HYDROLYSED FORMULAS FOR ALLERGY PREVENTION

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Short title: Hydrolysates and allergy prevention

Funding: There was no funding for the research

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal’s Web site (www.jpgn.org).
ABSTRACT

Aim. The aim of this review is to provide recommendations on the use of hydrolysates in infants when formula feeding is initiated.

Methods. We performed an overview of reviews followed by a systematic review of subsequently published trials.

Results. We did find eight systematic reviews; only one study of limited quality was published afterwards. Certain extensively hydrolyzed casein and certain partially hydrolyzed whey formulas are appropriate for reducing the risk of allergy in infants at high risk when formula feeding is initiated.

Conclusion. In high risk infants, when breastfeeding is not possible, hydrolysates of documented safety and efficacy have an indication in infant feeding up to the age of 4 to 6 months.

Key-words: allergy, hydrolysate, infant nutrition, prevention
INTRODUCTION

In healthy infants and in infants with high risk for developing allergy, exclusive breastfeeding for about 6 months is a desirable goal. Hydrolyzed formulas contain cow milk proteins (CMPs) that are subjected to chemical and enzymatic hydrolysis to reduce the molecular weight, the peptide size, and consequently, the allergenicity of the proteins. The differentiation between extensively hydrolyzed and partially hydrolyzed formulas is generally done by i) molecular weight profile and ii) clinical demonstration of reduced allergenicity. The protein molecular weight profile is an analytical classification measure that offers a straightforward differentiation between intact, partially and extensively hydrolyzed protein formulas (1). The methods use molecular weight markers that enable to qualify and quantify the proteins/peptides as % of total protein. The most important protein fractions present in cow milk (whey, casein) are used for the hydrolysis process rather than whole CMP (2). Whole cow milk-based formulas contain proteins in the range of 14 kD (α-lactalbumin) to 67 kD (bovine serum albumin). Partially hydrolyzed formulas (pHF) contain reduced oligopeptides that have a molecular weight of generally less than 5 kD (ranges between 3 kD and 10 kD); and peptides in extensively hydrolysed formula (eHF) have, in >90%, a molecular weight of <3 kD (2,3). Both pHFs and eHFs consist of a wide range of peptide sizes. Protein molecular weight profile only enables to differentiate the protein characteristics of formulas, but does not determine the allergenic formula properties. Moreover, there is no regulatory definition of eHFs and pHFs.

In addition, commercially available whey pHF (pHF-W) contain 18% of peptides greater than 6 kD, while eHFs contain between 1% and 5% greater than 3.5 kD. Peptides need to be in the range of 10 kD to 70 kD (predominantly 10 kD to 40 kD) to be able to act as an allergen (4,5).
The degree of hydrolysis may be characterized by biochemical techniques, such as the spectrum of peptide molecular weights or the ratio of alpha amino nitrogen to total nitrogen (6). Assuming the theory that the shorter the peptides, the less allergenic the product, much work has been done to determine the molecular weight of residual peptides in the hydrolysates (7). As a practical guideline for the industry, the appropriate cutoff for the absence of larger peptides has been determined to be approximately 1.5 kD (7).

The term "hypoallergenicity" or "HA" does not have a globally uniform interpretation. In the European Union, the term is associated with the health claim "Reduction of risk to allergy to milk protein" as defined by "Commission Directive 2006/141/EC of 22 December 2006 on infant formulae and follow-on formulae and amending Directive 1999/21/EC". eHFs comply with the above conditions too and are also "HA". However, these are used for "the dietary management of cow milk allergy". In the USA the term “HA” is a health claim that requires premarket approval by FDA (similar in Canada). Basically only eHFs are considered "HA" and thus can be used for the dietary management of CMPA. Because the wording "hypoallergenicity", abbreviated as “HA”, does have such a different meaning in different parts of the world, we should no longer use the wording "hypoallergenic" in scientific papers to avoid confusion, but rather use "partial" or "extensive" hydrolysates.

Despite the evidence available, there is still uncertainty regarding the choice, if at all, of a hydrolyzed formula in the feeding of infants as well as uncertainty regarding the actual efficacy to prevent allergy of a particular formula. Efficacy and safety should be established especially for cow milk protein hydrolyzed formulas, as factors such as the protein source, hydrolysis method, and degree of hydrolysis that often depend on the manufacturer contribute to differences among hydrolysates.
While acknowledging that breast feeding is the recommended feeding for infants with and without risk of developing allergy (3,8), the authors joined forces to provide recommendations on the use of hydrolysates in infants when formula feeding is initiated.

The objective of this statement was  

1) to systematically review and update data on the efficacy and safety of using a CMP hydrolyzed formula of any degree of hydrolysis compared with a standard infant formula in reducing the risk of allergy in healthy infants at high risk for allergy or in those without a risk;  

2) to formulate recommendations.
METHODS

An overview of reviews followed by a systematic review of subsequently published trials was carried out. The guidelines from the Cochrane Collaboration for overview of reviews, as well as comments by Smith et al. (9), were followed for the overview of reviews. All relevant systematic reviews/meta-analyses of randomized controlled trials (RCTs) and quasi-RCTs were considered for inclusion. The participants in the included trials had to be infants at high risk of developing allergy, as assessed by a family history (the presence of allergy in at least one parent and/or sibling) and/or other markers (as determined by the study investigators), or without any risk. The included trials compared use of formulas based on cow milk protein hydrolysates with standard infant formula or follow-on formula. The primary outcomes of interest in included trials were those related to allergic disease such as all allergic diseases, including atopic eczema/atopic dermatitis, gastrointestinal symptoms, food allergy/hypersensitivity, respiratory symptoms (wheezing and/or asthma), allergic rhinitis, and urticaria (if reported together); atopic eczema/atopic dermatitis; respiratory symptoms (wheezing, asthma as diagnosed by a physician), allergic rhinitis, food allergy/hypersensitivity, urticaria, and anaphylaxis. Search methods are outlined in the online-only appendix (http://links.lww.com/MPG/A301).

RESULTS

Overview of reviews

Eight systematic reviews with or without a meta-analysis met the inclusion criteria (Alexander & Cabana 2010 (10) Alexander et al. 2010 (11), Baumgartner et al. 1998 (12), Hays & Wood 2005 (13), Foisy et al. 2011 (14), Osborn & Sinn 2006 (Cochrane review (15), Osborn & Sinn 2005 (16), Szajewska & Horvath 2010 (17)). Two reviews (Baumgartner et al. and Hays & Wood) included trials co-authored by the investigator (RK Chandra) whose data have been
questioned (18), thus, these reviews were excluded. Two reviews (Foisy et al. (14), Osborn & Sinn 2007(15)) covered data included in the 2006 Cochrane review, and therefore, were excluded. Finally, one review (Alexander et al. 2010) (11)) was a duplicate of the same data that were published in another journal at the same time (Alexander & Cabana 2010 (10)), thus, this review was also excluded. The three included reviews (Alexander & Cabana 2010 (11), Osborn & Sinn 2006 (Cochrane review) (15), and Szajewska & Horvath 2010 (17)) and methodological quality of the reviews are described in Tables 1 & 2. Both the reviews of Osborn & Sinn 2006 (15) and Szajewska & Horvath 2010 (17) included unpublished data. Of importance, Szajewska & Horvath 2010, obtained unpublished data from clinical trials from the Nestle Nutrition Institute, while no data were obtained from other formula manufacturers. Osborn & Sinn 2006 contacted the authors to obtain unpublished data from other manufacturers as well.

**Hydrolyzed formulas and allergy risk:** The Cochrane Review (15) showed that compared to human milk feeding, feeding a hydrolyzed formula (all types) from birth onwards during the first few days of life in low risk infants resulted in no significant difference in infant allergy or childhood cow milk allergy (CMA). Compared to cow milk formula, there was no benefit of short-term feeding (average four days) of a hydrolyzed formula (all types). One large quasi-RCT reported a reduction in infant CMA of borderline significance in low-risk infants (1 RCT, n=3473; RR 0.62, 95% CI 0.38, 1.00). Compared to standard cow milk formula, prolonged (in the first four to six months of life) feeding with a hydrolyzed formula (all types) in high-risk infants resulted in a significant reduction in infant allergy (7 RCTs, n=2514 infants; RR 0.79, 95% CI 0.66, 0.94) and a significant reduction in CMA (1 RCT, n=67; RR 0.36, 95% CI 0.15, 0.89). The duration of intervention in the “long-term” prevention studies was four to six months; the different reviews define this as “prolonged feeding”. There were no significant differences between groups in the incidence of childhood
allergy, infant eczema, childhood eczema incidence and prevalence, and in infant or childhood asthma, rhinitis, and food allergy. Subgroup analysis of trials blinded to the formula revealed no significant difference in infant allergy or childhood allergy incidence between groups. No eligible trial examined the effect of four to six months HF feeding beyond early childhood on allergy. Compared to cow milk formula, feeding with a partially hydrolyzed formula (any type) showed a significant reduction in infant allergy (7 RCTs, n=1482; RR 0.79, 95% CI 0.65 to 0.97) but not in childhood allergy, infant or childhood asthma, eczema, or rhinitis. One small RCT showed a significant reduction in cow milk allergy (1 RCT, n=67; RR 0.36, 95% CI 0.15 to 0.89). Compared to standard cow milk formula, there was no clear effect of feeding extensively hydrolyzed formula (any type) on any of the outcomes. Infants fed an eHF compared with a pHF had a significant reduction in food allergy (2 RCTs, n=341; RR 0.43, 95% CI 0.19 to 0.99), but there was no significant difference between groups in all allergy or any other specific allergy incidence. Compared to cow milk formula, four to six months feeding with an extensively hydrolyzed casein formula was associated with a significant reduction in childhood allergy incidence (1 RCT, n=431, RR 0.72, 95% CI 0.53 to 0.97), a significant reduction in infant eczema (3 RCTs, n=1237, RR 0.71, 95% CI 0.51 to 0.97), and a significant reduction in childhood eczema incidence (1 RCT, n=431, RR 0.66, 95% CI 0.44 to 0.98) and prevalence (1 RCT, n=431, RR 0.50, 95% CI 0.27 to 0.92). Compared to cow milk formula, four to six months feeding with an extensively hydrolyzed whey formula resulted in no significant difference in the outcomes of any allergy, asthma, and eczema.

Methodological concerns included small sample sizes in many studies and methodological limitations such as unclear randomization, unclear allocation concealment, and no true blinding. Also, often the effects were not clear when analysis was restricted to trials with blinding of measurement to study formula or to studies of adequate methodology.
**Partially hydrolyzed whey formulas and allergy risk:** In one systematic review (Alexander & Cabana 2010)(10), eighteen articles representing 12 independent study populations met the inclusion criteria. Among them, 6 studies representing 4 infant populations were considered methodologically superior. For atopic dermatitis, meta-analysis of all reviewed studies that specifically reported data for atopic dermatitis and studies that reported outcomes that included atopic dermatitis (eg. atopy, skin symptoms) showed that feeding with pHF--W statistically significantly reduced the risk of atopic manifestations (11 trials, SRRE 0.56, 95% CI 0.4 to 0.77). Meta-analysis of studies of higher methodological quality also documented significant risk reduction (4 trials; SRRE 0.45, 95% CI 0.30 to 0.70). The effect was consistent, regardless of study design, infant population, follow-up time, or study location. The authors concluded that feeding with pHF instead of cow milk formula reduced the risk atopic dermatitis in infants with a family history of allergy.

Similar conclusions were reached by the authors of the second review (Szajewska & Horvath)(17). The 12 populations described in the 15 publications involving 3284 participants (1027 in the pHF groups and 2257 in the control groups) were eligible for inclusion. Sample sizes ranged from 30 to 2252 patients. Follow-up ranged from 6 months up to 6 years. One of the largest trials (the German Infant Nutrition Intervention study [GINI study]) was assigned a ‘yes’ for 4 criteria on the validity scale (adequate sequence generation, allocation concealment, blinding, and incompleteness of outcome data addressed), and one trial was assigned a ‘yes’ for 3 criteria. The remaining trials had a number of methodological limitations.

For all allergic diseases (7 RCTs), using a random-effects model, use of pHF-W was statistically significantly more effective in reducing the risk of all allergic diseases (incidence) compared with standard formula at 3 to 6 months (5 RCTs, RR 0.48, 95% CI 0.23 to 1.00), at
one year (4 RCTs; RR 0.62, 95% CI 0.45 to 0.85; NNT=12), and at 30 to 36 months (1 RCT; RR 0.42, 95% CI 0.19 to 0.90) but not at 2 years (2 RCTs). There was evidence of statistical heterogeneity at 3 to 6 months ($I^2=58\%$).

For atopic dermatitis or atopic eczema (8 RCTs), using a random-effects model, the use of pHF compared with standard formula statistically significantly reduced the incidence of eczema at one year (4 RCTs; RR 0.68, 95% CI 0.48 to 0.98; $I^2=0\%$), but not at 4 to 6 months (5 RCTs), 2 years (3 RCTs), nor 30 to 36 months (2 RCTs).

There were no statistically significant differences between pHF-W and eHF-W nor eHF-C formula in the risk reduction for all allergic diseases nor for atopic dermatitis or atopic eczema. Sensitivity analyses did not significantly alter these results.

The authors concluded that pHF-W was effective, compared with standard formula, in preventing allergy, particularly atopic dermatitis or atopic eczema, in children at a high risk of allergy at most time points. However, these findings should be interpreted with caution due to methodological concerns. The strongest evidence came from a well-designed and conducted, publically funded RCT (GINI Study).
Results overview

See Tables 3 to 6 for detailed results.

Studies Identified after the Systematic Review/Meta-analysis

We identified one single-blind RCT designed to assess the effect of using a pHF-W at weaning on the risk of allergic disease that was published subsequent to the latest meta-analyses (19). At the age of 2 years, 575 (93%) infants out of 620 were followed-up, and at 6 to 7 years, 495 (80%). Feeding with pHF compared with CMF did not significantly affect the risk of developing any allergic disease at 0-1 year (OR 1.02, 95% CI 0.67 to 1.54) or at 0-2 years (OR 1.21, 95% CI 0.81 to 1.8). There was no difference between the group fed pHF and the group fed CMF for the secondary outcomes within the first 2 years and at 6-7 years. There are methodological issues that call for cautions, including the unclear reason for publishing the results 15 years after collecting the data, outcome assessment through telephone interviews with parents, and changing definitions of outcome parameters compared to previous publications on this cohort (20).
CONCLUSION/RECOMMENDATION

- Certain extensively hydrolyzed casein and certain partially hydrolyzed whey formulas are appropriate for reducing the risk of allergy in infants at high risk when breastfeeding is not or no longer possible and formula feeding is initiated.

- Formulas with documented safety and efficacy should be the preferred choice (as shown in the tables). Many formulas currently available differ from those used in clinical trials due to further modifications. Worldwide, not all products are available everywhere. One could consider that it might be preferable to use a “non-studied hydrolysate” rather than “no hydrolysate” in such a case.

- Since hydrolyzed formulas have not been studied in the prevention of allergy in low risk infants they cannot be recommended in this group.
DECLARATION OF INTERESTS

C Agostoni has participated as a clinical investigator or speaker for Soremartec, Nestle Nutrition Institute, and Nutricia.

J Bhatia serves on the Advisory Board of the Nestle Nutrition Institute, and has given lectures for Abbott Nutritional Institute and Mead Johnson Nutritionals.

R Shamir has participated as a clinical investigator, or advisory board member, or consultant or speaker for Abbott, Danone, Enzymotec, Ferrero, Nestle Nutrition Institute, Nutricia and Teva.

AM Staiano did not report any potential conflict of interest.

H Szajewska has participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for Abbott, Arla, Biogaia, Biocodex, Danone, Dicofarm, Hipp, Nestle, Nestle Nutrition Institute, Nutricia, Mead Johnson, Merck, and Sequoia.

Dominique Turck has participated as a clinical investigator or speaker for Danone and Nestlé.

Y Vandenplas has participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for Abbott Nutrition, Biogaia, Biocodex, Danone, Hero, Nestle Nutrition Institute, Nutricia, Mead Johnson, Merck, Orafti, Phacobel, Sari Husada, United Pharmaceuticals, Wyeth and Yakult.
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