



New Developments in the Treatment of Cow's Milk Allergy



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Cow's milk allergy (CMA) is a relatively common condition in infants, with a reported incidence of 1-7.5%.¹ However, prevalence estimates can vary due to the broad spectrum of symptoms and the absence of specific diagnostic tools, making definitive diagnosis challenging.¹ CMA can be classified as IgE-mediated, non-IgE-mediated, or a combination of both.¹ IgE-mediated allergies typically trigger reactions within minutes of ingesting cow's milk, whereas non-IgE-mediated reactions can develop between 2 to 72 hours.² The primary systems affected include the skin, gastrointestinal tract and respiratory system.

To confirm a diagnosis and minimise overdiagnosis, a short-term elimination of cow's milk is recommended, followed by a reintroduction challenge. If breastfeeding is not an option, specialised hypoallergenic formulas are used as alternatives to standard infant formulas. These include extensively hydrolysed formulas (EHF), amino acid-based formulas (AAF), and soy-based formulas. Extensively hydrolysed rice protein formula's (HRFs) have been used in Europe since the early 2000s, and are now available in the UK.^{3, 4}

Why hydrolysed rice formula?

Hydrolysed rice infant formula is a suitable choice due to the low allergenicity of rice as a grain and the absence of cross-reactivity between cow's milk and rice.⁴ In contrast, other mammalian milks and soya milk have been found to pose a risk of cross-reactivity, making them less suitable for infants with CMA.³ This makes rice-based formulas a viable alternative for those requiring a hypoallergenic diet.

The rice proteins in these formulas undergo enzymatic hydrolysis, which breaks them down into smaller,

water-soluble peptides and enhances its absorption efficiency.² Since rice protein differs from human milk protein, these formulas are supplemented with essential amino acids, such as lysine, threonine and tryptophan, to ensure a balanced amino acid profile comparable to human milk.² Additionally, the energy content and lipid profile of hydrolysed rice formulas are similar to standard infant formulas, making them nutritionally adequate for infant growth and development.²

What do the guidelines say?

In 2024, DRACMA (Diagnosis and Rationale for Action Against Cow's Milk Allergy) recommended hydrolysed rice formulas as a first-line management option, alongside other EHF, for formula-fed infants with IgE- and non-IgE-mediated CMA. HRFs are likely to be well tolerated in cases of mild-to-moderate CMA, as they do not contain any cow's milk protein. See **Figure 1**. Furthermore, HRFs could be considered when other extensively hydrolysed formulas trigger a reaction, as cow's milk protein extensively hydrolysed formulas will still have 10-30% of residual cow's milk protein and extensively hydrolysed rice formulas are free from cow's milk protein.⁵⁻⁹ In 2026 a decision tree, developed by a group of UK experts, was published as a tool to support UK clinicians in determining when HRF should

be the preferred choice.¹⁰ A simple summary of this guidance can be found in **Figure 2**.

Growth & tolerance

Two studies have shown that healthy infants fed hydrolysed rice formulas exhibit normal growth patterns comparable to those of infants fed standard infant formula or those meeting World Health Organization (WHO) growth standards.² Additionally, several studies evaluating growth in infants with CMA who consumed rice hydrolysates have reported healthy growth patterns and good catch-up growth.² Notably, most of the studies focused on children with IgE-mediated cow's milk protein allergies or with infants who had confirmed allergy by either oral food challenges or double-blind controlled food challenges.²

Figure 1: Flow diagram to confirm or exclude cow's milk allergy

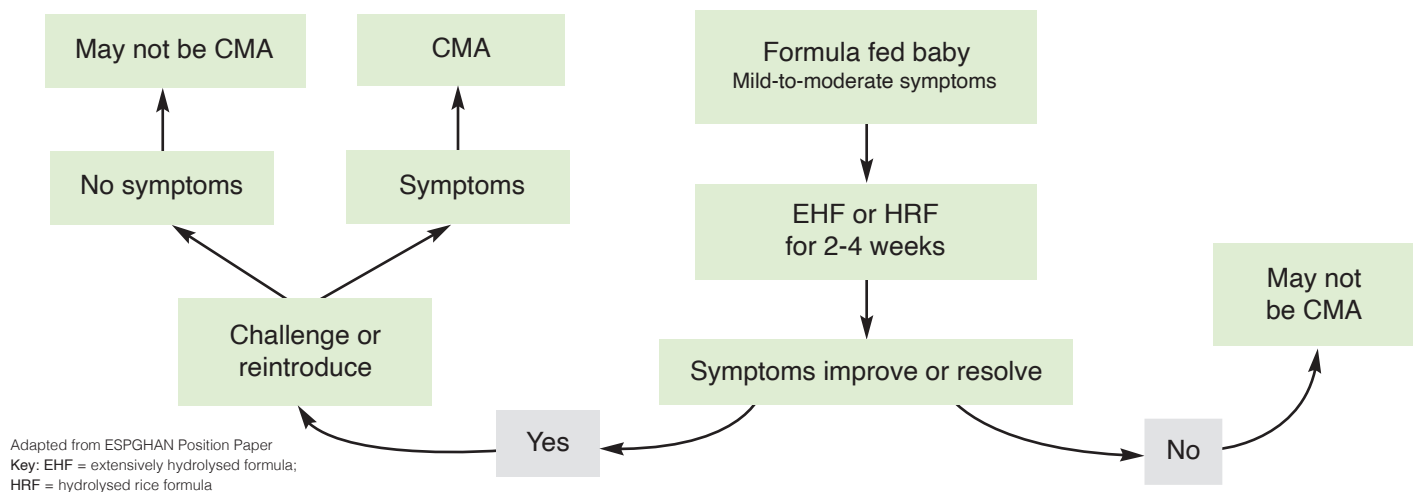
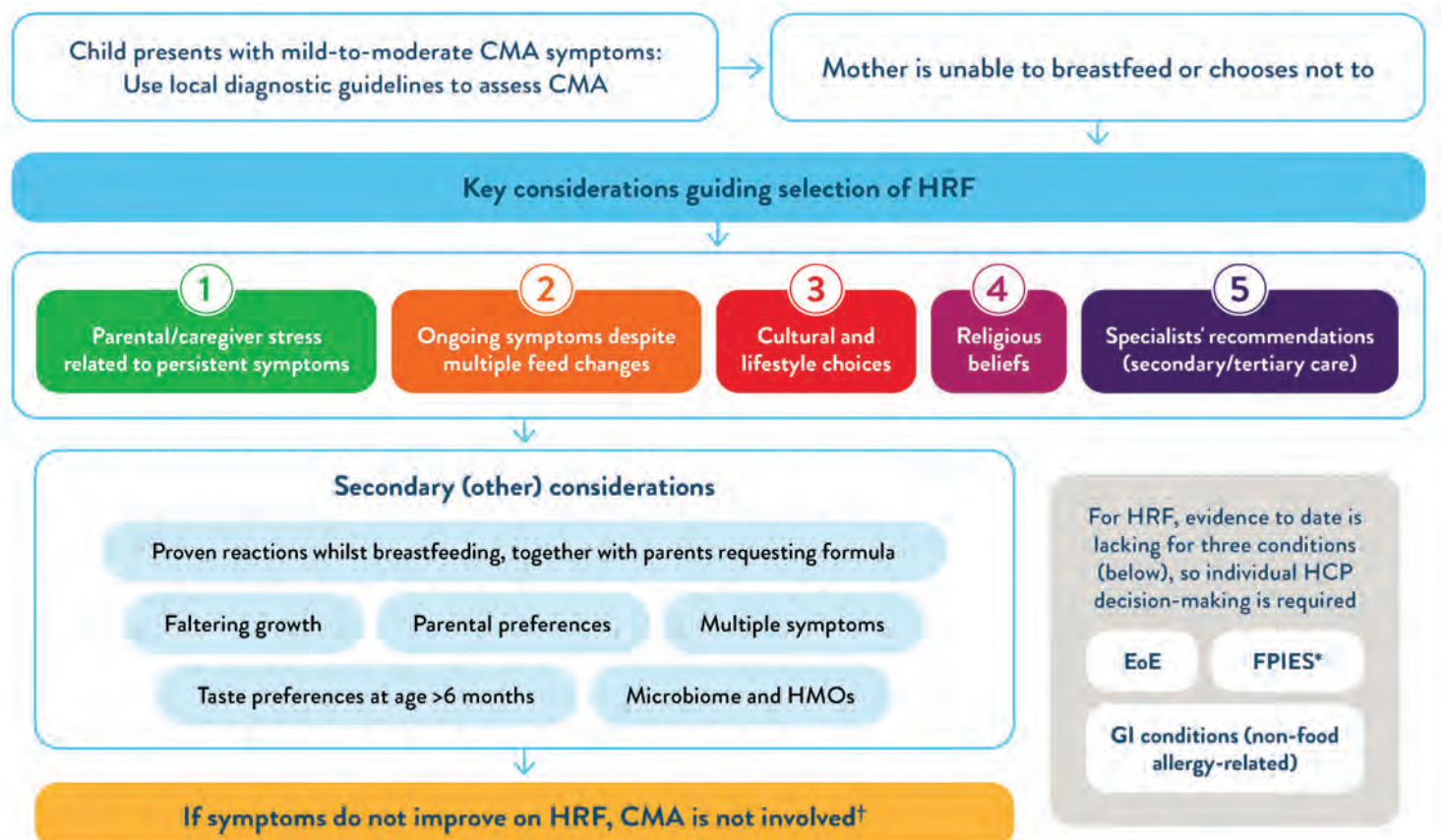


Figure 2: Guidance for when HRF may be the preferred option for the management of CMA



Adapted from Makwana N, et al. Nutrients. 2026;18,1225.

*DRACMA guidelines state: "In infants with milk- or rice-related FPIES, or in whom tolerance of rice is unknown, it is more beneficial not to use HRF until more evidence is available." The expert panel noted this reflects limited data and the reported frequency of rice-related FPIES.

†As advised in the most recently available (2024) ESPGHAN algorithm at the time of publication. The expert panel noted this reflects limited data and the reported frequency of rice-related FPIES

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Safety considerations

A potential concern with rice-based infant formulas is their arsenic content. Arsenic exists in both organic and inorganic forms and is naturally present in the environment, including rock, soil and groundwater.¹¹ Meyer *et al.* analysed HRF sourced from Italy, France and Belgium, measuring arsenic levels in the dry formula powder. They then compared these levels to the average arsenic intake for infants and toddlers, as reported by the European Food Safety Authority (EFSA) and found them to be within safe limits.¹¹ Levels in inorganic arsenic in all the HRF samples tested very low and similar to that reported by Vela *et al.* for cow's milk infant formula, but slightly higher than that reported by Jackson *et al.* using a different analysis platform.⁴ However, it is important to note that the measured arsenic levels only accounted for the dry formula powder and did not include the potential contribution of arsenic from the water used to prepare the formula. Since drinking water can also contain varying amounts of arsenic, this should be considered when reconstituting infant formula.

Another consideration is that although the rice grain is considered hypoallergenic, it can be a trigger for food-protein induced enterocolitis syndrome (FPIES). FPIES is a non-IgE mediated food allergy that typically presents within 1-4 hours after the trigger food ingestion.³ The symptoms include lethargy, pallor and excessive vomiting.³ A severe reaction can result in metabolic acidosis, hypothermia and hypotension.³ The whole rice grain has been reported to be a potential trigger for FPIES but to date there have been no reported FPIES reactions to an extensively hydrolysed rice protein.

Useful considerations

Some parents may prefer having an option of a formula that is free from cow's milk and other animal proteins and are following a vegetarian or plant-based diet. These infant formulas are also suitable for Halal and Kosher diets, making them a viable option for patients with specific religious dietary requirements. It is important to note that some of these formulas cannot be classified as vegan due to either the vitamin D source and/or the human milk oligosaccharides (HMOs) in the formula. The HRF that is available in the UK does contain HMOs, but the vitamin D source is plant-based.

HMOs are abundant in breastmilk and have a prebiotic effect which is beneficial to the infant microbiome and can lead to improved gut barrier and potentially reduce infections.^{6, 12} HMOs make up a large component of breastmilk and thus it would be plausible to consider adding them to formulas to improve their likeness to breastmilk.⁶ The safety of these biosynthesised HMOs being added to formulas have been investigated. In a prospective randomised control performed by Marriage *et al.* (2015) healthy infants who were fed a formula containing 2'-fucosyllactose (2'-FL) were found to have no differences in growth or tolerance (stools frequency and consistency and vomits) when compared to the formula feed that did not contain 2'FL. They did however find a reduction in parent reported cases of eczema and respiratory tract infections.¹³ HMOs are likely to demonstrate a positive impact on the gut microbiome and immunity.¹³

Conclusion

The landscape of cow's milk allergy management continues to evolve, with HRF emerging in the UK as a promising alternative to other EHF's. The low allergenicity, nutritional adequacy and dietary preferences makes them an attractive option for non-breastfed babies with CMA. These formulas have been used and tolerated in Europe for decades and have supported normal growth and development and are recommended as first line for management of CMA by DRACMA and ESPGHAN.^{1, 3}

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