A Systematic Review of the Role of Hydrolyzed Infant Formulas in Allergy Prevention

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Objective: To critically examine the published literature to determine whether feeding hydrolyzed infant formulas from birth has a role in allergy prevention.

Data Sources: We identified data through a MEDLINE search using allergy prevention and infant formulas as indexing terms. The search was restricted to 1985 through the present, English-language articles, and human subjects.

Study Selection: Criteria for inclusion in the review were prospective controlled trials published in peer-reviewed journals.

Data Extraction: Symptoms of allergy were defined and observed by health care providers (physicians and nurses).

Data Synthesis: Nine published trials evaluated the use of extensively hydrolyzed formulas, 12 evaluated the use of partially hydrolyzed formulas in high-risk infants, and 1 evaluated the use of partially hydrolyzed formulas in an unselected infant population. The reports compared hydrolyzed formulas with breastfeeding, cow’s milk formulas, soy formulas, and combinations thereof. The cohort of studies consistently showed reductions in the cumulative incidence of atopic disease from 12 to 60 months of age among high-risk infants fed extensively hydrolyzed casein formulas or partially hydrolyzed whey formulas vs cow’s milk formulas. No studies showed an increase in allergy risk with any hydrolyzed formulas.

Conclusions: Extensively hydrolyzed casein formulas and partially hydrolyzed whey formulas are appropriate alternatives to breast milk for allergy prevention in infants at risk. Because atopic disease in children cannot be predicted, the use of these formulas in the general population should be considered, and one must weigh cost, compliance, and long-term benefits.

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THE PREVALENCE OF FOOD ALLERGY AMONG INFANTS AND YOUNG CHILDREN IS ESTIMATED TO BE 5% TO 6% AND SEEMS TO BE INCREASING, PARTICULARLY IN DEVELOPED COUNTRIES.1-3 FOOD ALLERGY CAUSES SIGNIFICANT MORBIDITY, INCLUDING SEVERE AND EVEN LIFE-THREATENING ALLERGIC REACTIONS, AND IS A HUGE BURDEN FOR PATIENTS AND FAMILIES. GIVEN THESE FACTS, THERE HAS BEEN A GREAT DEAL OF INTEREST IN MEASURES THAT MIGHT HELP TO PREVENT THE DEVELOPMENT OF FOOD ALLERGY, ESPECIALLY IN HIGH-RISK CHILDREN.

HISTORICALLY, PREVENTION EFFORTS HAVE RELIED ON THE EARLY IDENTIFICATION OF HIGH-RISK INFANTS AND THE AVOIDANCE OF POTENTIAL ALLERGENS THROUGH THE FIRST 1 TO 2 YEARS OF LIFE. THE EXPECTATION IS THAT SENSITIZATION MAY BE REDUCED OR ELIMINATED THROUGH AVOIDANCE, ALTHOUGH AN EQUALLY APPEALING APPROACH WOULD BE TO DEVELOP STRATEGIES TO ENHANCE THE DEVELOPMENT OF IMMUNOLOGIC TOLERANCE TO MAJOR FOOD ALLERGENS. GIVEN THE DIFFICULTY IN IMPLEMENTING THESE AVOIDANCE DIETS, IT MAKES SENSE TO TARGET THOSE INFANTS DEEMED TO BE AT HIGHEST RISK.

However, it is also clear that children without obvious risk factors for atopic disease may develop food allergy,4 which suggests that a simpler strategy implemented in the general population would be preferred.

BACKGROUND

PREDICTING ATOPIC DISEASE IN CHILDREN

Several laboratory approaches for the identification of high-risk children have been studied, including cord blood IgE levels, cytokine levels, eosinophil counts, and specific genetic markers.6,7 However, none of these have proven to be sufficiently superior to the family history and as a result are not recommended for use in clinical practice. The family history, therefore, remains the most useful and practical method to identify the allergy-prone infant.8,9 Allergic disease in one parent increases the likelihood of allergy in a child, and allergic disease in both parents or in a parent and a sibling further increases those odds.
to between 40% and 70%. Despite the predictive value of parental history, it is not always available. Most infants at risk, with or without a family history of atopic disease, go unidentified.

**ORAL TOLERANCE**

While sensitization is the process by which one develops an immunologic hypersensitivity after allergen exposure, oral tolerance describes the induction of immunologic hyporesponsiveness after ingestion of a food antigen. Oral tolerance therefore permits exposure to foreign proteins, such as cow’s milk proteins, without developing hypersensitivity. In the normal situation, lower-molecular-weight proteins processed by the gut-associated lymphoid tissue induce oral tolerance without sensitization. The induction of oral tolerance depends on the form and dose of antigen exposure and the age at exposure. Although breast milk can contain food proteins that lead to allergic sensitization, these formulas pose an increased risk compared with breast milk. Partially hydrolyzed formulas (pHFs) have lower-molecular-weight proteins than cow’s milk formulas (CMFs) and were developed with this goal in mind. Research to support this theory is limited to animal data and preliminary human data. Experiments in rats, conducted by Fritsche, showed that feeding a pHF significantly suppressed β-lactoglobulin–specific IgE and IgG antibody production and mast cell response compared with extensively hydrolyzed formulas (eHFs). Among infants, Vaarala et al showed that CMFs resulted in sensitization and tolerance, whereas eHFs did not induce sensitization or tolerance; furthermore, sensitization depended on the infant’s age at exposure. These limited studies suggest that, while eHFs are an excellent alternative for children who are already sensitized to cow’s milk proteins, they may not induce tolerance to the same degree as pHFs.

**HYDROLYSATE FORMULAS IN ALLERGY PREVENTION**

Hydrosylate formulas have been traditionally used for the treatment of food allergies and intolerances and more recently for preventing atopic disease in high-risk infants. The extensively hydrolyzed casein formulas available in the United States include Nutramigen (Mead Johnson & Co, Evansville, Ind), Alimentum (Ross Products Division/Abbott Laboratories, Columbus, Ohio), and Pregestimil (Mead Johnson & Co). The only partially hydrolyzed whey formula available in the United States is Nestlé Good Start Supreme (Nestlé USA, Glendale, Calif). Cow’s milk proteins are subjected to chemical and enzymatic hydrolysis to reduce the molecular weight, the peptide size, and, consequently, the allergenicity of the proteins. The hydrolysate formulas are generally categorized into eHFs and pHFs based on the degree of hydrolysis and length of the remaining peptides.

**PROFESSIONAL GUIDELINES**

Guidelines summarizing the approach to allergy prevention in high-risk infants have been presented by the American Academy of Pediatrics (AAP) and the European Society for Paediatric Allergology and Clinical Immunology and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition. These recommendations are summarized in Table 1. This review focuses on what role hydrolysate formulas may play in allergy prevention and whether there is a difference between eHFs and pHFs in this role.

**SEARCH STRATEGY**

We identified studies that evaluated the role of hydrolysate formulas in allergy prevention through a MEDLINE search using allergy prevention and infant formulas as indexing terms. We re-

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**Table 1. Summary of Recommendations for Primary Prevention of Food Allergy by the American Academy of Pediatrics (AAP) and the European Society for Paediatric Allergology and Clinical Immunology and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPACI/ESPGHAN)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>AAP§</th>
<th>ESPACI/ESPGHAN§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition of high-risk infants</td>
<td>Family history in both parents or in a parent and sibling</td>
<td>Family history in a parent or sibling</td>
</tr>
<tr>
<td>Maternal pregnancy diet</td>
<td>Not recommended, with possible exception of peanut avoidance</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Exclusive breastfeeding</td>
<td>6 mo</td>
<td>4-6 mo</td>
</tr>
<tr>
<td>Maternal lactation diet</td>
<td>Eliminate peanuts and tree nuts (consider eliminating eggs, cow’s milk, and fish)</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Avoidance of soy formulas</td>
<td>Yes</td>
<td>Use a formula with confirmed reduced allergenicity</td>
</tr>
<tr>
<td>Hypoallergenic formula for bottle-fed high-risk infants</td>
<td>Use eHFs or possibly pHFs when not breastfeeding</td>
<td>Use eHFs or possibly pHFs</td>
</tr>
<tr>
<td>Hypoallergenic formula for supplementation</td>
<td>Use eHFs or possibly pHFs</td>
<td>Use a formula with confirmed reduced allergenicity</td>
</tr>
<tr>
<td>Delayed introduction of solid foods to infant</td>
<td>Delay all for at least 6 mo, cow’s milk for 12 mo, eggs for 24 mo, and peanuts, tree nuts, and fish for 36 mo</td>
<td>Start at fifth month of life</td>
</tr>
</tbody>
</table>

Abbreviations: eHFs, extensively hydrolyzed formulas; pHFs, partially hydrolyzed formulas.
restricted the search to English-language articles and human subjects. Additional studies were identified from cross-referencing.

**REVIEW CRITERIA**

We reviewed all published reports of prospective controlled trials evaluating hydrolysate formulas in allergy prevention that were published in peer-reviewed journals from 1985 to the present. We critically evaluated methods of randomization, blinding, duration of the dietary intervention, identification and verification of allergic symptoms, analysis of results, and support for conclusions made. We looked at the quality of the studies and the results obtained to determine whether each body of published research supports a role for hydrolysate formulas in allergy prevention.

**RESULTS**

### EXTENSIVELY HYDROLYZED FORMULAS

Extensively hydrolyzed formulas contain peptides with molecular weights less than 3000 Da. They meet the American Academy of Allergy and Immunology’s definition of hypoallergenicity. Extensively hydrolyzed formulas effectively relieve symptoms in more than 90% of patients with cow’s milk allergy (CMA), with only occasional reports of hypersensitivity reactions. The AAP’s and the European Society for Paediatric Allergology and Clinical Immunology and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition recommend eHFs for allergy prevention.

From 1985 to the present, 9 published reports on 8 patient cohorts prospectively evaluated eHF for allergy prevention in high-risk infants.11,18-25 Table 2 summarizes the details of the methods and results of some of these published reports. The reports compared eHFs with breastfeeding (BF), CMFs, soy formulas, pHFs, and combinations thereof. Eight of the 9 studies evaluated casein hydrolysate formulas, whereas 1 study20 assessed casein hydrolysate and whey hydrolysate formulas. For the purpose of this review, when we refer to eHFs, we are referring to extensively hydrolyzed casein formulas. Seven reports11,18,21,23,24 evaluated eHF as a supplement to BF, while 2 studies22,25 evaluated eHF as an exclusive diet in infants at high risk of atopy. In total, all of the trials reported a lower cumulative incidence of atopy, or a lower prevalence of atopy, among infants supplemented with eHFs compared with infants supplemented with CMFs, and these results were comparable to those of BF alone.

Variations in methods make it difficult to directly compare the results of these studies. All of these studies recruited infants at high risk of atopy, but the definition of high risk varied. The studies attempted to randomize and blind the formula assignments when or if BF was insufficient, but complete randomization was impossible because of ethical concerns about interfering with BF. The studies differed in the duration of the dietary intervention, with only 1 study25 meeting the AAP’s recommendation for exclusive formula feeding until 6 months of age. The studies also differed greatly in maternal and infant dietary restrictions, from no restrictions to specific allergen avoidance through 36 months of age. The studies differed significantly in the allergy symptoms recorded and the diagnostic measures that were used, ranging from an assessment of eczema alone22 to the use of skin prick tests, serum antigen-specific IgE levels, open food challenges, and double-blind placebo-controlled food challenges (DBPCFCs). Two studies22,25 prospectively compared eHFs with pHFs and BF in infants at high risk of atopy. These studies are discussed in more detail with the pHF studies in the next subsection titled “Partially Hydrolyzed Formulas.” Halken et al24 found a significantly lower incidence of CMA in infants receiving eHFs compared with those receiving pHFs, although the cumulative incidence of allergic symptoms was similar among groups.

A 2003 study20 prospectively compared eHFs with pHFs and CMFs among high-risk infants in Germany. The infants were randomized to receive eHFs, extensively hydrolyzed whey formulas, pHFs, or CMFs as a supplement to breast milk during the first 4 months of life. This was the only study that evaluated extensively hydrolyzed whey formulas. Among children 12 months of age, the authors reported significantly diminished atopic manifestations in the group fed eHFs compared with CMFs. The groups fed eHFs and pHFs had significantly less atopic dermatitis compared with CMFs, and results from the extensively hydrolyzed whey formula group were not different from those of the group fed CMFs. The differences found in this study suggest that factors such as the protein type and method of hydrolysis may play important roles in determining the protective effect. This study used well-defined definitions of atopy, including open food challenges and DBPCFCs; however, the study formulas were not fed exclusively for 6 months.

In summary, the data support a protective effect for eHFs, but the research falls short of meeting the AAP’s criteria for evidence of allergy prevention because the eHF were usually used as a supplement to BF and allergy symptoms were not sufficiently evaluated with DBPCFCs. Extensively hydrolyzed formulas are significantly more expensive and less palatable than standard CMFs, which makes compliance with exclusive feeding of eHFs difficult for many families.

### PARTIALLY HYDROLYZED FORMULAS

Partially hydrolyzed formulas were first developed in 1985 for use in infants with formula intolerance. The initial formula was a whey protein hydrolysate in which the peptides have molecular weights in the range of 3000 to 10,000 Da. The pHFs do not meet the AAP’s definition of hypoallergenicity because they have not been shown to relieve symptoms in most patients with established CMA and are not recommended for treatment of CMA. Recently, the AAP, the European Society for Paediatric Allergology and Clinical Immunology, and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition acknowledged a potential role for pHFs in the primary prevention of atopic disease. Like eHFs, pHFs have not met the AAP’s criteria for allergy prevention because of differences in allergy symptom scoring and a lack of studies with sufficient DBPCFCs. However, studies27,28 have been completed with pHFs as the exclusive diet for 6 months that demonstrated a significantly lower cumulative incidence of atopy over time com-
The table provides a detailed comparison of the methods and outcomes for various studies evaluating extensively hydrolyzed formulas (eHFs) for allergy prevention in infants at high atopic risk. Here is a brief summary of the key points:

- **Source**: The studies included are by Chandra et al., Zeiger et al., Mallet and Henocq, Halken et al., Oldaeus et al., and von Berg et al.
- **Population**: The number of infants varied from 158 to 221, with specific criteria for atopy or parental history.
- **Randomization**: Some studies used double-blind randomization, while others did not.
- **Blinding**: Blinding was used in some studies to prevent bias.
- **Formulas**: BFs, CMFs, and eHFs were compared in the studies.
- **Feeding Restrictions**: Various dietary interventions were used, including no solids until 12 mo, BF alone until 4 mo, and specific restrictions on diet or environment.
- **Symptoms**: Eczema, asthma, conjunctivitis, and other allergic symptoms were assessed.
- **Basis for Diagnosis**: DBPCFCs, SPT, blood IgE level, and other diagnostic methods were used.
- **Results and Conclusions**: The outcomes varied, with some studies showing a significant reduction in atopy and allergic symptoms with eHFs.

**Abbreviations**: BF, breastfeeding; BM, breast milk; CMF, cow’s milk formula; DBPCFCs, double-blind placebo-controlled food challenges; eHF, extensively hydrolyzed formula; eHF-W, extensively hydrolyzed whey formula; GI, gastrointestinal; pHF, partially hydrolyzed formula; SCORAD, Severity Scoring of Atopic Dermatitis; SPT, skin prick test.

From 1990 to the present, 12 published reports involving 10 separate study populations prospectively evaluated partially hydrolyzed whey formulas in allergy prevention, and 1 study evaluated partially hydrolyzed casein formula. Table 3 gives the details of the methods and results of these published reports. The reports compared partially hydrolyzed whey formulas with BF, CMFs, soy formulas, eHFs, and many combinations thereof. Thirteen reports evaluated pHFs in infants at high risk of atopy, 1 of which compared pHFs as part of a prevention program in an unscreened infant population.

Each of these trials reported a reduction in the cumulative incidence of atopy in infants fed pHFs (exclusively or as a supplement to BF) compared with infants fed CMFs, and these results were comparable to those of BF alone. Seven separate investigative groups prospectively evaluated pHFs compared with CMFs in infants at high risk of atopic disease. Only one study by Marini et al. attempted to randomize and often to double-blind formula assignment when or if BF was insufficient.

As with the studies of eHFs, variations in methods make it difficult to compare the results of the studies of pHFs. Variations include provision of an adequate sample size, differences in the definition of high risk, issues with randomization, duration of the dietary intervention (range, 3–6 months), maternal and infant dietary restrictions (ranging from no restrictions to allergen avoidance recommended through 24 months of age), environmental

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**Table 2**: Prospective Trials Evaluating Extensively Hydrolyzed Formulas (eHFs) for Allergy Prevention in Infants at High Atopic Risk

<table>
<thead>
<tr>
<th>Source</th>
<th>Population</th>
<th>Randomization</th>
<th>Blinding</th>
<th>Formulas</th>
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<th>Basis for Diagnosis</th>
<th>Results and Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chandra et al.</td>
<td>221 infants with single-parent history of atopy</td>
<td>Yes except BF</td>
<td>Double blind except BF</td>
<td>eHF vs CMF</td>
<td>Formula exclusively for 6 mo, no solid foods before 6 mo, BF mothers with restrictions avoided milk, eggs, fish, peanuts, and shellfish for 6 mo or duration of BF</td>
<td>Eczema</td>
<td>Eczema score</td>
<td>↓ Eczema with eHF vs soy or CMF at 18 mo</td>
</tr>
<tr>
<td>Zeiger et al.</td>
<td>288 infants with at least 1 parent with history of atopy</td>
<td>Yes</td>
<td>BF and eHF vs BF and CMF</td>
<td>Formula for 6 mo, no maternal diet restrictions, and unrestricted diet after 4 mo; the group fed eHF had maternal restrictions during lactation, solid foods delayed until 6 mo, major allergens restricted up to 36 mo (environmental restrictions also); the group fed CMF had no maternal or infant restrictions on diet or environment, except no solid foods until 4 mo</td>
<td>Atopic dermatitis, urticaria, Gi disease, asthma, and allergic rhinitis</td>
<td>Examination and IgE level</td>
<td>↓ Atopy with eHF vs CMF at 12 mo; total SPT and SPT to milk ↓ in the group fed pHF at 24 mo; at 7 y, no differences remained</td>
<td></td>
</tr>
<tr>
<td>Mallet and Henocq</td>
<td>177 infants with allergy history in first-degree relative</td>
<td>Yes</td>
<td>BF and eHF vs CMF and BF</td>
<td>Formula and BF through 4 mo, no maternal diet restrictions, and unrestricted diet after 4 mo</td>
<td>Asthma, recurrent wheezing, atopic dermatitis, urticaria, food allergy, colic, and Gi symptoms</td>
<td>Examination and IgE level</td>
<td>↓ Point prevalence of atopy was ↓ with eHF vs CMF at 24 mo</td>
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<tr>
<td>Halken et al.</td>
<td>158 infants with biparental history of atopy or single-parent history and high cord blood IgE level</td>
<td>Yes</td>
<td>BF and eHF, unfiltered formula, and BF vs BF alone</td>
<td>BF or formula for 6 mo, restricted solid foods and cow's milk proteins until 6 mo, and no maternal restrictions</td>
<td>Asthma, allergic rhinitis, obvious cow's milk allergy</td>
<td>Examination and IgE level</td>
<td>↓ No difference in cumulative incidence of cow's milk allergy among the 3 groups at 18 mo</td>
<td></td>
</tr>
<tr>
<td>Oldaeus et al.</td>
<td>155 infants with biparental history of atopy or single-parent history and high cord blood IgE level</td>
<td>Yes at weaning except BF</td>
<td>Yes</td>
<td>BF and eHF, BF and pHF, BF, and CMF vs BF alone</td>
<td>Maternal restrictions of cow's milk and eggs; no solid foods until 4 mo; cow's milk after 9 mo; and eggs, citrus, and fish after 12 mo</td>
<td>Asthma, atopic dermatitis, Gi symptoms, rhinitis, and conjunctivitis</td>
<td>Clinical, results of SPT, IgE level, open food challenges, and DBPCFCs</td>
<td>↓ Asthma in the groups fed pHF and eHF vs CMF at 24 mo; atopic disease was 51% with eHF, 64% with pHF, 84% with CMF, and 67% with BF</td>
</tr>
<tr>
<td>von Berg et al.</td>
<td>2252 infants with first-degree relative with atopy</td>
<td>Yes</td>
<td>Double blind except BF</td>
<td>BF and eHF, BF and pHF-W, BF, and CMF vs BF and CMF</td>
<td>No maternal restrictions, no solid foods until 4 mo, and BF and formula exclusively for 4 mo</td>
<td>Atopic dermatitis, urticaria, and Gi symptoms</td>
<td>Clinical, SCORAD results of SPT, open food challenges, and DBPCFCs</td>
<td>↓ Asthma in the groups fed eHF and pHF vs CMF at 12 mo</td>
</tr>
</tbody>
</table>

Abbreviations: BF, breastfeeding; BM, breast milk; CMF, cow’s milk formula; DBPCFCs, double-blind placebo-controlled food challenges; eHF, extensively hydrolyzed formula; eHF-W, extensively hydrolyzed whey formula; Gi, gastrointestinal; pHF, partially hydrolyzed formula; SCORAD, Severity Scoring of Atopic Dermatitis; SPT, skin prick test.
Table 3. Prospective Trials Evaluating Partially Hydrolyzed Formulas (pHF) for Allergy Prevention in Infants at High Atopic Risk

<table>
<thead>
<tr>
<th>Source</th>
<th>Population</th>
<th>Randomization</th>
<th>Blinding</th>
<th>Formulas</th>
<th>Feeding Restrictions</th>
<th>Symptoms</th>
<th>Basis for Diagnosis</th>
<th>Results and Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marini et al, 1990</td>
<td>116 Infants, both parents with IgE disease</td>
<td>Odd/even</td>
<td>No</td>
<td>BF vs pHF</td>
<td>Mothers avoided eggs and decreased cow’s milk proteins, infants had no history of atopy</td>
<td>Dermatitis, urticaria, wheezing, laryngeal edema, rhinitis, conjunctivitis, angioedema, and GI symptoms</td>
<td>Examination and IgE level</td>
<td>No significant difference with pHF vs BF</td>
</tr>
<tr>
<td>Chandra and Hamed, 1991, and Chandra, 1997</td>
<td>216 Infants with first-degree relative with atopy</td>
<td>Yes</td>
<td>Double blind</td>
<td>CMF vs soy vs pHF vs BF</td>
<td>Mother’s diet unrestricted, formula fed exclusively for 6 mo and hypoallergenic weaning diet after 6 mo</td>
<td>Eczema, wheezing, rhinitis, GI symptoms, and colic</td>
<td>Examination, results of SPT, IgE level, and DBPCFCs</td>
<td>↓ Atopic symptoms with BF and pHF vs soy and CMF at 12, 18, and 60 mo</td>
</tr>
<tr>
<td>Vandenplas et al, 1992, and Vandenplas et al, 1995</td>
<td>58 Infants with 2 first-degree relatives with atopy</td>
<td>Yes</td>
<td>Double blind</td>
<td>pHF vs CMF</td>
<td>Exclusively formula fed to 4 mo, then added grated apple, normal diet after 6 mo</td>
<td>Vomiting, diarrhea, colic, eczema, wheezing, rhinitis</td>
<td>Examination, results of RAST and SPT, and open food challenges</td>
<td>Cow’s milk protein sensitivity ↓ with pHF vs CMF at 6 and 12 mo; ↓ atop in 6 mo; ↓ atop in atopic groups less than 6 mo</td>
</tr>
<tr>
<td>Willems et al, 1993</td>
<td>122 Infants with high blood cord IgE level or family history of atopy</td>
<td>No</td>
<td>Single blind</td>
<td>pHF vs CMF</td>
<td>Exclusively formula fed for 3 mo</td>
<td>Eczema, asthma, bronchitis, rhinitis, GI symptoms, and sleeping difficulties</td>
<td>Examination</td>
<td>Only 67 infants followed protocol, ↓ atop in PHF vs CMF at 3 and 12 mo</td>
</tr>
<tr>
<td>Marini et al, 1996</td>
<td>359 Infants with biparental atopy</td>
<td>Yes</td>
<td>Double blind</td>
<td>BF vs pHF vs CMF vs BF and pHF vs BF and CMF; intervention vs nonintervention</td>
<td>BM or formula fed exclusively for 5–6 mo, mother’s diet restricted (low cow’s milk proteins)</td>
<td>Dermatitis, wheezing, urticaria, GI symptoms, and rhinitis</td>
<td>Examination, open food challenges, and results of RAST and SPT</td>
<td>↓ Atopy with BF and pHF vs CMF at 1 and 2 y; all intervention groups less than nonintervention groups</td>
</tr>
<tr>
<td>Oldaeus et al, 1997</td>
<td>155 Infants with biparental atopy or single-parent history and high blood cord IgE level</td>
<td>Yes at weaning except BF</td>
<td>Yes</td>
<td>BF and eHF, BF and whey-hydrolyzed pHF, BF and CMF vs BF alone</td>
<td>Maternal restrictions of cow’s milk and eggs, no solid foods until 4 mo; cow’s milk after 4 mo, and eggs, citrus, and fish after 12 mo</td>
<td>Asthma, atopic dermatitis, GI symptoms, rhinitis, and conjunctivitis</td>
<td>Clinical results of SPT, IgE level, open food challenges, and DBPCFCs</td>
<td>↓ Atopy with eHF and eHF vs CMF at 18 mo; atopic disease was 51% with eHF, 64% with PHF, 84% with CMF, and 67% with BF</td>
</tr>
<tr>
<td>Porch et al, 1998</td>
<td>130 Infants with high blood cord IgE level and parental history of atopy</td>
<td>Yes</td>
<td>Double blind</td>
<td>eHF vs pHF vs soy vs BF</td>
<td>Exclusively formula or BM fed for 4 mo; excluded eggs, milk, peanuts, and shellfish until 12 mo</td>
<td>Vomiting, diarrhea, atopic dermatitis</td>
<td>Examination, parental reports, and open food challenges</td>
<td>Allergy symptoms and challenges the same among groups at 2, 4, 6, and 12 mo</td>
</tr>
<tr>
<td>Exl et al, 1998</td>
<td>1098 Infants recruited from all births</td>
<td>No</td>
<td>No</td>
<td>BF and pHF vs BF vs CMF</td>
<td>GI symptoms, upper respiratory tract infection and otitis media; wheezing; chronic cough; asthma; and eczema</td>
<td>Examination</td>
<td>Cumulative symptoms at 6 mo 28% with pHF vs 57% with CMF (odds ratio, 0.3); 34% with BF and pHF vs 46% with BF and CMF (odds ratio, 0.6)</td>
<td></td>
</tr>
</tbody>
</table>

(continued)

recommendations for allergy prevention (such as no smoking, pets, or day care), symptoms that were recorded, and diagnostic methods. The outcomes are also difficult to compare because some authors reported the cumulative incidence of atopic disease, while others reported the point prevalence or number of atopic patients. Information regarding individual symptoms such as eczema, asthma, and CMA were presented inconsistently across studies. Despite these differences, however, the overall data demonstrate a reduction in the cumulative incidence of atopic disease in infants fed partially hydrolyzed whey formulas vs CMFs. Two recent studies prospectively compared pHFs with eHFs and BF. In these studies, the hydrolysate formulas were not compared with CMFs because the authors considered it unethical to feed CMFs to infants at high risk of atopy. Although Halken et al reported a statistically significant difference in CMA incidence be-
META-ANALYSES OF HYDROLYSATE FORMULAS IN ALLERGY PREVENTION

Two meta-analyses evaluating pHF in allergy prevention were published in the literature. In 1998, Baumgartner et al reported odds ratios for developing atopic disease that were significantly less than 1 when comparing pHFs with CMFs. More recently, Osborn and Sinn concluded that “there is some evidence that prolonged supplementation with hydrolyzed formula as opposed to cow’s milk formula reduces the risk of allergy” and suggested that there was “insufficient evidence” that eHFs have any advantage over pHFs.

Prospective controlled trials examining eHFs and partially hydrolyzed whey formulas for allergy prevention among high-risk infants demonstrate significant reductions in the cumulative incidence of atopic disease through the first 1 to 5 years of life compared with feeding CMF. However, based on the studies reported to date, neither eHFs nor pHFs meet the AAP’s criteria for evidence of allergy prevention because in studies that exclusively fed partially hydrolyzed whey formulas for 6 months, the allergy symptoms were not sufficiently evaluated with DBPCFCs. Notably, partially hydrolyzed whey formulas are comparable in price and palatability to CMFs and are available as starter formulas in the United States.

### Table 3. Prospective Trials Evaluating Partially Hydrolyzed Formulas (pHF) for Allergy Prevention in Infants at High Atopic Risk (cont)

<table>
<thead>
<tr>
<th>Source</th>
<th>Population</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Halken et al.24</td>
<td>478 Infants with biparental atopy or single-parent history and high blood cord IgE level</td>
<td>Date of birth</td>
<td>Double blind</td>
<td>eHF vs pHF vs BF</td>
<td>BM with or without formula for 4 mo, unrestricted thereafter</td>
<td>Wheezing, rhinitis, conjunctivitis, dermatitis, and urticaria</td>
<td>Examination, parental reports, and open food challenges</td>
<td>Atopy the same among groups through 18 mo, cow’s milk allergy significantly different (1.3% with BF, 0.6% with eHF, and 4.7% with pHF)</td>
</tr>
<tr>
<td>Chan et al.25</td>
<td>153 Infants with first-degree relative with atopy</td>
<td>Yes</td>
<td>Single blind</td>
<td>pHF vs CMF</td>
<td>Formula fed exclusively for 4 mo, unrestricted wearing diet followed until 30 mo</td>
<td>Eczema, wheezing, and urticaria</td>
<td>Examination and IgE level</td>
<td>Eczema with pHF vs CMF at 3, 6, 12, and 24 mo, not significant at 30 mo; wheezing was less but not significant; no difference in serum IgE levels between groups</td>
</tr>
<tr>
<td>von Berg et al.26</td>
<td>2252 Infants with first-degree relative with atopy</td>
<td>Yes</td>
<td>Double blind except BF</td>
<td>BF and eHF, BF and eHF-W, BF and pHF vs BF and CMF</td>
<td>No maternal restrictions, no solid foods until 4 mo, BF and formula exclusively for 4 mo</td>
<td>Atopic dermatitis, urticaria, gastrointestinal symptoms</td>
<td>Clinical, SCORAD, results of SPT, open food challenges, and DBPCFCs</td>
<td>Atopy with eHF, atopic dermatitis with eHF and pHF vs CMF at 12 mo</td>
</tr>
</tbody>
</table>

Abbreviations: BF, breastfeeding; BM, breast milk; CMF, cow’s milk formula; DBPCFCs, double-blind placebo-controlled food challenges; eHF, extensively hydrolyzed formula; eHF-W, extensively hydrolyzed whey formula; GI, gastrointestinal; pHF, partially hydrolyzed formula; RAST, radioallergosorbent test; SCORAD, Severity Scoring of Atopic Dermatitis; SPT, skin prick test.
actions, including DBPCFCs. Despite these limitations, the AAP, the European Society for Paediatric Allergology and Clinical Immunology, and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition recommend feeding eHFs to infants at high risk of atopic disease when BF is insufficient. Furthermore, these groups acknowledge that pHFs have a potential role in allergy prevention. Most of the studies addressed allergy prevention only in high-risk populations. However, in general practice, most infants manifesting atopic symptoms may not have been identified as high risk, whether or not they had a positive family history for the disease. It could be beneficial to broaden the use of eHFs or partially hydrolyzed whey formulas for allergy prevention in the general population, weighing potential benefits against the issues of cost, compliance, and palatability. In that regard, although the studies in the literature do not provide overwhelming evidence, they suggest that partially hydrolyzed whey formulas may serve as a reasonable first defense against allergic disease in the general population. Partially hydrolyzed whey formulas are comparable in nutrition, price, and palatability to traditional CMFs and are available as starter formulas for newborns.

Because most studies were conducted in high-risk infants, to determine the potential allergy prevention role in the general population, we need additional prospective randomized controlled trials comparing pHFs, eHFs, and CMFs using clinical scoring systems and DBPCFCs to define atopic disease in the general infant population. In addition, it seems as if different hydrolysate formulas have different potentials for allergy prevention, which appear to depend on factors beyond the degree of protein hydrolysis. Therefore, to demonstrate benefits, specific hydrolysate formulas need to be individually evaluated in clinical trials.

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REFERENCES