

Hydrolyzed Formula for Every Infant?

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Hydrolyzed formulas (HFs) are presently used primarily in infants that cannot be exclusively breastfed and those with documented cow's milk (CM) allergy, and for primary prevention of allergic disease. HFs are increasingly being used worldwide (table 1), begging the question if HFs may be recommended as the optimal choice for all standard-risk, full-term infants who are not exclusively breastfed.

From the regulatory standpoint, all extensively HFs (eHFs) in the United States and Canada are approved for use only under physician supervision, thus not approved or commercialized for routine use in healthy infants. Only one of the partially HFs (pHFs) which contains 100% whey partially hydrolyzed with trypsin is approved, marketed and commercialized as a routine-use infant formula for healthy term infants. In Europe, eHFs fall under the category of food for special medical purposes, also meant for use under medical supervision, but pHFs in Europe have been commercialized for routine use for a number of years. However, the most recent directive from the European Food Safety Authority states that only pHFs containing 100% whey using a specific hydrolysis process are appropriate for use as routine formulas for healthy term infants.

Data regarding the nutritional adequacy of modern-day HFs are scarce and lack long-term data suggesting that growth in infants fed HF versus intact protein formula (IPF) is different. There may be theoretical concern that partially hydrolyzed protein is both absorbed and metabolized faster than intact protein; whether this has any impact on the health outcomes of infants is unknown, but available data from eHFs are reassuring.

While human breast milk is the optimal source of nutrition for multiple reasons, a 2006 systematic review determined there were no comparable long-term studies regarding the prolonged use of HFs versus breastfeeding [1]. There are studies, however, that have examined the use of various formulas as a primary source or supplement to reduce the risk of atopic disease. Meta-analyses of formula consumption and the risk of atopic dermatitis (AD) have found that infants fed pHF compared to

Table 1. Select pHFs and eHFs available globally for infants (2015)

Country	Nestlé		Abbott		Mead Johnson	
	pHFs	eHFs	pHFs	eHFs	pHFs	eHFs
USA	pHF-W: Gerber® Good Start® Gentle/Soothe/Gentle for Supplementing	eHF-W: Gerber® Extensive HA™	pHF-WC: Similac® Total Comfort™	eHF-C: Similac Expert Care® Alimentum®	pHF-WC: Enfamil® Gentlease™/Reguline™	eHF-C: Pregestimil® Nutramigen®
	Good Start					Nutramigen
China	NAN HA	Althéra/Alfaré	Similac total Comfort		Enfamil Qingshu	Nutramigen
Mexico	Nan HA 1/ NAN HA 2	Althéra/Alfaré		Alimentum	Enfamil HA	Pregestimil/ Enfamil Nutramigen
Italy	NIDINA HA	Althéra/Alfaré	N/A		N/A (discontinued)	Nutramigen/ Pregestimil
France	GUIGOZ HA	Althéra/Alfaré	N/A		N/A (discontinued)	Nutramigen
Germany	BEBA HA	Althéra/Alfaré	N/A			Nutramigen
Nordic countries	NAN HA	Althéra/Alfaré				Nutramigen/ Pregestimil
Poland	NAN HA				Enfamil HA Digest	
Spain	NAN HA	Althéra/Alfaré				Nutramigen/ Pregestimil
Switzerland	BEBA HA	Althéra/Alfaré	N/A			
Russia	NAN HA	Alfaré/Alfaré Allergy' – brand name for Althéra	Similac HA			Nutramigen

Table 2. Should HF's be considered for routine use in healthy, term infants who cannot be breastfed?

Point of debate	Pro	Con
Regulatory status	Per US, Canadian and European regulatory agencies, pHF-W meets requirements for routine use Other HF's do not	Data for many HF's are outdated, and hydrolyzation methods have changed, resulting in different HF compositions; therefore, data on modern-day HF's as a category are lacking
Allergenicity	Europe: pHF's and eHF's considered 'hypoallergenic' North America: pHF-W may claim allergy risk reduction	Europe and North America: eHF's not for routine use even if demonstrated efficacy for allergy risk reduction or management of CM allergy Always for use under medical supervision
Metabolism	The metabolic consequences of different peptide formations in HF's from industrial hydrolysis are unknown, but based on published data, there is insufficient evidence to consider HF's as potentially harmful to term infants	New peptides with unknown functions are formed during industrial hydrolysis, and peptides normally formed by digestion of milk proteins may be absent, which could result in different bioactive peptides with different effects
Absorption	Adequate short-term growth has been demonstrated for all or most current HF's Select HF's have well-documented growth studies and health follow-up for up to 10 years No adverse safety issues identified by regulatory agencies	Long-term data are insufficient regarding absorption, blood metabolites and hormonal responses of various HF's vs. breastfeeding In preterm infants, weight gain rates were lower with older HF's

Table 2. (continued)

Point of debate	Pro	Con
Gastric emptying	In term infants, some HFs induce gastric emptying closer to breast milk than IPFs In preterm infants, decreased transit time promoted feeding tolerance	Some HFs likely result in faster gastric emptying based on several small studies, which may negatively affect gastric digestion
Gut maturation	There are insufficient data to conclude that HFs delay gut maturation compared to IPFs	There are insufficient data to conclude that HFs accelerate gut maturation compared to IPFs
Allergy prevention	If breastfeeding is insufficient or not possible for the first 4–6 months of life, the use of certain HFs has been shown to reduce the risk of developing AD in high-risk infants	While some studies have not shown a beneficial effect with the use of certain HFs for allergy prevention, systematic review and meta-analysis generally support their use
Cost-effectiveness	There are sufficient data to suggest that pHF-W given to formula-fed infants at high risk for AD is cost-effective for the prevention of AD in several countries	Studies not done for most HFs The costs of formulas vary significantly among countries, making it difficult to incorporate this into a global decision-making process

IPF had a lower risk of AD [2, 3], but there are significant limitations to these studies, making conclusions about the general use of HFs problematic. Some of the strongest evidence for use of HFs for allergy prevention comes from the German Infant Nutritional Interventional (GINI) study, which followed 945 high-risk newborn infants in a randomized trial investigating the effects of breastfeeding supplemented with one of four formulas, CM, whey-based pHF (pHF-W), whey-based eHF (eHF-W) or casein-based eHF (eHF-C), in the first 4 months of life [4]. Feeding with either pHF-W or eHF-C had a preventive effect on the cumulative incidence of AD in high-risk children that lasted until 10 years, the current point of published data; however, it should be noted that the primary preventive effect on AD by using either pHF-W or eHF-C was seen within the first 2 years of life, with no significant change in effect in the remaining 8 years. Additional trials are needed in high-risk infants to confirm these findings.

Costs should be considered in decision-making regarding the choice of the formula, but global comparison of this is difficult given large cost differences in different countries. Data suggest that pHF given to infants who are not exclusively breastfed is a cost-effective intervention for the prevention of atopic disorders, such as AD [5], though the question has been raised that the impact of allergy prevention in studies using HFs is limited to AD prevention, which implies that these preventive effects cannot be generalized to other allergic diseases in the atopic march, such as asthma and allergic rhinitis.

Despite the issues raised here (table 2), the desire to provide concrete recommendations of widespread HF use needs to be assessed carefully so as not to overstate claims of benefit. Long-term studies are needed to investigate the feasibility of HF as a routine feeding option for healthy, standard-risk infants. Because of the paucity of data for pHFs or eHFs, the routine use of HFs for every infant as an equivalent option to breastfeeding or IPF cannot be supported at present based on available scientific evidence.

References

- 1 Osborn DA, Sinn J: Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. *Cochrane Database Syst Rev* 2006;4: CD003664.
- 2 Alexander DD, Cabana MD: Partially hydrolyzed 100% whey protein infant formula and reduced risk of atopic dermatitis: a meta-analysis. *J Pediatr Gastroenterol Nutr* 2010;50:422–430.
- 3 Szajewska H, Horvath A: Meta-analysis of the evidence for a partially hydrolyzed 100% whey formula for the prevention of allergic diseases. *Curr Med Res Opin* 2010;26:423–437.

- 4 von Berg A, Filipiak-Pittroff B, Kramer U, et al: Allergies in high-risk schoolchildren after early intervention with cow's milk protein hydrolysates: 10-year results from the German Infant Nutritional Intervention (GINI) study. *J Allergy Clin Immunol* 2013;131:1565–1573.
- 5 Spieldenner J, Belli D, Dupont C, et al: Partially hydrolysed 100% whey-based infant formula and the prevention of atopic dermatitis: comparative pharmacoeconomic analyses. *Ann Nutr Metab* 2011;59(suppl 1):44–52.