mgr Agata Klementyna Stróżyk

Streszczenie w języku angielskim

From guidelines to clinical practice – the management of cow's milk protein allergy in children

Cow's milk protein allergy (CMA) is one of the most common food allergies in children. The gold standard of CMA diagnosis is oral food challenge performed after a period of elimination diet in formula-fed child and/or breastfeeding mother. If clinical symptoms occur following the ingestion of cow's milk proteins after the earlier period without symptoms during the elimination diet, it may be treated as proof of CMA. Treatment of CMA is mainly based on elimination diet that excludes all products containing any cow's milk proteins, or those who may lead to cross reactions. In formula-fed infants, the replacement of the formula with adequate hypoallergenic formula – extensively hydrolysed formula (EHF) or amino-acid formula (AAF) is necessary.

Correct diagnosis of CMA, implementation of appropriate elimination diet and follow-up of a tolerance acquisition to cow's milk proteins is essential for adequate psychomotor and social functioning of children with CMA, family functionality and quality of life and allergic march risk. The COVID-19 pandemic limited many diagnostic procedures (especially performance of oral food challenge) and therapeutic (incorrect choice of milk substitutes, e.g. the inclusion of plant-based beverages), that limited correct recognition and follow-up of patients with CMA. At the same time, experts highlight the risk of overdiagnosing CMA in children, that may be associated with the assessment of many symptoms remaining physiologic for this child's development period (i.e., constipation, gastroesophageal reflux) as related to allergy, without any confirmation by means of oral food challenge, e.g. the diagnosis is limited to skin and/or against specific immunoglobulin E (sIgE) testing.

Some of the experts doubt in not only the adherence, but also in the credibility of guidelines for diagnosis and management of CMA. The main issues are: limited strength of scientific evidence, assessment of physiological symptoms in infants as indisputably related to CMA, insufficient or lack of distinguished recommendations for management of infants with CMA who are breastfed and/or formula-fed, and a conflict of interest of guidelines co-authors. In the recent years, unjustified elimination diet in breastfeeding mothers of children with CMA became controversial.

As a part of this international discussion, we attempted to assess the quality of the guidelines from the last 10 years (2010-2020) and its adherence by Polish doctors. Project was planned in four steps: (1) the aim of the first was to assess the quality of guidelines on diagnosis and management of CMA in children and/or adults; (2) followingly, we attempted to evaluate the adherence of Polish doctors to the guidelines on diagnosis and management of CMA; (3) the aim of the third step was to summarize scientific evidence on the efficacy and safety of using EHF of whey and/or casein proteins in management of children with CMA; (4)

the last step was to review the literature regarding the use of elimination diet in children with CMA with practical guidelines for doctors.

The project consists of four publications: (1) a systematic review of guidelines on diagnosis and management of CMA in children and/or adults published in 2010-2020 years, with the use of the tool 'The Appraisal of Guidelines for Research and Evaluation' (AGREE II); (2) a cross-sectional study with the use of online questionnaire that assessed the adherence of doctors to recommendations on diagnosis and management of children with CMA and their sources of knowledge; (3) a systematic review of randomized controlled trials assessing the efficacy and safety of using the extensively hydrolyzed cow's milk proteins (whey [EHWF] or casein [EHCF]) formula in the management of children with CMA; (4) a review that summarizes the use of elimination diet in children with CMA.

For the systematic review assessing the quality of guidelines on diagnosis and management in children and/or adults with CMA, five medical databases were searched, including: MEDLINE, EMBASE, ISI Web of Science, World Health Organization Global Index Medicus and Turning Research into Practice, and guidelines repositories from January 2010 to April 2021. Only the guidelines developed by the scientific societies or institutions were included. Their quality was assessed with the AGREE II tool. It consists of 23 items grouped into six domains: (1) scope and purpose, (2) stakeholder involvement, (3) rigor of development, (4) clarity of presentation, (5) applicability, (6) editorial independence; and, subjective overall guideline assessment. Each item was assessed using a 7-point Likert assessment scale (where 1 means 'strongly disagree' and 7 is 'strongly agree'). Subsequently, for the each assessed item and domains, the scores were summed up and calculated as a percentage of the maximum possible value (using the equation provided by the AGREE II consortium; maximum possible value was 100%). The recommendations of the included guidelines were also summarized.

The Inclusion criteria were met by 12 guidelines. The majority of the guidelines were of good or very good quality (median scores for assessed domains, with one exception, exceeded 60%). The weakest domain was rigor of development (a median score was 30%), which assessed the process of collection and summarizing of the scientific evidence, and methods used for the formulation and update of recommendations. Identified limitations in this domain included: unclear description of the strength of the evidence for the included guidelines (i.e., methods used for the systematic search of medical literature, assessment of strength and limitations of the scientific evidence), and the procedure of guidelines update (including whether and when it is planned). In planned guidelines updates, societies should include systematic summary and assessment of the scientific evidence with the use of the recommended tool, i.e., GRADE (The Grading of Recommendations Assessment, Development and Evaluation). The strength of the evaluated guidelines was the clarity of presentation (median score was 92%), which assesses whether: recommendations are specific and unambiguous; different options for the management of the health condition are presented; and key recommendations are easy to find. The findings of this systematic review and the summary of recommendations were used by the teams of DRACMA (Diagnosis and Rationale for Action against Cow's Milk Allergy) and Polish Society of Paediatric Gastroenterology

Hepatology and Nutrition (PSPGHAN) experts during the development of guidelines updates [*World Allergy Organ J., 2022; 15, 100613*].

The second publication is a cross-sectional study that assessed the adherence to guidelines on diagnosis and management of CMA by Polish doctors. In the study, an anonymous questionnaire was used, which was previously used in a similar paper evaluating the doctors experience in the United Kingdom.

The adapted polish version of the questionnaire included 19 one- and multiple choice questions regarding the overall characteristics of the study population and the assessed outcomes, including two clinical cases. The study participants were Polish doctors who consult children diagnosed with CMA. Recruitment was performed between January 15 and March 10 2020, with the use of random sample size, through the contact with the members of the Allergic Section of PSPGHAN and a platform that enables education and cooperation between doctors (Konsylium24.pl).

A study involved 605 doctors; the majority of them were pediatricians working in general practice. Only a minority of respondents performed oral food challenge to confirm the diagnosis of CMA. Most of the participants correctly recommended the use of EHF as a first-line treatment in children with mild or moderate symptoms of CMA. However, less than a half of respondents advised amino-acid formula in children with severe CMA (anaphylaxis). Moreover, only half of the participants performed oral food challenge to assess the tolerance acquisition to cow's milk proteins. Main sources of the knowledge on diagnosis and management of CMA were national and international conferences, workshops and books.

To summarize, the study revealed that there is a discrepancy between the practice of Polish doctors who consult primary care patients and the guidelines on diagnosis and management of CMA. It is suggested that further educational activity among Polish doctors (i.e., with the use of conferences and workshops), is necessary to enhance their awareness and the level of guidelines adherence. Moreover, the study findings directed the experts who were developing the PSPGHAN guidelines to highlight the role of oral food challenge and tolerance acquisition assessment in the management of pediatric patient with CMA [*Int Arch Allergy Immunol., 2022; 25:1-8*].

The third publication is a systematic review of randomized controlled trials that summarized the scientific evidence on the efficacy and safety of the use of EHWF and/or EHCF in children with CMA. Three electronic databases: Cochrane, MEDLINE and EMBASE had been searched up to February 2020. Trials assessing the efficacy and safety of extensively hydrolyzed cow's milk proteins formula (EHWF or EHCF) compared to any other formula in children with CMA (regardless of mechanism and diagnostic criteria) were included. Studies evaluating the efficacy of EHF containing probiotics and/or prebiotics were also considered for this review. Each type of EHF was assessed separately. The primary outcomes were differences in mild-to-moderate allergic reactions, severe allergic reactions and adverse events rate. The risk of bias was evaluated with the use of the first version of Cochrane tool for assessing the risk of bias.

The inclusion criteria were met by 15 studies in 18 publications (1285 children). In the majority of studies, due to high heterogeneity, analyses were performed narratively. No substantial differences were found with regard to assessed outcomes between groups

receiving the EHWF compared to amino-acid formula. There was no study investigating the effect of the use of EHCF compared to amino-acid formula, and the EHWF compared to EHCF. For the EHCF, there was no difference in the growth compared to the soy formula; but, in one study, there was a development of secondary sensitization in both groups. Seven studies assessed the use of EHF containing different probiotics. For comparison of EHWF containing *Lactobacillus rhamnosus* GG (LGG) with the same formula without the probiotic the evidence was limited (2 trials). In two trials assessing the efficacy of EHCF use containing LGG compared to identical formula without the probiotic there was a difference between groups for any allergic manifestation, eczema, urticaria and rhinoconjunctivitis. There was also a higher probability of tolerance acquisition to cow's milk proteins (cumulative incidence) for use of EHCF containing LGG compared to the same formula without the probiotic within 12 months (2 trials); 24 and 36 months (one trial). For other formulas containing probiotics, there was no difference between the groups in assessed outcomes.

The findings of this systematic review suggest that EHF are well-tolerated by children with CMA. However, the evidence was insufficient to indicate the superiority of one formula over the other with regard to the type of hydrolyzed proteins (whey or casein), and the addition of the probiotic (LGG, B. *lactis* Bb12 or L *casei* CRL431/B lactis Bb12) [*Clin Exp Allergy., 2020; 50 :766-779*].

The last publication in the publication cycle is a review of the literature regarding the elimination diet in children with suspicion or diagnosis of CMA. The paper serves as a support for pediatricians and dietitians in implementation of the Polish recommendations. The work summarizes the overall guidance of the elimination diet used for diagnostic and treatment purposes with regard to the management stage of children with CMA. The role of patient education before the introduction of the elimination diet, the follow-up of patient's adherence to the therapeutic diet and the assessment of tolerance acquisition to cow's milk proteins in children with CMA were underlined. The recommended substitutes of products containing cow's milk proteins in the infant and post-infant periods as well as the nutritional risk associated with non-balanced cow's milk-free diet were also discussed. A tables summarizing selected permitted and unpermitted food products during the cow's milk-free diet and comparing the hypoallergenic formula available on the Polish market were added [*Stand. Med. Pediatr., 2022; 19: 363-374*].

To summarize the full research project, it should be stated that:

1. The majority of the guidelines on the diagnosis and management of CMA developed by the scientific societies or institutions were of good quality; the weakest domain for all publications was the rigor of development.
2. There was a discrepancy between the practice of Polish doctors consulting children with CMA in primary care and the recommendations on diagnosis and management of CMA; further educational activity among Polish doctors is recommended.
3. Extensively hydrolyzed cow's milk proteins formulas (of whey and/or casein proteins) are well-tolerated by children with CMA, however, the scientific evidence does not allow to indicate the superiority of one formula over other formulas.

4. A practical paper for doctors and dietitians summarizing the rules of the use of elimination diet in children with CMA was developed.