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Review article

Partially hydrolyzed formula in non-exclusively breastfed infants: A systematic review and expert consensus

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ABSTRACT

Objectives: Guidance and evidence supporting routine use of partially hydrolyzed formula (pHF) versus intact cows' milk protein (CMP) formula are limited in non-exclusively breastfed infants. The aim of this review was to better clarify issues of routine use of pHF in non-exclusively breastfed infants who are not at risk for allergic disease by using a systematic review and Delphi Panel consensus.
Methods: A systematic review and Delphi consensus panel (consisting of eight8 international pediatric allergists and gastroenterologists) was conducted to evaluate evidence supporting growth, tolerability, and effectiveness of pHF in non-exclusively breastfed infants.
Results: None of the studies reviewed identified potential harm of pHF use compared with CMP in non-exclusively breastfed infants. There was an expert consensus that pHF use is likely as safe as intact CMP formula, given studies suggesting these have comparable nutritional parameters. No high-quality studies were identified evaluating the use of pHF to prevent allergic disease in non-exclusively breastfed infants who are not at risk for allergic disease (e.g., lacking a parental history of allergy). Limited data suggest that pHF use in non-exclusively breastfed infants may be associated with improved gastric emptying, decreased colic incidence, and other common functional gastrointestinal symptoms compared with CMP. However, because the data are of insufficient quality, the findings from these studies have to be taken with caution. No studies were

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identified that directly compared the different types of pHF, but there was an expert consensus that growth, allergenicity, tolerability, effectiveness, and clinical role among such pHF products may differ.
Conclusions: Limited data exist evaluating routine use of pHFs in non-exclusively breastfed infants, with no contraindications identified in the systematic review. An expert consensus considers pHFs for which data were available to be as safe as CMP formula as growth is normal. The preventive effect on allergy of pHF in infants who are not at risk for allergic disease has been poorly studied. Cost of pHF versus starter formula with intact protein differs from country to country. However, further studies in larger populations are needed to clinically confirm the benefits of routine use of pHF in non-exclusively breastfed infants. These studies should also address potential consumer preference bias.

Introduction

Childhood atopic diseases are becoming increasingly common in both high- and low-income countries [1] and are a major public health concern [2]. Family history has long been considered an important risk factor for atopic disease [3]. However, >50% of allergic children have no family history of atopy [4,5]. The role of family atopic history as a risk factor for the development of food allergy remains unclear in light of recent studies of peanut and egg allergy [6].

Partially hydrolyzed formulas (pHFs) were originally developed to have enhanced tolerability and reduced allergenicity compared with intact cows' milk protein (CMP) formula and potentially may have benefit in decreasing the occurrence of atopic diseases [2,7]. pHFs are used worldwide in healthy infants, and in certain countries, they are used for the potential prevention of eczema through age 2 y in infants who may be at high risk of allergy [7]. The Food and Drug Administration (FDA) allows marketing of pHF in the United States for this potential indication. Current guidance on the routine use of pHF versus intact CMP formula in healthy infants who are not exclusively breastfed is limited and sometimes conflicting (Table 1). The European Commission (EC) [8], the European Food Safety Authority (EFSA) [9], the Codex Alimentarius Commission [10], the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) [11] and Health Canada emphasize the importance of scientific data to demonstrate that a product meets the infant's nutritional needs and safety requirements. The FDA [12] and the EFSA [9,13] have provided frameworks supporting qualified claims of pHFs as routine feeding options for healthy infants. In the United States, pHFs are subject to the requirements of the Infant Formula Act (21 USC 350 a), and all health claims for the formula must be evaluated by the FDA [12]. The EC directive 2016/127 and EFSA Scientific Opinion mandate that pHF safety and suitability should be established by clinical

Table 1
Summary of guidance on the routine use of partially hydrolyzed formula versus intact cows' milk protein formula

Guidance [Reference number]	Definition of infant formula and other relevant information	Protein specifications for standard and partially hydrolyzed infant formulas
FDA [12]	• "A food which purports to be or is represented for special dietary use solely as a food for infants by reason of its simulation of human milk or its suitability as a complete or partial substitute for human milk" (FDA regulations define infants as persons ≤ 12 mo old) • "The use of 100% whey pHF is safe and lawful"	Standard formula • Range: ≥ 1.8 and ≤ 4.5 g/100 kcal • No protein with a biological quality <70% of casein shall be used
European Commission directive 2016/127 [8]	• "Foodstuffs intended for particular nutritional use by infants during the first months of life and satisfying by themselves the nutritional requirements of such infants until the introduction of appropriate complementary feeding" • Formulas "must satisfy the nutritional needs of healthy infants as established by generally accepted scientific data"	Formula manufactured from protein hydrolysates • Range: ≥ 1.86 and ≤ 2.80 g/100 kcal • Nutritional safety and suitability of all infant and follow-on formula manufactured from protein hydrolysates should be clinically tested (if do not comply with the criteria laid down in European Commission directive 2016/127)
European Food Safety Authority Scientific Opinion [9]	• "Formulae must be safe, and suitable to meet the nutritional requirements and promote the growth and development of infants"	Formula manufactured from protein hydrolysates • Range: ≥ 1.8 and ≤ maximum of 2.8 g/100 kcal • Safety and suitability of each specific formula containing protein hydrolysates should be established by clinical studies
Codex Alimentarius Commission [10]	• "A product based on milk of cows or other animals or a mixture thereof and/or other ingredients which have been proven to be suitable for infant feeding" • "A breast-milk substitute specially manufactured to satisfy, by itself, the nutritional requirements of infants during the first months of life up to the introduction of appropriate complementary feeding"	Standard formula and pHF • Range: ≥ 1.8 and ≤ 3.0 g/100 kcal • pHF containing <2.25 g of proteins/100 kcal should be clinically tested
European Society for Pediatric Gastroenterology, Hepatology, and Nutrition [11]	• "A product based on milk of cows or other animals and/or other ingredients which have been proven to be suitable for infant feeding." • The nutritional safety and adequacy of infant formulas should be scientifically demonstrated to support normal anthropometric growth and development of infants	Standard formula and pHF • Range: ≥ 1.8 and ≤ 3 g/100 kcal • pHF containing <2.25 g of proteins/100 kcal should be clinically tested
Health Canada [12]	• Clear differentiation between CMP formula and FSMP • FSMP are intended for use only under medical supervision, which include formulas for the dietary management of various conditions and formulas for preterm infants • FSMP are not intended for healthy, term infants	Standard formula and pHF • Range: ≥ 1.8 and ≤ 4 g/100 kcal • Protein in these formulas may be whole-milk protein; a combination of casein and whey proteins; or just one of these proteins. Some or all of the protein may be partially hydrolyzed

CMP, cows' milk protein; FSMP, formula for special medical purposes; pHF, partially hydrolyzed formula
Adapted from Vandenplas et al. 2016 [7]

evaluation [8,9]. Data from systematic reviews and meta-analyses remain mixed in supporting that pHF containing 100% whey protects against development of atopic dermatitis in early childhood (infancy and toddlerhood) [2,14–17]. There are limited data regarding routine use of pHFs (e.g., use as an option as a primary infant formula) in non-exclusively breastfed infants and other not at-risk populations.

To better clarify issues of routine use of pHF in non-exclusively breastfed infants who are not at risk for allergic disease, a panel of pediatric allergy, gastroenterology, and nutrition experts was convened to explore this topic using a systematic review and Delphi Panel consensus. The panel's findings are reported herein.

Methods

To systematically evaluate the evidence regarding the routine use of pHF in non-exclusively breastfed infants not considered at- risk for the development of allergic disease, an international panel of pediatric allergists (n = 5) and gastroenterologists (n = 3) from the Asia-Pacific region (Australia, Malaysia: n = 1 each), Europe (Belgium, Germany: n = 1 each), Middle East (United Arab Emirates: n = 1), and North or Latin America (United States: n = 2, Mexico: n = 1) was assembled. Routine use was defined as use of a pHF as an option for primary infant formula in a standard-risk (e.g., not at risk for allergic disease), non-breastfed child. The group was asked to conduct a systematic literature review on the topic, and use the Delphi method to provide consensus opinion to back the literature review findings and to supplement any gaps in the literature on the subject.

Systematic literature search

A systematic literature search of the MEDLINE database up to September 2016 was performed using the search terms shown in Supplementary Tables 1 and 2 to inform the Delphi consensus process. No search restrictions were applied. Resulting publications were manually screened for potential relevance by the expert panel, with duplicates removed, and additional publications were identified from cross-referencing. The outcome of the search strategy is shown in Supplementary Figure 1. We identified 231 citations for final inclusion in this systematic review, falling under the general outcomes of formula definition; growth, tolerability, and general infant development; allergenicity and allergic disease prevention; prior systematic reviews and clinical practice guidelines; and health economics of pHF use.

Delphi consensus method

To better frame and organize discussion regarding the findings of the systematic review, a Delphi panel [18,19] was conducted among the expert panel. Based on the systematic literature search, a three-stage process was followed [18,19], with experts completing a first-round questionnaire on topics including defining terms around pHFs for routine use as we defined; evidence on growth, gastrointestinal (GI) tolerability, and effectiveness for potential allergy risk reduction; cost-benefits of pHF use; guidelines on pHF use; and clinical practice. First-round responses were summarized and presented to the experts, who could then revise their opinions, if desired. The questionnaire was amended for a second evaluation round, involving further refinement of the experts' responses and rating of answers on a 5-point Likert scale. After completion of the second round, the experts met to discuss the findings and generate or finalize a consensus of opinion on topics, where possible. Consensus was defined as ≥75% agreement among experts (n ≥ 6). Questionnaire responses from each round were anonymously collected to minimize any potential bias from the influence of dominant individuals and/or group pressure for conformity [18].

The findings from the systematic literature search and Delphi consensus project were used as the basis for development of this narrative review and summary of the consensus on these topics. Per group consensus, it was decided that no meta-analysis would be attempted given considerable heterogeneity in the available data (specifically that data were limited, where available these involved use of different formulations of pHF, and different populations were studied). As such, it was also decided that this document would not attempt to make summary statements or qualified recommendations with GRADE evidence weighting. The panel sponsor had no role in the Delphi process and no involvement with drafting of the manuscript. Experts were chosen based on their expertise on infant nutrition or allergy disease prevention, and not chosen based on any relationship with the sponsor. Before submission, the sponsor was allowed to view the manuscript exclusively for regulatory purposes related to consistency with current approved product indications but otherwise had no decision making related to the content.

Results

Definition of terms

Twelve publications were identified in the systematic review that discussed the protein contents of infant formula, to define and differentiate pHF from other formulas, and to define hypoallergenicity with respect to an infant formula.

Intact protein versus hydrolyzed protein formulas

Specifically, intact protein formulas are not treated in any way to break down native proteins into smaller peptides (e.g., by hydrolyzation). In contrast, hydrolyzed formulas are composed of a protein base and degraded to a variable extent (partially or extensively) by enzymes, heat, pressure or ultrafiltration to increase tolerance and digestibility and possibly reduce allergenicity and immunogenicity on the basis that the lesser degrees of intact protein content is associated with enhanced immunologic tolerability. Both casein and whey hydrolyzed formula products exist worldwide. There was unanimous expert consensus regarding the accuracy of these definitions.

The literature suggests that residual cows' milk immunoglobulin (Ig)E and T-cell epitopes can remain after hydrolysis, and could be recognized by the immune systems of some individuals [20]. Peptides as small as 10 to 15 amino acids can bind to IgE and T cells [21,22]. There are multiple IgE-binding epitopes in both whey and casein that fall within this size range [22]. However, it is estimated that allergens must be ≥25 to 30 amino acids for crosslinking of IgE receptors and activation of a proinflammatory immune response [21]. No studies were identified that recommended pHF as appropriate for use in treatment of allergic diseases. Multiple studies were identified that indicated that extensively hydrolyzed formula (eHF) may be considered for prevention or management of allergic disorders such as atopic dermatitis (AD) or cow's milk protein (CMP) allergy-related symptoms. There was unanimous expert agreement on these points.

The extent of the size of remaining casein or whey peptides after hydrolysis determines whether the formula is deemed a pHF or eHF. The literature review noted that regardless of protein base, pHFs typically contain peptides of average molecular weight <5 kDa, whereas eHFs are composed of >90% of peptides with molecular weight ≤3 kDa [23]. Although the expert panel agreed with the literature regarding definition of formula type by size of the hydrolyzed formulas, there was also consensus that the definition of a pHF should be based on established, clear guideline standards, such as the existing EC directives and regulations [8], FDA Guidance for Industry [12], or ESPGHAN guidelines to promote maximal consistency in product labeling [11].

Avoidance of terminology related to "hypoallergenicity"

We noted multiple definitions in the literature describing the term *hypoallergenic*, and no clear consistency in what this definition implied. In Europe, the term *hypoallergenic* denotes a formula with reduced allergenicity related to the cow's milk protein base, which includes both eHF and pHF [24,25]. In the United States, the term *hypoallergenic* refers to a formula that is used for treatment or primary prevention of CMP allergy; therefore, *hypoallergenicity* is also defined more stringently (i.e., under double-blind, placebo-controlled conditions, 95% confidence that 90% of infants with documented CMP allergy will not react with defined symptoms to the formula) [26]. Thus, both eHF and pHF could be considered hypoallergenic under these definitions. There was expert consensus that the term *hypoallergenic* should be avoided when discussing infant formulas because it is ambiguous and potentially confusing.

Overall effects of pHFs

Twenty-six publications identified in the systematic review discussed the growth and safety of pHF use. The systematic literature review identified no studies that demonstrated harm in use of pHF in any population, including routine use in non-exclusively breastfed infants not at risk for the development of allergic disease. Although outside the context of our population of interest, the most current Cochrane systematic review of hydrolysates for the prevention of infant allergy and food intolerance found no adverse effects on infant growth associated with hydrolyzed formulas in any of the studies included for analysis [27]. In a prospective, double-blind, controlled, non-inferiority trial of healthy infants (N = 335) randomized to intact CMP formula or whey pHF (pHF-W) for 60 d, no significant between-group difference in frequency of serious adverse events was observed [28]. Parent-reported formula intake, and physician-assessed weight gain and tolerance (fussiness, gas, stool consistency, and incidence of diarrhea or constipation) were similar, regardless of formula use [28]. In another randomized, double-blind study, daily weight gain over 4 mo did not significantly differ between healthy infants who were breastfed full-term or those receiving pHF-W or intact whey-predominant CMP formula (N = 205) [29]. Growth parameters at 6 wk and 3 and 6 mo also did not differ in unselected infants who were exclusively breastfed, or in whom breastfeeding was supplemented or replaced with pHF-W use (N= 564) in a cohort study [30]. As well, although outside our population of interest the ongoing follow-up of the German Infant Nutritional Intervention (GINI) cohort study has demonstrated no significant differences in absolute or World Health Organization–standardized body mass index trajectories through the first 10 y of life in children at high risk of atopy who were breastfed (n = 448) or received pHF-W (n = 118), whey eHF (eHF-W; n = 123), or intact CMP formula (n = 127) [31].

The panel had unanimous consensus that sufficient growth data exist to conclude that infants fed pHF grow within normal limits and that as a consequence, there is no harm in using a pHF over an intact CMP formula in infants who are not exclusively breastfed. pHFs appear to result least in similar data as intact CMP formula, with comparable nutritional parameters, although there are no similar long-term studies involving pHF use in healthy children without a familial risk for atopy. The panel also unanimously agreed that sufficiently powered, randomized controlled trials are needed to evaluate both short-term nutritional outcomes and long-term developmental and health outcomes for routine pHF use [7].

GI tolerability and digestive comfort of pHFs

The literature review identified 92 publications that discussed overall pHF tolerability (16 publications) and specific aspects of GI tolerability (29 publications for "GI tolerability," 15 publications for colic, 32 publications regarding prebiotic or probiotic supplementation). Both prospective, randomized studies and an observational study were identified that support the association of certain pHFs with both potentially improved gastric emptying and beneficial effects on common functional GI symptoms (e.g., colicky symptoms, regurgitation, functional constipation). However, data were of insufficient quality and limited because of potential confounding factors (e.g., changes in carbohydrate, fat composition, and additives) to draw firm conclusions, and few were felt to be specific to the general population of interest [32].

In a prospective, randomized study of infants aged <1 y (N = 28) with gastroesophageal reflux, mean values for gastric emptying after a single feed of casein-predominant formula, soy formula, or pHF-W were 39.7%, 44.6%, and 48.5%, respectively. A significant difference in gastric emptying time was observed between casein-predominant formula and pHF-W ($P < 0.05$) [33]. In a double-blind, randomized crossover study in healthy newborns (N = 17) fed intact CMP formula, pHF, or eHF, gastric emptying was significantly faster in the eHF group than in the intact CMP formula and pHF groups (median of 46 versus 55 and 53 min, respectively; $P < 0.05$ for both comparisons). There was no significant difference between emptying times for pHF and intact CMP formula [34]. However, both studies involved small samples and were of inadequate power.

No randomized clinical trials were identified as demonstrating the efficacy of pHF-W in infantile colic [32]. Similarly, there were no studies identified evaluating the efficacy of pHF-W as a solitary intervention in infants with constipation [32]. A prospective, double-blind, crossover trial in exclusively formula-fed infants with regurgitation (N = 12) who previously failed to improve with thickened or hydrolyzed formulas, prokinetic and acid-blocking drug medication showed that a pHF-W combined with two thickeners significantly decreased regurgitation and crying compared with a thickened casein-predominant formula [35]. The review identified 32 publications regarding prebiotic and probiotic supplementation in pHF, but found that current evidence is insufficient to show clear clinical benefits from adding prebiotics or probiotics to pHFs to influence the outcome of functional GI disorders. A systematic review by the ESPGHAN Committee on Nutrition concluded in 2011 that based on the limited available evidence, administering prebiotic- or probiotic-supplemented formulas to healthy infants does not raise any safety concerns, although this is not recommended as a routine practice [36]. The World Allergy Organization advised in 2015 that although currently available evidence does not indicate that probiotic supplementation reduces the risk for developing allergic outcomes in children, it likely has a net benefit, resulting primarily from eczema prevention [37].

In evaluating the evidence, there was expert consensus from the Delphi panel that pHFs have acceptable GI tolerability for routine use as defined herein, and that there is no current evidence supporting benefit associated with probiotic supplementation in pHFs. Furthermore, the panel had consensus agreement that better designed studies are needed to help determine optimal probiotic dose and strain, as well as adjust for potential confounding from other formula ingredients such as vitamin D.

Value of pHFs in reducing allergy risk

In all, 190 studies were identified dealing with the allergy-related manifestations including prevention (107 publications for atopic dermatitis, 51 for food allergy, and 32 for asthma). In addition, a majority of the 31 previously published clinical guidelines or systematic reviews on pHF use specifically discussed pHF use for allergy prevention. There were no studies or prior systematic reviews or clinical guidelines identified that supported potential allergy prevention benefit associated with routine use of a specific pHF-W in not at-risk populations. Data on this subject has been exclusively studied only in the at-risk population, and are not without some controversy as not all studies have universally concluded nor demonstrated a preventative benefit (associated with a reduced risk for development of atopic dermatitis through age 2) in intention-to-treat populations. Thus, meta-analyses and systematic reviews have offered conflicting results of pooled data regarding such benefits [2,14–17,38]. The literature search noted multiple potential definitions of "at risk" or "high risk" for the development of allergic disease, complicating delineation of a consistent population being studied. Risk defined by primary relative

or family history of any allergic disease has been the primary definition used in most of the published literature. However, newer criteria used in the recent food allergy early introduction trials have also specifically defined risk by either the presence of egg allergy or severe atopic dermatitis, presence of IgE (food-specific or general), or just on the presence of severity of atopic dermatitis, and de-emphasizes the presence of any family history of allergic disease. The family history-based definition has been used in two prevention studies specific to egg allergy, and all of the studies using hydrolyzed formula for possible prevention of multiple possible atopic manifestations. The newer risk definitions have been used in trials of early intervention specific to the development of either egg or peanut allergy. This may possibly account for the heterogeneity in the baseline definition of risk.

The panel reached unanimous consensus that there may be limited instances in which data could potentially be extrapolated from at-risk populations to the general population. However, there was unanimous consensus that additional data are needed to confirm any potential allergic risk-reducing benefit ascribed to a particular pHF formula in non–at-risk populations. Moreover, there was unanimous consensus that for prevention of allergic disease, data from at-risk populations should not be extrapolated to a non–at-risk population. More importantly, the panel reached unanimous consensus that there is inconsistency in the definition of high risk, making comparison between trials more difficult, and necessitating a firmer consensus on a more standardized definition to even study any potential allergy related risk-reducing potential associated with pHF for routine use so that study populations are clearly delineated [39].

Limitations in extrapolating data on hydrolyzed formulas to non-studied populations

The systematic review identified multiple references that suggested that although there are commonalities within the types of eHF and pHFs sold, these may have distinct properties and should not be considered economic substitutes of one another. A recent peptidomic analysis of four commercially available eHFs showed that their peptide profiles differ and are distinct from each other. Each profile provides a descriptive and recognizable signature, determined by the specific hydrolysis process used for each product [40]. These findings support the consensus that individual pHFs and other hydrolyzed-formula products should not be considered the same without trials clearly demonstrating non-inferiority. This was also influenced to some degree by discussion regarding if data from older clinical trials still hold value in comparison with more modern trials, considering that infant ormula recipes may have evolved since those studies were performed. There was consensus that although subtle modification of existing pHFs (e.g., addition of probiotics, prebiotics, polyunsaturated fatty acids, or vitamin D) would likely not have any clinically relevant negative effects, and comparisons between these modern and older infant formulas would remain valid. However, there was consensus that alterations in the hydrolysis process of an existing pHF would likely necessitate new testing to determine any effects such changes may have on its established clinical effectiveness. There was unanimous consensus that it is inappropriate to extrapolate the effectiveness of specific individual hydrolyzed formulas to other populations that have been untested. As well, there was unanimous consensus that the potential allergy prevention benefit has been noted only with a particular pHF-W product and that such benefits should not be extrapolated to all pHFs (and must be independently studied) when considering design of future studies for the non–at-risk target population.

Timing of use of pHF

From among 45 publications identified that specifically dealt with pHF use and infant growth or development, no studies specifically identified describing a specific, appropriate age for pHF use in terms of an upper age limit or a specific time of introduction that has proven superior to another time. There was unanimous consensus of the Delphi panel that an upper age limit for pHF consumption is not required, provided the formula given is still considered appropriate for the infant's age and developmental stage. However, the timing for commencing pHF consumption was considered important, with all experts agreeing that the highest potential value in starting pHF use occurs in the first 6 mo of life if children cannot be exclusively breastfed, with markedly less value if starting >6 mo, and likely no value if starting >12 mo given that non-breastfed infants transition to non-formula sources of nutrition at about a year of age notwithstanding a comorbidity that necessitates a specific formula.

Health economics research on pHFs

Alhtough 15 publications were identified in the systematic review related to the cost-effectiveness of pHF use, no study was identified that studied and supported any cost-effectiveness of routine pHF use as we have defined *routine*. Cost savings from pHF use have mainly been demonstrated from reduction in atopic dermatitis (AD) in at-risk populations—an argument that presently has no translation to populations not at risk [7]. There was consensus that routine use of pHF as defined, although often more expensive initially than intact CMP formula, could conditionally have long-term cost benefits through potential prevention of functional GI disorders [41]. It was felt such savings could arise from avoiding the need for increased medical consultations and use of treatments, as well as indirect savings related to possible decreased productivity, absenteeism, and other negative effects on the parent. There was unanimous consensus that the current cost-savings models related to pHF-W use are highly dependent on the validity of findings from the GINI study, which only applies to a narrowly defined population of at-risk children [42,43]. However, one US-focused analysis was identified that estimated that administering pHF-W rather than intact CMP formula to all infants not exclusively breastfed (and not exclusively at risk) infants, could result in annual societal savings of ~US $750 million [44]. However, it is difficult to make a strong recommendation regarding the cost-effectiveness of pHF-W versus standard infant formula because the cost of formula varies from country to country. In the United States, the cost of pHF-W and starter formula is quite similar, whereas in France, pHF-W is 50% more expensive that standard starter formula with intact protein [7].

pHF use: Current guidelines and regulatory aspects

No literature was identified that suggested that pHF would not be an appropriate starter formula compared with intact CMF. From a regulatory perspective, pHFs are an accepted starter formula for infants who cannot be exclusively breastfed, and this is echoed by current guidelines (Table 1). However, these recommendations are limited by being based mainly on clinical studies involving use in a selected high-risk population, extrapolated to more general potential use. Only the EFSA [13], ESPGHAN [11] and European Academy of Allergy and Clinical Immunology [45] guidelines currently consider that specific pHFs and other hydrolyzed formulas may vary in their clinical effectiveness [42]. Although no study was identified that compared the superiority or inferiority of different pHFs, there

was consensus that protein standards for pHFs may be defined differently by organizing and regulatory bodies, and by country, and that individual hydrolyzed formulas, including pHFs, are not considered to be the same with regard to proven effectiveness and tolerability. There also was unanimous consensus that choice of pHF as a routine starter formula may be a preference-sensitive decision on behalf of the infant's parents.

Discussion

Exclusive breastfeeding during the first 4 to 6 mo of life is the recognized first choice for infant nutrition and development, but is not always possible. Infant formulas, in particular those derived from cows' milk, are a commonly used substitute for breastfeeding, but there is a plethora of products available, some chosen by consumer preference, and some with specific medical uses indicated in certain conditions, supported by varying levels of clinical evidence and limited guidance.

This group was tasked with performing a systematic literature review exploring the routine use of pHF in the general population. Foremost, no data suggest harm from routine use in non–at-risk populations, and this was unanimously backed by the expert consensus. The bigger issue was lack of compelling data for benefit, either from the literature or from expert consensus. Data weakly suggest that routine pHF use may be associated with possible improvements in functional GI disorders, and data support pHF use is not associated with apparent deficits in growth and development. The literature search yielded little else—no studies were identified regarding allergy in this population, no studies were identified suggesting an optimal time for introduction of pHF or specific cost-benefit analysis of the routine use of pHF outside the at-risk population, no studies were identified that compared differing forms of pHF that could be used for these outcomes, and overall there was a rather inconsistent definition of *hypoallergenic* used in the literature. Accordingly, considering the available data in the literature, there was consensus that, given a setting where this conceivable real-world issue may not be appropriate or financially feasible to investigate through a well-designed clinical trial, use of pHF in non–at-risk populations may be more a practical matter of patient preference for the parent.

This process resulted in a narrative systematic review, with no meta-analysis performed given the heterogeneity of the data. We also made no attempt at making a formal GRADE-based recommendation for such use of pHF. A consensus of a Delphi panel with international representation was used to supplement the gaps in evidence. We feel this dual process is a strength of this review. In evaluating the available data, there were no studies identifying harm, a point with which there was unanimous consensus. There were limited potential benefits, mainly related to data related to functional GI tolerability, which despite poorer quality evidence, the expert consensus was that there could be some benefit associated with such use. However, routine use of pHF could not be recommended for allergy prevention, given no data and a clear consensus that such use needed to be rigorously evaluated (in particular given controversial potential benefits in the at-risk population for which meta-analyses have vacillated) [46]. Furthermore, the expert consensus denoted a need for better clarification of what an "at-risk" population constituted to better delineate the "non–at-risk" population for selection before future study should be undertaken. There was consensus that inclusion of validated disease-specific measures in future clinical trials may facilitate better evaluation of infant formula effectiveness, in particular across differing types of populations.

The present review and consensus concluded that not all pHFs and hydrolyzed formulas are equivalent and that comparability across different formulas is limited, and there was unanimous group consensus that this has not always been recognized by policymakers. The group agreed that the recent systematic review and meta-analysis from the *British Medical Journal*, which did not find any benefit for allergy prevention of pooled pHF and eHF data, compared with intact CMP formula [17], is a prime example of potential issues that may arise from not considering differences in the specific nature of individual pHFs, which may be a limiting factor to the conclusion of that particular review, compared with other reviews. Therefore, a need for high-quality, prospective, independently funded clinical trials that investigate the effect of specific pHFs still remains, regardless of the study population (at risk or not).

Conclusions

The literature review noted, and the expert panel agreed, that pHFs derived from different source proteins should not be considered equivalent. Infants fed pHF-W grow within normal range. However, use of pHF in populations not at risk has not been associated with any preventative or protective benefit, given that demonstration of such benefit related to particular pHF products (versus intact CMP formula in infants for the first 4– to 6 mo of life who are not exclusively breastfed) has only been studied and demonstrated (in some cases inconsistently) in populations at risk for the development of allergic disease. It is not possible to make a conclusion about cost-effectiveness given the huge variation in cost of pHF-W compared with starter formula with intact protein [7]. Thus, future studies are necessary to address whether such use in populations not at risk has any similar benefit. There was strong unanimous consensus that use of pHF products in the population not at risk would be safe given no risks or known hazards of this practice were identified and this consensus is potentially aligned with possible caregiver preference to try these products as available market options.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nut.2018.05.018.

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