New Developments in the Treatment of Cow's Milk Allergy

Lauren Arpe, Registered Dietitian, BSc Diet and Post Grad Diploma, Principal Paediatric Dietitian, Great Ormond Street Hospital, UK

Cow's milk protein allergy (CMPA) 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] CMPA 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 CMPA.[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]

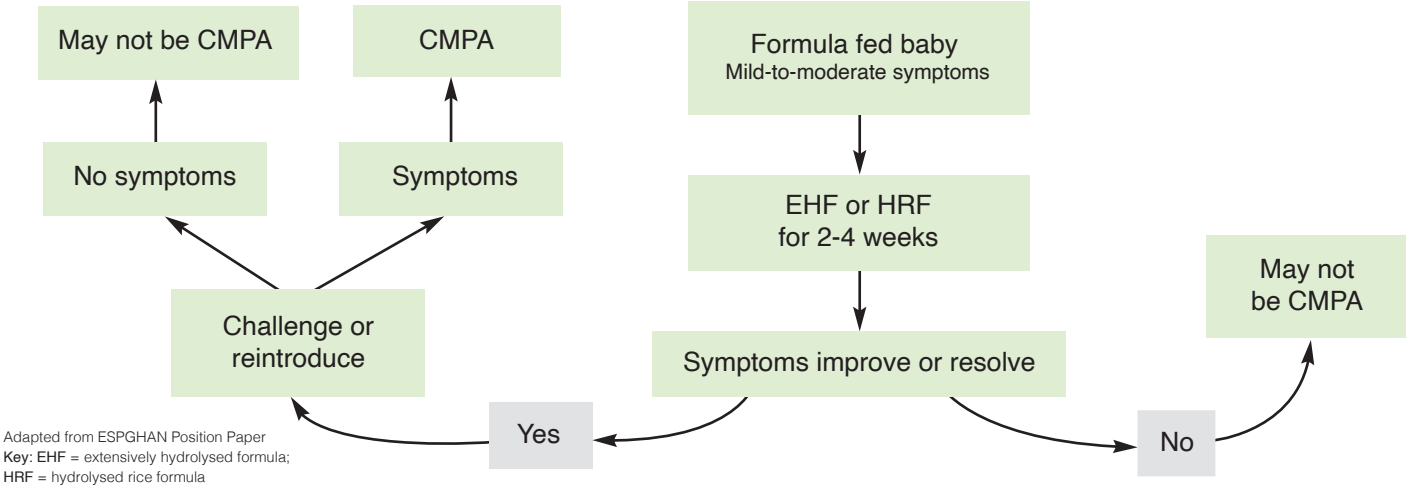
What do the guidelines say?

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 EHFs, for formula-fed infants with IgE- and non-IgE-mediated CMPA. HRFs are likely to be well tolerated in cases of mild-to-moderate CMPA, 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]

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 CMPA 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] See **Table 1**.

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



Adapted from ESPGHAN Position Paper
Key: **EHF** = extensively hydrolysed formula; **HRF** = hydrolysed rice formula

Table 1: Studies supporting growth in infants with CMPA and healthy infants[10-15]

Study	Length of study	Population	Age	Outcome
D'Auria *et al.* 2003 Randomised pilot study	6 months	16 infants with CMPA confirmed by OFC	6-14 months	Growth and protein status similar between HRF and SF groups
Agastoni *et al.* 2007 Randomised, prospective trial	6 months	125 infants with CMPA	6-12 months	Comparable improvement in weight for age z-score between EHRF and SF between 6-12 months
Giradet *et al.* 2013. Prospective, multicentre open study	5 months	78 healthy infants without CMPA	1-6 months	HRF supported weight, length, and head circumference (WHO child growth standards)
Lasekan *et al.* 2006 Prospective, randomised double-blind clinical trial	16 weeks	65 healthy infants	1-4 months	HRF – good weight, length and head circumference compared to std infant formula
Reche *et al.* 2010 Prospective, open and randomised clinical trial	21 months	92 infants diagnosed with IgE mediated CMPA	1-10 months	Weight and length similar to HRF and EHF group up to 18 months
Vandenplas *et al.* 2014 Prospective study	6 months	42 infants with CMPA	0-16 weeks	HRF catch up weight gain in 1st month. Normal wt-age, wt-lt and BMI z scores for 6 months

*Hydrolysed rice formula, soya formula, extensively hydrolysed formula

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.[16] 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.[16] 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, 17] 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.[18] HMOs are likely to demonstrate a positive impact on the gut microbiome and immunity.[18]

Conclusion

The landscape of cow's milk allergy management continues to evolve, with HRF emerging in the UK as a promising alternative to other EHFs. The low allergenicity, nutritional adequacy and dietary preferences makes them an attractive option for non-breastfed babies with CMPA. 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 CMPA by DRACMA and ESPGHAN.[1, 3]

"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, 17]"

References: **1.** Bognanni A, *et al.* (2024). World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guideline update – XII – Recommendations on milk formula supplements with and without probiotics for infants and toddlers with CMA. World Allergy Organ J.; 17(4): 100888. **2.** Dupont C, *et al.* (2020). Hydrolysed Rice Protein-Based Formulas, a Vegetal Alternative in Cow's Milk Allergy. Nutrients; 12(9): 2654. **3.** Vandenplas Y, *et al.* (2024). An ESPGHAN Position Paper on the Diagnosis, Management, and Prevention of Cow's Milk Allergy. J Pediatr Gastroenterol Nutr.; 78(2): 386-413. **4.** Meyer R, *et al.* (2018). Low inorganic arsenic in hydrolysed rice formula used for cow's milk protein allergy. Pediatr Allergy Immunol.; 29(5): 561-563. **5.** De Boissieu D, Matarazzo P, Dupont C. (1997). Allergy to extensively hydrolysed cow milk proteins in infants: identification and treatment with an amino acid-based formula. J Pediatr.; 131(5): 744-747. **6.** Caffarelli C, *et al.* (2002). Determination of allergenicity to three cow's milk hydrolysates and an amino acid-derived formula in children with cow's milk allergy. Clin Exp Allergy.; 32(1): 74-79. **7.** Meyer R, Groetch M, Venter C. (2018). When should infants with cow's milk protein allergy use an amino acid formula? A practical guide. J Allergy Clin Immunol Pract.; 6(2): 383-399. **8.** McLeish CM, MacDonald A, Booth IW. (1995). Comparison of an elemental with a hydrolysed whey formula in intolerance to cow's milk. Arch Dis Child.; 73(3): 211-215. **9.** Latcham F, *et al.* (2003). A consistent pattern of minor immunodeficiency and subtle enteropathy in children with multiple food allergy. J Pediatr.; 143(1): 39-47. **10.** D'Auria E, *et al.* (2003). Nutritional value of a rice-hydrolysate formula in infants with cow's milk protein allergy: a randomized pilot study. J Int Med Res.; 31(3): 215-222. **11.** Agostoni C, *et al.* (2007). Growth of infants with IgE-mediated cow's milk allergy fed different formulas in the complementary feeding period. Pediatr Allergy Immunol.; 18(7): 599-606. **12.** Girardet JP, *et al.* (2013). Growth and tolerance in infants fed an infant formula based on hydrolysed rice proteins. Arch Pediatr.; 20(3): 323-328. **13.** Lasekan JB, *et al.* (2006). Growth, tolerance and biochemical measures in healthy infants fed a partially hydrolysed rice protein-based formula: a randomized, blinded, prospective trial. J Am Coll Nutr.; 25(1): 12-19. **14.** Reche M, *et al.* (2010). The effect of a partially htdrolysed formula based on rice protein in the treatment of infants with cow's milk protein allergy. Pediatr Allergy Immunol.; 21(4 Pt 1): 577-585. **15.** Vandenplas Y, De Greef E, Hauser B, Paradice Study Group. (2014). Safety and tolerance of a new extensively hydrolysed rice protein-based formula in the management of infants with cow's milk protein allergy. Eur J Pediatr.; 173(9): 1209-1216. **16.** Bocquet A, *et al.* (2019). Efficacy and safety of hydrolysed rice-protein formulas for the treatment of cow's milk protein allergy. Arch Pediatr.; 26(4): 238-246. **17.** Reverri EJ, *et al.* (2018). Review of the clinical experiences of feeding infants formula containing the human milk oligosaccharide 2'-fucosyllactose. Nutrients.; 10(10): 1346. **18.** Marriage BJ, *et al.* (2018). Infants fed a lower calorie formula with 2'FL show growth and 2'FL uptake like breast-fed infants. J Pediatr Gastroenterol Nutr.; 61(6): 649: 658.