An ESPGHAN position paper on the diagnosis, management and prevention of cow's milk allergy.

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Potential conflict of interest

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

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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 was published in 2012. This position paper provides an update on the diagnosis, treatment and prevention of CMA with focus on gastrointestinal manifestations. After reaching consensus on the manuscript, statements were formulated and voted on.

What is new

- Available evidence on the role of dietary practice in the prevention, diagnosis and management of CMA was updated and recommendations formulated..
- New sections were added on nutrition, growth, cost, and quality of life.

Keywords: amino acid formula; breastfeeding; cow's milk allergy; diagnosis; functional gastrointestinal disorder; elimination diet; extensive hydrolysate; formula feeding; IgE; management; oral food challenge; partial hydrolysate; prevention; soy formula; rice hydrolysate

Abbreviations

AAF	amino acid (based) formula
APT	atopy patch test
BAT	basophil activation test
BCAA	branched chain amino acid
CM	cow's milk
CMA	cow's milk allergy
DBPCFC	double-blind placebo-controlled food challenge
eHF	extensively hydrolysed formula
GI	gastrointestinal
EAACI	European Academy of Allergy and Clinical Immunology
EFSA	European Food Safety Authority
EoE	eosinophilic esophagitis
EGIDs	eosinophilic gastrointestinal disorders
FGIDs	functional gastrointestinal disorders
FPIAP	food protein induced allergic proctocolitis
FPIES	food protein induced enterocolitis syndrome
HRF	hydrolysed rice formula
IgE	Immunoglobulin E
L	Lacticaseibacillus
LCPUFA	long chain poly-unsaturated fatty acid
OFC	oral food challenge
OIT	oral immune therapy
RCT	randomised controlled trial
SPT	skin prick test
WAO	World Allergy Organisation
WG	working group

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131 # Statements

	Statement	Mean / median	votes
1	The prevalence of cow's milk allergy (CMA) is influenced by regional differences and diagnostic procedures, and ranges from less than 0.5% to 4.9%.	8.9 / 9	8; 9 (12x)
2	Within the gastro-intestinal (GI) tract, non-IgE CMA can manifest with entities such as food protein induced allergic proctocolitis (FPIAP), food protein induced enterocolitis syndrome (FPIES), eosinophilic gastrointestinal (GI) disorders.	8.7 / 9	7(2x); 9(11x)
3	FPIAP is, in most cases, a benign, easily recognised condition that may not need treatment in breastfed infants.	8.4 / 9	6;7(2x); 8;9(9x)
4	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)
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)
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 oral food challenge (OFC) can be considered in order to help confirm the diagnosis.	8.8 / 9	7; 9(12x)
7	CMA is considered a possible factor in the pathogenesis of eosinophilic gastrointestinal disorders (EGIDs).	8.9 / 9	7;8(3x); 9(9x)
8	CMA is considered a possible factor in the pathogenesis of eosinophilic oesophagitis (EoE), and, where the index of suspicion is high oesophageal biopsies should be taken whilst	8.3/ 9	6;7(3x); 9(9x)

	on a CM containing diet.		
9	Some patients with suspected FGIDs can improve with a CM elimination regardless of CMA.	4.3 / 5	0(2x);1;2; 4;5(3);7(3); 9
10	Some patients with suspected FGIDs can improve with a CM elimination regardless of CMA, but there are no specific tests to allow clarification of the diagnosis by discriminating between CMA and functional gastrointestinal disorders (FGIDs).	7.8 / 9	4(2x); 7(2x); 8; 9(9x)
11	In patients not responding to conventional therapies for functional GI disorders (FGIDs), CMA can be considered and patients trialled on a time limited elimination diet which should be followed by an OFC.	8.4 / 9	6;7; 8(3x); 9(8x)
12	In patients not responding to conventional therapies for gastro-oesophageal reflux (disease) (GOR(D)), CMA can be considered and patients trialled on a time limited elimination diet during 2-4 weeks which should be followed by an OFC.	8.8 / 9	8(3x); 9(10x)
13	In infants who present with crying and irritability there is insufficient data to recommend a time-limited CM elimination diet followed by an OFC.	8.4 / 9	6;7; 8(3x); 9(8x)
14	There is insufficient data to support infant colic occurring as a single manifestation of CMA.	8.4 / 9	6;7;8(2x); 9(8x)
15	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 can be trialled which should be followed by an OFC.	7.9 / 9	4;7(3x); 8(4x); 9(5x)
16	In patients not responding to conventional therapies for constipation, including laxatives in optimal dosage, CMA can	7.9 / 8	6;7(4x); 8(3x);

	be considered, and a time limited elimination diet can be started which should be followed by an OFC.		9(5x)
17	When treatment for functional abdominal pain disorders is being initiated, CMA can be considered, and a time limited elimination diet be started which should be followed by an OFC.	3.5 / 3	0(3x); 1(2x); 2;4;5; 6(2x);8;9
18	In patients not responding to other standard treatments for functional abdominal pain disorders, there is sufficient evidence to recommend a time limited CM elimination diet followed by an OFC.	3.9 / 5	0(3x); 1(3x); 5;6; 7(3x); 8(2x)
19	In patients not responding to other standard treatments for functional abdominal pain disorders, there is insufficient evidence to recommend a time limited CM elimination diet followed by an OFC.	6.5 / 7	2;4(2x); 5(2X); 7(3);8; 9(4x)
20	There is insufficient evidence regarding a higher risk of infectious disease in infants with CMA.	8.3 / 9	5;7;8(3x); 9(8x)
21	Absence of family history does not exclude the possibility of CMA.	8.8/9	8(2x); 9(11x)
22	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)
23	The Cow's Milk-associated Symptom Score (CoMiSS) is an awareness tool for CMA.	8.5 / 9	6;7;8; 9(10x)
24	The CoMiSS initial score 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)
25	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)

26	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)
27	In formula fed infants, a CM derived extensively hydrolysed formula (eHF) is the first choice for a diagnostic elimination diet.	8.8 / 9	8(2x); 9(11x)
28	Only CM derived eHFs tested in randomized clinical trials should be used.	8.6 / 9	7(2x);8; 9(10x)
29	There are insufficient comparative trials to make a recommendation whether to use whey versus casein hydrolysates.	8.8 / 9	8(3x); 9(10x)
30	In patients with CMA and severe diarrhoea and/or with severe malnutrition, the transient use during 2-4 weeks of a formula without lactose may be preferred.	7.0 / 8	0;5(2x); 7(3x); 8(3x); 9(4x)
31	In formula fed infants, amino acid-based formula (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)
32	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)
33	Although less studied than CM based eHFs, rice hydrolysed formulae (RHFs) can be considered as an alternative for a diagnostic elimination diet.	7.4 / 8	1;5;6; 7(2x);8(2x); 9(6x)
34	Soy infant formula should not be used as the first choice for the diagnostic elimination diet but can be considered in some	7.6 / 9	0;6;7(2x);

	cases for economic, cultural and palatability reasons.		8(2x); 9(7x)
35	In IgE mediated allergy, the response to the diagnostic elimination diet is to be expected within 1 to 2 weeks.	8.8 / 9	8(2x); 9(11x)
36	In non-IgE mediated allergy, the response to the diagnostic elimination diet is to be expected within 2 to 4 weeks.	8.7 / 9	7;8;9(11x)
37	A double-blind placebo controlled food challenge (DBPCFC) is the gold standard for confirming a diagnosis of CMA.	8.9 / 9	8;9(12x)
38	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)
39	In IgE-mediated CMA, the OFC test should be supervised by trained medical health care professionals	8.8 / 9	7;8; 9(11x)
40	The DBPCFC is recommended for unclear cases and research purposes.	8.8 / 9	8(2x); 9(11x)
41	The result of a negative DBPCFC should be confirmed by an OFC of a regular age-appropriate serving to exclude delayed reactions.	8.4 / 9	6;7; 8(3x); 9(8x)
42	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)
43	Elevation of total IgE does not generally contribute to the diagnosis of CMA.	8.8 / 9	8(2x); 9(11x)
44	Elevated specific IgE (sIgE) and skin prick test (SPT) show sensitisation to CMP, but do not confirm CMA, whose diagnosis is based on the presence of symptoms.	8.8 / 9	8(2x); 9(11x)
45	The negative predictive values (NPVs) of sIgE and SPT are high in IgE mediated allergy.	8.5 / 9	7;8(4x); 9(8x)
46	The atopy patch test (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)

47	Currently, component resolved diagnostics and basophil activation test (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)
48	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)
49	IgG-antibodies against CMP 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.	8.9 / 9	8(1x); 9(12x)
50	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)
51	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)
52	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)
53	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)
54	Professional dietary counselling 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)
55	Close monitoring of growth is mandatory in children with CMA as they may suffer from growth faltering.	8.8 / 9	8(2x); 9(11x)

56	Irrespective of efficacy for the treatment of CMA, nutritional adequacy of available formulae is confirmed by the approval of the formula by the relevant national and international regulatory authorities assuming the intake is sufficient.	8.8 / 9	7; 9(12x)
57	In formula fed infants, a CM derived eHF is the first choice for a therapeutic elimination diet.	8.9 / 9	8; 9(12x)
58	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)
59	Partially hydrolysed CM based formulae are not indicated in the treatment of CMA.	8.8 / 9	7;8; 9(11x)
60	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)
61	RHFs can be considered as an alternative to CM derived eHF for a therapeutic elimination diet.	7.8 / 8	5(2x);7(3x); 8(2x);9(6x)
62	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)
63	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 (eg. milk containing biscuits).	8.8 / 9	8(3x); 10(9x)
64	Standardization of the home challenge applying the milk ladder adapted to local dietary habits is recommended.	8.8 / 9	8(3x); 10(9x)
65	The provision of oral immune therapy in selected patients with persistent IgE-mediated CMA should be limited to specialized centres.	8.8 / 9	8(2x); 9(11x)

66	Breastfeeding should be promoted for its multiple benefits, although its preventive effect on CMA has not been consistently documented.	9 / 9	9(13x)
67	Dietary restrictions, other than those warranted for the pregnant woman herself, are not indicated during pregnancy to prevent CMA.	9 / 9	9(13x)
68	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)
69	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)
70	In general, supplements of CM formula in breastfed infants are not recommended.	8.9 / 9	8; 9(12x)
71	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 for preventing CMA.	8.3/9	4;7; 8(2x); 9(9x)
72	The role of RHF for preventing CMA has not been studied.	8.8/9	7; 9(12x)
73	For infants with a documented family history of allergic disease who cannot be exclusively breastfed, there is evidence against recommending soy formula for preventing CMA.	8.5/9	7(3x); 8; 9(9x)
74	There is insufficient evidence to recommend the use of probiotics, prebiotics or synbiotics studied so far for CMA prevention.	8.8/9	7; 9(12x)
75	There is insufficient evidence to recommend the use of long chain poly-unsaturated fatty acids (LCPUFAs) for CMA prevention.	8.8/9	7; 9(12x)
76	Vitamin D supplementation has no role in CMA prevention.	8.8 / 9	7;

			9(12x)
77	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)
78	CMA may lead to substantial impairments in quality of life, both of the children and their caregivers.	8.8 / 9	8; 9(12x)

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Introduction

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 three categories: IgE-mediated, non-IgE-mediated and mixed. CMA is one of the most common food allergies worldwide. The diagnosis and management of CMA remain a clinical challenge due to the absence of a sensitive and specific diagnostic tool. Moreover, its clinical presentation is non-specific. ESPGHAN published a guideline on the diagnosis and management of CMA in 2012 (1). Since then, new data became available making it necessary to update the ESPGHAN recommendations. Both over- and under-diagnosis carry a nutritional risk, including faltering growth and micronutrient deficiencies, and have a negative impact of the quality of life of the infant and its family.

Methods

We evaluated evidence from systematic reviews and meta-analyses regarding prevalence, pathophysiology, symptoms, and diagnosis of CMA published after the previous ESPGHAN document (1). Medline was searched from inception until May 2022 for topics that were not covered in the previous document.

After finalisation of the manuscript, the most important conclusions and recommendations were summarized in "statements" and all authors voted on each of them with a score between 1 and 9; a score of $\geq$ 6 was arbitrarily considered as agreement. The higher the score, the stronger the agreement. The statements and the voting results are listed at the end of the manuscript. If four or more panel members voted < 6, there was < 75% consensus, and the statement was rejected.

Pathophysiology

Information on pathophysiology can be found as supplementary material.

Prevalence of cow's milk allergy

The true prevalence of CMA remains controversial for its subjective perception is far more frequent than the actual prevalence of confirmed CMA. 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 (2).

The most reliable epidemiologic data are from birth cohorts that are free from selection bias (3). Specific and precise data come from the EuroPrevall study which reports oral food challenge (OFC) proven CMA across Europe (4). A total of 9,336 (77.5%) from an initial cohort of 12,049 children were followed up to the age of two years, and CMA was suspected in 358 children and confirmed in 55 leading to an overall incidence of 0.54% (95% CI 0.41-0.70) (4). National incidences varied and ranged from <0.3% (in Lithuania, Germany and Greece) to 1% (in the Netherlands and UK) (AZ4). Of all children with CMA, 23.6% had no CM-specific serum IgE, especially those from the UK, Netherlands, Poland and Italy (AZ4). Interestingly, 69% (22/32) of the CM-allergic children that were re-evaluated one year after the diagnosis tolerated CM, ranging from 57% of those children with IgE-mediated CMA to 100% of the children with non-IgE mediated CMA (4).

According to old data, the prevalence of CMA during infancy was 1.9% in a Finnish study, 2.16% in the Isle of Wight (United Kingdom (UK)), 2.22% in a study from Denmark, 2.24% in the Netherlands, and up to 4.9% according to data from Norway (3). 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 (5). The incidence of CMA in exclusively breastfed infants is in the range of 0.4% to 0.5% according to two trials (level I evidence) (6,7) but might be as high as 2.1% (level II evidence) (8).

As part of the EuroPrevall study (4), the cumulative incidence of food hypersensitivity in 823 children followed up to 2 years of age in Hampshire (UK) for CMA was 2.4 % (1.4-

3.5) and for non-IgE-mediated CMA the cumulative incidence was 1.7 % (9). It remains unanswered as to 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 *versus* caesarean section), feeding, pollution and the administration of medication such as antibiotics and proton pump inhibitors early in life (10).

CMA also occurs in older children. Patient reports of presumed CMA range between 1 and 17.5%, 1 and 13.5%, and 1 to 4% in pre-schoolers, in children 5 to 16 years of age and adults, respectively (1). CM-specific IgE 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 (1). 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 (11). A double-blind placebo-controlled food challenge (DBPCFC) confirmed the diagnosis in <1% (12). A narrative review reported an overall pooled estimate of self-reported CMA of 6.0% (95% confidence interval (CI): 5.7-6.4) (13). However, the prevalence of food challenge defined CMA was ten times lower: 0.6% (0.5-0.8) (13).

Statement 1	Mean/ median	votes
The prevalence of cow's milk allergy (CMA) is influenced by regional differences and diagnostic procedures, and ranges from less than 0.5% to 4.9%.	8.9 / 9	8; 9(12x)

Clinical presentation of cow's milk allergy

Because of the impact on long-term health, the diagnosis of CMA should only be made on the basis of a complete history, physical examination, and anthropometric assessment (14). 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

immediate-onset IgE-mediated, usually within minutes following ingestion. In non-IgE mediated allergy, the onset of symptoms is delayed and develop usually after ≥2 h, usually between 6 and 72 hours (15,16). Venter et al. categorized CMA symptoms as mild, moderate and severe (15,16). 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 (16). 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) (16). 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 (16). 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, gastrointestinal (13-34%) and respiratory (1-8%). Up to one infant in four presents with a combination of symptoms involving more than one organ or system.

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)

Legend: ^ patients may also present with mixed IgE and non-IgE symptoms; * none of the symptoms is specific; ° unrelated to infection.

GI symptoms may be driven by an interplay of factors such as oesophagitis and GI inflammation, dysmotility, visceral hyperalgesia, dysbiosis and others (17).

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 (10,14,15,18-20). According to epidemiological data, the expected overlap between CMA and gastro-oesophageal reflux (GOR) can be observed in less than 1% of breastfed or formula fed infants (21). The prevalence of CMA in infants with functional gastrointestinal disorders (FGIDs), e.g. colic and regurgitation, now referred to as disorders of gut-brain interaction by the Rome IV criteria, is controversial with a natural resolution in the majority of cases around the fifth month of life for colic and one year of life for regurgitation (22-24). 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 (25,26). Regarding gastrointestinal (GI) symptoms, FPIAP and FPIES are conditions that need special mention.

Statement 2	Mean / median	Votes
Within the gastro-intestinal (GI) tract, non-IgE CMA can manifest with entities such as food protein induced allergic proctocolitis (FPIAP), food protein induced enterocolitis syndrome (FPIES), eosinophilic gastrointestinal (GI) disorders.	8.7 / 9	7(2x); 9(11x)

Food protein induced allergic protocolitis

Food protein-induced allergic proctocolitis (FPIAP; formerly known as allergic or eosinophilic proctocolitis) often presents with haematochezia or persistent mucus-streaked

diarrhoea in an otherwise healthy young infant (27). 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 (28-30). FPIAP usually begins within the first weeks of life and resolves in late infancy in most cases. FPIAP is characterised by inflammation of the distal colon in response to one or more food proteins through a mechanism that does not involve IgE. Whether treatment of FPIAP is needed or not is debated (27,31-33). The management of mild FPIAP should be limited to observation during the first month of haematochezia (31) as it is generally a benign and a self-limiting disorder despite marked mucosal abnormality on endoscopy.

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 (29,30), 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 (34), this has not been studied. CM formula fed infants should be treated with a diagnostic elimination diet and challenge, in line with the recommendations.

Statement 3	Mean / median	votes
FPIAP is, in most cases, a benign, easily recognised condition that may not need treatment in breastfed infants.	8.4 / 9	6; 7(2x); 8; 9(9x)

Food-protein induced enterocolitis syndrome

Food protein-induced enterocolitis syndrome (FPIES) is a non–IgE-mediated food allergy with CM being one of the most commonly reported triggers (35). 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 (35). FPIES is still underdiagnosed despite being considered a potential medical emergency. Acute FPIES typically presents in infancy with

repetitive protracted emesis approximately 1 to 4 hours after food ingestion. 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 to 10 hours of ingestion and can be present for up to 24 hours (36-40). 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 (36,37,41-43). Symptoms of acute FPIES usually resolve 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 (35).

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 (35). Chronic FPIES is uncommon and reported more frequently in Japan and Korea (38,40). It develops after repeated ingestion of the triggering food, and presents as chronic/intermittent emesis, watery diarrhoea, and failure to thrive, potentially leading to dehydration and shock (35,43,44). Hypoalbuminemia and poor weight gain can hint to the presence of chronic CM-induced FPIES in young infants with persistent GI symptoms (45). 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 (35). The diagnosis of FPIES primarily based on a clinical history of typical characteristic signs and symptoms with improvement 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 (35). Therefore, if only a single FPIES episode has occurred, a diagnostic OFC should be considered to confirm the diagnosis. OFC is helpful to consider 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 (35).

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 oral food challenge (OFC) can be considered in order to help confirm the diagnosis.	8.8 / 9	7; 9(12x)

Eosinophilic gastrointestinal disorders

Eosinophilic gastrointestinal disorders (EGIDs) are characterized by increased eosinophil counts on tissue biopsies responsible for clinical findings such as abdominal pain, nausea, vomiting, and diarrhoea (46). 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 (47-53). 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 (54,55).

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

Eosinophilic oesophagitis

Eosinophilic oesophagitis (EoE) is characterized by a) oesophageal symptoms including feeding intolerance, GORD, dysphagia and food impaction, and b) 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 (56). There is a similar increase in incidence and prevalence as in other allergic conditions (57). Multiple studies support the central role of allergy in the aetiopathogenesis of EoE based on three pieces of evidence: 1) the association of an allergic history and/or correlation with other allergic manifestations in children with EoE; 2) the fact that the majority of children with EoE respond to dietary exclusion (58); 3) the existence of animal models of allergy with sensitization and allergen exposure associated with the development of oesophageal mucosal eosinophilia (59). 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% to 90% of cases and in almost all studies CM is the most common food trigger (60-66). 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 (67,68). After a diagnostic elimination diet, normalization of histology has to be ascertained.

Statement 8	Mean/ median	votes
CMA is considered a possible factor in the pathogenesis of eosinophilic oesophagitis (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 functional gastrointestinal disorders

The prevalence of CMA in infants with FGIDs is controversial. In infants presenting with GI symptoms associated with CM intake, prevalence is estimated at approximately 20-25% of all infants (69-71). Although pathophysiology differs, whether these symptoms are considered as a FGID or a non-IgE mediated allergy is related to the background of the

355 consulted health care professional (HCP). A family history of allergy, the involvement of
356 several organ systems (digestive, cutaneous, respiratory), a younger age, the lack of
357 improvement after usual therapeutic measures for FGIDs increases the likelihood of non-
358 IgE mediated CMA (1,14,15,18-20). GI symptoms may be driven by an interplay of factors
359 such as oesophagitis and GI inflammation, dysmotility, visceral hyperalgesia, and dysbiosis
360 (17). In some infants, food allergens play a role as triggers for FGIDs that occur in
361 association with other GI, respiratory, or skin manifestations as well as poor growth
362 (25,26).
363 The cumulative prevalence of FGIDs, such as regurgitation, constipation, dyschezia and
364 colic in infants is estimated to be around 25%. The prevalence of FGIDs is much higher
365 than that of CMA. CM elimination often results in improvement of symptoms, although
366 this may partially be ascribed to the natural course or a placebo effect and needs to be
367 interpreted with caution. In some situations, it may be difficult to separate allergic reactions
368 from FGIDs because i) some symptoms and signs of functional disorders and allergy are
369 similar, ii) there is no sensitive and specific diagnostic test for a FGID or for (non IgE-
370 mediated) allergy, and iii) in both conditions, symptoms improve by elimination diet.
371

Statement 9	Mean / median	votes
Some patients with suspected FGIDs can improve with a CM elimination regardless of CMA.	4.3 / 5	0(2x);1; 2;4;5(3); 7(3);9
Statement 10		
Some patients with suspected FGIDs can improve with a CM elimination regardless of CMA, but there are no specific tests to allow clarification of the diagnosis by discriminating between CMA and functional gastrointestinal disorders (FGIDs).	7.8 / 9	4(2x); 7(2x); 8;9(9x)
Statement 9&10: One member considers FGIDs out of the spectrum of CMA		
Statement 11		
In patients not responding to conventional therapies for functional GI disorders (FGIDs), CMA can be considered and patients trialled on a time limited elimination diet which should be followed by an OFC.	8.4 / 9	6;7; 8(3x); 9(8x)

Gastro-oesophageal reflux (disease)

To confirm the diagnosis of CMA in infants presenting with GOR and/or colic, it is recommended to eliminate CM for 2 to 4 weeks, especially before treatment with acid suppressors for GOR (5,14,72). Breastfeeding should be encouraged while the mother may be advised to exclude CM in her diet for 2 to 4 weeks and reintroduce CM thereafter. A maternal exclusion diet can potentially lead to early cessation of breastfeeding (73). In formula fed infants, 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 (25,74,75), indicating that the improvement may not be related to CMA.

Statement 12	Mean/ median	votes
In patients not responding to conventional therapies for gastro-oesophageal reflux (disease) (GOR(D)), CMA can be considered and a time limited elimination diet can be started which should be followed by an oral food challenge (OFC).	8.8 / 9	8(3x); 9(10x)

Irritability, crying and infant colic

Approximately 20% of parents consult a HCP because their infants present with excessive crying and irritability, which are described as infantile colic. Infantile colic is a common distressing condition characterised by excessive crying in the first few months of life. The aetiopathogenesis of infantile 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 (76). Acupuncture and the use of soy infant formula are currently not recommended (76). 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 (77). 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 (AZ77). Benefits reported for hydrolysed formulae are inconsistent (AZ77). However, in this Cochrane Review infantile 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" (AZ77). But the definition of infantile colic was adapted in the Rome IV criteria and made less stringent: for clinical purposes, infantile colic 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 infant failure to thrive, fever, or illness (22). However, for research purposes the definition is still more strict: 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 (22).

Statement13		
In infants who present with crying and irritability there is insufficient data to recommend a time-limited CM elimination diet followed by an OFC.	8.4 / 9	6;7; 8(3x); 9(8x)
Statement 14		
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 15		
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 can be trialled which should be followed by an OFC.	7.9 / 9	4;7(3x); 8(4x); 9(5x)
One panel member estimated that the wording "additional symptoms" was of no added value.		

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% (78). A number of studies have reported an association between CM consumption and constipation (79-93). 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, two randomised 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 (80,87,94).

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 (85). These factors (e.g. pain, proctitis, fissures, increased anal sphincter tone, etc.) resolve after a CMP elimination diet (85). The joint guideline for functional constipation from the European and North American Societies for Pediatric Gastroenterology, Hepatology, and Nutrition published in 2014 suggests, based on expert opinion, a 2- to 4-week trial of avoidance of CMP in the child with intractable constipation (94).

Statement 16	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 can be started which should be followed by an OFC.	7.9 / 8	6;7(4x); 8(3x);9(5x)

Functional abdominal pain disorders

In a case-control study, Saps et al. 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 FIGD (7 with irritable bowel syndrome (IBS) and 2 with functional dyschezia) compared to none of an age-matched control group without history of CMA (95). Pre-schoolers with a history of allergic disease (including food allergy) also have an increased risk for IBS in school age (96). 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 odd's ratio (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) (97). 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 (98).

Schappi et al. 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 (99). Eosinophils and mast cells within the lamina propria were increased in the children with atopy and were shown to degranulate rapidly (P <0.05) 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 (99).

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 (100). More evidence is needed to clarify the role of allergy and immune activation in the pathogenesis of FAPDs in children.

Statement 17	Mean / median	votes
When treatment for functional abdominal pain disorders is	3.5 / 3	0(3x);1(2x);

being initiated, CMA can be considered, and a time limited elimination diet be started which should be followed by an OFC.		2;4;5; 6(2x); 8;9
Statement 18		
In patients not responding to other standard treatments for functional abdominal pain disorders, there is sufficient evidence to recommend a time limited CM elimination diet followed by an OFC.	3.9 / 5	0(3x); 1(3x); 5;6; 7(3x);8(2x)
Statement 19		
In patients not responding to other standard treatments for functional abdominal pain disorders, there is insufficient evidence to recommend a time limited CM elimination diet followed by an OFC.	6.5 / 7	2;4(2x); 5(2X); 7(3);8; 9(4x)

Increased risk for infectious disease

The high rate of respiratory infections in early life has a major impact on healthcare 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 (101). Outcome of trials suggest that an elimination diet supplemented with prebiotics, probiotics and synbiotics may decrease the frequency and severity of mainly respiratory tract but also gastrointestinal infections and reduce antibiotic intake (101). GI, skin, respiratory and ear infections affect significantly more children with CMA than those without, increasing by 74% ($p < .001$), 20% ($p < .001$), 9% ($p < .001$), and 30% ($p < .001$) respectively (102). 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 ($p < .001$) (102).

Statement 20	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)

One member estimates that the is sufficient evidence in literature that shows an increased prevalence of infections in infants with CMA

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 (103). 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, $p = 0.025$) (104). However, infants without family history can also develop allergies (104), and overall allergy without a family history, outnumber those with one. 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 (104). Confounding variables such as pollution and the administration of medication such as antibiotics and proton pump inhibitors early in life (105,106). 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 gastrointestinal microbiome development (106, 107).

Statement 21	Mean / median	votes
Absence of family history does not exclude the possibility of CMA.	8.8 / 9	8(2x); 9(11x)
Statement 22		
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 tools

The CM-related Symptom Score (CoMiSS^{TM}) was developed to alert HCPs to the possibility of CMA being responsible for excessive crying, regurgitation, stool pattern changes as well as skin and respiratory symptoms. 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 best documented awareness tool (108). 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% (108). CoMiSS was reported to be a simple and operable method to screen for CMA, though there may be a risk of under-diagnosis when CoMiSS≥12 is used as the criterion for early identification of CMA in Chinese infants (109). The impact of genetic or regional difference on CMA symptoms needs to be further studied. An updated CoMiSS cut-off of ≥ 10 has been proposed as awareness for CMA (110). A multi-disciplinary task force of the European Academy of Allergy and Clinical Immunology developed a paediatric diet history tool, with the goals to develop a structured approach to connect symptoms, suspected foods and dietary intake (111), Another awareness tool, based on 25 questions has been tested in 43 infants aged up to 2 years (112). 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 (112). 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 (113). The latter two scores were, however, not further evaluated.

Statement 23	Mean / Median	votes
The Cow's Milk-associated Symptom Score (CoMiSS) is an awareness tool for CMA	8.5 / 9	6;7;8; 9(10x)
Statement 24		
The CoMiSS initial score 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 cow's milk allergy

Diagnostic cow's milk elimination diet

Symptoms and signs of CMA involve skin (urticaria, angioedema, atopic eczema/dermatitis), gastrointestinal (i.e., vomiting, colic, abdominal pain, diarrhoea, constipation), respiratory (rhinorrhoea, sneezing, cough, dyspnoea) to systemic reactions (cardiovascular collapse) (114). Reactions are mostly triggered by milk ingestion, but can also be triggered by inhalation and skin contact (114). A proper diagnosis of CMA should always start with an "allergy-focused clinical history" and a complete physical examination (15). Attention should be given to the presenting symptoms and signs that may be indicating possible CMA. Information regarding the infant's feeding history and the personal and familial history of allergic disease should be asked for.

If CMA is suspected, a diagnostic elimination for 2 to 4 weeks is recommended. Improvement will be faster in IgE mediated than in non-IgE mediated allergy. In severe atopic dermatitis, the diagnostic elimination diet may take 6 up to 8 weeks before improvement (115). There is only evidence for the use of CM based eHFs for diagnostic elimination diet; RHFs and soy formula are possibly as well efficacious, but they cannot be recommended because of lack of evidence.

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 e.g. psychological factors, an OFC with an objective unequivocal reaction is sufficient for the diagnosis of CMA (1, 116,117). 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 (117-119). 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 25	Mean / Median	Votes
The response to a diagnostic elimination diet followed by an OFC is the	8.9 / 9	8;

corner stone for the diagnosis of CMA.		9(12x)

Diagnostic elimination diet in breastfed infants

Exclusively breastfed infants with non-IgE mediated CMA may react to protein from the maternal diet (120). It is well-established that food proteins, such as egg, soya, cow's milk and wheat, are detectable in breastmilk for many hours or days after ingestion. (121). Eight peptide sequences of bovine β -lactoglobulin had significantly higher levels in milk from allergic mothers than in milk from non-allergic mothers (122). Dietary bovine β-lactoglobulin may be absorbed through the intestinal barrier and secreted into human milk (122). This seems to be significantly higher in allergic mothers and may have consequences for the development of the immune system of their breastfed infant (122). 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 (123). Up to 20% of the breastfed infants have spontaneous resolution of symptoms such as rectal bleeding without any changes in the maternal diet (120).

Breastfeeding with maternal elimination diet for CM may be considered for 2 to 4 weeks (124). 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 (125). 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 (126-128). When symptoms improve the mother should reintroduce CM in her diet.

Exceptionally, in very severe cases, a temporal introduction of AAF may be warranted. Mothers should be encouraged to express breastmilk 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 26	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, extensively hydrolysed formulae (eHF) are the first choice for CMA management, whereas amino acid-based formulae (AAF) are reserved for more severe cases and/or impaired nutritional status (1,129) (**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. In the presence of severe diarrhoea, lasting longer than a week, lactase deficiency may be suspected, and a lactose-free eHF may be temporary preferred. We refer to an international consensus report to define severity and management of diarrhoea (130). We could not find studies related to the usage of medium chain triglycerides in the event of CMA related diarrhoea.

Table 2: Properties of different hydrolyzed formulae, amino acid formula and soy infant formula (131).

	Protein	Carbohydrate	Lipids	Comments
Partially hydrolyzed formula	oligopeptides from hydrolyzed cow's milk proteins [whey and/or casein with MW < 5000 Dalton (Da) (range 3000-10000 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 <1500Da) 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

The American Academy of Pediatrics defines partially hydrolysed formulae (pHF) as those containing oligopeptides with a molecular weight of <5000 Da and extensively hydrolysed formulae (eHF) as those containing peptides with a molecular weight <3000 Da (132). The American Academy of Pediatrics and the 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, the nutritional composition and the residual allergenicity of the hypoallergenic formula (15). CMP 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 (133). 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 (134). Significant residual beta-lactoglobulin or casein-derived immunogenic peptides or proteins found in some eHF products suggests incomplete hydrolysis and/or contamination during manufacturing (134). However, if these differences in hydrolyzation process and peptide size also result in a different clinical outcome has been poorly studied. A comparative trial did not show a difference in efficacy between a whey (with probiotics - this product was never commercialised) and a casein eHF with probiotics (135). The eHFs evaluated to date appear to be well-tolerated by most children with CMA (136). However, published studies do not allow for any conclusion regarding one formula to be superior to another formula for CMA management (136).

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 whey eHF (137). Data from the UK report a 29% failure rate of some eHFs (138). Conversely, the efficacy of some other eHFs was reported to be equal to that of AAF (139). 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 (120). There is no consensus on minimal and maximal duration of a diagnostic elimination diet. If symptoms persist, the diet needs to be carefully re-evaluated as potential food allergens may have been missed or another diagnosis is considered (114).

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) failure to thrive; iii) multiple and severe complex GI food allergies; iv) acute and chronic severe FPIES; v) eosinophilic esophagitis not responding to an extended exclusion diet or not eating solids; vi) to avoid any risk of sensitization; vii) symptom persistence on eHF (even partially) (114, 140, 141).

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 healthcare system (142). 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 (143). In the "step-down" concept an AAF is used as therapeutic elimination diet, and when the OFC is positive, an eHF is used for the therapeutic elimination diet (143). A Turkish guideline also recommends the step-down approach (144). Finally, there are Chinese consensus papers of gastroenterologists and dermatologists recommending AAF as diagnostic elimination diet (145,146).

Hydrolysed rice formulae (HRFs) have become more available and are an alternative option for the treatment of CMA as they do not contain any CMP (147-151), although there are only limited data of their use for diagnostic elimination diet in suspected CMA. Although the arsenic content of RHF are reported to be within the recommended limits, and HRFs were evaluated as safe by the ESPGHAN Nutrition Committee, the arsenic content is not mentioned in the majority of the commercialised HRFs (152). To date, no data exist on the efficacy of HRFs in infants not tolerating eHF as an alternative to AAF (131).

Soy protein based infant formulae contain enzymatically hydrolysed soy protein isolate. The reason to use soy isolate is for technical and protein quality reasons. Soy formula also

664 contains phytate, aluminium, and phytoestrogenic isoflavone at levels not present in milk-
665 based formulae, although in the last few decades there has been a significant reduction of
666 these components. Aluminum and estrogens are present in breastmilk, and the latter are
667 increased in mothers who consume large amounts of soy (153). Global evaluation of the
668 impact of modern soy formulae on human development suggests that their use is not
669 harmful (154,155).
670
671 A commentary by the ESPGHAN Committee on Nutrition (156) and a clinical report by the
672 AAP (157) recommended, based on the study by Klemola et al (158) and Zieger et al (159),
673 against the use of soy infant formula especially below the age of 6 months because of the
674 risk of co-allergy. The age limit was proposed based on data from a small subgroup of 20
675 infants (158). Klemola et al reported later that all children with co-allergy between CM and
676 soy had non-IgE mediated allergy (160). Zieger et al concluded that 14% of infants with
677 IgE-CMA were also allergic to soy (159). However, this study included 99 children from 5
678 US centres, of which not all had a positive SPT or detectable or very low soy sIgE (159).
679 So, co-allergy between CM and soy is rare in IgE mediated CMA, and soy infant formula
680 can also be considered as an alternative option (159,160). However, in non-IgE mediated
681 CMA co-allergy is more frequent, although data suggesting this association mainly come
682 from the USA. In an Italian study in 21 infants with atopic dermatitis due to CM
683 hypersensitivity, 20/21 cleared symptoms with soy formula (one refused to drink soy)
684 (161). A possible secondary sensitization to soy was found in one infant in whom dietary
685 therapy alone was not effective (161). In another Italian study in 66 children with FPIES,
686 none had coexisting CM and soy allergies (162). In a Korean study, patients with positive
687 soy-specific IgE accounted for 18.3% of 224 children sensitized to CMP (163). The
688 prevalence of sensitization to soy decreased with age (36.8% in the first year, 16.4% in the
689 second year, and 13.7% in the third year of life) (163). Of 21 CMA patients, 42.9% (n=9)
690 had soy allergy (mean age 10.3 months) (163). However, US studies report that about 30%
691 to 50% of infants with FPIES react to both CM and soy, whereas most non-US studies
692 report a far smaller percentage (164). Soy infant formula is less commonly used in non-IgE
693 mediated allergy. Of note, in many European countries, the availability of soy formula has
694 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 27	Mean / Median	Votes
In formula fed infants, a CM derived extensively hydrolysed formula (eHF) is the first choice for a diagnostic elimination diet.	8.8 / 9	8(2x); 9(11x)
Statement 28		
Only CM derived eHFs tested in randomized clinical trials should be used.	8.6 / 9	7(2x);8; 9(10x)
Statement 29		
There are insufficient comparative trials to make a recommendation whether to use whey versus casein hydrolysates.	8.8 / 9	8(3x); 9(10x)
Statement 30		
30A. In patients with CMA and severe diarrhoea and/or with severe malnutrition, the transient use during 2-4 weeks of a formula without lactose may be preferred.	7.0 / 8	0;5(2x); 7(3x); 8(3x); 9(4x)
B. In patients with CMA severe diarrhoea and/or with severe malnutrition, the transient use during 2-4 weeks of a formula with lactose and with medium chain triglycerides (MCTs) may be preferred.	4.4 / 4	0(2x);1; 2;3(2x);4; 6;7(2x); 8(3x)
The difference between Statement A and B concerns the role of MCTs. It was estimated that there is no evidence "against" but also no evidence "in favour". Three panel members considered there was sufficient evidence in favour of the MCTs.		
Statement 31		
In formula fed infants, amino acid-based formula (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 32		

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 33		
Although less studied than CM based eHFs, rice hydrolysed formulae (RHFs) can be considered as an alternative for a diagnostic elimination diet.	7.4 / 8	1;5;6; 7(2x); 8(2x); 9(6x)
Two panel members estimate that there is insufficient evidence to consider RHF as an option for a diagnostic elimination diet		
Statement 34		
34A. 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)
34B. 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 and cultural reasons.	6.9 / 8	1(2x); 7(4x); 8(3x); 9(4x)
The difference between Statement A and B concerns strong difference in opinion regarding "palatability" as an acceptable reason or not to put an infant on soy formula.		

Oral food challenge

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

The milk OFC should start with a very small dose (eg. 1 ml) and increase stepwise to a significant volume of at least 100 ml (1; 114). In IgE-mediated CMA, the OFC should be supervised by trained HCPs. 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. 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 (1).

The parents should be prepared to document any late reactions. An OFC should always be performed under supervision by an HCP. Patients should be observed for at least 2 hours following the maximum dose. 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 (1). Intravenous access is only necessary in selected cases, but always if a severe or systemic reaction is likely.

The DBPCFC is the gold standard for the diagnosis of food allergy (1,117). 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 in clinical practice. A DBPCFC is preferentially used 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 (1). 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 one week in a double-blind way in order to detect late reactions to CM (165). A negative DBPCFC should be confirmed by a negative open OFC with a regular age-appropriate serving (1, 116) 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

Table 3. Algorithm for oral food challenge (adapted from ref 165).

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

738

Statement 35	Mean / Median	Votes
In IgE mediated allergy, the response to the diagnostic elimination diet is to be expected within 1 to 2 weeks.	8.8 / 9	8(2x); 9(11x)
Statement 36		
In non-IgE mediated allergy, the response to the diagnostic elimination diet is to be expected within 2 to 4 weeks.	8.7 / 9	7;8; 9(11x)
Statement 37		
A double-blind placebo controlled food challenge (DBPCFC) is the gold standard for confirming a diagnosis of CMA.	8.9 / 9	8; 9(12x)
Statement 38		
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 39		
In IgE-mediated CMA, the OFC test should be supervised by trained medical health care professionals	8.8 / 9	7;8; 9(11x)
Statement 40		
The DBPCFC is recommended for unclear cases and research purposes.	8.8 / 9	8(2x); 9(11x)
Statement 41		
The result of a negative DBPCFC should be confirmed by an OFC of a	8.4 / 9	6;7;

regular age-appropriate serving to exclude delayed reactions.		8(3x); 9(8x)
Statement 42		
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 Specific IgE 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 (114).

In a systematic review and meta-analysis by the EAACI (166), atopy patch test (APT), skin prick test (SPT) and specific IgE (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 (87% (95% CI 75–94) sIgE. 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 CMP or a SPT with CM are useful in the diagnostic workup, although these tests have a low specificity leading to overdiagnosis (167).

The concordance between SPT and sIgE in CMA is variable but never high (168-170). The choice of test is guided by local availability and relative and absolute contraindications for the SPT (114,171), which include severe eczema/dermographism, 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 (172,173). 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 (114,174).

A positive SPT or elevated specific IgE demonstrates sensitization to CMP, but do not prove CMA. The NPV of both is >90% for IgE-mediated CMA (171). 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 (171). Young infants may initially have a negative SPT and absence of CMP-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 (114164,171). A 3 mm cut-off for the SPT results a high sensitivity and NPV, but yields a low specificity and PPV, and thus may lead to overdiagnosis (167). The PPV is > 95 % for a wheal size above ≥8 mm or > 6 mm for children younger than 2 years (167).

Statement 43		
Elevation of total IgE does not generally contribute to the diagnosis of CMA.	8.8 / 9	8(2x); 9(11x)
Statement 44		
Elevated specific IgE (sIgE) and skin prick test (SPT) show sensitisation to CMP, but do not confirm CMA, whose diagnosis is based on the presence of symptoms.	8.8 / 9	8(2x); 9(11x)
Statement 45		
The negative predictive values (NPVs) of sIgE and SPT are high in IgE mediated allergy.	8.5 / 9	7;8(4x); 9(8x)

Atopy patch test

At present, there are insufficient studies demonstrating advantages of the APT over SPT or sIgE (114,166,171,175) in part due to the lack of standardized test substances. Therefore, APTs are not recommended for routine diagnosis of food allergy (114).

Statement 46	Mean / Median	votes
The atopy patch test (APT) is not recommended for the routine	8.6 / 9	6;8(2x);

diagnosis of non-IgE mediated CMA mainly due to insufficient evidence for reproducibility and efficacy.		9(10x)

Component resolved diagnostics and basophil activation test

Component resolved diagnostics is an emerging diagnostic tool that detects sIgE to allergenic molecules or the epitope of the allergen (171,176). 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 (177). 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 (177).

The basophil activation test (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 (178, 179). The PPV for the threshold of CD203c expression was 85.7% for milk and 75.0% for casein (178). The BAT demonstrated higher specificity and NPV than the SPT and sIgE, while retaining sensitivity and PPV (114). 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 (114).

Statement 47	Mean / Median	votes
Currently, component resolved diagnostics and basophil activation test (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 GOR 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 (21,180-182), but are not diagnostic as these findings can be found in other upper GI pathologies. Lower GI endoscopy findings are non-specific, including focal mucosal erythema, loss of vascular patterns, erosions, ecchymosis, and lymphoid nodular hyperplasia (28,181-183). Lymphoid nodular hyperplasia is a common finding in infants with CMA and may be found in the colon and/or terminal ileum (184).

Lozinsky et al. showed that 89.3% (236/264) of infants had eosinophils (between 5 and 25 per high-power field) in their colonic biopsies (28,53,185). Mennini et al. emphasize the importance of eosinophil quantification in different colonic segments (28). In neonatal transient eosinophilic colitis, endoscopy and histology findings are the same as in CMA, but bleeding is self-limited and ceases without CM elimination diet (186).

To date, there are no specific recommendations on the timing and necessity of colonoscopy in children suspected to have CMA (28). In a cohort of 730 children aged 1 to 18 years undergoing colonoscopy because of rectal bleeding, allergic colitis was found in 3.3% of cases (187).

Statement 48	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)

Other biological markers

A number of alternative diagnostic approaches are popular among complementary and alternative medicine practitioners, e.g. bioresonance, kinesiology, iridology, hair analysis, cytotoxic test, and IgG and IgG4 levels (114). These tests are currently not validated and cannot be recommended for the diagnosis of food allergy (114). 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 (114).

Other 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 (167, 188). In a recent paper including 30 infants aged 0 to 9 months with CMA, levels of faecal calprotectin were higher in CMP allergic than in healthy infants at diagnosis but differences did not reach statistical significance ($\underline{P}$ = 0.119)(188). 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). Prospective studies with larger populations are needed to establish the value of faecal calprotectin as a biomarker of CMA.

Statement 49	Mean / Median	votes
IgG-antibodies against CMP 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 in children with cow's milk allergy

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) (189). 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. Long lasting elimination diets, especially over the age of one year, can be associated with nutritional deficiencies, eating disorders and changes in taste preferences (190,191). Elimination diets have also a negative impact on taste development and preferences (192,193).

In infants, it is possible to propose an alternative formula, while in older children suggesting suitable substitutes is challenging. Extensively hydrolysed or cow's milk free formulae improve the quality of the CMP free diet, particularly regarding intake of vitamin D, vitamin E, energy, protein, calcium, iron and zinc (194,195). 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.
Among older children with food allergies, such as CM, intakes under milk-free diets differ significantly from a milk-consuming diet with respect to calcium, riboflavin, zinc and niacin (196,197). 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) (196,198200). 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 (190,201). Particular attention must be paid to protein-energy intake (190), as Meyer et al. found that only 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 (202). 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 (191,203). This occurs despite the contribution of subtle inflammation and abnormal intestinal permeability, that may affect absorption and utilization of nutrients, and adds to the nutritional risk in these children (191,204,205).

Also, lipid and carbohydrate intakes may be inadequate during an exclusion diet, and alternative sources should be used in older children (196,197,203). In a cohort of 91 children with a mean age of 18.9 months (SD 16.5-21.3), the plasma levels of linoleic,

886 docosahexaenoic and arachidonic acid warrant particular attention being lower compared to
887 controls (203).
888
889 The supplementary dose of elemental calcium can vary from 500 mg/day in infancy and
890 toddlerhood to 1000 mg/day or more during adolescence, remaining below the maximum
891 tolerable dose according to the recommended intake per age (190). Regarding vitamin D
892 supplementation, patients at risk for vitamin D deficiency had a daily requirement of 400–
893 1000 IU in the first years of life and 600–1000 IU from 1 to 18 years (206).

894 To prevent malnutrition in children excluding CM, professional dietary advice is essential
895 to ensure appropriate substitution of dairy products. Several studies have found improved
896 nutrient intake in CMA children who receive dietary advice from a dietitian (194,204).
897

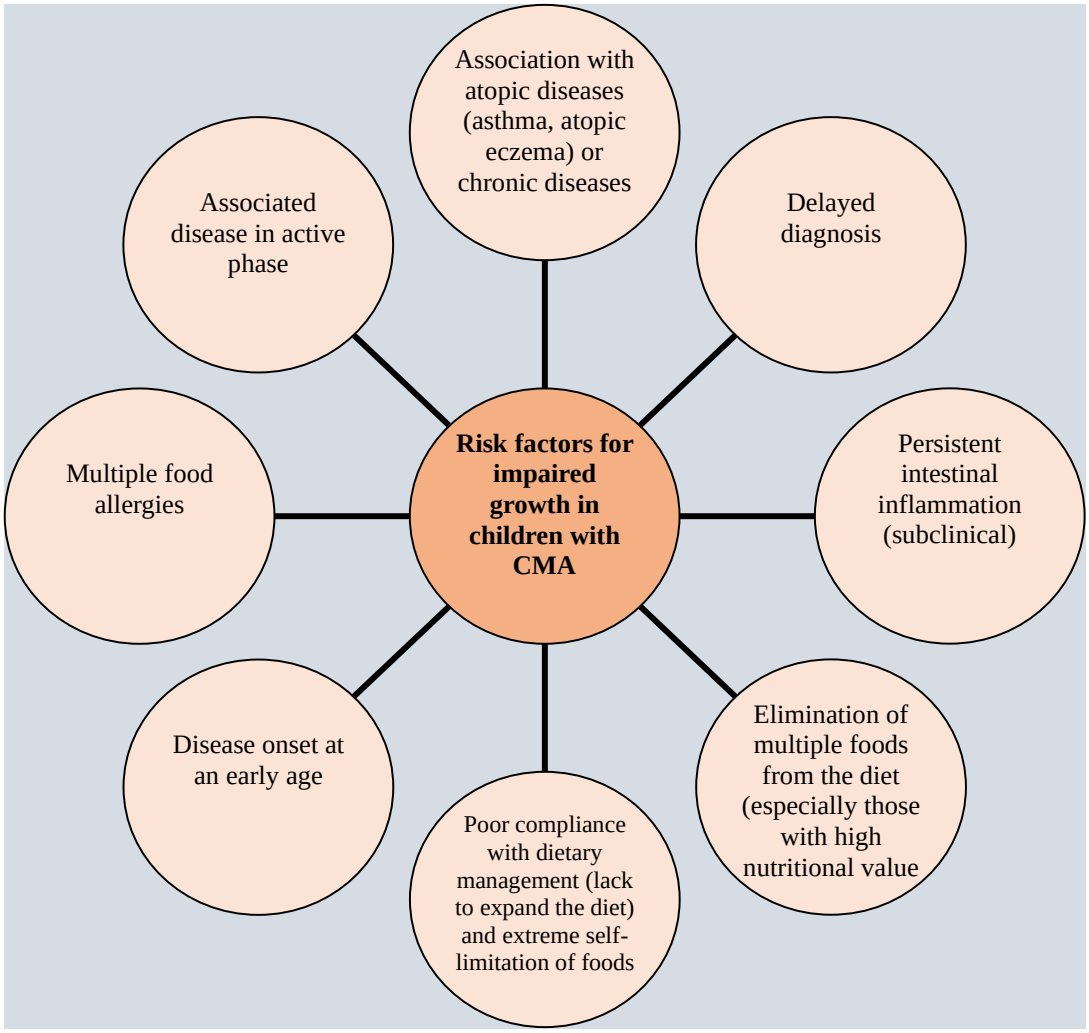
Statement 50	Mean / Median	votes
Professional dietary counselling should be offered to mothers on CM elimination diets. Supplements of calcium and vitamin D are recommended for lactating mothers.	8.8 / 9	8(2x); 9(11x)
Statement 51		
Complementary feeding should be introduced at the same age as in children 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 52		
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 53		
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 54		
Professional dietary counselling 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 cow's milk allergy

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 (207) (**Figure 1**). Final adult height (n:87) was shown to be lower in those with CMA compared to healthy controls (205).

Figure 1. Risk factors for impaired growth in children with CMA.



Children with CMA and eczema show an impaired height compared to healthy controls and this was mostly associated with the severity of eczema (208,209). 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 (207,210).

Clinical trials have investigated the effect of different formulae on growth. In one prospective randomized trial in infants with CMA, in 84 soy fed infants and 84 extensively hydrolysed whey formula (eHF-W) fed infants growth was within reference values (211). Another study prospectively examined growth in four groups (breastmilk, soy formula, casein hydrolysate, rice hydrolysate) of infants with CMA, between the age of 6 and 12 months (212). No between-group differences in growth were found, but all four groups

showed negative values for both weight-for-age (WA) and height for age (HA) Z-scores at 6 months (212). Infants fed the two hydrolysed formulae showed a better weight gain between the age of 6 to 12 months (212).

An RCT with 65 children aged between 5 and 12 months fed with two different types of formulae (AAF, eHF-W) compared to controls showed a difference in WA Z-scores between the two CMA groups and the healthy control group at T0 and after 3 months of follow up (213). The authors concluded that long-term use of eHF-W and AAF are safe and lead to normalization of anthropometric parameters without considerable alterations in protein metabolism (213).

Feeding with eHF-C was associated with a transient lower weight gain during the first year of life (214). Children on an elimination diet presented higher frequency of picky eating and higher scores of feeding problems (215). Picky eating was associated with lower values of weight-for-age z-scores (215). A significantly higher number of foods are eliminated from the diet in children with CMA and feeding difficulties than in children without feeding difficulties (216). In the UK, children with food allergies are more underweight than the general population, which appears to be linked to the number of foods excluded (217). Also in the USA, children with CMA weigh significantly less than children without CMA (218,219). However, variables such as genetic background or insurance may be confounding this observation. In the families with a commercial insurance, children with CMA were significantly shorter (mean height z-score = 0.06; P = .01) and weighed less (mean weight z-score -0.1; P = .006) than children without food allergies (mean height z-score = 0.42; mean weight z-score = 0.07) (218). In contrast, children with food allergies and state insurance were not smaller in height or weight compared with children without food allergies. Among white subjects, there was a significant effect of food allergies on height and weight (ANOVA for height P = .012, for weight P = .0036) that was not observed for Hispanic/Latino, black, or Asian subjects (218).

A recent systematic review analysed seven RCTs conducted in infants with confirmed CMA fed both with AAF with and without synbiotics (*Bifidobacterium breve* M16-V and prebiotics) (220). All studies showed adequate growth parameters at baseline and after treatment, however, in only two studies growth was a primary outcome. Another systematic review and meta-analysis showed that adequate growth was observed through the study

duration; however, in only two studies growth was a primary outcome (220). A prospective study (AZ201) 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 (221).

Statement 55	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 formulae for cow's milk allergy

There is a relatively wide choice of nutritionally adequate formulae in infants with CMA: eHF (whey or casein), plant-based formulae (hydrolysed rice and soy-protein formulae) and AAF (222). The European Food Safety Authority requires for all newly marketed hydrolysates at least one RCT demonstrating non-inferiority in growth compared to a standard formula (222).

Protein

According to European Regulation 2016/127, the protein range of hydrolysed formulae 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) (223). In particular, minimum and maximum values for essential amino acids should be similar to breast milk (223) and special considerations for amino acids should be addressed such as e.g. sulphur containing amino acids for soy- and branched chain amino acids (BCAAs) for rice-based formulae (224).

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 (225). There may be different rates of digestion, absorption and

metabolism of amino acids. In hydrolysed formulae, the concentration of free amino acids is about 100 times higher than in standard formulae (226), mainly represented by BCAAs and glutamate (227). After ingestion of hydrolysed proteins an increase in blood urea levels has been observed (228).

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 (229). From a satiety perspective, intact protein suppresses ghrelin levels to a greater extent than hydrolysed protein (230). 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 (231).

Lipids

There is no evidence for requirements of essential fatty acids or medium chain triglycerides (MCT) in formulae for the treatment of CMA, although regarding MCT, beneficial effects have been suggested (232-235). A recent in vitro study investigated the digestion of MCT at different concentrations of 0, 20, 30, and 55% and showed no differences (236).

Carbohydrates

Historically, it was technically almost impossible to manufacture lactose that was strictly CM free. In 2010, ~70 % of hypoallergenic formulae were lactose-free and contained glucose polymers instead (1). 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 (211), and some biotechnologically produced structures identical to those present in breast milk (Human Identical Milk Oligosaccharides; HiMOs)

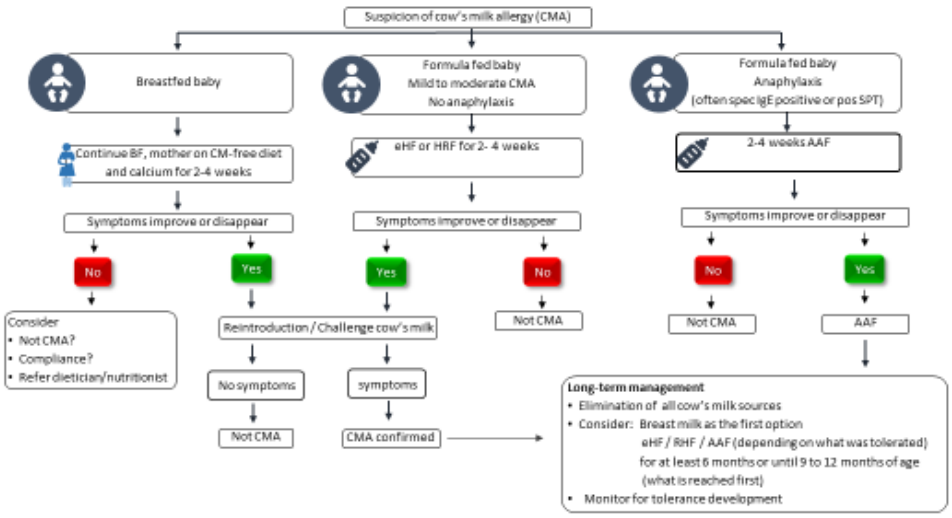
are added to some therapeutic formulae (237). Further studies are needed to evaluate the efficacy and nutritional value of HMO-supplemented formulae.

Statement 56	Mean/Median	votes
Irrespective of efficacy for the treatment of CMA, nutritional adequacy of available formulae is confirmed by the approval of the formula by the relevant national and international regulatory authorities assuming the intake is sufficient.	8.8 / 9	7; 9(12x)

Dietary treatment of cow's milk allergy in practice

Dietary treatment depends on if the infant is exclusively or partially breastfed, or exclusively formula fed. As for the duration of the treatment, the ESPGHAN practical guideline of 2012 (**Figure 2**) should be at least for 6 months or up to the moment when the infant reaches 12 months, whatever is reached first (1). Diversification or complementary feeding should be introduced at the same age as in children without CMA (1,165). The introduction of foods should follow the same recommendations as for those without CMA.

Figure 2. Practical algorithm to manage an infant with CMA.



SPT: skin prick test ; BF: breastfeeding ; AAF: amino acid based formula ; E(R)HF: extensive (rice) hydrolysate formula

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 breastmilk is not available, a CM based eHF is the first option (1,132,157,238,239). 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. Partially hydrolysed formulae are not recommended in the treatment of CMA (222). Recent data show that eHFs supplemented with probiotics (*Lacticaseibacillus rhamnosus* GG, *Bifidum breve* xx), prebiotics (fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS) and HMOs (2'-FL, LNnT) are well tolerated, although an increased efficacy has not been demonstrated systematically. There is no recommendation for the addition of "biotics" to a therapeutic elimination diet.

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 (128). Weaning food is recommended to be CMP-free until tolerance is confirmed by an OFC (120). The elimination diet should be thoroughly monitored to exclude hidden 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 (140). 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 (240).

There is good evidence that HRFs are an alternative for eHFs as therapeutic elimination diet (148-151), but there are insufficient RCTs with HRFs.

As discussed before, soy protein based formula is not recommended for infants < 6 months (58), 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 to 0.5 % for the general population, 0.4 to 3.1 % for the referred population, and 0 to 12.9 % for allergic children (241).

There is no place for any other animal milk with intact protein in CMA (242,243). The significant homology between milk from cow, sheep and goat results in cross-reactivity (244). However, mare's or donkey's milk may be tolerated by some individuals (243,244), but 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 (242, 245).

Statement 57	Mean / Median	votes
In formula fed infants, a CM derived eHF is the first choice for a therapeutic elimination diet.	8.9 / 9	8; 9(12x)
Statement 55		
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 59		
Partially hydrolysed CM based formulae are not indicated in the treatment of CMA.	8.8 / 9	7;8; 9(11x)
Statement 60		
60A. Regarding the therapeutic elimination diet, AAF should be reserved for infants with an absent or partial response to eHF.	8.0 / 9	2;7(2x); 9(10x)
60B. 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)

Two members of the panel had strong contradictory opinions regarding including "severe cases" or not as indication for AAF as therapeutic formula.		
Statement 61		
RHFs 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)
Two panel members estimated that the lack of RCTs for RHF justify a negative voting.		
Statement 62		
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)
Similar to "soy for diagnostic elimination diet", there is a strong opinion of one panel member that "palatability" is not an acceptable reason for soy infant formula.		

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 (1). 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" (15) starting with small amounts of baked milk. As heating changes the structure of the peptides, patients may tolerate baked milk (33, 246-251). Home introduction protocols are safe in non-IgE mediated food allergy (**Table 4**) (252).

Table 4. Patient-specific factors for home challenge using a milk ladder (adapted from 252).

- 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 (eg, preschool) are preferred, though not without risk, since older patients may be prone to persistence of allergy and suffer from co-existing allergies

However, standardization of the home challenge is recommended (253). 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 63	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 (eg. milk containing biscuits).	8.8 / 9	8(3x); 10(9x)
Statement 64		
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

Oral immune therapy (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 (254). Indications and safety of oral immunotherapy (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 (254-256). EoE is diagnosed in 5.3% of children during OIT in children with CMA (256). OIT in children with severe and persistent CMA deserves consideration, but currently this approach should be reserved for selected patients and restricted to specialized centers.

Statement 65	Mean / Median	votes
The provision of oral immune therapy 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 cow's milk allergy

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 (257). 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 (258).

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 (259), 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 like LEAP and other studies) (260).

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 (261,262). 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 (261).

Statement 66	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 67		
Dietary restrictions, other than those warranted for the pregnant woman herself, are not indicated during pregnancy to prevent CMA.	9 / 9	9(13x)

Avoiding early introduction of cow's milk formula

There is no evidence for dietary restriction in a breastfeeding mother to prevent CMA (258).

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 Host et al and led to the concept of "dangerous bottle" (of CM formula) given at maternity ward and increasing the risk of CMA (263).

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 (257). The absolute effect ranged from a 22% decrease to a 2% increase in the prevalence of food

allergy, with a low level of evidence (257). There is, however, controversy with regards to the effects of brief early exposure to CM formula. Another systematic review identified one RCT (264) 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 (257,264). 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 (265). Wide confidence intervals call for caution in interpreting these results. In a subsequent RCT (266), 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, $P < 0.001$).

According to a prospective cohort study involving 6,209 exclusively breastfed infants followed from birth for CMA, one of the significant risk factors for presence of CM specific IgE was the exposure to CM protein in the maternity ward (8). Breastfed infants receiving CM formula supplementation (45.8% of neonates less than 24h-old) had a 7.03 times increased risk to develop CMA than those exclusively breastfed (267). In an open non-blinded clinical trial on breastfeeding supplemented with AAF of CM formula (5 ml/day up to 5 months of age), the CM fed group breastfeeding with or was sensitizised to CM (IgE level >0.35 IU/mL) at the infant's second birthday 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) (264). Sakihara et al 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 (266). In an observational case-control study, additional bottle feeding in the maternity ward increased the risk for CMA compared to age-matched controls (265).

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 (266). There are

no publications showing a beneficial effect of the introduction of a CMF during the first 3 days of life.

Statement 68	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)
One panel member considers there is sufficient evidence that early introduction of CM formula increases the risk for CMA		
Statement 69		
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 70		
In general, supplements of CM formula in breastfed infants are not recommended.	8.9 / 9	8; 9(12x)

Protein hydrolysates

A recent 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 (257). 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 (257).

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 (268). 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 (268).

Although the effect of hydrolysed formulae on food allergy remains unclear, these formulae 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 (269). 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 (270). This trial involved 2252 healthy infants who were randomized to one of three hydrolysed formulae [pHF-W; eHF-W; eHF-C] or a formula based on intact CM as a reference to be fed during the first four 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 to 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 (270).

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

Statement 71	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 for preventing CMA.	8.3 / 9	4;7; 8(2x); 9(9x)
One panel member considers there is sufficient evidence for certain pHFs		
Statement 72		
The role of RHF for preventing CMA has not been studied.	8.8 / 9	7;9(12x)

Soy-based formula

Soy-based formulae are made from soy protein isolate and do not contain CMPs or lactose. In one 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) (271).

Statement 73	Mean / Median	votes
For infants with a documented family history of allergic disease who cannot be exclusively breastfed, there is evidence against recommending 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 (257). However, the evidence is very uncertain.

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 (272,273). 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 (274).

Statement 74	Mean / Median	votes
There is insufficient evidence to recommend the use of probiotics, prebiotics or synbiotics studied so far for CMA prevention.	8.8 / 9	7; 9(12x)

Long chain poly-unsaturated fatty acids

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 (275). 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 (275). 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 (257). 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 (257).

Statement 75	Mean / Median	votes
There is insufficient evidence to recommend the use of long chain poly-unsaturated fatty acids (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 (257). 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 76	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 (2). 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 (2). Complementary

bottles given at maternity hospitals to newborns who will later be exclusively breastfed increases the risk of developing CMA (265,276). In some prevention trials randomisation was allowed up to the age of 1 month, meaning that a number of infants were fed intact CMP before inclusion in the trial (277). Sensitisation to CMP may also develop through skin contact (278).

Economic cost of cow's milk allergy

Individuals with food allergies make increased use of healthcare services leading to substantial economic costs in addition to the physical health burden caused by anaphylaxis (279). 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 (280).

Both eHF and AAF are more expensive than standard infant formulae (281). 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 (282). 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 (283).

Morais et al. propose using AAF in the diagnostic elimination diet of infants with suspected CMA (143). 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 (143). Using an AAF as the initial treatment for CMA can potentially release limited hospital resources for alternative use within the paediatric healthcare system in the Australian healthcare system (142).

Cost of formulae 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, AAF 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 RHF are needed.

Statement 77	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 (279). 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 (284). Among food allergic children, those with CMA have a lower quality of life compared to children with easily avoidable allergens (e.g., nuts) (285,286). CMA individuals who tolerate baked milk products report a better quality of life due to fewer dietary restrictions (285).

In their review, Antolin-Amerigo et al. 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 (287). 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. 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 (288). 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 (AZ266).

Statement 78	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)

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Supplementary material

1. Pathophysiology

According to the European Academy of Allergy and Clinical Immunology (EAACI) and World Allergy Organization (WAO) nomenclature, a hypersensitivity reaction to CM can be defined as CMA if it involves immunological mechanisms (1). Immune-mediated adverse food reactions are the consequence of failure to develop or maintain food tolerance and can be classified into three main categories: 1) immunoglobulin E (IgE)-mediated, 2) non-IgE-mediated, and 3) mixed mechanisms of food allergy (2). CMA constitutes an abnormal response of the body's immune system towards CMP, which are recognized as a potential threat. CM contains more than 20 protein fractions. The significant allergens belong to casein (α-s1-, α-s2-, β-, and κ-casein) and whey proteins (α--lactalbumin and β-lactoglobulin) (3). Many individuals with CMA have a sensitivity to both caseins and whey proteins (4). Although most children with CMA are allergic to several CM components, the most common reaction is to casein. Over 50% of patients have antibodies against casein, β-lactoglobulin, and/or α-lactalbumin (5).

Symptoms that are 'immediate' (quick to appear) involve deficient immune regulation and polarization of milk protein-specific effector T cells towards type-2 T helper cells, leading to signaling of B-cells to produce CM-specific IgE (6, 7). CM-specific IgE bind to the surface of tissue mast cells and blood basophils. Upon re-exposure to CM, CM-antigenic proteins bind to and cross-link these cell surface–bound IgE, leading to the release of symptom-inducing mediators, such as histamine and leukotrienes (1). Typically, allergic symptoms occur within minutes after consuming CM up to two hours afterwards. This type of reaction is described as IgE-mediated CMA. In non-IgE-mediated CMA, symptoms are 'delayed' (slow to appear). Non-IgE-mediated allergy, outside of food protein-induced allergic proctocolitis and eosinophilic oesophagitis, is not well understood, leading to variations in the diagnosis and management thereof (8). The immune response in non-IgE-mediated CMA is less well characterized, but involves cellular mechanisms (1). Symptoms typically develop two hours after consumption but can take up to 72 hours. If CM is repeatedly consumed in the diet, the immune system will be continuously triggered resulting in symptoms over days or even weeks.

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2. Statements

Statements were developed and discussed within the whole group by e-mail exchange and during a virtual on-line meeting. Nevertheless, during the first voting round some panel

members proposed changes to the original statements. The changes in the statements are listed below.

	Statement	Mean / Median	Votes
4	Acute FPIES is a potential medical emergency whose accurate diagnosis remains a challenge and is **solely** based on symptoms and their timing.	8.0/9	4;5; 8(4x); 9(7x)
	Two members rejected the statement because of the word "solely" since it excludes a standardized OFC, which is helpful in unclear cases and for assessment of tolerance development and outgrowth of FPIES. It was proposed to either omit the word "solely" and re-vote or add that comment.		
9	As there are no specific tests to discriminate between CMA and functional gastrointestinal disorders (FGIDs), some patients with suspected FGIDs can improve with a CM elimination diet regardless of CMA.	7.5/9	4;5(2x);6; 7(2x);9(7x)
	3/13 disagreed; although the statement was accepted, opinion among the panel members differs. Rewording of the statement was proposed for re-voting.		
13A	In infants who present with crying and irritability there is **insufficient** data to recommend a time-limited CM elimination diet followed by an OFC.	8.4 / 9	6;7; 8(3x); 9(8x)
13B	In infants who present with crying and irritability there is **sufficient** data to recommend a time-limited CM elimination diet followed by an OFC.	2.2 /1.5	0 (4x); 1(3x); 2;4(2x); 5(3x)
	The panel voted strongly negative on the statement that there sufficient evidence to trial a CM-elimination diet in infant presenting with crying and irritability		
27	In case of diarrhoea, a formula without lactose and medium chain triglycerides is preferred.	6.5/7	0;4;5;6(2x); 7(3x);8(3x); 9(2x)
	Although initially approved as statement, during the voting 5 members considered the was no evidence for or against medium chain triglycerides. The statement was		

	re-worded for a second voting rounds.