

Specialty Infant Formulas for Milk Allergy: Current Choices and Unmet Needs

Yvan Vandenplas, MD, PhD^{1,*}

Sophie Nutten, MD, PhD²

Address

¹KidZ Health Castle, UZ Brussel, Vrije Universiteit Brussel, Laarbeeklaan 101, 1090, Brussels, Belgium
Email: yvan.vandenplas@uzbrussel.be

²Department of Gastrointestinal Health, Nestlé Research Center, Lausanne, Switzerland

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Abstract

Purpose of Review Literature on the different options for the management of cow's milk allergy (CMA) was reviewed. Literature was searched using databases to find original papers and reviews on this topic.

Recent Findings Amino acid based infant formula (AAF) is the most effective dietary treatment of CMA. However, because of the high cost, guidelines recommend extensively hydrolyzed formula (eHF) with a clinical proof of efficacy as the first choice option. In many parts of the world, rice hydrolysates are an alternative option. Soy infant formula can sometimes still be considered, in the absence of more suitable products. Yet, about 10 to 15% of infants allergic to cow milk will also react to soy. Thickened eHF and AAF may be helpful in infants presenting also with troublesome regurgitation. Partially hydrolyzed formula or infant formula with intact protein from other animals is no option. Finally, oral immune therapy is indicated in some children with persistent CMA.

Summary eHF remains the first option for the treatment of most patients with CMA. Recent data on induction of oral tolerance in CMA infants are interesting and deserve further research.

Introduction

Exclusive breastfeeding is universally regarded as the first choice for infant feeding in the first months of life, but will not be discussed further in this manuscript, which focuses on specialty formula-fed infants

with cow's milk allergy (CMA). Although there is no hard evidence that the prevalence of CMA itself increases, that of allergic diseases involving the gastrointestinal (GI), the respiratory tract and the skin does increase worldwide [1, 2]. The estimated prevalence of

CMA ranges between 1.9 and 4.9%, of which about half is IgE mediated and half not [3, 4]. However, incidences as low as 0.5% (95% CI 0.4–0.7) and 0.6% (95% CI 0.5–0.8) for a food-challenge-defined prevalence of CMPA has been reported [4, 5•].

Hypo-allergenic formula

CMA is a reproducible clinically adverse immune-mediated reaction to one or more cow's milk proteins. Different immune mechanisms (IgE-mediated, non-IgE mediated or combination of the two) have been described. Non-IgE mediated has been far less studied than IgE-mediated allergy and immune mechanisms are still not fully understood, yet evidence suggests that these reactions are probably T cell mediated; this entity is also referred to as "hypersensitivity" [6].

Much more parents perceive symptoms associated with cow's milk than the reported incidence of CMA, since parents report an incidence of up to 17% [7]. Infant formula has been developed for the management of CMA, and they are often referred as "hypo-allergenic." Yet, the wording "hypo-allergenic formula" should preferably be avoided, unless a generally accepted definition is introduced, because it has a different meaning in various parts of the world. In Europe, hypo-allergenic formula means a formula that contains hydrolyzed protein and thus a reduced allergenicity, and covers as well partial as extensive hydrolysates. In the USA, hypo-allergenic formula refers to a formula that is tolerated by at least 90% of the children with CMA, with a 95% confidence interval.

Management of CMA symptoms

The vast majority of infants suspected to suffer CMA will be formula-fed and present with a combination of symptoms [8]. Most guidelines recommend an extensively whey or casein-based hydrolyzed cow milk based infant formula (eHF) with clinical proof of efficacy for 2 to 4 weeks, as the first therapeutic option [3, 7–9] (Table 1, treatment recommendations). If the symptoms do not improve with an eHF, then CMA is unlikely. No guideline or recommendation indicates a preference for a whey- or casein-based eHF. However, since most of the eHFs are cow milk based, failure does occur if infants allergic to one or more of the residual peptides. According to literature, this may occur in up to 5 or even 10% [3].

However, the recommendation to position eHF as the preferred option over amino acid-based formula (AAF) is inspired by financial aspects (Table 2). If cost would not be a factor to consider, it is likely that all guidelines would recommend AAF as the preferred option, at least for a period of 2 to 4 weeks.

Table 1. Therapeutic recommendations according to different guidelines

	Australia, Dracma, ESPGHAN		
	1st choice	2nd choice	Differences
GI syndromes	eHF	AAF	Australia: soy as first option in infants > 6 months
Proctocolitis	eHF	AAF	
Eos Eso	AAF		
Immediate food allergy	eHF	AAF	Australia: soy as first option in infants > 6 months
FPIES	eHF	AAF	
Atopic eczema	eHF	AAF	Australia: soy as first option in infants > 6 months
Urticaria	eHF	AAF	
Constipation	eHF	AAF	
Heiner syndrome	AAF	eHF	

AAF is cow milk protein free, since it is purely made from amino acids, and thus not using “cow milk” at all in the manufacturing process. If a strict AAF diet does not result in an improvement of the symptoms, the patient does not suffer CMA. AAF is recommended in formula-fed infants if the presenting symptoms are anaphylaxis or eosinophilic esophagitis, or when the child does not improve with an eHF and CMA is a likely diagnosis or when the cost/benefit analysis is in favor of an AAF. However, eHFs have been reported to be effective in adults with eosinophilic esophagitis caused by cow milk [10]. If infants refuse to drink an eHF, AAF may be indicated as well [3, 5•, 11]. In case of anaphylaxis, a challenge with an eHF should be performed after 6 to 9 months or when the infant is 1 year old in a hospital environment before cow milk is (re-)introduced [3, 12•]. AAF has possibly different long-term nutritional effects than eHFs [11, 13, 14•]. Recently, nutritional deficiencies such as hypophosphatemia and bone disease have been reported with one AAF [14•].

Most of the eHFs are derived from cow milk and result from hydrolysis and heat treatment of proteins to highly decrease and ideally abolish the allergenicity of the resulting peptides.

Table 2. Average cost of formula in Belgium

	€/400 g
Standard infant starter formula	8–9
Partial (whey) hydrolysate	10
Extensive cow milk hydrolysate	17–20
Rice hydrolysate	14
Amino acid formula	42–45

Cow's milk (CM) contains two fractions of proteins: casein and whey proteins, both with allergenic properties. Milk allergenicity can be reduced by various processes such as heat and enzymatic hydrolysis. Manufacturing processes (source of protein, duration of treatments, enzymes and temperature used, combination with ultra-filtration or pressure, etc.) differ for each product. As a consequence, all products are different, contain different peptide size and amino acid sequence and thus present different remaining allergenicity. An individual infant may react to one hydrolysate and tolerate another. Importantly, the characteristics and clinical effect of one eHF cannot be extrapolated to another.

No clear and universal definition of eHFs exists, which was reflected in recent publications mentioning the peptide profile heterogeneity of eHFs and its potential impact on their functionality [15, 16]. Definitions are based on molecular weight of peptides, preclinical testing, and clinical testing. The American Academy of Pediatrics (AAP) defines an extensively hydrolyzed formula as a formula containing only peptides with a molecular weight of <3000 Da [17], when the British Society for Allergy and Clinical Immunology (BSACI) recommends to use hydrolysate with "the greatest percentage of peptides under 1000 Da" [18]. In IgE-mediated allergy, symptoms are induced by the release of inflammatory mediators and cytokines (such as histamine and TNF- α) after cross-linking of the high affinity IgE receptor (Fc ϵ RI) on mast cells and basophils by allergenic epitopes. This reaction is complex and involves different parameters [19]. The cross-linking of Fc ϵ RI requires that at least 2 IgE molecules bind to the allergen, which consequently must contain at least IgE binding sites of approximately 15 amino acid residues long theoretically, in order that the antibody binding can occur [20]. Discontinuous epitopes also exist which renders this picture more complex and less precise in terms of length of epitopes able to trigger an IgE-mediated reaction. Anyway, peptide size is recognized as being one key element linked to an allergic reaction. Complementary preclinical methods have been developed to assess residual allergenicity of hydrolysates. Animal models [21•, 22], mouse basophil activation test [23], or humanized basophil cell line degranulation assay [24] have been described and allow differentiation between intact, partially hydrolyzed and extensively hydrolyzed formula, as well as, for some methods, between different extensively hydrolyzed formula. These various complementary methods are with no doubt necessary to characterize and ensure quality management of hydrolysates. Yet, they have not been proven predictive of reactions in CMA infants and successful well-designed trials are still the ultimate proof of efficacy.

Efficacy of hydrolysates can also be explained by their immunomodulatory properties. Hydrolysates were reported to enforce the intestinal epithelial barrier, to promote T cell differentiation and decrease inflammation [12•]. Some studies also suggest that eHF may influence pathogen recognition receptors signaling. Some peptides in eHF bind to TLR2 and TLR4, influence cytokine production and may modulate immune responses in children with CMA [12•].

Palatability of infant formula is also an important aspect to be taken into account. Generally speaking, eHF has a bitter taste than AAF but differences in palatability of eHF have been described and are linked to the amount of bitter

peptides obtained through hydrolysis or presence versus absence of lactose for example [25, 26].

Thickened extensive hydrolysates and amino acid-based formula

Thickened eHF and AAF are commercially available [27, 28] to treat simultaneously CMA and infant regurgitation. CMA is a differential diagnosis in infants presenting with GERD symptoms [29]. A diagnosis of CMA is considered in up to one third of the pediatric cases with signs and symptoms of GERD [30].

Whether an eHF is thickened or not seems not to be relevant in CMA; however, when the challenge test is negative, the thickened eHF is more effective in reducing regurgitation than the non-thickened one [27]. Up to now, no allergic reaction to the thickening agent has been reported.

Rice hydrolysates

Rice hydrolysates are free of CMP allergens and are less expensive than cow milk-based eHF. Of note, the definition of extensively vs partially hydrolyzed is even vaguer for rice-based products, as the hydrolysis step is needed for technical reasons (solubility) as well. If an eHF is too expensive, not available, or if the infant refuses to drink it, an extensively hydrolyzed rice formula (eRHF) is an adequate option, based on their good nutritional profile and excellent clinical efficacy [31–33]. One eRHF was indeed recently shown to fulfill the requirements of 90% efficacy with a 95% confidence interval and has been shown to be nutritionally adequate [31]. Partially hydrolyzed rice formula (pRHF) exists as well. In general, the risk of contaminants such as heavy metal and pesticides is higher in rice-based products. Typically, the content of arsenic may be a safety issue limiting the use of rice. The Food and Drug Administration (FDA) has warned that some rice products, such as rice feed thickeners and cereals, may have a high content of arsenic. However, rice infant formula is securely controlled and has been shown to have an arsenic content within the legal limits. The arsenic content in rice-based infant formula should be determined and declared on the label [34]. Importantly, rice drinks (sometimes incorrectly labeled as rice milk), which are distributed in some healthcare shops, are not nutritionally adequate for infants.

Soy infant formula

Soy infant formula is no longer available in Europe, while it still holds an important market share in the USA and other parts of the world. Soy infant formula is nutritionally adequate, and whether its use should be limited to infants older than 6 months or not because of the content of isoflavones is heavily debated. Isoflavones have been shown to induce estradiol-like effects in animal models [35]. The World Allergy Organization Diagnosis and Rationale for Action against Cow's Milk Allergy (WAO-DRACMA) guidelines recommend cow milk-based eHF over soy infant formula in IgE-mediated CMA [7]; the Australian guidelines recommend soy infant formula even as first option in some conditions in infants older than 6 months (Table 1), and according to the

American Academy of Pediatrics, soy infant formula may be considered as a valid second choice option after eHF since 10 to 14% of the CMA infants will also develop a soy protein allergy with a higher incidence in non-IgE-mediated CMA than in IgE-mediated CMA [36]. According to a recent meta-analysis, the prevalence of soy allergy was 0.5% in the general population, but the prevalence of sensitization after the use of soy infant formula was 8.7% [37]. In some parts of the world, a partially hydrolyzed soy infant formula is commercialized, although its therapeutic efficacy has not been tested. Altogether, given the debate on the safety of soy infant formula, eRHF seems a better option.

What are not options?

The residual allergenicity of the peptides in partially hydrolyzed formula (pHF), which are not intended for management of CMA symptoms, is indeed too high to recommend the use of this kind of formula in the treatment of CMA. A pHF is tolerated by less than half of infants with CMA [38]. However, pHF may be a good option in the management of functional gastrointestinal disorders if CMA is not suspected [39]. The cross-reactivity of cow's milk with milk from other animals such as sheep and goat is far too high to consider IF based on the latter in the management of CMA [40]. Thus, goat's milk infant formula may be a valid alternative to cow's milk-based infant formula, but cannot be recommended in the treatment of CMA. Significant cross-sensitization to milk proteins derived from animals such as cow, goat, and sheep exist in patients allergic to CMP, but far less so than the milk proteins tested from animals such as mare (donkey), horse, or camel [41]. Camel and mare milk have not been evaluated as possible options [42–44], but ass milk (donkey milk) in particular has been shown to be effective in managing CMA symptoms [44, 45]. The risk of contamination with cow's milk should not be underestimated, as there are rarely dedicated production lines for alternative milks. However, none these milks are commercialized as suitable for infants with CMA and thus are nutritionally not adapted to the requirements of infants. While consumption of unprocessed cow milk in young infants protects against respiratory infections [46], it can as well not be recommended in infants for nutritional reasons. Finally, the epitopes in raw, cooked, or baked milk differ [47•, 48] and baked milk was reported to be tolerated in children with eosinophilic esophagitis as presentation of CMA [49].

Gut microbiota

There is increasing evidence that resident microbial communities in the human gastrointestinal tract, airway, and skin contribute to health and disease. More specifically, a role of microbiome in allergy has been studied during the last four decades.

Advances in science and technology and specifically the possibility now to catalog microbiota and define imbalances in microbial communities (referred as dysbiosis) has led to recent publications, which suggest that modifying the microbiome to the host's advantage could prove to be an approach for preventing and/or treating allergic disease. For example, enrichment of Clostridia and Firmicutes in gut microbiome

positively correlated to resolution of milk allergy [50•]. Microbial metabolites (including short chain fatty acids (SCFA)) are end-products of dietary fiber fermentation by the intestinal microbiota and have recently been demonstrated to regulate allergic inflammation [51].

Extrapolation from in preclinical studies suggests that supplementing infant formulas such as eHF with prebiotics or probiotics such as *Lactobacillus* (L.) *rhamnosus* GG or *Bifidobacteria* (B.) *breve* may offer an additional benefit [52]. Many therapeutic formulas are supplemented with pre- and/or probiotics. Administration of L. GG to children under the age of 2 years suffering from eczema and with a challenge-proven food allergy has been shown to result in a significant decrease in the eczema score [53]. But negative results were reported as well [54]. L. GG has been shown to substantially increase memory B cells and stimulate interferon- γ secretion in infants with CMA and with IgE-associated dermatitis, but not in healthy infants. In infants with colitis, supplementation of a casein eHF with L. GG significantly enhanced the recovery of the inflammation in the colonic mucosa in comparison to the same hydrolysate without the probiotic [55]. In the group that received the probiotic, fecal calprotectin and the number of infants with ongoing occult blood in stools after 1 month were significantly smaller [55].

While promising results have been published, there is currently no positive recommendation from international scientific medical societies to use prebiotics or probiotics for treatment of food allergy and discrepant recommendations [56].

One study showed that addition of lactose to an eHF modulated the composition of the gut microbiota and increased SCFA in infants with CMA [57]. Considering the numerous beneficial effects described for SCFA, these data, while still preliminary, argues in favor of a beneficial effect of lactose for the development of a healthy gut microbiota. In the meantime, it is technically feasible to add lactose to eHF with no detectable residual milk proteins.

Induction of oral tolerance

The primary goal in the treatment of CMA is, of course, for the symptoms to disappear. However, subsequently to the improvement of symptoms, the second, and almost equally important objective, is to acquire oral tolerance. Yet, no established guidelines or protocols on how to proceed with this aspect of the treatment are available today.

Oral tolerance is a state of systemic unresponsiveness and is the default response to food antigens in the gastrointestinal tract and subsequently plays a critical role in preventing disorders such as food allergy. While the process is still not fully uncovered, we have a pretty good understanding of the immune mechanisms involved [58•, 59••]. A major role of a specific subset of dendritic cells has been demonstrated and is involved in induction of regulatory T cells. T cell anergy can also contribute to oral tolerance. The microbiota also plays a role in the development of oral tolerance, through regulation of macrophages and innate lymphoid cells which contribute to the regulatory phenotype of the dendritic cells.

Cow milk peptides

The hypothesis that exposure to cow's milk protein residue (to mimic oral tolerance induction) in CMA infants would favor acquisition of tolerance is still debated. One study described no difference in tolerance acquisition to CMP between groups receiving either an eHF or a RHF [60] and one other showed that patients not exposed to cow's milk protein residue (under soy formula or RHF) achieved tolerance earlier than patients on eHF [61]. More studies are needed to answer this specific question especially because the design of these two latter ones are debatable due to the heterogeneity of the groups including different brands of soy and eHF, which are known to contain different peptides.

Immunotherapy

Food immunotherapies involve oral, sublingual, epicutaneous, or subcutaneous administration of small amounts of native or modified allergens to induce immune tolerance [62]. The oral immunotherapy approach (OIT) generally follows the same principles as immunotherapy of other allergic disorders and involves the administration of small increasing doses of food during an induction phase followed by a maintenance phase with regular intake of a maximum tolerated amount of food. OIT for cow's milk allergy has been shown to be effective in several studies [63], yet adverse reactions occur frequently, especially during the escalation phase for the protocol, requiring epinephrine in a number of cases. Studies combining OIT with omalizumab could be useful to decrease adverse reactions [64–66].

Because it is better tolerated than milk in patients with CMA, baked milk has also been used in OIT [67, 68] and may potentially accelerate desensitization. Only few studies using sublingual (SLIT) or epicutaneous (EPIT) immunotherapy have been reported for cow's milk [69, 70]. These two approaches were less effective but safer than OIT, leading to less severe adverse events. The question of the development of long-term tolerance after a memory immune response has been generated is still open, but mechanistic studies of OIT trials have shown shared pathways in oral tolerance and OIT, with a role of Tregs and anergy [71–73]. Multicentric and randomized-controlled studies are needed to answer still open questions including optimal dose, ideal duration of immunotherapy, degree of protection, efficacy for different ages, severity and type of food allergy responsive to treatment [62].

There is also a potential role for probiotics in inducing immune tolerance. An eHF supplemented with *L. casei* CRL431 and *B. lactis* Bb-12 failed to accelerate tolerance [74]. The negative effect may be linked to strain efficacy since in one other trial that compared an eHF without and with *L. GG*, a double-blind placebo-controlled food challenge was negative in 54% of the infants without *L. GG* and in 81% of the infants receiving *L. GG*. These findings may prove innovative in the therapeutic approach to treating infants with CMA by accelerating the acquisition of tolerance [75]. Data suggest that *L. GG* promotes tolerance in infants with CMA, in part, by influencing the strain-level bacterial community structure of the infant gut and possibly by increasing fecal butyrate levels [76].

Studies demonstrate that an AAF with synbiotics is safe and well tolerated and promotes normal growth when fed to healthy full-term infants as the sole

source of nutrition and is hypoallergenic in subjects with CMA [77]. A nutritionally complete AAF including a prebiotic blend of fructo-oligosaccharides and the probiotic strain *Bifidobacterium breve* M-16V improves the fecal microbiota of infants with suspected non-IgE-mediated CMA [78]. Yet, impact on tolerance acquisition has not been demonstrated.

Unmet needs of current available formula

From the practical point of view, the bitter taste of eHF may be considered as major shortcoming of the formulas, with potential impact on compliance and acceptance, and an improvement of the taste profile should be considered. Formula taste should be considered regarding the acceptance of the infant and not consider interpretation of smell and taste by adults. Overall, these formulae are more costly than standard formula. Lowering the cost without jeopardizing the quality of the formula, as well as systems for having them reimbursed would be welcomed. Since there is consensus that eHF are specific, resulting in recommendations by different scientific organizations and key opinion leaders that “only these formulae should be recommended that have been clinically tested,” the healthcare professional as well as the consumer should be better informed if a formula was clinically tested or not. Another possibility would be that a formula is only allowed to come on the market if it has been clinically tested. However, although being prerequisite, the clinical trials generally only provide a snapshot with a single test based on a single production batch and reproducibility in day-to-day manufacturing is key to ensure product safety and quality, supported by diligent processes for quality control.

From the scientific point of view, formula originating from other protein sources might be of interest as this may result in a greater efficacy, lower cost, and better taste. Soy and rice are examples, but other commonly available protein sources such as potato could be of interest as well.

The advantages of the manipulation of the gastrointestinal microbiome with pre- (including the benefits of lactose and HMOs) and probiotics should be further studied. Finally, much more research is needed on the best way to induce the development of oral tolerance. Manipulation of the gut microbiota is only one way. The answers to these question will modify formula composition. It might also be necessary to have dedicated formulas for the management of CMPA with the lowest possible risk profile and separate solutions to induce tolerance.

Conclusion

According to the guidelines and recommendations, cow milk-based eHF remains the preferred therapeutic choice, while AAF is reserved for the most severe cases. RHF are becoming more popular, since their efficacy is excellent and nutritional parameters are adequate.

Manipulation of the gut microbiota may enhance the development of oral tolerance. If the administration of small amounts of cow milk peptides also result in the development of oral tolerance needs further validation. If the absence of cow milk peptides, as is the case with AAF and RHF, would result in a delayed development of oral tolerance needs further evaluation as well, but

seems not the case according to the data available today. The hypothesis that management of CMA would first preferable be started with cow milk protein free formula, followed by cow milk based eHF, followed in turn by small amounts of cow milk, baked or not, supplemented or not with pre- and/or probiotics, to enhance tolerance development is a challenging thought which deserves to be evaluated.

Compliance with Ethical Standards

Conflict of Interest

Y Vandenplas has participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for Abbott Nutrition, Biocodex, CHR Hansen, Danone, Nestle Health Science, Nestle Nutrition Institute, Nutricia, Mead Johnson Nutrition, Schär, United Pharmaceuticals, Wyeth. S Nutten is a Nestec Ltd. employee.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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