



Making Informed Choices for the Nutritional Management of Infants with Cow’s Milk Allergy

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Meeting Summary

Cow’s milk allergy (CMA) is a common allergy in early childhood that is frequently misdiagnosed and inadequately treated. In this symposium, held during the 57th Annual Congress of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), a panel of experts described the latest European guidelines for the diagnosis and treatment of CMA (ESPGHAN 2024), including the recommendation to use extensively hydrolysed formula (EHF) at first line in infants with mild-to-moderate CMA who are not breastfed. Factors for clinicians to consider when prescribing a tailored diet for patients in this population were discussed, such as type of protein, degree of hydrolysis, and immune factors.

Although hydrolysis breaks down proteins into short peptides that have reduced allergenicity, the residual levels of longer peptides vary considerably between EHF's available for the management of CMA. Initial data were presented from a blinded study that aims to characterise EHF's, including longer peptides and aggregates that may have the potential to cause an IgE-mediated reaction. The results to date indicate considerable compositional variability between products.

Further research is needed to support the introduction of standardised methodology for characterising EHF, together with clinically relevant read-outs. Such research will help set standards for EHF manufacturing and provide information that will help clinicians in selecting the most appropriate EHF for infants and young children with CMA.

Introduction

Mikael Kuitunen, Associate Professor and Consultant Paediatric Allergist, Helsinki University Hospital, Finland, explained that CMA, an immune reaction to whey or casein proteins in cow's milk, is one of the most common allergies presenting in early childhood.¹ Symptoms of CMA usually occur rapidly after the ingestion of cow's milk, and mainly involve the skin, respiratory tract, and gastrointestinal tract.² They can range in intensity from mild to severe, with anaphylactic reactions representing the most severe response.² Prevalence rates vary, which may be due to different methods of reporting.³ Epidemiological studies using double-blind placebo-controlled food challenge (DBPCFC) report a prevalence of CMA during infancy of <1%; however, the prevalence perceived by parents is much greater, at about 10%.³

CMA is frequently misdiagnosed and inadequately treated in infants and young children.³ Diagnosis of CMA, especially non-IgE CMA, in this age group can be challenging, as many presenting symptoms, such as colic, gastro-oesophageal reflux, and change in stool consistency, are non-specific and overlap with disorders of gut-brain interaction.^{3,4} Overdiagnosis of CMA occurs far more frequently than underdiagnosis.³

In a study at a maternity hospital in Finland, parental suspicion of CMA was reported in 10% (622/6,209) of healthy newborns given supplementary infant formula soon after delivery.⁴ Symptoms subsided in

40% (247/622) of these infants after eliminating cow's milk from their diet, and 48% (118/247) subsequently had a positive response to a challenge with cow's milk.⁴ This indicates an overall incidence of challenge-proven CMA of 1.9% in the study population.⁴ Infants who developed delayed gastrointestinal symptoms, such as colic, irritability, regurgitation, vomiting, food refusal, and diarrhoea³ within 5 days of reintroducing cow's milk were frequently not detected as CMA-positive through more objective tests (skin-prick test, patch test, elevated serum cow's milk-specific IgE, elevated serum eosinophil cationic protein).⁴

In a broader study, based on the pan-European EuroPrevall birth cohort, parental suspicion of CMA was reported in 3% (358/12,049) of infants. CMA was subsequently confirmed in 15% (55/358) of these infants in a DBPCFC, resulting in an overall incidence of challenge-proven CMA of 0.54%. The prevalence of both CMA in general, and IgE-mediated CMA specifically, varied between countries, and this may be partly explained by the use of different methodologies.^{3,5}

Recent guidelines from ESPGHAN recommend that diagnosis of CMA in infants in clinical practice should be based on a brief elimination diet (by the mother, if breastfeeding) followed by reintroduction/challenge with cow's milk if symptoms improve.³ It is important to note that breastfeeding should be continued in breastfed infants suspected of CMA.³ Infants with confirmed CMA should be monitored for the development

of oral tolerance to cow's milk,³ and this recommendation is supported by data indicating that among infants diagnosed with IgE-mediated CMA, tolerance may develop within 12 months of eliminating cow's milk from the infant's diet.⁶

Kuitunen explained that the therapeutic management of challenge-confirmed CMA should include avoidance of cow's milk and foods containing cow's milk by the infant/young child, following an individualised strategy, and (if not being breastfed) the use of an appropriate choice of hypoallergenic formula.¹ Parents/carers should be provided with information regarding reading and interpreting food allergen labels, including precautionary allergen warnings, selecting safe and nutritious substitute foods, monitoring nutritional intake and growth, and identifying and treating acute severe allergic reactions.¹

It's Not Just About Removing the Cow's Milk Protein

Lucy Jackman, Great Ormond Street Hospital, London, UK, reiterated that some of the symptoms of CMA are common in infants.⁷ She described a UK study that used the international Milk Allergy in Primary Care (iMAP) guidelines to identify possible non-IgE-mediated CMA symptoms, investigating the frequency of these symptoms among 1,303 exclusively breastfed 3-month-old infants.⁷ The study found that one in 11 infants had ≥ 2 'severe' iMAP symptoms, and three in four had mild/moderate iMAP symptoms.⁷ Jackman stressed that overdiagnosis is common in primary care, because the process of the four 'Rs' (Remove, Replace, Reintroduce, Relapse) is not always completed (Jackman, personal communication).

The WHO recommends exclusive breastfeeding for the first 6 months of life, and breastfeeding alongside complementary feeding for up to 2 years of life.¹ Breastmilk provides the vast majority of an infant's nutritional needs, including macronutrients of carbohydrate,

protein, and fat.⁸ Vitamins D and K may be insufficient in breastmilk and infants sometimes require supplementation.⁸ Breastmilk also provides non-nutritional bioactive substances that can have a prolonged impact on an infant's growth and development, gut microbiome, and immune function.⁹ These substances include hormones (e.g., insulin, ghrelin, etc.), human milk oligosaccharides (HMO), and immunomodulatory components (e.g., cytokines, growth factors, antibodies, etc.).⁹

Among infants with confirmed CMA, breastfeeding remains the optimal source of milk.³ However, if breastfeeding is not possible, or the mother chooses not to breastfeed, an EHF is recommended at first line.³ Hydrolysed rice formula can also be considered as an alternative, while the option of an amino-acid-based formula is reserved for infants with more severe CMA or those who do not respond to EHF.³ Soy-based formula, based on hydrolysed soy protein isolate, contains some substances, such as phytate, aluminium, and phytoestrogenic isoflavone, at higher concentrations than are found in milk-based formulas.³ While soy formulas are not considered to be harmful to human development, ESPGHAN and the American Academy of Pediatrics (AAP) recommend against its use in infants aged <6 months due to the risk of co-allergy between soy and cow's milk, mainly in infants with non-IgE-mediated CMA.³ The decision of which formula to use should be based on the nutritional composition of the formula and its residual allergenicity, and the individual infant's symptoms.³

Composition of Extensively Hydrolysed Formulas

The macro and micronutrient content of hypoallergenic infant formulas, such as EHF, are tightly governed by recommendations in the EU to ensure nutritional adequacy.¹⁰ However, Jackman stressed that they may vary significantly in their wider composition, such as their protein source, protein/peptide length, carbohydrate source, fat source, and additives like pre and probiotics.¹¹⁻¹³

Hydrolysed cow's milk proteins

CMA reactions occur when circulating antibodies recognise conformational or linear epitopes on the surface of cow's milk proteins.¹⁴ Hydrolysis is a process by which chemical or enzymatic methods are applied to break down polypeptide chains in these proteins, modifying their allergenicity.¹⁵

Advances in hydrolysis techniques mean that the processes used to produce EHF's have evolved. Formulas available on the market today can therefore be produced using different methods, resulting in variable levels of hydrolysis.¹² As such, it is possible that some products labelled as EHF may not be appropriate for use in CMA.¹²

There is currently no clear consensus on what constitutes an EHF, with the AAP defining an EHF as a formula where "most of the nitrogen is in the form of free amino acids and peptides <1.5 kDa,"¹⁶ and the British Society for Allergy and Clinical Immunology (BSACI) advising that an EHF with "the greatest percentage of peptides <1 kDa" may be preferable for CMA.¹³ Not all infants with CMA achieve symptom resolution when they switch to an EHF,^{17,18} and it has been hypothesised that the observed residual allergenicity relates to the peptide size distribution of different EHF's.¹²

In a physicochemical study in 2019, commercially available EHF's were analysed to detect residual cow's milk peptides of >1.2 kDa, which are potentially allergenic.¹² While the majority (89–100%) of peptides were <2.4 kDa, some formulas retained peptides >1.2 kDa, and there was notable variability in peptide size profiles between EHF products and even between batches of the same product.¹² These findings underscore the need to develop guidelines for the minimum requirements for EHF products.¹⁹

Lactose

The carbohydrate component of breast milk predominantly consists of lactose, which is readily digested in almost all infants.⁸ Some EHF products contain lactose, while others do not.¹³ The most recent ESPGHAN guidelines recommend the temporary use of a lactose-free EHF during a diagnostic

elimination diet in infants with suspected CMA and severe diarrhoea lasting longer than a week (suggestive of lactase deficiency).³ However, they also state that "adverse reactions to lactose in CMA are not supported in the literature, and complete avoidance of lactose in CMA is no longer warranted."³

Lactose in breastmilk plays an important role in developing the function of the gastrointestinal tract from birth and maintaining the composition of the intestinal microbiota.⁸ This is an important consideration when selecting an EHF, as allergic infants have been shown to have dysbiosis.²⁰

Jackman described a prospective study in which infants with DBPCFC-confirmed CMA (n=16) received a lactose-free EHF for 2 months followed by an identical lactose-containing EHF for 2 months.²⁰ Healthy, gender-matched infants were used as controls (n=12). The addition of lactose to EHF significantly increased the counts of *Bifidobacteria/Lactobacillus* (p<0.01) and decreased the counts of *Bacteroides/Clostridia* (p<0.05), reaching counts similar to those in healthy controls.

Another important role of lactose is to support the absorption of minerals and calcium.¹¹ In another prospective study, 18 healthy, full-term infants aged 8–12 weeks received lactose-free partially hydrolysed formula (PHF) for 2 weeks, followed by lactose-containing PHF.²¹ The presence of lactose in formula was shown to significantly increase the absorption of calcium (p<0.01); however, the absorption of calcium from both formulas was adequate for the calcium needs of full-term infants.

Finally, the inclusion of purified lactose may improve the palatability of EHF for infants and young children.^{3,22,23}

Human milk oligosaccharides

HMOs are the third-most abundant solid component of breast milk.⁸ HMOs are indigestible carbohydrates that play an important prebiotic role in the development of intestinal microbiota after birth.⁸ Breast milk contains over 200 structurally different

HMOs, which can be categorised into neutral fucosylated HMO, acidic sialylated HMO, and neutral non-fucosylated HMO.²⁴ Breast milk promotes the growth of specific *Bifidobacterium* species in the infant intestine, which ferment HMOs to produce short-chain fatty acids. These fatty acids create a low pH environment in the colon, encouraging the growth of beneficial bacteria and inhibiting pathogens.²⁴ They also protect against infection, have anti-inflammatory properties, and strengthen the intestinal epithelial barrier.²⁴

Non-human oligosaccharides, such as galactooligosaccharides and fructooligosaccharides, have been added to infant formula for many years to reproduce some of these prebiotic effects.^{3,25} However, these oligosaccharides are structurally very different from HMOs, and since most of the known biological effects of HMOs are structure-specific, it is possible that they may not provide the same health benefits.²⁵

More recently, advances in biotechnology have made it possible to replicate HMOs that are structurally identical to those found in human milk.^{3,25,26} These 'human-identical' HMOs are added to some therapeutic formulas.³

In a randomised, multicentre study of non-breastfed infants with CMA (N=194), an exploratory analysis of the data compared the effects of an EHF supplemented with two HMOs (2'-fucosyllactose [2'-FL] and lacto-N-neotetraose [LNnT]) versus a control EHF (without HMO supplementation) on the faecal microbiome.²⁷ The addition of the HMO increased intestinal *Bifidobacteria* and slowed microbiome maturation, particularly when used before 6 months of age.

Safety and hypoallergenicity

Several studies have demonstrated the safety and tolerability of EHF's supplemented with HMOs and lactose in infants and young children with CMA.²⁸⁻³⁰ In one randomised crossover study, children (2 months–4 years; N=67) with CMA underwent a DBPCFC with an EHF containing 2'-FL and LNnT (test formula) and a non-HMO-containing EHF (control formula). Both formulas contained

highly purified lactose.²⁸ Both the test and control formulas were tolerated by 98.4% of participants, confirming clinical hypoallergenicity. In another randomised study, the growth of full-term infants aged 0–6 months was compared between those given an EHF containing 2'-FL and LNnT (test formula; n=94) or a non-HMO-containing EHF (control formula; n=96).²⁹ Both formulas contained highly purified lactose. At the 4-month follow-up, daily weight gain for the test formula was noninferior to the control formula ($p < 0.005$), indicating that the addition of HMO did not impact growth.²⁹ Infants in the HMO group also had a lower incidence of upper respiratory tract infections and ear infections.²⁹

Are All Protein Hydrolysates the Same?

Clare Mills, University of Surrey, UK, reiterated that EHF's are a heterogeneous group of products,¹² and explained why it is important to clarify the definition of an EHF.

Clinically Relevant Cow's Milk Allergens

Caseins and whey proteins are the most clinically relevant cow's milk allergens.³¹ The majority (approximately 80%) of the protein in cow's milk is formed of caseins, which assemble into micelles around calcium phosphate molecules.^{14,32} β -lactoglobulin and α -lactalbumin are the most abundant whey proteins.¹⁴ Patients with CMA have an immune reaction to casein, and many also react to whey proteins.¹⁴

All of these proteins contain both conformational and linear IgE epitopes.¹⁴ While heating cow's milk can modify the allergenicity of conformational epitopes by denaturing/unfolding proteins, this has little to no effect on the allergenic potential of cow's milk because linear epitopes remain unaffected.¹⁴ Since hydrolysis uses chemical or enzymatic processes, it can break down proteins into smaller peptides,¹⁴ disrupting both conformational and linear epitopes.

Cow's milk-based hydrolysed formula can be either partially or extensively hydrolysed (PHF or EHF).³ As already noted, there is no international consensus for the definition of these two types of formula, but PHF is generally composed of peptides <5 kDa, whereas EHF is generally composed of peptides <3 kDa.³³ Studies have shown that PHF based on either casein or whey may retain IgE epitopes.^{34,35} However, even among EHF marketed for the management of CMA, the peptide molecular weight distribution can vary considerably.¹²

It has been recommended that minimum clinical evidence requirements should be developed for formulas intended for CMA, and that the analytic methods used to detect residual allergens should be standardised.¹²

Physicochemical Analysis of Extensively Hydrolysed Formula

Mills presented initial data from a study conducted by Surrey University in association with Nestlé Health Science (Vevey, Switzerland) and the Waters Corporation (Milford, Massachusetts, USA). This blinded study aimed to characterise EHF's in terms of the presence of structures with the potential to cause an IgE-mediated reaction, including residual intact proteins, peptides large enough to encompass a sequential IgE epitope (12–15 amino acids), and peptide aggregates. A total of eight EHF's (EHF-1 to EHF-8) and one PHF (control) were assessed using a variety of methods, including SDS-PAGE, gel permeation chromatography, and mass spectroscopy.

When the formula samples were subjected to SDS-PAGE, which denatures proteins and separates them by size, the PHF showed a broad range of peptide sizes ranging up to around 100 kDa, indicating the unsuitability of this product for CMA. While the majority of EHF samples consisted of peptides <6kDa, EHF-1 and EHF-2 showed a peptide profile similar to that of the PHF, indicating that they contained a mixture of intact, aggregated protein and large peptides.

Further analysis with high-performance liquid chromatography (HPLC) confirmed

the SDS-PAGE results, showing that EHF-1 and EHF-2 contained a high relative abundance of peptides >1.2 kDa (40.5% and 37.0%, respectively), with the PHF sample showing a relative abundance of 51.2% of these larger proteins (Figure 1). Specific immunoassays showed that EHF-1 contained residual casein, and both EHF-1 and EHF-2 contained residual β -lactoglobulin.

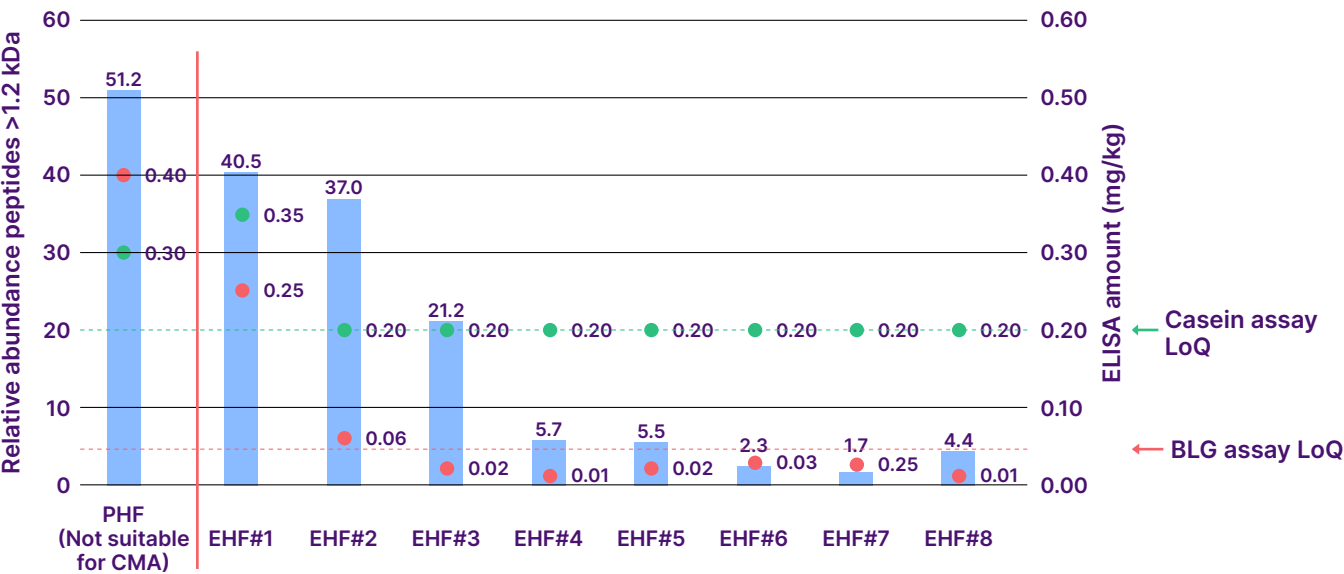
The samples were also subjected to liquid chromatography ion mobility mass spectrometry (LC-IM-MS). Principal components analysis of their peptide profiles showed distinct clustering of the PHF sample with EHF-1, the EHF-2 sample with EHF-3, and the remaining 5 EHF samples together, reflecting the number and size of the peptides in the formulas. These similarities and differences may be due to different starting materials and hydrolysis processing parameters.

Mass spectrometry of the EHF samples showed a wide range of peptide distribution profiles, both in terms of the total number of cow's milk protein derived peptides per sample and the number of large peptides ≥ 3 kDa (Figure 2). Mass spectrometry of the peptide mass profiles specific to β -lactoglobulin showed that PHF and EHF-1, -2, and -3 contained the greatest number of β -lactoglobulin peptides, and EHF-8 had the fewest. Most β -lactoglobulin peptides were <2.5 kDa; however, a small number of peptides >3 kDa were identified in all samples except EHF-8. Since a 3 kDa filter was used in the preparation of all the tested EHF formulas, these peptides are likely to be aggregates that formed after filtration.

When the samples were assessed for the abundance of a specific β -lactoglobulin peptide known to contain an IgE epitope (⁸⁵KKIIAEKTKIPAVFKIDAL NENKVLVLDTDYKKYLLF¹²¹), the levels of this peptide varied considerably between the EHF samples, with a higher relative normalised abundance found in EHF-1, -2, and -5, and undetectable levels in EHF-8.

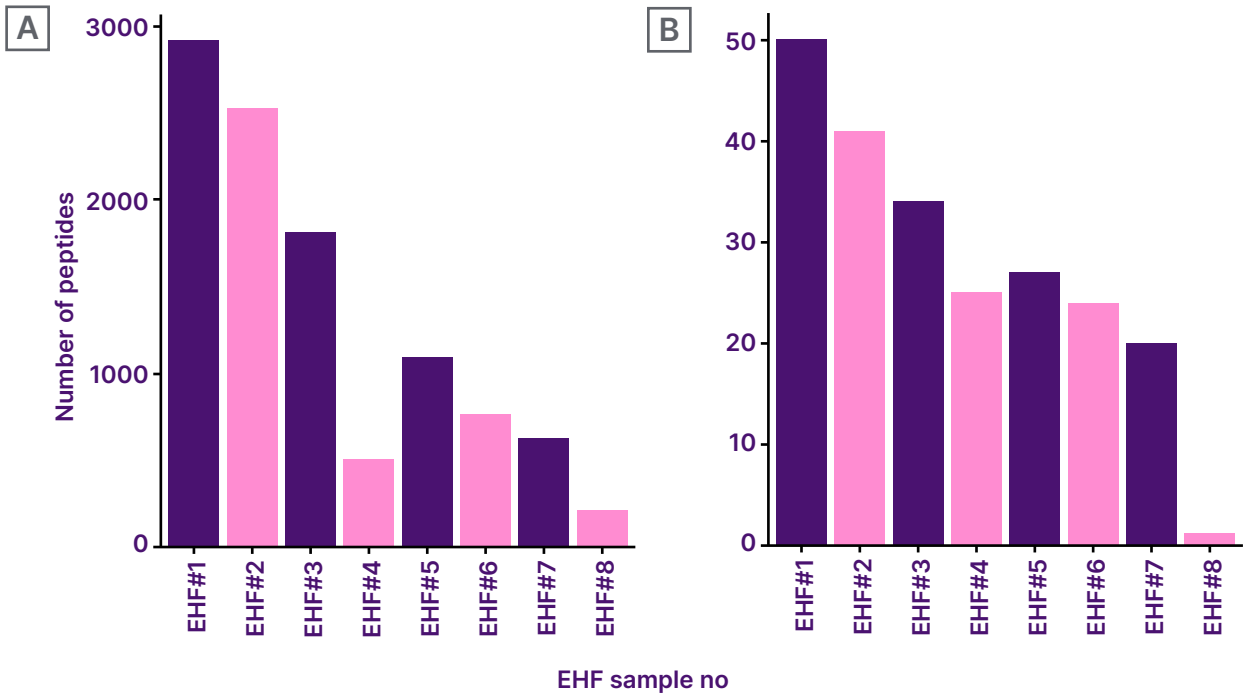
Mills concluded that the compositional variability of the EHF samples in terms of peptides may explain why some EHF can cause symptoms in infants and young children with CMA.^{17,18} It also

Figure 1: Residual intact peptides and proteins determined by high-performance liquid chromatography and specific immunoassay.



BLG: β -lactoglobulin; CMA: cow's milk allergy; EHF: extensively hydrolysed formula; LoQ: lower limit of quantification; PHF: partially hydrolysed formula.

Figure 2: Peptide distribution profiles for different samples of extensively hydrolysed formula profiled by mass spectrometry.



A) Total number of cow's milk protein-derived peptides. B) Number of large peptides ≥ 3 kDa.
EHF: extensively hydrolysed formula.

highlights that the peptide profile of some products characterised as an EHF more closely resemble that of PHF, which is not considered to be suitable for infants with CMA.

While this physicochemical analysis focused on the removal of epitopes with the potential to induce an allergic reaction in susceptible infants, Mills explained that residual peptides of cow's milk protein may also include smaller T cell epitopes that would be immunologically active, and may be important for tolerance induction.³⁶

Future functional studies are needed to confirm the results of this physicochemical analysis using biological samples. These clinical data will be able to guide the introduction of standardised tests capable of identifying EHF products suitable for CMA, which in turn may support clinicians in selecting the right EHF for each child. Mills stressed that any discussion of standardisation in EHF products should involve multiple stakeholders, including patients, clinicians, manufacturers, medical societies, regulators, and researchers.

CONCLUSION

Breast milk is the recommended mode of feeding for all infants, including those with CMA. If formula is used, an EHF based on cow's milk or a hydrolysed rice formula should be selected.³ EHF's vary considerably by protein type and peptide profile, and the inclusion of components such as lactose and HMOs.^{3,12,13,25,26} While it is important not to avoid lactose unnecessarily in formula for patients with suspected CMA,³ a personalised choice of formula should be based on nutritional composition, residual allergenicity, and an infant's symptoms.³

It is important to note that not all commercialised EHF products have undergone formal characterisation and testing in the laboratory and clinical trials.¹⁹ The development of minimum technical and regulatory requirements for EHF products therefore remains an unmet need.¹⁹

References

- Venter C et al. World Allergy Organization (WAO) diagnosis and rationale for action against cow's milk allergy (DRACMA) guidelines update – XVI - Nutritional management of cow's milk allergy. *World Allergy Organ J.* 2024;17(8):100931.
- Tosca MA et al. Molecular allergy diagnostics in children with cow's milk allergy: prediction of oral food challenge response in clinical practice. *J Immunol Res.* 2023;2023:1129449.
- Vandenplas Y et al. An ESPGHAN position paper on the diagnosis, management, and prevention of cow's milk allergy. *J Pediatr Gastroenterol Nutr.* 2024;78(2):386-413.
- Saarinen KM et al. Diagnostic value of skin-prick and patch tests and serum eosinophil cationic protein and cow's milk-specific IgE in infants with cow's milk allergy. *Clin Exp Allergy.* 2001;31(3):423-9.
- Schoemaker AA et al. Incidence and natural history of challenge-proven cow's milk allergy in European children--EuroPrevall birth cohort. *Allergy.* 2015;70(8):963-72.
- Chatchatee P et al. Tolerance development in cow's milk-allergic infants receiving amino acid-based formula: a randomized controlled trial. *J Allergy Clin Immunol.* 2022;149(2):650-8.
- Vincent R et al. Frequency of guideline-defined cow's milk allergy symptoms in infants: secondary analysis of EAT trial data. *Clin Exp Allergy.* 2022;52(1):82-93.
- Kim SY et al. Components of human breast milk: from macronutrient to microbiome and microRNA. *Clin Exp Pediatr.* 2020;63(8):301-9.
- Brockway MM et al. Human milk bioactive components and child growth and body composition in the first 2 years: a systematic review. *Adv Nutr.* 2024;15(1):100127.
- Official Journal of the European Union. Commission Delegated Regulation (EU) 2016/127. n.d. Available at: https://eur-lex.europa.eu/eli/reg_del/2016/127/oj/eng. Last accessed: 23 May 2025.
- Martin CR et al. Review of infant feeding: key features of breast milk and infant formula. *Nutrients.* 2016;8(5):279.
- Nutten S et al. Peptide size profile and residual immunogenic milk protein or peptide content in extensively hydrolyzed infant formulas. *Allergy.* 2020;75(6):1446-9.
- Luyt D et al. BSACI guideline for the diagnosis and management of cow's milk allergy. *Clin Exp Allergy.* 2014;44(5):642-72.
- Fiocchi A et al. World Allergy Organization (WAO) diagnosis and rationale for action against cow's milk allergy (DRACMA) guidelines. *World Allergy Organ J.* 2010;3(4):57-161.
- Pereira RN et al, "Chapter eight - tackling food allergens - the role of food processing on proteins' allergenicity," Toldrá F (ed.), *Advances in Food and Nutrition Research* (2023), Academic Press, pp.317-351.
- American Academy of Pediatrics (AAP). Committee on Nutrition. Hypoallergenic infant formulas. *Pediatrics.* 2000;106(2 Pt 1):346-9.
- Petrus NCM et al. Remaining symptoms in half the children treated for milk allergy. *Eur J Pediatr.* 2015;174(6):759-65.

18. Chauveau A et al. Immediate hypersensitivity to extensively hydrolyzed formulas: an important reminder. *Pediatr Allergy Immunol.* 2016;27(5):541-3.
19. Nutten S et al, "Chapter four - design, quality, safety and efficacy of extensively hydrolyzed formula for management of cow's milk protein allergy: what are the challenges?" Toldrá F (ed.), *Advances in Food and Nutrition Research* (2020), Academic Press, pp.147-204.
20. Francavilla R et al. Effect of lactose on gut microbiota and metabolome of infants with cow's milk allergy. *Pediatr Allergy Immunol.* 2012;23(5):420-7.
21. Abrams SA et al. Calcium and zinc absorption from lactose-containing and lactose-free infant formulas. *Am J Clin Nutr.* 2002;76(2):442-6.
22. Miraglia Del Giudice M et al. Flavor, relative palatability and components of cow's milk hydrolysed formulas and amino acid-based formula. *Ital J Pediatr.* 2015;41:42.
23. Maslin K et al. Palatability of hypoallergenic formulas for cow's milk allergy and healthcare professional recommendation. *Pediatr Allergy Immunol.* 2018;29(8):857-62.
24. Dinleyici M et al. Functional effects of human milk oligosaccharides (HMOs). *Gut Microbes.* 2023;15(1):2186115.
25. Bode L et al. Structure-function relationships of human milk oligosaccharides. *Adv Nutr.* 2012;3(3):383S-91S.
26. Nestlé Health Sciences. Althéra HMO: Hypoallergenic Formula. n.d. Available at: <https://www.cowsmilkallergy.com/hcp/hypoallergenic-formulas/althera-hmo>. Last accessed: 22 May 2025.
27. Boulangé CL et al. An extensively hydrolyzed formula supplemented with two human milk oligosaccharides modifies the fecal microbiome and metabolome in infants with cow's milk protein allergy. *Int J Mol Sci.* 2023;24(14):11422.
28. Nowak-Węgrzyn A et al. Confirmed hypoallergenicity of a novel whey-based extensively hydrolyzed infant formula containing two human milk oligosaccharides. *Nutrients.* 2019;11(7):1447.
29. Vandenplas Y et al. Effects of an extensively hydrolyzed formula supplemented with two human milk oligosaccharides on growth, tolerability, safety and infection risk in infants with cow's milk protein allergy: a randomized, multi-center trial. *Nutrients.* 2022;14(3):530.
30. Marriage BJ et al. Infants fed a lower calorie formula with 2'FL show growth and 2'FL uptake like breast-fed infants. *J Pediatr Gastroenterol Nutr.* 2015;61(6):649-58.
31. Edwards CW, Younus MA, Cow milk allergy [Internet] (2024) Treasure Island: StatPearls Publishing. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK542243/>. Last accessed:
32. Holt C. A quantitative calcium phosphate nanocluster model of the casein micelle: the average size, size distribution and surface properties. *Eur Biophys J.* 2021;50(6):847-66.
33. Greer FR et al. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics.* 2008;121(1):183-91.
34. Bernard H et al. Specificity of IgE antibodies from patients allergic to goat's milk and tolerant to cow's milk determined with plasmin-derived peptides of bovine and caprine β -caseins. *Mol Nutr Food Res.* 2012;56(10):1532-40.
35. Xu L et al. Influence of whey protein hydrolysis in combination with dextran glycation on immunoglobulin E binding capacity with blood sera obtained from patients with a cow milk protein allergy. *J Dairy Sci.* 2020;103(2):1141-50.
36. Goh A et al. Differences between peptide profiles of extensive hydrolysates and their influence on functionality for the management of cow's milk allergy: a short review. *Front Allergy.* 2022;3:950609.