Journal of Indonesian Specialized Nutrition
e-ISSN: xxxx-xxx

The Importance Factors in Selecting Extensively Hydrolyzed Formulas for Cow's Milk Allergy Management

Erika Wasito[1*], Laksmi Murti[1]

[1]Danone SN Indonesia, Jakarta, Indonesia

**Correspondence:* *erika.wasito@danone.com

***ABSTRACT*:** Current guidelines recommend extensively hydrolyzed formulas (eHF) as the first choice for infants with mild to moderate cow's milk allergy (CMA) symptoms. Different eHF producers may apply different technical processes that can influence the end characteristics of the products, the efficacy and effectiveness in CMA management. This review aims to summarizes references and reports to indicate the importance factors that should be considered in selecting eHF available in the market for CMA treatment. The most important factor is the clinical evidence on tolerance level of the eHF formula above 90% among allergic children or the efficacy and effectiveness in CMA management. Other factors are the composition of protein molecular size in the end product and the long history of usage of the product in the population with positive feedback from more than 90% healthcare professionals that could indicate as the real-world evidence.

Keywords- Cow's milk allergy, extensively hydrolyzed formulas, food allergy, infants, pediatrician

INTRODUCTION

Cow's milk allergy (CMA) is one of food allergy that commonly occurs in infants less than 1 year old (NICE, 2019). The infants and children with CMA are at high risk of nutrition deficiencies, therefore they need appropriate nutrition and allergy management (Robbins et all, 2014). Indonesian Pediatric Society (Ikatan Dokter Anak Indonesia - IDAI) has developed a guideline on diagnosis and management of CMA that recommends continuing breastfeeding and maternal avoidance of any cow's milk and its products. Infants and children that has received complementary food should also completely avoid cow's milk protein either in the form of milk or milk products (IDAI, 2014). Based on The Indonesia Agency of Drug and Food Control (BPOM-RI), there are two medical treatments for patients with CMA: treatment with extensively hydrolyzed formulas (eHF) and amino-acid-based formula (AAF). Extensively hydrolyzed formulas (eHF) are suitable for patients with mild to moderate

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CMA symptoms, whilst AAF is recommended for severe CMA symptoms (BPOM, 2020; Host & Halken, 2014).

In 2020, BPOM-RI launched new regulations about Formula for Special Medical Purposes for cow's milk allergy, where 95% of the total protein should have a molecular weight of ·1500 Daltons and protein with molecular weights 6000 Daltons should not exceed 0.5% of total protein.4 Further than this criteria, it is interesting to explore other important factors of eHF as treatment for mild to moderate CMA symptoms.

RESEARCH METHODS

This study used a descriptive research method with a literature analysis approach. Data were collected from various literature sources, such as scientific articles, medical journals, reference books, and other academic resources related to the research topic. Information on factors that are important in the selection of extensive hydrolysate formulas was analyzed and compiled. Data from the literature was analyzed descriptively. Important factors influencing the selection of an extensive hydrolysate formula will be identified and described in detail. The analysis includes an understanding of how these factors are interconnected and influence the formula selection decision.

RESULTS AND DISCUSSION

Cow's milk allergy (CMA)

Cow's milk allergy (CMA) is an immunological adverse clinical reaction to a protein in cow's milk.1 About 50-70% of cow's milk allergy symptoms occur as skin manifestation, 50-60% cause gastrointestinal disease and 20-30% occur as respiratory tract allergic disease. However, CMA symptoms decrease with age from infancy to adulthood reflecting the change in immune response. By the age of 1 year old, the risk of CMA decreased by 45-50%, and about 60-75% at the age of 2 years old, and about 85-90% at the third year (Host & Halken, 2014).

As an immunological response, CMA occurs as a result of dysregulation in the immune system with immunoglobulin E (IgE)-mediated or not-IgE-mediated. Hypersensitivity reaction occurs when protein in cow's milk responds to antibody.1 Therefore, the key management of cow's milk allergy is complete avoidance of cow's milk and milk products. Cow milk contains proteins that can cause an allergic reaction such as caseins (casein (alpha-s1-, alpha-s2-, beta-, dan kappa-casein) and whey (beta-lactoglobulin dan alpha-lactalbumin).6,7 The allergy symptoms in IgE-mediated occurs when allergen epitope link with IgE receptors in mast cells and basophil, leading to the release of histamine and cytokine (e.g. histamine dan TNF-α). The molecular weight of protein peptides is one of the important factors that associated with protein allergenicity that cause the allergic reaction. Protein allergenicity

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can be reduced with a process that can destroy the protein epitope responsible in the bonding of allergen and IgE receptors, for example through heat treatment that can disrupt the vast majority of allergenic epitopes due to protein denaturation (Nutten et all, 2020). The heating process of beta-globulin causes an intermolecular disulfide-bond and an forms aggregate with other protein in foods that results in reduction of beta-lactoglobulin allergenicity (Bartuzi et all, 2017).

Cow's milk protein modification through multiple processes including extensive protein hydrolysis, heat treatment, enzymatic, and ultrafiltration during manufacturing of eHF, is designed to remove and reduce allergenic peptides in cow's milk protein hence producing hypoallergenic or non-allergenic milk products (IDAI, 2014; Park & Haenlein, 2013).

Hypoallergenic formula can be recommended for non-breastfed infants with CMA, however global standard on the criteria that should be fulfilled as Hypoallergenic formula is not available. American Academy of Pediatrics (AAP) has defined that Hypoallergenic formula is a formula tolerated by 90% of infants with CMA, with a 95% confidence interval in a prospective randomized or double-blind, control placebo trials. Meanwhile, in Europe and Indonesia, the Hypoallergenic formula is defined as formula with hydrolysate protein, which are extensively hydrolysed formulas (eHF) and partially hydrolysed formulas (pHF) (IDAI, 2014; Nutten et all, 2020; Park & Haenlein, 2013; D'Auria et all, 2021).

Many institutions, namely The European Society of Pediatric Allergy and Clinical Immunology (ESPACI), The European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), and American Academy of Pediatrics (AAP), stated that extensively hydrolyzed formulas are safe and can be recommended for children with CMA, even though the formula might still contain clinically significant antigens.10 The definitions of extensively hydrolyzed formulas based on the cut off of peptide molecular weight peptide are also different in many countries because there are limited clinical evidence on peptide molecular weight that strongly proven in preventing or reducing allergic reaction in infant or children with CMAs. Refers to AAP, eHF is a formula containing peptides with molecular weights of <3000 Da, while the British Society for Allergy and Clinical Immunology (BSACI) recommend eHF with peptides molecular weights of <1000 Da for CMA treatment. According to The European Commission Directive, 2006/141/EC on infant formula and follow-on formula, the immuno-reactive protein should be limited to less than 1% of total Nitrogen.7,9 In Indonesia, the eHf should contain protein with molecular weights of 500 Daltons at least 95% of total protein and protein with molecular weights of < 6000 Daltons should be not more than 0,5% total protein (BPOM, 2020).

Besides the cow's milk protein modification to reduce allergy reaction, the nutrition composition of eHF should contain carbohydrates, fat, and micronutrients e.g. iron to meet the adequacy of nutrients. These formulas can be used to support the growth and development of infants and young children with CMA who are prone to growth faltering (Nutten et all, 2020; Agostoni et all, 2016; Borschel et all, 2018). Based on the above discussion, a hydrolysis process to reduced protein allergenicity of cow's milk is important in a formula for CMA management. The composition of total

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nutrients in should also be carefully formulated to support the growth and development among infants and young children with CMA.

Evidence on Extensively hydrolyzed formulas

A reserach by (Miraglia et all, 2015) study the effectiveness of extensively hydrolyzed formulas compared to partially hydrolyzed formulas among children with CMA. The research used two extensive hydrolyzed formula and one partially hydrolyzed formula. The study showed that the extensive hydrolyzed formulas were tolerated by 94% and 97% of children with CMA, while partially hydrolyzed formula was tolerated by 64% CMA children. The tolerance toward formulas were shown by the absence of allergy reaction and negative skin prick tests, after formula consumption. Giampetro study showed the hydrolysis protein was the main factor that determine the allergenicity of formulas (Meyer et all, 2018). Both extensive hydrolyzed formulas fulfilled the criteria of AAP as hypoallergenic formula that can be tolerated by at least 90 % of CMA children, but partially hydrolyzed formula could not be categorized as hypoallergenic formula for CMA management (Dupont et all, 2018).

Another study showed lower incidence of CMA among infants who consume extensive hydrolyzed formula (0,6% of the population) compared to partially hydrolyzed formula (4,7%). The evidence shows that the eHF being used in the study is effective in preventing CMA (Vandenplas, 2017). Other studies showed a significant reduction in CMA incidence in the first 18 months of life by combining eHF and a free cow's milk protein diet restriction in infants with hight risk of atopy (Hubbard et all, 2022).

Based on the above evidence, extensive hydrolyzed formula in general is well tolerated and effective in CMA management. However, specific clinical evidence for respective eHF is important because different hydrolysis process might impact the tolerability level and the efficacy of the extensive hydrolysate formula.

Extensively hydrolyzed formulas used by Indonesian Pediatricians

Doctors and pediatricians are the important key decision maker to recommend an eHF for the patients. Their experience with a certain eHF product tolerance and efficacy in their patients might influence their decision in selecting the eHF product. In October 2021, a survey has been conducted to 105 pediatricians in Indonesia, about their experience in using a known eHF product that has been available in Indonesia since 2008. About 43% respondents work in a private hospital, and 36% of work in government affiliates hospitals and 21% in private clinics. The survey found majority of pediatricians (83%) recommend the eHF for CMA management with mild to moderate allergic symptoms. Most pediatricians (98%) agree that the specific eHF is effective in CMA treatment, especially reducing CMA

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symptoms in gastrointestinal (99%), respiratory system (94%) and skin (95%). Most pediatricians (97%) agree that the allergic symptoms become better after the intervention with the specific eHF (Neurosensum, 2021). The good experiences are important to develop confidence in recommending a specific eHF for CMA management of their patients.

CONCLUSION

Extensive hydrolyzed formula in general is recommended in allergy management with mild to moderate symptoms. Many clinical studies have evaluated the efficacy of eHF in the management of CMA and the result could be specific for the studied product due to different technology process. In conclusion, the protein molecular weight, the clinical evidence on the tolerance, efficacy and effectiveness are important factors in selecting an extensive hydrolyzed formula. Furthermore, personal experience of healthcare professionals in a specific eHF is important factor in recommending a specific product for allergy management.

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