk of food allergy compared to whole protein CM formula (273). For pHF (5 RCTs involving 3572 infants), the absolute effect ranged from a 34% decrease to an 11% increase. For eHF (5 RCTs involving 3221 infants), the absolute effect ranged from a 4% decrease to a 2% increase. There was little to no evidence that one type of hydrolysed formula was more effective than another (273).

Similarly, a Cochrane review found that in high-risk infants who are unable to be completely breastfed, there is no evidence to support feeding with a hydrolysed formula compared with CM formula for prevention of allergic disease, including CMA (285). The quality of evidence was very low for all outcomes. Very low-quality evidence indicated that short-term use of an eHF compared with a CM formula may prevent CMA in infancy (285).

Although the effect of hydrolysed formulas on food allergy remains unclear, these formulas may reduce the risk of other allergic diseases such as eczema. A systematic review showed that pHF (100% whey) compared to CM formula reduced the risk for allergic diseases, particularly atopic dermatitis/eczema, among children at high risk (286). One of the studies that contributed the most to the pooled results is the German Infant Nutritional Intervention study (GINI study), a large, well-designed and conducted RCT with a 20-year follow-up period (287). This trial involved 2252 healthy infants who were randomized to 1 of 3 hydrolysed formulas [pHF-W; eHF-W; eHF-C] or a formula based on intact CM as a reference to be fed during the first 4 months of life if exclusive breastfeeding was not possible. A reduced cumulative incidence of atopic dermatitis was found among infants who received the pHF-W or eHF-C versus CM formula during a 20-year follow up. In addition, after 16–20 years of follow-up, the prevalence of asthma after puberty in a high-risk population was lower in both the eHF-C and pHF-W groups (288). Based on human intervention studies, EFSA stated that no conclusions could be drawn on the efficacy of the infant formula in reducing the risk of developing atopic dermatitis (289). The panel determined that there is no established cause-and-effect relationship between the consumption of the infant formula under evaluation and the reduction in the risk of developing atopic dermatitis in infants with a family history of allergy.

HRF cannot be recommended for preventing CMA because of lack of evidence.

Statement 66	Mean/ median	Votes
For infants with a documented family history of allergic disease who cannot be exclusively breastfed, there is insufficient evidence to recommend the routine use of pHF, eHF-Whey, eHF-Casein or AAF for preventing CMA.	8.3/9	4; 7; 8 (2x); 9 (9x)
Statement 67		
The role of HRF for preventing CMA has not been studied.	8.8/9	7; 9 (12x)

Soy-Based Formula

Soy-based formulas are made from soy protein isolate and do not contain CMs or lactose. In 1 RCT (involving 620 infants), soy-based formula compared with conventional CM formula did not reduce CMA risk (CMA cumulative incidence 0–2 years; RR: 1.35; 95% CI: 0.48–3.81) (290).

Statement 68	Mean/ median	Votes
For infants with a documented family history of allergic disease who cannot be exclusively breastfed, there is no evidence to recommend soy formula for preventing CMA	8.5/9	7 (3x); 8; 9 (9x)

Probiotics, Prebiotics and/or Synbiotics

A recent systematic review found that no prebiotic, probiotic or synbiotic administered during pregnancy, breastfeeding and/or infancy had an effect on food allergy in infancy and early childhood (273). However, the evidence is very limited.

Of note, some meta-analyses have suggested that probiotics (as a group) may be effective in preventing eczema, particularly if the probiotics are administered both pre- and post-natally (291,292). In contrast, a meta-analysis focusing on a single probiotic, *Lacticaseibacillus* (formerly known as *Lactobacillus*) *rhamnosus* GG, concluded that there was no evidence that this specific probiotic would result in a reduction of atopic eczema (293).

Statement 69	Mean/ median	Votes
There is insufficient evidence to recommend the use of pro-, pre- or synbiotics studied so far for CMA prevention.	8.8/9	7; 9 (12x)

Long Chain Poly-Unsaturated Fatty Acids (LCPUFAs)

Despite critical gaps in our current knowledge, it is increasingly apparent that dietary intake of fatty acids may influence the development of inflammatory and tolerogenic immune responses (294). A lack of pre-study serum fatty acid level assessments in clinical studies significantly limit the ability to compare allergy outcomes across studies and to provide clear recommendations at this time (294). A recent systematic review found that fish oil supplementation during pregnancy or in infants had no effect on the risk of food allergies, but the evidence was very weak (273). However, the administration of fish oil during both pregnancy and lactation may reduce the risk of food allergy in children at high risk (food allergy cumulative incidence 0–1 year; RR: 0.13; 95% CI: 0.02–0.95; $P < 0.05$). Wide confidence intervals call for caution in interpreting these results (273).

Statement 70	Mean/ median	Votes
There is insufficient evidence to recommend the use of LCPUFAs for CMA prevention.	8.8/9	7; 9 (12x)

Vitamin D

A 2020 systematic review identified 3 RCTs on the effects of vitamin D supplementation on food allergy. Vitamin D supplementation during pregnancy (food allergy cumulative incidence 0–3 years: RR: 1.92; 95% CI: 0.57–6.5), during lactation (food allergy cumulative incidence 0–2 years: RR: 3.42; 95% CI: 1.02–11.77; $P < 0.05$), or infancy (food allergy cumulative incidence 0–1 year; RR: 1.33; 95% CI: 0.75–2.33) had little to no effect on food allergy in early childhood (273). In none of these studies CMA was evaluated. The certainty of evidence was very low for all studies. Again, wide confidence intervals call for caution in interpreting these results. Vitamin D supplementation is recommended for every infant but has no role in CMA prevention.

Statement 71	Mean/ median	Votes
Vitamin D supplementation has no role in CMA prevention.	8.8/9	7; 9 (12x)

Confounding Variables

The many confounding variables in the pathogenesis of allergy may contribute to the differences between animal studies, where all variables are controlled, and trials in infants. The mode of delivery, perinatal administration of antibiotics to the mother or infant and feeding all influence the GI microbiota and the risk of developing allergy (7). An important feature characterizing epigenetically-mediated processes is the existence of a time frame where the induced effects are the strongest and, therefore, most crucial (7). Complementary bottles given at maternity hospitals to newborns who will later be exclusively breastfed might increase the risk of developing CMA (283,295). In some prevention trials randomization was allowed up to the age of 1 month, meaning that a number of infants were fed intact CM before inclusion in the trial (296). Sensitization to CM may also develop through skin contact (297).

ECONOMIC COST OF CMA

Individuals with food allergies make increased use of health care services leading to substantial economic costs in addition to the physical health burden caused by anaphylaxis (298). In a recent review, Dierick et al showed that the socioeconomic burden of allergic diseases is considerable. In children, this is especially true for food allergies impacting quality of life as well as direct and indirect costs. They, however, found limited data on the effects of inadequate management (287).

Both eHF and AAF are more expensive than standard infant formulas (299). In a study that included the case records of 145 AAF fed infants and 150 matched eHF-fed infants from a nationally representative database of patients in the UK, the authors found that starting treatment of CMA with an eHF was the most cost-effective option (300). Similarly, a Turkish panel of experts calculated the total 2-year direct medical costs associated with CMA, including physician visits, laboratory tests, and treatment and showed that first line use of AAF was associated with higher medical costs by 2 years (301).

Morais et al (166) propose using AAF in the diagnostic elimination diet of infants with suspected CMA. The hypothesis is that infants who do not respond to AAF do not suffer from CMA. The authors conclude that using this strategy from the perspective of the Brazilian Public Healthcare System has lower costs and results in an increased number of symptom-free days (166). Using an AAF as the initial treatment for CMA can potentially release limited hospital resources for alternative use within the paediatric health care system in the Australian health care system (166).

Cost of formulas differ from country to country due to different actual purchase costs and reimbursements. If reimbursement is not considered, AAFs are more expensive than eHFs. However, even with reimbursement AAFs are more expensive to the health system. A step-down approach will lead to an increased (and unneeded) use of AAF, since many parents will refuse a challenge test (even with an eHF). At equal cost, there is no evidence what the best option is: step-up or step-down approach. As a consequence, data regarding the cost/benefit ratio of HRF are needed.

Statement 72	Mean/ median	Votes
The choice of formula for the treatment of CMA should take into consideration cost and availability of the therapeutic formula.	8.8/9	8; 9 (12x)

QUALITY OF LIFE

CMA can be a source of parental and family stress (298). The stress of daily food allergy management and the limited treatment options impact family relationships and often limit social activities, contributing to an impaired quality of life (302). Among food allergic children, those with CMA have a lower quality of life compared to children with easily avoidable allergens (e.g. nuts) (303,304). CMA individuals who tolerate baked milk products report a better quality of life due to fewer dietary restrictions (303).

In their review, Antolín-Amérigo et al (305) conclude that tools designed to assess the impact of food allergies on health-related quality of life should always be part of the diagnostic work up. The authors suggest that health-related quality of life may be the only meaningful outcome measure suitable and available for food allergies.

In a recently published paper, Protudjer et al (306) studied the impact of the coronavirus pandemic on the health-related quality of life of Canadian children with food allergies and anxiety levels of their families. While daily food allergy management was better during the pandemic, the authors showed that anxiety was more prevalent among those families with children with a food allergy compared with controls. Mothers of children with food allergy reported poorer health-related quality of life (281).

Statement 73	Mean/ median	Votes
CMA may lead |to substantial impairments in quality of life, both of the children and their caregivers.	8.8/9	8; 9 (12x)

LIMITATIONS

The author list was chosen by Council and the Committees of Nutrition and Gastroenterology, and limited to paediatric gastroenterologists with a specific interest in CMA. The differences in the organization of primary care throughout Europe (in some countries primary care is only done by paediatricians, in other countries by family doctors/general practitioners; differences in reimbursement of formulas) made the inclusion of these colleagues not feasible. Moreover, these differences in health care systems and languages would be a limitation to include "parent organizations". Given the fact that CMA is frequently presented and managed by primary care and that data from clinical trials in primary care are limited, the quality of evidence regarding all aspects of CMS is low. The potential conflicts of interest of all authors are clearly listed. Almost all authors have been involved in clinical trials or advisory boards of infant formula companies, albeit not limited to CMA.

CONCLUSIONS

CMA may lead to substantial impairments in quality of life in children and their caregivers. Accurate diagnosis, avoiding under- and overdiagnosis, is mandatory but remains challenging due to the lack of specific symptoms and adequate diagnostic tests. Awareness tools have been developed to reduce the risk of under-diagnosis, however they should not be considered as diagnostic tools. Reintroduction of CM protein in non-IgE-mediated allergy and OFC in IgE-mediated allergy are the "gold standard" diagnostic tests, yet these are often not performed by caregivers. As a result, there is a risk of overdiagnosis and the implementation of long-term elmination diets, posing potential nutritional risks. The choice of formula for the treatment of CMA should take into consideration cost and availability of the therapeutic formula. Cow's milk eHF is the first choice treatment option, but HRF can be considered as an alternative option. Soy could be an option in specific circumstances.

Given the diagnostic challenges, prevention would be preferable but unfortunately, there is insufficient evidence to recommend any effective prevention strategy.

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