

When Should Infants with Cow's Milk Protein Allergy Use an Amino Acid Formula? A Practical Guide



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Cow's milk protein allergy (CMPA) is the most common food allergy in childhood and its prevalence ranges between 1.9% and 4.9%. Most children present with CMPA at age less than 1 year and therefore may require a hypoallergenic formula in the absence of breast milk. Hypoallergenic formulas include both extensively hydrolyzed formula (EHF) and amino acid formula (AAF). For most children with a CMPA, an EHF will be sufficient for symptom resolution, as reflected in current guidelines, but there is a subset of children with CMPA where an AAF may be indicated. The appropriate use of an AAF is a highly debated topic, because there is a significant fiscal burden to either the health care system or the parents. From the literature, the following themes were identified as *possible* reasons for choosing an AAF: (1) symptoms not fully resolved on EHF, (2) faltering growth/failure to thrive, (3) multiple food eliminations, (4) severe complex gastrointestinal food allergies, (5) eosinophilic esophagitis, (6) food protein–induced enterocolitis syndrome, (7) severe eczema, and (8) symptoms while breast-feeding. Each of these themes was critically reviewed using all available published data and found that using an AAF in height growth faltering may be indicated. In addition, patients who end up on an AAF often present with multisystem involvement, requiring multiple food eliminations and fall within the more severe spectrum of gastrointestinal allergies. In eosinophilic esophagitis, all current recommendations support the use of an AAF as first-line approach, and in children with anaphylaxis, despite limited evidence an AAF is recommended because of the potential risk for a severe reaction. The use of an AAF in children who are breast-fed remains a highly controversial topic and at all times breast-feeding should be supported in children with CMPA. This article provides a practical guide that is evidence based for health care professionals to the use of AAF. © 2017

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INTRODUCTION

Published data indicate that there appears to be an increase in the prevalence of food allergies, with recent figures from some developed countries pointing toward a prevalence of 10%.¹ The most common food allergens in childhood include cow's milk, hen's egg, nuts, soya, wheat, and fish,² but cow's milk protein allergy (CMPA) remains the most common worldwide presentation of food allergy, with a prevalence ranging between 1.9% and 4.9%.³ Most children present with CMPA at age less than 1 year, which is the time when nutritional reliance on breast milk or cow's milk formula is the highest. If breast milk is not available, a hypoallergenic formula is required, which is highly controlled for nutritional content and tolerance in infants allergic to cow's milk. By definition, hypoallergenic formulas are tolerated by 90% of children with CMPA with a 95% CI and are divided according to the degree of protein hydrolysis: extensively hydrolyzed formula (EHF), which contains short peptides (most below 1500 Da), and amino acid formula (AAF), which provides protein in the form of amino acids.⁴ Studies have shown that between 2% and 18% (average 10%) of children with the immediate-type, IgE-mediated CMPA continue to react to an EHF.⁵⁻⁷ Therefore, for most children with CMPA, an EHF will be sufficient for symptom resolution, as reflected in current guidelines, but there is a subset of children with CMPA where an AAF may be indicated.^{8,9}

The appropriate use of an AAF is a highly debated topic, because there is a significant fiscal burden to either the health care system or the parents, with AAF costing on average 40% more than EHF in both the United Kingdom and the United States. Understandably this cost will vary between countries, different brands, and local contracts.¹⁰ Many insurance companies or health care authorities will not cover the cost of hypoallergenic formulas, especially after the child reaches the age of 12 months. In addition to the cost associated with AAF, other considerations in the debate around the appropriate use of AAF include tolerance induction, optimal growth, and patient safety. There is paucity of data on the impact of hypoallergenic formulas on quality of life, but a survey by Lozinsky et al¹¹ found significant distress reported by parents due to the delay in optimal symptom management. It would therefore make sense to identify

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Abbreviations used

AAF- Amino acid formula
 AD- Atopic dermatitis
 CMPA- Cow's milk protein allergy
 EFH- Extensively hydrolyzed formula
 EoE- Eosinophilic esophagitis
 ESPGHAN- European Society for Paediatric Gastroenterology,
 Hepatology and Nutrition
 FPIES- Food protein–induced enterocolitis syndrome
 SCORAD- SCORing Atopic Dermatitis

those patients requiring an AAF from the onset to improve time to symptoms resolution and reduce the distress of families that have to cope with children with ongoing symptoms. This article therefore aimed to review published literature on the appropriate use of AAF to provide health care professionals with practical guidance on when this is indicated.

IDENTIFICATION OF STUDIES

We performed a PubMed (<https://www.ncbi.nlm.nih.gov/pubmed>) search for peer-reviewed, published articles in English language (1980 to August 2017) including guideline publications on the management of CMPA using hypoallergenic formulas. We used the following search terms (single and in combination): hypoallergenic formula/feed, AAF/feed, elemental formula/feed, amino acid formula/feed, and/versus EHF/feed, EHF whey/EHF casein, semi-elemental formula/feed, and cow's milk allergy and food allergy. Only systematic reviews, randomized controlled trials, prospective nonrandomized studies, before and after clinical trials, and observational studies were included; case studies based on single cases were not included in this review and studies testing the hypoallergenicity of formulas, whether they conform to current guidelines, were also excluded unless they included a comparison to an EHF. Once publications were identified, they were reviewed by all the authors to identify studies that specifically addressed indications for an AAF or compared an AAF with an EHF. From the literature, the following themes were identified as possible reasons for choosing an AAF and are discussed in more detail in subsequent sections: (1) symptoms not fully resolved on an EHF, (2) faltering growth/failure to thrive, (3) multiple food eliminations, (4) severe complex gastrointestinal food allergies, (5) eosinophilic esophagitis (EoE), (6) food protein–induced enterocolitis syndrome (FPIES), (7) severe eczema, and (8) symptoms while breast-feeding.

When symptoms do not fully resolve on an EHF

The most common reason for recommending an AAF is poor symptom resolution after an average time of 4 weeks (recommendations range from 2 to 6 weeks) using an EHF for the management of CMPA.^{3,9,12,13} Current guidelines are all in agreement that following the failure of an EHF (in conjunction with optimal dietary elimination of all cow's milk–containing foods) an AAF should be trialed.^{3,8,9,13,14} Several studies have documented a subset of children who do not have optimal symptomatic improvement on an EHF, despite complete elimination of cow's milk. With IgE-mediated CMPA, the average failure of around 10% of children on an EHF seems to be universally accepted on the basis of published data; however, the failure of symptom relief in those with delayed CMPA affecting

the gastrointestinal tract and the skin is also beginning to be recognized. de Boissieu et al⁷ reported in 1997 a group of 16 children who continued to have eczema and gastrointestinal symptoms (presumed non–IgE-mediated allergies) on both whey and casein-based EHF but improved on an AAF, but when EHF was reintroduced, symptoms recurred. Since then additional studies have also identified a subset of patients who continue to react on an EHF.^{5,6,15,16} In 1997, Vanderhoof et al¹⁷ published a study on children with suspected non–IgE-mediated allergies who did not have symptom resolution with milk elimination on a casein EHF for an average of 40 days (range, 10–173 days). Infants were then switched to an AAF and from this cohort, 25 children were rechallenged after 2 weeks on the AAF and 32% tolerated the EHF without reoccurrence of symptoms; hence, 68% continued to require an AAF. More recently, the same authors observed 30 infants, with mainly non–IgE-mediated CMPA (although some had IgE sensitization to milk), who had been on EHF formula for at least 2 weeks before the first study visit. The patients in this study had a history of weight loss and persistent allergic manifestations defined as at least 1 of the following symptoms: atopic dermatitis (AD), bloody stool, diarrhea, rash, vomiting. Patients were changed to an AAF and followed for 12 weeks at which time mean gastrointestinal symptom score improved from 22.4 to 8.4 ($P < .001$). In addition, a significant improvement was found in AD, both in the number of infants experiencing AD and in the mean AD score (32.73 to 9.04; $P = .015$) in 7 of the 13 patients still experiencing AD. The above studies raise important questions; first, whether there is a cohort that may tolerate an EHF on reintroduction after full symptom resolution on an AAF, and second the length of time with ongoing symptoms before a change onto an AAF should be considered. Stepping down from an AAF to an EHF has not been studied; however, Morais et al¹⁸ have recently assessed the cost-effectiveness of using an AAF formula as first line to achieve full symptom resolution and after 6 weeks switching to an EHF, which was shown to be more cost-effective. Although most guidelines provide 2 to 4 weeks as an optimal time for symptom resolution, a recent publication by Chebar Lozinsky et al¹² has found that in non–IgE-mediated gastrointestinal allergies 4 weeks of optimal elimination may be required. Studies in which a switch to an AAF was made within 2 weeks because of suboptimal symptom resolution may have allowed for insufficient time for this to occur.

Further studies in which an AAF led to symptom resolution are summarized in Table 1 (5 non–IgE-mediated allergy, 1 mixed IgE and non–IgE-mediated allergy, and 1 IgE-mediated allergy). Not all studies have used the criterion standard double-blind challenge method to confirm CMPA but many have included a single- or double-blind challenge to EHF, soya formula, and/or AAF following symptom resolution on cow's milk elimination diet. Nevertheless, there does seem to be a trend toward higher failure of an EHF in patients with non–IgE-mediated gastrointestinal CMPA. This observation has been substantiated by a previous systematic review by Hill et al²² in 2007 who found that children with more complex non–IgE-mediated gastrointestinal allergies seemed to benefit from an AAF. However, the authors of that systematic review did not define what was deemed as “more complex” non–IgE-mediated gastrointestinal manifestations, which has led to confusion regarding the appropriate use of AAF. Published data indicate that not all children will require an AAF, but also that multiple

TABLE I. Summary of studies comparing tolerance of EHF and AAF

Author	Type of study	Number recruited	Patient characteristic	Outcome
Sampson et al ¹⁹	Prospective randomized double-blind, placebo-controlled food challenges to cow's milk, AAF, and EHF	28 recruited 26 included (2 developed tolerance), 16 underwent SPT to the formulas	Age 11 mo-12 y IgE-mediated CMPA . Confirmed through double-blind, placebo-controlled challenge—6 of 26 were not challenged because they had severe anaphylactic reactions	AAF: 3 of 16 positive SPT result to AAF 0 of 26 reacted to AAF on challenge EHF: 5 of 16 positive SPT result to first brand of EHF casein 8 of 16 positive SPT result to second brand of EHF casein 1 of 26 reacted to EHF casein (skin rash, respiratory symptom, and vomiting)
de Boissieu et al ⁷	Prospective nonrandomized study Confirmation of CMPA through challenges not mentioned	16	Infants (age not specified) had ongoing gastrointestinal and/or skin symptoms on EHF. All were treated for gastroesophageal reflux. Suspected non-IgE-mediated allergy	13 of 16 showed symptom improvement when an AAF was introduced and when challenged to an EHF, symptoms recurred
de Boissieu and Dupont ¹⁶	Prospective nonrandomized study. Confirmation of CMPA through challenges not mentioned	22	Infants (mean age at referral to the unit, 4.7 ± 3.7 mo). Predominant gastrointestinal symptoms and 6 of 22 had AD. Suspected non-IgE-mediated allergies	After 1 mo on AAF, all children were challenged to EHF and reacted to this feed; 9 of 22 reacted with only gastrointestinal symptoms to the EHF but in 13 of 22 children in addition to gastrointestinal symptoms, failure to thrive, angioedema, and AD occurred. The latter also reacted to multiple other foods
Hill et al ²⁰	Prospective study: all patients on AAF but challenged with parental choice of either EHF casein/whey or soya formula. The challenge sequence was randomized and blinded. Confirmation of CMPA through challenges not mentioned	18 enrolled but only 10 had EHF as challenge formula (7 soya formula and 1 cow's milk)	Median age, 7.5 mo (range, 3-14 mo) Children with suspected non-IgE-mediated CMPA	0 of 18 reacted to AAF 10 were challenged to EHF (6 of 10 reacted to EHF): 2 of 6 vomiting and diarrhea 2 of 6 diarrhea 1 of 6 vomiting 1 of 6 diarrhea, vomiting, and eczema 7 were challenged to soya formula: 6 of 7 reacted 1 was challenged to cow's milk: tolerated
Caffarelli et al ⁵	Randomized controlled cross-over: AAF to EHF casein and EHF whey. CMPA confirmed through challenge	20 but not all crossed over to other formulas	Median age, 2.6 y (range, 11 mo-9 y) Children had challenge-confirmed mixed IgE and non-IgE-mediated CMPA	2 of 10 had AD on AAF 16 were challenged EHF whey (3 of 16 reacted): 1 of 16 vomiting 1 of 16 AD 1 of 16 rash/skin symptoms EHF casein (1 of 16 reacted): 1 of 16 diarrhea

(continued)

TABLE I. (Continued)

Author	Type of study	Number recruited	Patient characteristic	Outcome
Vanderhoof et al ¹⁷	Prospective nonrandomized. Confirmation of CMPA through challenges not mentioned	28 recruited and 25 crossed over	Age range, 22 to 173 d. Infants with suspected non-IgE-mediated CMPA who did not have symptom resolution on EHF casein	After 2 wk on AAF all children had symptom improvement; 25 of 28 were challenged with EHF casein again: 8 of 25 tolerated EHF casein but 17 of 25 redeveloped symptoms
Vanderhoof et al ²¹	Prospective multicenter observational study. Confirmation of CMPA through challenges not mentioned	30	Infants at mean age of 6.6 mo, who failed EHF with persistent allergic manifestation and weight loss; 76% IgE negative and most symptoms were gastrointestinal (vomiting) and 41.7% had AD. Mainly non-IgE-mediated allergy	Statistically significant improvement in all residual allergic manifestations (skin and gastrointestinal) in terms of both number of symptoms and symptom severity

SPT, Skin prick test.

Bold indicates confirmation of the allergy and type of allergy.

feed changes, poor symptom resolution, and input from multiple health professionals all contribute to a fiscal burden.²³ It is therefore desirable to have a better definition in regard to the type of patient who may require an AAF (see section “Interpreting results and guidance for health care professionals”).

Faltering growth in food allergy

Several studies have highlighted concerns in regard to growth in children with food allergies with low weight-for-age,²⁴ but more concerning low height-for-age.²⁵⁻²⁷ Current data indicate that between 7% and 24% of children with food allergies have stunting (defined by a height-for-age <-2 SD).²⁸⁻³⁰ In developed countries, the prevalence of stunting in the food-allergic community ranges between 9% and 14% but this can increase to almost 25% of non-IgE-mediated CMPA in developing countries as demonstrated by Vieira et al.³⁰ Stunting in early life does not only impact on long-term height growth but has also been shown to be linked to poor cognitive outcome in later age (ie, in reading, mathematics).^{31,32} As early as 1998, Isolauri et al³³ reported on growth patterns in a cohort of children with both IgE- and non-IgE-mediated CMPA, highlighting a lack of linear catch-up growth in particular in children who had early onset of symptoms to cow's milk. Most patients in that study were on an EHF as milk replacement and volume consumption and nutrient intake was deemed sufficient for normal growth and development; therefore, inadequate nutritional intake was discounted as a cause for poor catch-up growth. The authors hypothesized that ongoing growth faltering might be related to persistent unnoticed inflammation of the gastrointestinal tract and/or the skin increasing nutrient requirements. Beck et al²⁸ have also found in the HealthNuts cohort that children with food allergy and AD were shorter and lighter throughout early childhood. The association between atopic comorbidities, low-grade inflammation, and growth requires more research to clearly identify the causal factors. Arvola et al³⁴ showed that in children with AD, gut barrier function improved with concomitant diminishing SCORing Atopic Dermatitis

(SCORAD) score after cessation of breast-feeding and starting of hypoallergenic formula (either EHF or AAF). It is therefore plausible that if symptoms affecting the skin or the gastrointestinal are ongoing, children continue to have poor growth relating to low-grade inflammation affecting gastrointestinal barrier function, with the latter leading to suboptimal nutrient absorption. The impact of low-grade inflammation itself on growth, related to residual cow's milk peptides in the formula, has not been explored in food allergy. Cytokines, also involved in ongoing allergic reactions, namely, IL-6 produced by macrophages and TNF- α , have been shown to have an impact on growth in other diseases.³⁵⁻³⁹ Borschel et al⁴⁰ studied children and infants with chronic diarrhea and recruited 2 groups, one 12 months or younger ($n = 27$) and another 12 months or older ($n = 19$). From the older cohort, 10 of 19 (53%) had food-allergic conditions and from the infants younger than 12 months, all ($n = 27$) were diagnosed with a food allergy or eosinophilic gastroenteritis (2 children with food allergies also had short gut syndrome). Children were changed to a specific test AAF from another AAF or EHF casein and partially hydrolyzed whey formula. Following this change, all significantly improved both weight and height, but in particular length increased in the infant cohort in which all had a food allergy. Of note is that this effect on height growth is not seen if an EHF and AAF are compared in a healthy infant population,⁴¹ implying that the pathophysiology is related to gut barrier function and/or ongoing inflammation.

Data from other pediatric populations highlight the importance of catch-up growth and the long-term benefit of optimizing growth earlier rather than later.^{42,43} Although most studies have found similar weight gain between EHF and AAF, many have indicated better linear catch-up growth in children with CMPA on an AAF.^{6,44,45} This has also been found in the systematic review on AAF by Hill et al²² in 2007. A more recent study by Vanderhoof et al,²¹ of infants who failed an EHF and were switched to an AAF, found that the weight gain velocity statistically significantly increased ($P < .001$) from a

mean weight of 6.322 kg to 7.472 kg, representing a change in z score from -1.6 z score at baseline to -1.1 after 12 weeks. Although the height gain velocity was also increased on the AAF, this did not reach statistical significance (65.32 cm to 69.96 cm, which translated into a z score of -0.7 to -0.4). The latter finding may be related to the relatively short time of follow-up where significant changes in height velocity may not yet be detected.

All current food allergy guidelines mention growth as a major complication of CMPA. The Diagnosis and Rational for Action against Cow's Milk Protein Allergy guidelines do not provide specific guidance on formula choice to support optimal growth, but the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines and guidelines from the United Kingdom (primary, secondary, and tertiary guidelines) specify a hypoallergenic formula choice in the presence of faltering growth.^{3,8,9,13,46} The Australian CMPA guideline suggests the use of an EHF instead of soya formula if faltering growth is present, and ESPGHAN and UK guidelines suggest the use of an AAF if faltering growth is present, with ESPGHAN mentioning in particular the presence of faltering growth with severe enteropathy.^{8,9,13,46} Many of the aforementioned guideline publications substantiated their suggestion on the basis of publications by Isolauri et al,³³ Niggemann et al,⁴⁴ and Hill et al.²² Although data are limited, height growth velocity seems to improve in particular in children who did not respond to an EHF. As such, if the child has growth faltering that does not resolve on EHF and other traditional nutrition interventions, an AAF should be considered even in the presence of improved allergic symptoms.⁴⁵

Multiple food elimination and AAF

Food-allergic children who have proven reactions to multiple foods have consistently been shown to fall within the more severe group of food allergy.^{21,20,47} Hill et al²⁰ described a cohort of 18 children who had improved on an AAF following reported hypersensitivity reactions to EHF/soya and on rechallenge (parents chose challenge formula) 6 of 7 reacted to soya, 6 of 10 reacted to EHF whey/casein formulas, and 1 tolerated cow's milk. In those who failed the EHF, parents reported multiple food allergies and reactions to, on average, 6 foods (range, 1-9), but these were not challenged within a controlled hospital environment. Similarly, de Boissieu and Dupont¹⁶ found in their cohort of 22 children who were intolerant to EHF (challenge based) that 13 of 22 also reacted to at least 4 other foods and that cohort also took a longer time to become cow's milk tolerant. In the cohort by Sicherer et al,⁴⁵ 29 of 31 children on an AAF were also avoiding multiple foods. All children from that study had delayed symptoms with a combination of vomiting and diarrhea, but 7 also had IgE sensitization (milk, soya, egg, nuts, wheat, barley) of which 4 had AD. Studies on growth have indicated that those who avoided 3 or more food allergens had consistently worse growth parameters and nutritional intake.^{24,25,48} Isolauri et al⁶ found that AAF was superior in achieving growth in children who were on multiple food elimination diets; however, that study was not designed to assess this impact, and it was a secondary finding (Table II).

Retrospective and prospective studies by Meyer et al⁵¹ and Chebar Lozinsky et al¹² on non-IgE-mediated gastrointestinal

allergic children indicate that most children had more than 3 foods eliminated and most were on an AAF for symptom resolution. As with the study by Isolauri et al,⁶ the latter 2 studies did not set out to study the impact of AAF on multiple food elimination diets; the findings were therefore observational. The study by Sampson et al,¹⁹ investigating the tolerance of an AAF versus EHF using double-blind placebo-controlled food challenges, reported that most children were also sensitized to other foods; however, in that study only 2 of 26 reacted to an EHF (Table III). de Boissieu and Dupont¹⁵ followed up both their cohorts from the publication in 1997 and 2000 for tolerance of EHF. They found that those with isolated EHF allergy (just with CMPA) tolerated the EHF on rechallenge much earlier (10.5 months) compared with children with more than 1 to 6 other food allergies (13.4 months) and more than 6 food allergies (20 months).

The systematic review on AAF in 2007 stated that an AAF was most probably indicated in children with multiple food allergies,²² but the conclusion was based on a small number of studies in which this was a concomitant finding. Other studies have shown that multiple food eliminations impact on growth and an AAF seems to play a positive role in regard to height growth velocity in children with cow's milk allergy.^{6,25,48} In most studies in which children had multiple allergies, it is very difficult to establish the impact of symptom and growth improvement on the basis of an AAF only versus other food eliminations. Only 1 study has prospectively followed patients up and indicated that children with multiple food elimination (outside of cow's milk) took a longer time to tolerate an EHF. It is therefore important to ensure that patients who eliminate cow's milk in addition to multiple other foods optimally eliminated the other allergens (because this may have an impact on symptom improvement) and if there are ongoing symptoms, consider whether they may benefit from an AAF, in particular if height growth is faltering and symptom resolution is not optimal.

Severe complex gastrointestinal manifestations of non-IgE-mediated food allergies

The term "complex gastrointestinal manifestations" was first used in the context of non-IgE-mediated gastrointestinal allergies by Hill et al²² in 2007. They used this term for children with more severe and complex CMPA, in particular those with non-IgE-mediated gastrointestinal symptoms (ie, enterocolitis or proctitis syndromes with faltering growth and eosinophilic gastrointestinal disorders) who seemed to benefit from an AAF. The observation that more children with non-IgE-mediated gastrointestinal allergies seem to react to an EHF is not new. In 1997 Vanderhoof et al¹⁷ highlighted for the first time failure on an EHF in children with non-IgE-mediated gastrointestinal food allergies. In that study, 28 children failed EHF casein and exhibited ongoing symptoms of bloody stools, vomiting, diarrhea, irritability, or failure to gain weight, or a combination of these symptoms. All improved on an AAF and histology from 20 patients varied from eosinophilic infiltration to normal, with no correlation between severity of inflammation and presenting symptoms. Several studies have since pointed toward a higher failure rate of an EHF in children with non-IgE-mediated CMPA affecting the gastrointestinal tract.^{21,52} Latham et al⁵² found that 29.7% of the children in their retrospective study with non-IgE-mediated

TABLE II. Summary of studies assessing growth on AAF

Author	Type of study	Number recruited	Patient characteristic	Outcome on growth
Niggemann et al ⁴⁴	Randomized controlled study. CMPA was confirmed through double-blind challenge	31 EHF 42 AAF	Median age, 5.7 mo (range, 1.6-9 mo) All children had confirmed CMPA and had eczema as primary symptom. 40 infants IgE-mediated allergy, 14 non-IgE-mediated allergy, 19 with mixed IgE- and non-IgE-mediated allergy	Height-for-age was statistically higher ($P = .04$) in children on AAF
Hill et al ²⁰	Prospective study: all patients on AAF but challenged with parental choice of either EHF casein/whey or soya formula. The challenge sequence was randomized and blinded. Confirmation of CMPA through challenges not mentioned	18 children	Median age 7.5 mo (3-14 mo) Children had a double-blind placebo-controlled food challenge to either soya, whey, or casein formula. Suspected non-IgE-mediated CMPA	4 of 18 had growth failure at the beginning of the study and demonstrated marked weight gain after AAF was commenced. The children who had growth failure also had multiple food hypersensitivities
Sicherer et al ⁴⁵	Prospective nonrandomized study. Diagnosis confirmed in 4 ways: (1) positive double-blind, placebo-controlled food challenge with CM, (2) a convincing history of acute, severe reaction after accidental ingestion with a positive test result for IgE antibody, (3) convincing history of a reaction with CM-specific IgE concentration of >31 kU/L, and (4) documentation of eosinophilic infiltration	31, of which 23 were already on AAF and 13 of 23 did not tolerate an EHF, 10 of 23 had an AAF due to multiple allergies 18 of 31 were followed up for growth	Median age, 23.3 mo (range, 6 mo to 17.5 y) Double-blind challenges to AAF or placebo (previously used hypoallergenic formula) IgE-mediated allergy	18 of 31 were followed up long-term for growth. No statistically significant difference in growth seen at the 4-mo visit, following introduction of new AAF
Borschel et al ⁴⁰	Prospective nonrandomized study. Confirmation of CMPA through challenges not mentioned	18 AAF	Children with chronic diarrhea (≥ 2 wk ≥ 4 stools) with any of the following diseases: EoE, food allergy, short gut syndrome, inflammatory bowel disease, protein maldigestion (10 of 18 had food-allergic conditions and those who had food allergy were infants). Suspected non-IgE in 10 of 18	Significant increase in weight for age and height for age was seen in all children. Impact on growth was bigger in the infants
Borschel et al ⁴¹	Double-blind randomized controlled study. Healthy infants—no challenge to cow's milk	213 randomized but 134 completed 112 d on the feed: 65 AAF 69 EHF	Healthy infants randomized at birth: 6.4 d for AAF 6.2 d for EHF Allergy status not applicable	No difference in weight, length, and head circumference

(continued)

TABLE II. (Continued)

Author	Type of study	Number recruited	Patient characteristic	Outcome on growth
Isolaurei et al ⁶	Randomized controlled follow-up study. CMPA confirmed through double-blind challenge	22 EHF 23 AAF	Infants with a mean age of 6 mo. All had eczema diagnosed by Hanifen criteria. Challenge-proven CMPA. Mixed IgE- and non-IgE-mediated allergy	Significant increase in weight ($P = .09$) and length for age in the AAF group ($P = .006$) when compared with the EHF group
McLeish et al ⁴⁹	Double-blind randomized controlled study. CMPA not confirmed through challenge	19 AAF and 16 completed 21 EHF and 13 completed it	Median age, 10 wk (range, 36–108 wk) Entry criteria: infants with persistent diarrhea on a cow's milk formula, persistent postenteritis diarrhea, or diarrhea following gastrointestinal surgery. Suspected non-IgE-mediated allergy in 28 of 40	Both groups were undernourished at the beginning of the study, but at 24 mo there were no statistical differences in growth between the 2 groups
Vanderhoof et al ²¹	Prospective multicenter observational study. Confirmation of CMPA through challenges not mentioned	30 on AAF	Children who failed EHF with persistent allergic manifestation and weight loss. All were provided with an AAF. Mainly non-IgE-mediated allergy	After 12 wk, significant increase in weight (+0.433 z score). Although not statistically significant, length was increased over this period as well
Canani et al ⁵⁰	Multicenter randomized controlled study. CMPA confirmed through double-blind challenge	21 AAF 19 EHF 25 standard formula	Children with proven CMPA —both IgE- and non-IgE-mediated	No differences found in length, weight, and head circumference between children on AAF and children on EHF compared with the healthy controls after 12 mo on the formula. No differences in protein metabolism outside of urea being significantly higher at 3 mo in the group on EHF

Bold indicates confirmation of the allergy.

gastrointestinal allergies were intolerant to an EHF, whereas McLeish et al⁴⁹ established that out of 13 infants with diarrhea on a cow's milk formula, 2 developed allergic colitis on an EHF. de Boissieu et al⁷ and Boissieu and Dupont¹⁵ performed 2 studies on the failure of EHF: in one study, 13 of 16 had ongoing gastrointestinal symptoms on an EHF and an AAF led to full symptom resolution and in the other also with children with predominantly gastrointestinal symptoms all 22 patients improved on an AAF. The problem remains that non-IgE-mediated gastrointestinal allergies are poorly defined outside of EoE and generally the pathophysiology is still not well understood.⁵³ Full symptom resolution often does not always occur in children on the more severe spectrum of non-IgE-mediated gastrointestinal allergies and may be due to continuing allergic inflammation, atopic comorbidities, or other causes that remain elusive, altogether.¹²

There is paucity of data to answer the question of why more children with non-IgE-mediated gastrointestinal allergies seem to require an AAF and although this has been linked to the ongoing gastrointestinal symptoms, a lot of questions remain. One important question that has not been studied is the length

of time required for symptom resolution on EHF versus AAF. There are currently no studies that compare a matched cohort of children with complex gastrointestinal allergies in a double-blind cross-over study using EHF and AAF. However, a recent *in vitro* study investigated T-cell proliferation and cytokine secretion resulting from different hypoallergenic formulas and found that the AAF studied did not induce T-cell proliferation or proinflammatory cytokine release.⁵⁴ Although this is an *in vitro* study, it may point toward important differences in tolerance of different hypoallergenic formulas with non-IgE-mediated CMPA. Nonetheless, the practical question remains for the health care professional: how do you define "complex" or "severe" gastrointestinal presentations or even for that matter identify with certainty immunologically mediated disease in the absence of tests and having to rely mainly on subjective symptom reporting? Although there is no existing classification on the severity of non-IgE-mediated gastrointestinal allergies, in the last decade EoE and FPIES in particular have received much attention in relation to the severity and dietary management including hypoallergenic formula use, which is discussed in further details below.

TABLE III. Use of AAF in patients requiring multiple food eliminations

Author	Type of study	Number recruited	Patient characteristic	Number of foods eliminated
Hill et al ²⁰	Prospective study: all patients on AAF but challenged with parental choice of either EHF casein/whey or soya formula. The challenge sequence was randomized and blinded. Confirmation of CMPA through challenges not mentioned	18 were randomly challenged to EHF or soya	Median age, 7.5 mo (range, 3-14 mo) Children with suspected non-IgE-mediated CMPA that stabilized on AAF	All children were referred with delayed reactions but 7 of 18 had positive SPT result/specific IgE to a combination of milk, egg, and nuts (although many had not been exposed). Adverse delayed reactions were reported to other foods including rice, wheat, and chicken in most children
Isolaure et al ⁶	Randomized controlled prospective follow-up study. CMPA confirmed through double-blind challenge	22 EHF 23 AAF	Mean age of 6 mo. All had eczema diagnosed by Hanifen criteria. 49% had positive SPT result to CM and 58% had positive patch test results to CM. Mixed IgE- and non-IgE-mediated allergy	On the basis of clinical symptoms, none of the children from either group were consuming egg. No intake of wheat, barley, rye, and oats for 68% in the EHF group and 65% in the AAF group, as well as restrictions on various fruits and vegetables in 31% of the children in the EHF group and 26% in the AAF group
Sicherer et al ⁴⁵	Prospective nonrandomized study. Diagnosis confirmed in 4 ways: (1) positive double-blind, placebo-controlled food challenge with CM, (2) a convincing history of acute, severe reaction after accidental ingestion with a positive test result for IgE antibody, (3) convincing history of a reaction with CM-specific IgE concentration of >31 kU/L, and (4) documentation of eosinophilic infiltration	31, of which 23 were already on AAF and 13 of 23 did not tolerate an EHF. 18 of 31 agreed to switch to new AAF	Median age, 23.3 mo (range, 6 mo-17.5 y) Blinded oral food challenge to AAF. IgE-mediated allergy	29 of 31 children in this study had >1 food allergy. 14 of 31 had ≥3 food allergies (all tolerated an AAF). Allergy to other foods included the following: Soy, 19 of 31 Egg, 16 of 31 Peanut, 10 of 31 Potato, 4 of 31 Gluten, 3 of 31 Meats, 2 of 31 Rice, 2 of 31 Banana, 1 of 31 Pea, 1 of 31
Sampson et al ¹⁹	Prospective randomized double-blind, placebo-controlled food challenges to CM, AAF, and EHF	28 recruited 26 included following challenge (2 developed tolerance)	Age 11 mo-12 y. IgE-mediated CMPA confirmed through double-blind challenge. All had SPT performed to other foods	SPT positive to the following: Egg = 23 of 28 children Peanut = 19 of 28 Other nuts = 9 of 28 Soya = 5 of 28 Beef = 2 of 28 Shellfish = 2 of 28 From this cohort 2 reacted to an EHF
de Boissieu and Dupont ¹⁶	Prospective nonrandomized study. Confirmation of CMPA through challenges not mentioned	22	Infants (mean age at referral to the unit, 4.7 ± 3.7 mo). Predominant gastrointestinal symptoms and 6 of 22 had AD. Suspected non-IgE-mediated allergies	9 of 22 were diagnosed as having only CM, soya, and EHF allergy and 13 of 22 children had in addition to the above at least 4 other food allergies (outside of CM, soya, and EHF allergy)

(continued)

TABLE III. (Continued)

Author	Type of study	Number recruited	Patient characteristic	Number of foods eliminated
de Boissieu and Dupont ¹⁵	Prospective nonrandomized. Confirmation of CMPA through challenges not mentioned	52 from 2 cohorts previously published ^{7,16}	Infants (mean age, 5.3 ± 3.8 mo). See Table I on patient characteristics from both de Boissieu studies ^{7,16}	All children in the study failed an EHF (as described in Table I) SPTs to all non-CM allergies were performed followed by single-blind oral challenge. 18 of 52 had isolated allergy to EHF (CMPA) 21 of 52 had allergy to <6 foods 13 of 52 had allergy to >6 foods Children with isolated EHF allergy tolerated an EHF on average at 10.5 mo, vs <6 and >6 foods at 13.4 and 20 mo, respectively

CM, Cow's milk; SPT, skin prick test.

Bold indicates confirmation of the allergy and type of allergy.

EoE and AAF. Symptom and histological remission on an AAF has been shown to be more than 90% in children with EoE and thus all current national and international guidelines as well

as the latest work group report from the American Academy for Allergy, Asthma & Immunology suggest the use of an AAF for this non-IgE-mediated allergic condition as first-line feed.⁵⁵

TABLE IV. Studies using elemental diet of AAF alone for EoE and remission rates

Study	Number of children	Remission	Further information
Kelly et al ⁵⁷	10 with GERD Age: median, 34.3 mo; range, 6-78 mo	Total resolution of symptoms (n = 8) Partial resolution of symptoms (n = 2)	Esophageal eosinophil counts decreased significantly from (median, 41; range, 15-100) to (median, 0.5; range, 0-22) (<i>P</i> = .005) after the AAF trial
Liacouras et al ⁵⁸	164 Age: median, 8.1 ± 4.3 y	Resolution in 160 of 164 (97.6%)	Based on n = 160 who improved: Eosinophils/hpf prediet: 38 ± 10.3; postdiet: 1.1 ± 0.5. White grapes/pure juice or apples/pure juice permitted alongside the AAF
Kagalwalla et al ⁵⁹	25 Age: mean, 6.4 y	22 of 25 (88%) in the AAF group achieved significant improvement in esophageal inflammation (<10 eosinophils/hpf)	The pretreatment and posttreatment peak eosinophil count was 58.8 ± 31.9 and 3.7 ± 6.5 (<i>P</i> < .001), respectively
Spergel et al ⁶⁰	151	AAF led to resolution in >95% of the patients	Resolution was defined as <15 eosinophils/hpf. The maximal eosinophil count in the most severely affected esophageal biopsy specimen was used to determine response to therapy
Rizo Pascual et al ⁶¹	17 9 y (range, 2 y and 8 mo to 14 y and 5 mo) but only 3 treated with AAF only	Remission in 3 of 3 patients	Remission was defined as <10 eosinophils/hpf
Henderson et al ⁶²	49 Age: median, 5.6 y (range, 0.9-19.7 y)	47 of 49 (96%) in remission (<15 eosinophils/hpf)	Median prediet: 51 (28- 90) and postdiet: 1 (0- 3.5)
Markowitz et al ⁶³	51 Age: median, 8.3 ± 3.1 y (range, 3-16 y)	All but 2 patients experienced improvement on the elemental diet	Median number of esophageal eosinophils/hpf decreased from 33.7 pretreatment to 1.0 after treatment (<i>P</i> < .01)

GERD, Gastroesophageal reflux disease.

Many argue however that an AAF has historically been used in EoE rather than being shown to be the best option in terms of hypoallergenic formula in this condition. Lucendo et al⁵⁶ showed in an adult EoE population that 88% of adults ($n = 17$) who demonstrated milk-triggered EoE remained in histologic remission when supplemented for 8 weeks with 400 mL EHF daily, while they still continued to eat their tolerated foods. However, no study to date has used an EHF alone in an attempt to induce EoE remission. [Table IV](#) summarizes current studies using an AAF for EoE indicating remission rates. In addition to these publications, several case reports exist but are not included in this review.⁶⁴⁻⁶⁶ No studies using EHF in children with EoE have been performed and this is therefore reflected in the guidelines.

FPIES and AAF. FPIES to cow's milk is a particular severe presentation of non-IgE-mediated gastrointestinal allergies. Most children present within 1 to 4 hours of the ingestion of cow's milk (one of the most common culprits) with the predominant symptom being severe profuse vomiting followed by, in many cases, diarrhea (with/without blood). Hypovolemia and shock in the severest of cases may also occur.⁶⁷ More recently chronic FPIES has also been described in the International Consensus Guidelines. This diagnosis is less well characterized than acute FPIES and is reported only in infants younger than 4 months with chronic/intermittent emesis, watery diarrhea, and faltering growth.⁶⁷ To date no randomized cross-over studies using EHF and AAF have been published in children with both acute and chronic FPIES and intolerance to EHF has been described only in prospective observational studies, retrospective reviews, and case studies.^{68,69} Sicherer et al⁷⁰ showed that out of 16 children with FPIES only 1 reacted to an EHF and in a more recent review of patients with FPIES, Caubet et al⁷¹ found that 38.5% members of their cohort were on an AAF whereas the rest were on an EHF; whether they reacted to the EHF or were just commenced on an AAF was not stated in that article. Similarly, an observational study on solid food FPIES reported that 65% were previously fed with either a casein EHF or AAF.⁷² Katz et al⁷³ questioned the need for either EHF or AAF because many in his cohort tolerated soya formula. However, soya-triggered FPIES is commonly reported in the United States and the United Kingdom.^{71,74} There is therefore no clear data on what formula to use as first line for FPIES. This is reflected in current guidelines, which often just specify the use of a "hypoallergenic formula," that is, EHF or AAF for FPIES, or recommend an EHF, unless it is associated with growth faltering (see section "[Faltering growth in food allergy](#)") in which case an AAF should be considered.^{8,9,67}

Severe atopic dermatitis and AAF

In the United Kingdom, the National Institute for Health and Care Excellence guidelines for AD in children recommend a 6- to 8-week trial of EHF or AAF for infants younger than 6 months with moderate or severe AD who have not responded to optimal treatment with emollients and mild topical corticosteroids, irrespective of being sensitized to cow's milk or not.⁷⁵ Most guidelines suggest the use of an EHF as first-line formula for AD; however, the question has been raised whether there is a cohort of children with severe AD who may not improve on an EHF and require an AAF. Kaczmarek et al⁷⁶ found in an oral challenge—confirmed population with CMPA that 32.8% of children with a mean SCORAD of 55.4 reacted to an EHF and

all but 1 improved on an AAF. In that study, the severity of the AD did not predict failure of an EHF; however, many also had exacerbation of gastrointestinal symptoms with an EHF. Conversely, the studies by Niggeman et al⁴⁴ and Isolauri et al⁶ have found no statistical difference in SCORAD in a mixed IgE- and non-IgE-mediated group on EHF versus AAF. The systematic review by Hill et al²² supports this finding that an AAF and an EHF were equally effective in resolving skin symptoms in uncomplicated CMPA. However, according to the assessment in that systematic review, there is a subgroup of children in which an AAF is indicated, such as in those who present with severe early-onset AD when breast-feeding (see section "[Symptoms while breast-feeding](#)"), and/or with faltering growth (see section "[Faltering growth in food allergy](#)") or when a trial of an EHF with optimal skin management is not sufficient for symptom resolution.^{7,21} The latter findings were based on 2 observational studies and 1 before and after clinical trial. A study by Leung et al⁷⁷ from 2004 was not included in the systematic review on AAF from 2007. In that study, children with AD (emollient treatment not specified), with a median age of 1.4 years, were randomly allocated to either an AAF or their standard formula (cow's milk or soya) and crossed over after 6 weeks. No statistically significant difference was seen between active and placebo in their SCORAD score. In addition, CMPA was not confirmed through an oral challenge and only 5 of 15 had a positive skin prick test result/specific IgE to cow's milk (rest to other allergens) in the aforementioned study. The outcome of that study carries an important message because it indicates a lack of benefit in using an AAF when CMPA has not been fully established to improve AD (in particular in the older child). See [Table V](#) for a summary on studies on AAF/EHF and AD. Current guidelines on CMPA vary in their recommendations: Diagnosis and Rational for Action against Cow's Milk Protein Allergy guidelines recommend an EHF as first-choice formula for AD and then AAF if symptom improvement does not occur (see section "[When symptoms do not fully resolve on an EHF](#)"),⁸⁰ and the British Society for Allergy & Clinical Immunology guidelines recommend the use of an AAF as first line in severe AD only in breast-fed infants.⁹ Nevertheless, there does seem to be some data implying that the combination of the skin and gastrointestinal tract may require more attention when choosing between hypoallergenic formulas (in particular if in combination with faltering growth and multiple eliminations).

Symptoms while breast-feeding

Breast milk remains the "criterion standard" source of nutrition for young children with CMPA and should be promoted whenever possible. Very limited data exist on the prevalence of reproducible clinical reactions to cow's milk protein in breast-fed children, which is thought to be around 0.5%.³ Although β -lactoglobulin originating from cow's milk can be detected in breast milk of 95% of lactating women, the amount is insignificant to many of the infants with mild to moderate CMPA.^{52,81,78,79} However, some children with CMPA are more sensitive to residual CMP and may react to the residue of β -lactoglobulin transferred through breast milk. There are currently no studies comparing breast milk to an AAF in regard to CMPA and because of ethical restrictions, no such studies will occur. Findings are therefore based on nonrandomized and observational studies. In a study by Hill et al,²⁰ 16 of 18 children developed gastrointestinal symptoms and eczema while being

TABLE V. Studies comparing EHF to an AAF in AD

Author	Type of study	Number recruited	Patient characteristic	Outcome on eczema
Niggeman et al ⁴⁴	Randomized controlled study. CMPA was confirmed through double-blind challenge	31 EHF 42 AAF	Median age, 5.7 mo (range, 1.6-9 mo) Eczema defined by criteria of Sampson ⁹⁹ and Seymour et al ¹⁰⁰ and severity assessed through SCORAD. 40 infants with IgE-mediated allergy, 14 non-IgE-mediated allergy, 19 with mixed IgE- and non-IgE-mediated allergy	No statistical difference in SCORAD before and after using EHF or AAF at 3 mo or 6 mo' time point after formula initiation
Isolaure et al ⁶	Randomized controlled prospective follow-up study. CMPA confirmed through double-blind challenge	22 EHF 23 AAF	Median age of 6 mo. All had eczema diagnosed by Hanifen criteria. Challenge-proven CMPA. Mixed IgE- and non-IgE-mediated allergy	Median SCORAD of 17 for EHF and 21 for AAF at the beginning of the study and at 8 mo this reduced to 5 and 4, respectively, in the EHF and AAF groups. There was no statistical difference between the groups before and at the end of the study
Palmer et al ⁷⁸	Prospective observational study. CMPA confirmed by oral challenge (took 2 wk)	67 children	Mean age of 11.34 ± 8.52 mo. All had eczema diagnosed by Hanifen and Rajka criteria. Open challenge-proven CMPA. Did not specify IgE-/non-IgE-mediated allergy status, but patients had a mix of gastrointestinal symptoms (colic, diarrhea, and reflux) and AD	Mean SCORAD 55.41 ± 17.4; 95% CI, 51.17-59.66 22 of 67 had intolerance reaction to an EHF: 17 of 22 to an EHF casein and 4 of 22 to an EHF whey and all but 1 child improved on an AAF. There were no differences in SCORAD (57.18 ± 16.59 vs 54.56 ± 17.90) between the groups failing/not failing the EHF, but the group that failed had a higher blood eosinophil count
Franke et al ⁷⁹	Randomized single-blind placebo- controlled study. Confirmation of CMPA through challenge did not occur	15 children	Median age, 1.4 y (IQR, 0.6-2.6 y). Children were consuming either cow's milk or soya formula. SPT/specific IgE to food allergens including cow's milk performed; 5 of 15 positive to cow's milk; rest positive to egg and/or soya. IgE-mediated allergy based on SPT/specific IgE only	The median changes for SCORAD and its area, intensity, and pruritus were not statistically significant during the active phase or the placebo phase

IQR, Interquartile range; SPT, skin prick test.

Bold indicates confirmation of the allergy and type of allergy.

breast-fed and of those, 12 reacted to an EHF. The level of residual β -lactoglobulin (0.84-14.5 μ g/L) in breast milk varies greatly, but studies indicate that the range is similar to that in EHF and it is therefore assumed that children with this level of sensitivity will continue to react to an EHF.^{6,7,81} An observational study by Latcham et al,⁵² not focusing on EHF or AAF, found that 55 of 121 mothers (47%) had exclusively breast-fed until weaning, and 41 of the children (14 of 44 immediate hypersensitivity responders and 27 of 77 delayed responders) developed gastrointestinal or skin symptoms while solely breast-fed. From the group with IgE-mediated food allergies, 11% settled on maternal elimination diet, while 34% did well on an EHF and 16% required an AAF. Conversely from the delayed non-IgE-mediated group, 16% settled on a maternal

elimination diets, 17% settled on an EHF, and 38% required an AAF. From both cohorts, therefore only 17% fully settled on a maternal elimination diet of cow's milk, possibly indicating multiple food allergies; however, additional food allergies were not reported in that study. In the study by Vanderhoof et al,¹⁷ 29% of children who failed an EHF and improved on an AAF exhibited symptoms while breast-feeding. A further study has described a cohort of children (n = 14) who continued to have symptoms of proctocolitis in spite of maternal elimination.⁸² All were switched to an AAF formula and improved. In that study, none were trialed on an EHF and therefore it is difficult to establish whether they would have tolerated this feed. This study also mentioned that in addition to the use of AAF formula all patients were on multiple food elimination diets.

TABLE VI. Use of AAF in relation to symptoms occurring while breast-fed

Author	Type of study	Number recruited	Patient characteristic	Symptoms in relation to breast-feeding
Berry et al ²⁴	Randomized controlled cross-over. Confirmation of CMPA through challenges not mentioned	18 were randomly challenged to EHF or soya	Median age, 7.5 mo (range, 3-14 mo) Children with suspected delayed CMPA that stabilized on AAF	16 of 18 patients had onset of non-IgE-mediated delayed symptoms that occurred while on breast milk; EHF/soya was introduced and they failed and symptom resolution occurred with AAF
Palmer et al ⁷⁸	Prospective observational study. CMPA confirmed by oral challenge	67 children	Mean age of 11.34 ± 8.52 mo. All had eczema diagnosed by Hanifen and Rajka criteria. Did not specify IgE-/non-IgE-mediated allergy status, but patients had a mix of gastrointestinal symptoms (colic, diarrhea, and reflux) and AD	Mean time of breast-feeding was 5.84 ± 6.01 mo (95% CI, 4.13-7.55). The shortest time of breast-feeding we noted in 4 infants with hypersensitivity to both EHF casein and whey but as a whole group there was no difference between those who failed an EHF and improved on an AAF
de Boissieu and Dupont ¹⁵	Prospective nonrandomized. Confirmation of CMPA through challenges not mentioned	28	Median age, 22-173 d. Children with suspected non-IgE-mediated CMPA who did not have symptom resolution on EHF casein	8 of 28 were breast-fed before being switched to an EHF casein that they failed and subsequently improved on an AAF
Sotto et al ⁸³	Retrospective observational study. Confirmation of CMPA through challenge did not occur	14	Age range, 21-90 d. Children presumed to have non-IgE-mediated allergic proctocolitis who continued to have symptoms on maternal elimination	Breast milk was stopped in all children and they were commenced on an AAF with symptom resolution. However, no EHF was trialed

Bold indicates confirmation of the allergy and type of allergy.

The UK guidelines suggest using an AAF formula in children who do not have symptom resolution on maternal elimination of cow's milk and the ESPGHAN guidelines mention that in breast-fed children with severe symptoms a hypoallergenic formula may be indicated, hinting toward the use of an AAF to stabilize symptoms.^{9,13} This recommendation is based on very limited data, which is acknowledged in the ESPGHAN guidelines, and remains a controversial topic. It is based on the theory that the level of β -lactoglobulin in an EHF will be similar to that detected in breast milk; however, one has to establish first if other allergens transferred through breast milk (ie, soya, egg) may be implied in ongoing symptoms, before such a step is even considered.⁸¹ The American Academy of Pediatrics and the World Allergy Organization (via the Diagnosis and Rational for Action against Cow's Milk Protein Allergy guidelines) do not make a distinction between the symptomatic breast-fed and nonsymptomatic breast-fed infant, or non-breast-fed infant in terms of substitute formula recommendations and as such many clinicians choose to use an EHF as first-line feed also in breast-fed infants.³ However, based on the limited data that have been published (Table VI), there may be a subset of breast-fed infants who may benefit from an AAF: those who exhibit severe delayed, complex non-IgE-mediated allergic symptoms

(skin and gastrointestinal tract), are breast-fed without symptom resolution on an optimal maternal elimination diet (potentially indicating multiple food allergies), and in particular if faltering growth is present. Table VI summarizes these studies.

Anaphylaxis

The reported frequency of milk-induced anaphylaxis (not anaphylaxis to EHF) varies from 0.8% to 9%.³ A study published in 2002 from the United Kingdom found that milk ingestion was the recorded cause of fatal anaphylaxis in 4 cases over more than 10 years, and was involved in 10.9% of fatal or near-fatal anaphylactic episodes.⁸⁴ To the knowledge of the authors, none of the aforementioned cases was related to an EHF. In the United States, 4 children died from fatal milk anaphylaxis from 2001 to 2006.^{85,86} In 1999, Sotto et al⁸³ documented 8 cases between 1985 and 1998 that developed intolerance reactions to EHF, of which 4 had an anaphylactic reaction. Similarly, in 1989, Businco et al⁸⁷ reported 5 cases of children having anaphylactic reactions to a whey EHF. Outside of these cases, there is paucity of data on the prevalence of anaphylaxis to EHF in children with CMPA, but personal communications with allergists have indicated that such cases do exist and therefore the ideal would be that children with this severity of

TABLE VII. Formulas suggested as first choice by guidelines

Clinical presentation	DRACMA ³	BSACI Guidelines ⁹	NIAID US Guidelines ¹⁴	ESPGHAN ^{13,95}
Anaphylaxis	AAF	AAF	No specific recommendation	AAF
Acute urticaria or angioedema	EHF	EHF	No specific recommendation	EHF
Atopic eczema/AD	EHF	EHF	No specific recommendation	EHF
EoE	AAF	AAF	The NIAID guidelines acknowledge that trials in EoE have shown symptom relief and endoscopic improvement in almost all children on AAF/elemental diet, though no specific recommendation on formula choice is made	AAF (as specified by current ESPGHAN guidelines on EoE)
Gastroesophageal reflux disease	EHF	EHF	No specific recommendation	EHF
Cow's milk protein–induced enteropathy	EHF	EHF unless severe in which case AAF	No specific recommendation	EHF but AAF if complicated by faltering growth
FPIES	EHF	AAF	Hypoallergenic formulas are recommended	EHF
Proctocolitis	EHF	EHF	No specific recommendation	EHF
Breast-feeding with ongoing symptoms (already on maternal elimination diet) or requiring a top-up* formula	No specific recommendation	AAF	No specific recommendation	With severe symptoms that are complicated by growth faltering, a hypoallergenic formula up to 2 wk may be warranted. In many countries, AAF is used for diagnostic elimination in extremely sick exclusively breast-fed infants. Although this is not evidence based, it is aimed at stabilizing symptoms

DRACMA, Diagnosis and Rational for Action against Cow's Milk Protein Allergy; NIAID, National Institute of Allergic and Infectious Diseases.

*Top-up formula is where a hypoallergenic formula is required because of insufficient breast milk or the inability to exclusively breast-feed.

reaction receive a hospital- based challenge to an EHF. Because this is not a feasible recommendation for many allergy centers,⁸⁸ most consensus guidelines have erred on the side of caution and have recommended AAF as first-line formula in children with confirmed cow's milk–induced anaphylaxis.^{3,8,9,14}

Limitations of current studies investigation of the use of AAF

There are significant limitations associated with the studies presented in this review; the most notable is that to date there are

only a few studies that have performed a direct comparison of AAFs and EHF and none of them included children with severe gastrointestinal food allergies, including EoE and FPIES, as well as set out to compare children on different formulas with multiple food allergies. In addition, this publication has included only those studies in which cow's milk was identified as the main culprit; many studies however included children with multiple other food allergies outside of cow's milk. Although these publications do give the impression that the change of formula (EHF to AAF) was the main reason for symptoms improvement, with

TABLE VIII. The overlap in symptoms reported in studies of children who benefited from an AAF over an EHF

Publications	Symptoms while breast-fed	Severe GI symptoms	Growth faltering	Multiple allergies	AD
Hill et al ²⁰	+		+	+	
Sicherer et al ⁴⁵		+		+	
Kaczmarek et al ⁷⁶		+			+
Isolauro et al ⁶			+	+	+
de Boissieu and Dupont ¹⁵		+	+		+
de Boissieu et al ⁷		+		+	+
Vanderhoof et al ¹⁷	+	+			
Lucarelli et al ⁸²	+	+		+	

GI, Gastrointestinal.

multiple food allergies, one cannot rule out that the elimination of other allergens and changes in the diet led to symptom improvement.

Furthermore, many studies that have crossed over/challenged to an EHF did not randomize the choice of formula and in 1 study the parents could choose the formula to which their child was challenged. Also, in 1 study, patients were enrolled after only 2 weeks of failing an EHF, which may be too soon for full symptom resolution to occur, in particular in patients with non-IgE-mediated gastrointestinal allergies and severe AD.¹² Many studies are retrospective or observational and lack formal food challenges to confirm intolerance to an EHF, and findings of intolerance to an EHF were often secondary observations. Confirming CMPA in delayed non-IgE-mediated gastrointestinal allergies remains difficult and gastrointestinal symptoms reported may therefore be ambiguous. The number of studies is low, due to the complexity of recruitment and often poor compliance with having to cross over to multiple feeds that may have different tastes. Last, comparative studies of EHF and AAF are often company sponsored, with only a limited number of independent studies available, which may bias outcome.

Current guidelines

In the last 10 years, 15 guidelines have been published in the English language worldwide on the diagnosis and management of CMPA.^{3,8,9,46,89-94} These guidelines in regard to both diagnosis and management are very similar and provide guidance on the diagnosis of CMPA and the management, including information on maternal elimination during breast-feeding, calcium and vitamin supplementation, and hypoallergenic formulas. Because most children present in early childhood with this allergy, in non-breast-fed children a hypoallergenic formula will be required. Table VII summarizes the recommendations for hypoallergenic formulas from major guidelines. In principle, these indicate that for most children with mild to moderate IgE-/non-IgE-mediated CMPA, an EHF is suggested; however, if they have severe IgE-mediated cow's milk-induced anaphylaxis or faltering growth in association with the more severe spectrum of non-IgE-mediated allergy (some specify this in association with enteropathy/hypoproteinemia), an AAF is indicated in most guidelines. Only the UK guidelines provide specific advice in regard to when a top-up formula is required with breast-fed children. The National Institute of Allergic and Infectious Diseases Guidelines for the Diagnosis and Management of Food Allergies¹⁴ recommend a hypoallergenic formula for the management of FPIES, based on demonstrating that most children tolerated EHF, recognizing that there are some children who can tolerate only an AAF and providing references for this in the guideline. In addition, they suggest that a failure on an EHF warrants the use of an AAF. The aforementioned suggestions are well substantiated by published evidence and are in line with international guidelines and most guidelines from other countries.^{3,8,9,46,91,92,96} It is important to note that a recent quality appraisal of CMPA guidelines, by recognized official professional bodies (ie, the European Academy of Allergy and Clinical Immunology, the British Society for Allergy & Clinical Immunology, the World Allergy Organization, the American Academy for Allergy, Asthma & Immunology), using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument, found that the overall quality score of these guidelines was more

than 60%, which was deemed as good quality and therefore recommended their use.⁹⁷

Interpreting results and guidance for health care professionals

From the presented data, the choice of an AAF following the failure of an EHF seems clear and this is reflected in all current guidelines. In 4 of the 6 studies in which an AAF was used either in comparison with an EHF or following the failure of an EHF, significant growth, in particular height growth, was seen. Because of the potential negative consequences of poor growth, the recommendation made in a number of the guidelines to use an AAF in children with CMPA and growth faltering seems to be warranted. The choice of an AAF in anaphylaxis (which is rare in infancy) is consensus based, and seems a reasonable precautionary recommendation in light of the severity of the possible reaction. Alternatively, for an infant who has experienced anaphylaxis, a physician-supervised challenge to EHF may also be recommended.

However, the other indications for an AAF commonly used in guidelines, including children who react while breast-feeding, severe AD, and multiple food allergies, are less clear. Publication showing the benefit of an AAF seem to describe a population of children not with a single stand-alone symptom (ie, severe AD) but a combination of overlapping symptoms (including growth faltering) and multiple food eliminations, and often occur in children who had these symptoms already while being breast-fed (Table VIII). The importance of establishing food allergies on the basis of an allergy-focused history was highlighted in a recent publication by the EAACI.⁹⁸ The information from our review indicates that the choice of an AAF instead of an EHF may lie in the history and *combination of symptoms*, rather than an absolute indication based on a single condition or a specific symptom. From our review, the following conditions warrant the use of an AAF:

- Failure on an EHF
- EoE
- Growth faltering, in particular with multisystem involvement (gastrointestinal tract/and or skin) and multiple food eliminations
- Anaphylaxis

CONCLUSIONS

The appropriate use of an AAF versus an EHF is a highly debated topic, in particular because it has a significant cost implication for health care systems and parents, but also because the well-being of the child with a CMPA needs to be taken into account. For most children with CMPA, an EHF will lead to symptom resolution, but there is a cohort that will require an AAF. On the basis of our literature review, children more likely to benefit from an AAF mostly show complex disease presentations (multiple foods involved, severe AD, and/or gastrointestinal symptoms), with growth issues. It is therefore important that health care professionals perform a detailed allergy-focused history to help them make this decision. A blanket approach for using an AAF is not advised, in particular with the emergence of new data of tolerance development using specific hypoallergenic formulas with addition of probiotics, prebiotics, and synbiotics, which may in future further influence formula choice.

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