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Consensus document on the primary prevention of cow's milk protein allergy in infants aged less than 7 days☆

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Abstract
Introduction: Cow's milk protein allergy (CMPA) is the most frequent food allergy in the first year of life. There is no clear consensus regarding its prevention. A recommendation to avoid CMP in the first week of life as a preventive measure in all infants, regardless of their atopic risk, has recently been published. The purpose of this document is to issue a recommendation on the use of extensively hydrolyzed CMP formulas in the first week of life for the primary prevention of CMPA.

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Methods: A group of experts was formed with members proposed by the Spanish Association of Pediatrics (AEP), the Spanish Society of Clinical Immunology and Allergology and Pediatric Asthma (SEICAAP), the Spanish Society of Pediatric Gastroenterology, Hepatology and Nutrition (SEGHNP) and the Spanish Society of Neonatology (SENEO). The group conducted a critical review of the evidence on the subject published in the last 10 years.
Results: The search yielded 72 studies, of which 66 were rejected for not meeting the inclusion criteria. The final review included 6 documents: 3 clinical trials and 3 systematic reviews, 2 of them with meta-analysis. There was no evidence of a statistically significant reduction in the incidence of CMPA in the infants who received hypoallergenic formulae or exclusive breastfeeding.
Conclusion: Based on the current evidence, it is not possible to draw clear conclusions about the effect of avoiding CMP in the first week of life for prevention of CMPA. Although there are data that suggest a certain beneficial effect of avoiding CMPA in atopic risk infants, these results are not conclusive enough to extend the recommendation to the general population.

PALABRAS CLAVE
Alergia a leche de vaca;
Prevención primaria;
Fórmula para lactantes

Documento de consenso en la prevención primaria de alergia a proteínas de leche de vaca en lactantes menores de 7 días de vida de su artículo

Resumen
Introducción: La alergia a las proteínas de la leche de vaca (APLV) es la alergia alimentaria más frecuente en el primer año de vida. No existe un consenso claro respecto a su prevención. Recientemente se ha publicado la recomendación de evitar estas proteínas en la primera semana de vida como medida de prevención en todos los niños, con independencia de su riesgo atópico. El objetivo de este documento es emitir una recomendación sobre el uso de fórmulas extensamente hidrolizadas de PLV en la primera semana de vida para la prevención primaria de la APLV.
Métodos: Se constituyó un grupo de expertos propuestos por la Asociación Española de Pediatría (AEP), la Sociedad Española de Inmunología Clínica y Alergología y Asma Pediátrica (SEICAAP), la Sociedad Española de Gastroenterología, Hepatología y Nutrición Pediátrica (SEGHNP) y la Sociedad Española de Neonatología (SENEO). Se realizó una revisión crítica de la evidencia publicada en los últimos 10 años sobre el tema.
Resultados: Se seleccionaron 72 estudios, de los cuales 66 fueron rechazados por no cumplir los criterios de inclusión. Se incluyeron en la revisión 6 documentos: 3 ensayos clínicos y 3 revisiones sistemáticas, 2 de ellas con metaanálisis. No se observó una reducción estadísticamente significativa en la incidencia de APLV en los grupos de lactantes que recibieron fórmulas hipoalergénicas ni lactancia materna exclusiva.
Conclusión: Con base en las evidencias existentes en la actualidad, no se pueden establecer conclusiones claras acerca del efecto de evitar las PLV durante la primera semana de vida en la prevención de la APLV. A pesar de existir datos que pudieran orientar a un cierto efecto beneficioso de su evitación en niños con riesgo atópico, estos resultados no son concluyentes ni generalizables a lactantes sin dicho riesgo.

Introduction

Cow's milk protein allergy (CMPA) amounts to 31.6% of the total food allergies diagnosed in children,[1] and it is the most prevalent one in the first year of life. Based on data from the EuroPrevall study,[2] 0.54% of children aged less than 2 years in Europe develop CMPA. In the Spanish population, the observed incidence of IgE-mediated cow's milk protein (CMP) in the first year of life is 0.36%.[3]

Unlike other food allergies, CMPA tends to be cured spontaneously. Most children develop tolerance by age 3 years, and tolerance is achieved earlier in forms that are not mediated by IgE. Clinical practice guidelines agree on the subject of CMPA diagnosis and management, but there is significant disagreement as regards its prevention.

Between 1999 and 2014, numerous societies advocated for the use of extensively hydrolised formulas (EHFs) for occasional supplementation of breastfeeding (BF) in chil-

dren at risk of atopic disease.[4–6] In 2015, large-scope observational studies were published that suggested that early introduction of potentially allergenic foods (milk, eggs, peanuts) reduced the incidence of allergy to the food.[7–9] The findings of these studies were consistent with the favourable outcomes of oral desensitization to milk and eggs in children with persistent allergy.

These findings revolutionised preventive strategies, and from 2016, changes were introduced to complementary feeding recommendations that applied not only to infants at risk of atopic disease, but to the general population. Introduction of these foods from age 4 to 6 months was recommended, in addition to the use of infant formulas (IF) with cow's milk protein for supplementation of BF in all children, independently of the risk of atopy.[10]

Recently, the European Academy of Allergy and Immunology (EAACI)[11] issued the recommendation to avoid consumption of IF in breastfeeding newborns in the first week of life as a measure for primary prevention of CMPA, independently of the risk of atopic disease. Proposed substitutes included water, donor human milk, elemental formulas (EF) and EHFs. In contrast, a consensus guidance developed by the American Academy of Allergy, Asthma, and Immunology (AAAAI), the American College of Allergy, Asthma, and Immunology (ACAAAI) and the Canadian Society for Allergy and Clinical Immunology (CSACI)[12] concluded that the routine use of any type of hypoallergenic formula to prevent food allergy or sensitization to food allergens should not be recommended.

In this document, we attempt to provide a critical review of the available evidence with the aim of offering a recommendation as regards the use of extensively hydrolysed CMP formulas in the first week of life for primary prevention of CMPA.

Material and methods

A working group was formed with experts proposed by the Asociación Española de Pediatría (AEP) and the Sociedad Española de Inmunología Clínica y Alergología y Asma Pediátrica (SEICAP), Sociedad Española de Gastroenterología, Hepatología y Nutrición Pediátrica (SEGHNP) and the Sociedad Española de Neonatología (SENEO). The following structured research question was formulated by consensus with the Patient, Intervention, Comparison, Outcome method (PICO)[13]: In term infants aged less than 1 week who are breastfed and need supplementation with formula, does the use of EHFs or CMP-free formulas decrease the risk of developing CMPA?

We conducted a review of the literature published in the past 10 years (2011-2021) restricted to English, French and Spanish articles in the PubMed. We used the following search terms: *cow's milk, allergy, prevention, guidelines, hydrolysate*. After reviewing the title and abstract, we selected the articles corresponding to systematic reviews, controlled clinical trials and observational studies. We excluded studies that did not include newborns with chronological ages of less than 1 week in the population under study.

The search yielded 72 studies, of which we excluded 66 due to not meeting the inclusion criteria or meeting the exclusion criterion. The review included 6 articles: 3 clinical trials and 3 systematic reviews, 2 of them with meta-analysis.

After the analysis of the retrieved literature, the principal author developed a final recommendation that was subjected to voting by all participants in the consensus process.

Results

Two of the articles[14,15] were published by the same research group and corresponded to an open randomised clinical trial in 312 infants at risk of atopic disease, with an intervention lasting 5 months and a follow-up period of 2 years. The intervention group (n = 151) was breastfed and received occasional supplements of EHF, avoiding IF at least the first 3 days of life. The control group (n = 156) was breastfed and received regular supplementation with IF (5–40 mL) from birth until 5 months of life. Fifteen infants in the intervention group (9.9%) exhibited sensitization compared to 27 in the control group (17.9%), which corresponded to an absolute risk reduction (ARR) of 0.079, with a 95% confidence interval (CI) of 0.157–0.002. However, among the limitations of the study, the authors noted that introduction of CMP after day 3 post birth could protect against the development of food allergies, including CMPA.

Another clinical trial analysed whether consumption of EHF compared to IF in the first months of life in children at risk of type 1 diabetes delayed or prevented the development of persistent asthma, allergic rhinitis and atopic eczema.[16] The results evinced an association between intake of EHF or more than one type of milk in the first days of life and subsequent development of persistent asthma. We did not consider this study for more detailed analysis, as it did not specifically assess the association with the development of CMPA.

A Cochrane review on the subject[17] identified 2 studies published before 2011. These studies assessed the effect of supplementation in infants in the first 3 to 4 days of life with EHF compared to IF. The first one, which included 129 infants (53 breastfed, 39 fed IF and 37 fed a casein hydrolysate formula), did not find differences in the overall incidence of allergic disease (relative risk [RR], 1.37; 95% CI, 0.33–5.71) or any specific allergic diseases, including CMPA, until childhood.[18] The other study[19] included 5385 healthy infants that required supplementation during the hospital stay: 1789 received IF, 1859 pasteurised human milk and 1737 a whey hydrolysate formula. The authors did not find a statistically significant reduction in the incidence of CMPA in the group given the whey hydrolysate formula (RR 0.62; 95% CI, 0.38–1.00) or the group that was breastfed (RR, 0.70; 95% CI, 0.44–1.12). There were significant differences when they compared the use of IF to the composite category of EHF and BF (OR, 1.5; 95% CI, 1.02–2.25), which remained significant in the multivariate analysis (adjusted OR, 1.54; 95% CI, 1.04–2.30).

The systematic review conducted by Boyle et al.[20] identified 3 clinical trials comparing supplementation with IF and supplementation with different types of hydrolysed formula (casein, whey, partially hydrolysed). The results of these studies are not pertinent to this review, as the intervention periods extended past the first week of life.

Table 1 Summary of included studies.

Article	Study design	Funding	Population at risk/without risk*	n	Intervention group	Control group	Variables under study	RR 95% CI	Results
Urashima	Open RCT	Government grant	At risk	312	156 term infants, breastfed and not breastfed, with supplementation with EF through 5 months (if >150 ml/day for 3 consecutive days, switched to IF). Supplementation with EF only in the first 3 days post birth	156 term infants, breastfed with supplementation with IF (>5 ml/day) through 5 meses	CMPA at 2 years	RR, 0.10 (0.01−0.77)	CMPA: IG, 0.7 % CMPA in hydrolysate group vs 3.6% CMPA in CG. Conclusion: CMP formula is a risk factor for CMPA, anaphylaxis and other food allergies
2019	2-year follow-up	Dairy Products Health Science Council y la Japan Dairy Association		RNT			Other food allergies		
Jama Pediatrics[14]							Risk of anaphylaxis due to food allergy Dx: IgE tests and OPT		
Japan Tachimoto	Open RCT	Dairy Products Health Science Council y la Japan Dairy Association	At risk	312	156 term infants, breastfed and not breastfed, with supplementation with EF through 5 months (if >150 ml/day for 3 consecutive days, switched to IF). Supplementation with EF only in the first 3 days post birth	156 term infants, breastfed with supplementation with IF (>5 ml/day) through 5 meses	Primary outcome: atopic sensitization	RR, 0.556 (0.308−1.002)	Atopic sensitization observed in 15 children in IG (9.9%) vs 27 in CG (17.9%), corresponding to an absolute risk reduction of −0.079, with a 95% CI of −0.157 to −0.002.
2020	2-year follow-up Extension period (EP) through 6 years			RNT			Secondary outcomes: anaphylactic reactions, worsening of atopic dermatitis, wheezing, allergic rhinitis		

Table 1 (*Continued*)

Article	Study design	Funding	Population at risk/without risk*	n	Intervention group	Control group	Variables under study	RR 95% CI	Results
Jama Netw Open[15] Japan Juvonem	Open RCT	Non-commercial	Without risk	129	Two groups: feeding regimen in first 3 days of life. All BF from day 4	3rd group:	Food allergen sensitization (CMPA), recurrent wheezing, atopic dermatitis	RR, 1.37 (0.33–5.71)	No differences in the overall incidence of allergic diseases (including CMPA) between any of the 3 groups
1996	3-year follow-up			RNT	- 39 IF	53 exclusive BF	Dx: IgE (blood samples at day 4 and months 2, 4, 8, 12 and 24 post birth)- skin prick test		
Acta Pediatrica[18] Sweden					- 37 EHF				
Saarinen KM 1999	Prospective randomised	Nutricia	Without risk	5389	Supplementation	824 exclusive BF	Questionnaire about parental history of symptoms of CMPA (urticaria, atopic dermatitis, vomiting, diarrhoea, failure to thrive, rhinitis o wheezing). Elimination from diet followed by IgE tests, skin prick tests and OPT	RR by group	No significant reduction in the incidence of CMPA in the group fed whey hydrolysate formula (RR, 0.62; 95% CI, 0.38–1.00), or the BF group (RR, 0.70; 95% CI, 0.44–1.12). Significant difference in the comparison of IF group vs the combined of EHF/BF group (OR, 1.5; 95% CI, 1.02–2.25) confirmed in the multivariate analysis (adjusted OR, 1.54; 95% CI, 1.04–2.30).
J Allergy Clin Inmunol[19] Finland				RNT	- 1758 IF - 1844 pasteurised human milk - 1715 whey EHF			-EHF: RR, 0.62 (0.38–1.00] -BF: RR, 0.70 (0.44–1.12)	

BF, breastfeeding; CG, control group; CI, confidence interval; CMP, cow's milk protein; CMPA, cow's milk protein allergy; Dx, diagnosis; EHF, extensively hydrolysed formula; EP, extension period; IF, infant formula; IG, intervention group; OPT, oral provocation test; OR, odds ratio; RCT, randomised controlled trial.

* Risk of atopy.

Last of all, the systematic review conducted by de Silva et al.[21] based its conclusions on a single clinical trial, the study by Urashima et al.[14] that we discussed earlier in this article. Table 1 summarises the main characteristics of the studies selected in the literature review.

Discussion

A review of the literature currently available showed that there are very few studies on which to base any type of recommendation. A critical reading of these studies revealed that they were of limited methodological quality. In particular, in the study by Urashima,[14] there is an important selection bias, as it only included infants with risk of atopy, which substantially limits the possibility of extrapolating its results to the general population. On the other hand, the intervention was heterogeneous, with considerable variability in the duration of the period in which CMP was avoided in the intervention group: CMP was introduced in the first 2 weeks post birth in 7.3% of the group, and only 12% maintained the restriction for 5 months. In addition, CMP was not eliminated from the maternal diet in either of the 2 groups. In short, the intervention was not clearly defined, which seriously compromises the validity of the study protocol, and therefore the reliability of its results.

There were also clear methodological deficiencies in the study by Saarinen.[19] The results were of marginal significance, with a CI that was close to zero in the comparison of the group that received supplementation with IF with the remaining groups, including those with supplementation with whey hydrolysate formula and pasteurised human milk. The significance continued to be marginal in the adjusted multivariate analysis. When it came to the multivariate analysis, the authors did not mention which variables were added to or eliminated in the adjustment of the model, which precludes proper assessment of the results. Still, it appears that the only variable included in the model was the variable the authors labelled ''obvious parental atopy''. The adjustment for this atopic risk variable may compromise the generalizability of the conclusions, since, given that there is no information on regression diagnostics, it is not possible to determine whether the authors took into account the potential effect of interactions between the variables included in the model.

We ought to highlight the main limitations of this consensus document. First of all, it does not take into account the potential effect of avoiding CMP in the prevention of other allergic manifestations. Secondly, the search was restricted to a single bibliographic source, the PubMed database of the National Library of Medicine of the United States. Lastly, we did not systematically assess the quality of the evidence of the reviewed studies.

In conclusion, based on the current evidence, it is not possible to establish clear recommendations as regards the exclusion of CMP in the first week of life for the purpose of preventing CMPA. Although there are data that suggest that avoiding CMP may be somewhat beneficial in children at risk of atopic disease, these results are not conclusive and cannot be generalised to infants without this risk.

Therefore, the working group recommends the following:

In the case some form of supplementation to breastfeeding is needed in the first week of life, it should not be provided routinely with extensively hydrolysed formulas or CMP-free formulas with the aim of preventing CMPA (100% agreement).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.anpede.2022.05.004.

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