

## Hypoallergenic Infant Formulas

**ABSTRACT.** The American Academy of Pediatrics is committed to breastfeeding as the ideal source of nutrition for infants. For those infants who are formula-fed, either as a supplement to breastfeeding or exclusively during their infancy, it is common practice for pediatricians to change the formula when symptoms of intolerance occur. Decisions about when the formula should be changed and which formula should be used vary significantly, however, among pediatric practitioners. This statement clarifies some of these issues as they relate to protein hypersensitivity (protein allergy), one of the causes of adverse reactions to feeding during infancy.

ABBREVIATION. IgE, immunoglobulin E.

Symptoms of food protein allergy include those commonly associated with immunoglobulin E (IgE)-associated reactions, such as angioedema, urticaria, wheezing, rhinitis, vomiting, eczema, and anaphylaxis.<sup>1</sup> Non-IgE-associated, immunologically mediated conditions have also been associated with the ingestion of cow's milk, soy, and other dietary proteins in infant feedings. These disorders include pulmonary hemosiderosis,<sup>2</sup> malabsorption with villous atrophy,<sup>3</sup> eosinophilic proctocolitis,<sup>4</sup> enterocolitis,<sup>5</sup> and esophagitis.<sup>6</sup> Finally, some infants may experience extreme irritability or colic as the only symptom of food protein allergy.<sup>7</sup> The prevalence in infancy of milk protein allergy is low—2% to 3%.<sup>8–10</sup> Thus, the use of hypoallergenic-labeled infant formulas, which cost as much as 3 times more than standard formulas, should be limited to infants with well-defined clinical indications. Adverse reactions to cow's milk associated with other conditions such as phenylketonuria and lactose intolerance may also be alleviated by the use of alternative formulas, although not necessarily those intended to treat infants with protein allergy.

## FORMULA DEVELOPMENT AND LABELING

Before new potential hypoallergenic formulas are tested in trials using human infants, comprehensive preclinical testing must be conducted to examine for toxicity and suitability to maintain a positive nitrogen balance and to attempt to predict whether infants allergic to cow's milk will react adversely to them. This testing should include efforts to determine the molecular weight profile of residual pep-

tides, the amount of immunologically recognizable material present, and the ability of the product to sensitize or provoke reactions in animal models of allergenicity.<sup>11–14</sup>

To establish the risk of hypersensitivity in infants, carefully conducted preclinical studies must be performed that demonstrate a formula may be hypoallergenic. The formula needs to be tested in infants with hypersensitivity to cow's milk or cow's milk-based formula and the findings verified by properly conducted elimination-challenge tests.<sup>15</sup> These tests should, at a minimum, ensure with 95% confidence that 90% of infants with documented cow's milk allergy will not react with defined symptoms to the formula under double-blind, placebo-controlled conditions.<sup>16</sup> Such formulas can be labeled hypoallergenic. If the formula being tested is not derived from cow's milk proteins, the formula must also be evaluated in infants or children with documented allergy to the protein from which the formula was derived. It is also recommended that after a successful double-blind challenge, the clinical testing should include an open challenge using an objective scoring system to document allergic symptoms during a period of 7 days.<sup>16</sup> This is particularly important to detect late-onset reactions to the formula.<sup>17</sup>

Any formula with residual peptides may provoke reactions in infants allergic to cow's milk.<sup>17,18</sup> Extensively hydrolyzed proteins derived from cow's milk, in which most of the nitrogen is in the form of free amino acids and peptides <1500 kDa, have been used in formulas for >50 years for infants with severe inflammatory bowel diseases or cow's milk allergy. These formulas, as well as the newer free amino acid-based formulas, have been subjected to extensive clinical testing and meet the standard for hypoallergenicity.<sup>19–21</sup>

Hypoallergenic formulas are intended for use by infants with existing allergic symptoms. Recently formulas have also been promoted to prevent the development of allergy in infants at high risk for developing allergic symptoms. The ability to determine which infants are at high risk is imperfect, although many markers, including elevated levels of cord blood IgE and serum IgE in infancy and an atopic family history, have been identified.<sup>22</sup> Because a family history of allergy is at least as sensitive and specific as any other marker,<sup>23</sup> infants from families with a history of allergy should serve as the study participants in clinical testing of formulas that claim the ability to prevent allergy from developing. These infants should be fed the formula exclusively from birth for at least 6 months under the conditions of a

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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controlled, randomized study and observed for at least 12 additional months. Allergic symptoms during the period of observation should be documented with a validated clinical scoring system and allergic symptoms verified by double-blind, placebo-controlled testing. When compared with infants fed a standard cow's milk formula, infants fed formulas that claim to prevent or delay allergy should have a statistically significant lower prevalence of allergy at the end of the observation period.<sup>16</sup>

#### CLINICAL PRACTICE TREATMENT

Breast milk is the optimal sole source of nutrition for healthy infants for the first 6 months of life. Breastfeeding should be continued for the first 12 months of life or longer. Although the incidence of food allergy is very low in breastfed infants compared with formula-fed infants, rare cases of anaphylaxis to cow's milk proteins have been reported in those breastfed as well as more frequent cases of cow's milk-induced proctocolitis.<sup>24–26</sup> The pathophysiology of these reactions in the breastfed infant is not well-understood. However, immunologically recognizable proteins from the maternal diet can be found in breast milk.<sup>27,28</sup>

Elimination of cow's milk, eggs, fish, peanuts and tree nuts, and other foods from the maternal diet may lead to resolution of allergic symptoms in the nursing infant. For those infants whose symptoms do not improve or whose mothers are unable to participate in a very restricted diet regimen and for formula-fed infants with cow's milk allergy, alternative formulas can be used to relieve the symptoms.

In infants allergic to cow's milk, milk from goats and other animals<sup>29</sup> or formulas containing large amounts of intact animal protein are inappropriate substitutes for breast milk or cow's milk-based infant formulas. Soy formulas have a long history as alternative formulas in infants who are allergic. Eight to 14% of infants with symptoms of IgE-associated cow's milk allergy will also react adversely to soy,<sup>30</sup> but reports of anaphylaxis to soy are extremely rare. Those infants allergic to cow's milk and who do not have an adverse reaction at the start of feeding on a soy formula tolerate it very well.<sup>31</sup> Thus, although soy formulas are not hypoallergenic, they can be fed to infants with IgE-associated symptoms of milk allergy, particularly after the age of 6 months.<sup>29</sup> There is a significantly higher prevalence of concomitant reactions between cow's milk and soy proteins (25%–60%) among those infants with proctocolitis and enterocolitis<sup>32</sup> and therefore soy is not recommended for the treatment of infants with these non-IgE-associated syndromes.<sup>31</sup>

Formulas based on partially hydrolyzed cow's milk proteins (1000–100 000 times higher concentrations of intact cow's milk proteins compared with extensively hydrolyzed protein) have provoked significant reactions in a high percentage of infants allergic to cow's milk<sup>33,34</sup> and are not intended to be used to treat cow's milk allergy. Extensively hydrolyzed formulas have also provoked allergic reactions in infants allergic to cow's milk,<sup>17,18</sup> but at least 90% of these infants tolerate extensively hydrolyzed for-

mulas as well as the more recently introduced free amino acid-based infant formulas. Although the majority of infants with colic will not respond to a hypoallergenic formula, those with severe colic may benefit from a 1- to 2-week trial of a hypoallergenic formula.<sup>7</sup>

#### PROPHYLAXIS

Recent studies, one a randomized and prospectively controlled study of preterm infants followed up for 18 months<sup>35</sup> and a second prospective non-randomized and uncontrolled study of full-term infants followed up for 17 years,<sup>36</sup> have demonstrated that breastfeeding exclusively for at least 6 months reduces the risk of later respiratory allergic symptoms and eczema. Although many of the studies that have examined the ability of breastfeeding to delay or prevent allergic disease have significant methodologic shortcomings,<sup>22,37</sup> the total of these studies suggests that breastfeeding exclusively has a protective effect, at least in high-risk infants and particularly if it is combined with maternal avoidance of cow's milk, egg, fish, peanuts and tree nuts during lactation.

More definitive prospective studies of the use of alternative formulas for allergy prophylaxis in high-risk infants are needed. However, the prospective studies available that utilized blinded food challenges to confirm allergic symptoms suggest that asymptomatic formula-fed infants at high risk for allergy given alternatives to cow's milk formulas may have a lower future risk of allergic disease or delayed onset of allergic symptoms. In one recently reported study, infants at high risk for allergy fed an extensively hydrolyzed formula or breastfed infants whose mothers avoided cow's milk, egg, and peanuts and did not introduce these foods into their infants' diets had a reduced prevalence of all allergic disorders at 1 year compared with the control group fed a standard cow's milk formula.<sup>38</sup> However, at 7 years of age there were no differences in allergic respiratory symptoms between the 2 groups.

A recent meta-analysis of all prospective controlled trials of a partially hydrolyzed formula showed a significant prophylactic effect of the partially hydrolyzed formula on the development of atopic symptoms at 60 months of age.<sup>39</sup> The studies analyzed did not all include confirmation of allergic symptoms by blinded challenge. In the only prospective study of allergy prophylaxis in high-risk infants that compared a partially and extensively hydrolyzed formula, only the extensively hydrolyzed formula prevented the development of allergy during the first 18 months of life in high-risk infants.<sup>40</sup> The other comparison groups in this study were fed a cow's milk-based formula or were breastfed exclusively for more than 9 months. Solid feedings were delayed until 4 months of age, and eggs, cow's milk, and fish were eliminated from the mothers' diets and their introduction delayed in their infants' diets until after the first year of life. Randomized prospective studies of soy protein-based formulas have not shown a preventive effect of these formulas on the development of allergy in high-risk infants.<sup>41,42</sup> No

published studies have examined the effectiveness of free amino acid-based formulas on allergy prevention in high-risk infants.

### CONCLUSION

Hypoallergenic formulas, like all formulas intended for infant feeding, must demonstrate nutritional suitability to support infant growth and development. To be labeled hypoallergenic, these formulas, after appropriate preclinical testing, must demonstrate in clinical studies that they do not provoke reactions in 90% of infants or children with confirmed cow's milk allergy with 95% confidence when given in prospective randomized, double-blind, placebo-controlled trials.

Extensively hydrolyzed and free amino acid-based formulas have been subjected to such studies and are hypoallergenic. Currently available, partially hydrolyzed formulas are not hypoallergenic. Carefully conducted randomized controlled studies in infants from families with a history of allergy must be performed to support a formula claim for allergy prevention. Allergic responses must be established prospectively, evaluated with validated scoring systems, and confirmed by double-blind, placebo-controlled challenge. These studies should continue for at least 18 months and preferably for 60 to 72 months or longer where possible.

### RECOMMENDATIONS

1. Breast milk is an optimal source of nutrition for infants through the first year of life or longer. Those breastfeeding infants who develop symptoms of food allergy may benefit from:
  - a) maternal restriction of cow's milk, egg, fish, peanuts and tree nuts and if this is unsuccessful,
  - b) use of a hypoallergenic (extensively hydrolyzed or if allergic symptoms persist, a free amino acid-based formula) as an alternative to breastfeeding. Those infants with IgE-associated symptoms of allergy may benefit from a soy formula, either as the initial treatment or instituted after 6 months of age after the use of a hypoallergenic formula. The prevalence of concomitant is not as great between soy and cow's milk in these infants compared with those with non-IgE-associated syndromes such as enterocolitis, proctocolitis, malabsorption syndrome, or esophagitis. Benefits should be seen within 2 to 4 weeks and the formula continued until the infant is 1 year of age or older.
2. Formula-fed infants with confirmed cow's milk allergy may benefit from the use of a hypoallergenic or soy formula as described for the breastfed infant.
3. Infants at high risk for developing allergy, identified by a strong (biparental; parent, and sibling) family history of allergy may benefit from exclusive breastfeeding or a hypoallergenic formula or possibly a partial hydrolysate formula. Conclusive studies are not yet available to permit defin-

itive recommendations. However, the following recommendations seem reasonable at this time:

- a) Breastfeeding mothers should continue breastfeeding for the first year of life or longer. During this time, for infants at risk, hypoallergenic formulas can be used to supplement breastfeeding. Mothers should eliminate peanuts and tree nuts (eg, almonds, walnuts, etc) and consider eliminating eggs, cow's milk, fish, and perhaps other foods from their diets while nursing. Solid foods should not be introduced into the diet of high-risk infants until 6 months of age, with dairy products delayed until 1 year, eggs until 2 years, and peanuts, nuts, and fish until 3 years of age.
  - b) No maternal dietary restrictions during pregnancy are necessary with the possible exception of excluding peanuts;
4. Breastfeeding mothers on a restricted diet should consider the use of supplemental minerals (calcium) and vitamins.

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