# Dietary prevention of allergy, atopy, and allergic diseases

***Key words:*** *Allergy, allergic diseases, atopy, IgE, cow's milk allergy, cow's milk formula, hydrolyzed formula, atopic eczema dermatitis syndrome, atopic eczema, nomenclature*

Avoidance has been one of the cornerstones of the treatment of allergic diseases. However, it is often difficult to avoid allergens completely. Early allergic symptoms, such as food allergy and "atopic dermatitis" (AD), are often the first manifestation of the so-called "atopic march"[1]—ie, the lifelong appearance of new allergies and allergic diseases caused by allergens to which the individual is exposed. Therefore, pediatricians in particular have focused on the prevention of allergic diseases in infancy.

In this issue of the Journal, the latest report on prevention of allergy by feeding non–breast-fed infants hydrolyzed cow's milk formula (HF) is published.[2] It is a major study on the question of whether or not eHF (extensively hydrolyzed cow's milk protein [CMP] formula—ie, CMP formula with much reduced allergenicity) and/or pHF (partially hydrolyzed CMP formula—ie, CMP formula with different degrees of allergenicity), as a supplement to breast-feeding, would prevent the development of allergy, atopy, or allergic diseases in infancy.

The authors conclude that "prevention of allergic diseases in the first year of life is feasible by dietary intervention but influenced by family history of AD"; accordingly, "[t]he preventive effect of each HF needs to be clinically evaluated."[2] What they showed, in fact, was that at least 1 eHF prevented the development of *atopic eczema/dermatitis syndrome* (AEDS)—this being the proposed name for AD. The second statement is not quite true, inasmuch as the preventive effect was at the limit of significance (as shown in the article's Table IV) and too many tests for significance were performed.

There are several points to be discussed in this editorial regarding the study by von Berg et al[2]: its design, its nomenclature, and its methods. The design, because I think the primary goal of a trial investigating the preventive effect of CMP avoidance would be to properly investigate the prevention of cow's milk allergy (CMA); the nomenclature, because the terms *atopic* and *atopic disease* were used inconsistently; and the methods, because I find some of them less relevant. I will also discuss the statistics presented.

*Abbreviations used*

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| AD: | Atopic dermatitis |
| AEDS: | Atopic eczema/dermatitis syndrome |
| CMA: | Cow's milk allergy |
| CMPF: | Cow's milk protein formula |
| CMP: | Cow's milk protein |
| DBPCFC: | Double-blind, placebo-controlled food challenge |
| HF: | Hydrolyzed cow's milk formula |
| eHF: | Extensively hydrolyzed CMPF |
| pHF: | Partially hydrolyzed CMPF |

Coca and Cooke[3] defined atopy as hypersensitivity with some common features: it is (a) hereditary, (b) limited to a small group of human beings, (c) different from "anaphylaxis" (Coca and Cooke used the term *allergy* to mean an altered reactivity), (d) "qualitatively an abnormal response" occurring only in particular (atopic) individuals, (e) clinically characterized by hay fever and bronchial asthma, and (f) associated with immediate-type (flare-and-wheal) skin reactions.[4] Thus, in their original definition of atopy, Coca and Cooke[3] included only allergic rhinitis and bronchial asthma. Later, Wise and Sulzberger[5] proposed the term *atopic dermatitis*. Furthermore, Coca and Cooke[3] were obviously unaware of the description by Prausnitz and Küstner[6] of the passive transfer of immediate hypersensitivity by serum in human beings. They did not know about the new class of antibodies—the IgE antibodies.[7] IgE-mediated allergic reactions to inhalant allergens were referred to by Pepys[8] as "atopic allergy." Today, the term *atopic* is often used synonymously with type 1 allergy,[9] or IgE-mediated allergy. However, pediatricians in particular use the terms *atopy* and *atopic* to describe individuals who have or tend to develop so-called "atopic diseases." Pediatricians have found the term *atopy* to be clinically useful. Often, "atopic disease" in the parents is used as an inclusion criterion in prospective epidemiologic trials—eg, that of von Berg et al,[2] which is reported in this issue. However, so-called "atopic diseases" are not always "atopic," as will be discussed.

Allergic symptoms include asthma, rhinoconjunctivitis, gastrointestinal immunologic diseases, and characteristic skin lesions, which are referred to as "atopic diseases." An "atopic" individual will develop a spectrum of "atopic diseases" during his or her lifetime, this being sometimes referred to as the "atopic march."[1] During infancy, gastrointestinal and eczematous skin symptoms dominate. Often, such symptoms are caused by food allergy. The first food allergy in westernized countries, CMA, often presents during the first months of life.[10] Actually, one third of infants developing CMA already show symptoms during lactation,[10] the allergy probably

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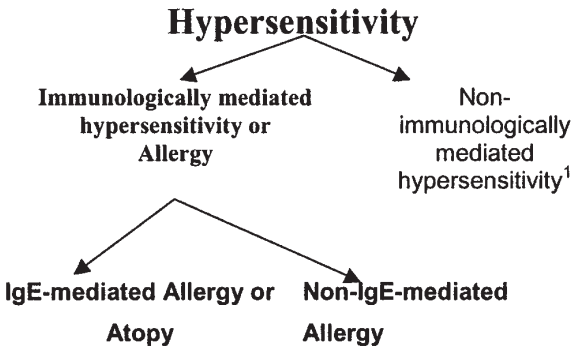


**FIG 1.** The nomenclature of hypersensitivity, allergy, and IgE-mediated (atopic) and non–IgE-mediated allergy, according to the nomenclature proposed by EAACI.[4]

being induced by CMP transferred via breast milk.[11] However, in a study by Host et al,[10] 9 of 9 infants who were solely breast-fed and developing CMA had been given CMF in the nursery. Thus, sensitization was probably due to early CMP intake.[10] After weaning, infants are dependent on CMF for their nutrition in westernized countries. To avoid CMP, eHF has for 60 years been given to infants with CMA. These HFs have also been tried for prophylaxis of CMA. The hypothesis has been that through avoidance of CMP, the first step in the "atopic march" would be avoided and the risk for future allergies—at least food allergies—would be reduced. In prospective trials with HF, there has been no influence on the development of allergic asthma,[12] and there still exists controversy regarding the effect of pHF supplementation on the development of CMA, other food allergies, and so-called "atopic," or (better) allergic, diseases.[11,13]

For the last 10 years it has been discussed whether eHF, which (to adults) has an unpleasant smell and taste, or pHF, which smells and tastes better and is therefore better tolerated by older children who have not previously received any supplementation, should be used for prevention by elimination. It has been claimed that pHF might induce tolerance because of the presence of some allergenic activity.[13] Recent data indicate a greater effect with eHF than with pHF in two[14,15] of 3 studies[14-16] with well-defined diagnostic criteria.[14]

The article by von Berg et al[2] stimulates some additional comments.

First, I would like to discuss the nomenclature of allergy/allergic diseases and atopy/"atopic diseases." As noted above, there has been some confusion regarding the use of the word *atopy*. Dermatologists have talked about "atopic dermatitis," and some have divided it into "atopic atopic dermatitis" and "non–atopic atopic dermatitis," in reference to individuals with IgE and individuals without IgE, respectively. This has been confusing. Furthermore, pediatricians in particular have talked about "atopy" in 2 different senses, some—eg, Pepys[8]—referring to individuals producing allergen-specific IgE antibodies and others—eg, Coca and Cooke[3]—referring to individuals with certain hereditary disease manifestations. Most confusing has been the matter of defining high-risk infants in trials such as that of von Berg et al.[2] In their report, as in many similar papers, retrospective data on heredity only—not on atopy but on allergic diseases—are used for the characterization of parents; other investigators have used either cord blood IgE[14] or skin testing/in vitro IgE antibody tests for the characterization of parents of children included in trials of this kind.

The European Academy of Allergology and Clinical Immunology recently proposed a new nomenclature for allergy and allergic diseases.[4] It includes the following important definitions:

- *Hypersensitivity* causes objectively reproducible symptoms or signs that are initiated by exposure to a defined stimulus at a dose tolerated by normal subjects; included are both immunologically mediated hypersensitivity and non–immunologically mediated hypersensitivity, as illustrated in Fig 1.
- *Atopy* is a personal or familial tendency to produce IgE antibodies in response to low doses of allergens (usually proteins) and to develop typical symptoms, such as asthma, rhinoconjunctivitis, or eczema/dermatitis.
- *Allergy* can be divided into IgE-mediated diseases and non–IgE-mediated diseases, and in general these should be referred to as *allergic diseases* rather than as "atopic diseases"; however, a person with an IgE-mediated disease can be referred to as an atopic individual or as having an atopic disease.

The reason for proposing the new nomenclature was to try to make it easier to understand what researchers and clinicians mean. An additional aim was to make it easier to interpret the results of clinical trials, especially the possible mechanisms. These definitions are important when the findings of von Berg et al[2] are examined. What these researchers show is that an allergic disease or syndrome (AEDS) is prevented in some infants; they do not show that an allergy—ie, CMA or symptoms caused by CMA—is reduced.

A proper design is crucial for the conclusions drawn from epidemiologic studies. Conclusive studies should be prospective, with well-defined inclusion criteria, relevant predefined outcome parameters, clinical investigations at fixed intervals and at symptoms, well-defined diagnostic criteria with respect to symptoms, a sufficient duration of follow-up, and a proper sample size for adequate statistical evaluation.

In the study by von Berg et al,[2] healthy newborns having at least 1 family member (mother, father, or biological sibling) with an allergic disease (according to a questionnaire) were included. In 1996, Hansen[17] defined high-risk infants as those with double parental heredity or single heredity (parent or sibling) combined with elevated cord blood IgE. There are other possibilities for defining children to be included in trials of this kind. However, the results will be influenced by the inclusion criteria. Therefore, to make it possible to compare results between studies, the same inclusion criteria should be used. The results obtained in the article by von Berg et al[2] cannot be compared with those reported by most other groups because

of differences in inclusion criteria. In my opinion, the criteria of Hansen[17] should be preferred, though to learn more, one should complement these criteria with tests of the parents to differentiate between IgE-mediated and non–IgE-mediated allergy and hypersensitivity without known immunologic background. The response to reduced allergen exposure or allergen stimulation might be influenced by whether the parent had an IgE-associated disease or a non–IgE-associated disease.

Another issue is the definition of outcome parameters and how the diagnosis of these parameters was achieved. In the study by von Berg et al,[2] outcome parameters were (a) "atopic manifestations," including mainly AEDS and gastrointestinal symptoms, and (b) separately, AEDS. AEDS was diagnosed clinically in a proper way, but without differentiation between atopic and nonatopic AEDS, which might be of importance. Nor was it established whether AEDS was caused by CMA, as verified by double-blind, placebo-controlled food challenge (DBPCFC) performed in close proximity to the time when symptoms appear. Thus, the most important diagnosis in this context, CMA, was not diagnosed properly, given that few CMP challenges were performed. This is remarkable, inasmuch as approximately one half of children with suspected CMA do not react to CMP at challenge.[18] Because the diagnosis of CMA was not established properly, the report does not give the information hoped for.

AEDS (AD) is a disease with at least 2 mechanisms: (1) atopic, or IgE-mediated, and (2) nonatopic, or (probably) cell-mediated (Fig 2). Host[18] found that 50% of children developing CMA, as defined by DBPCFC, had specific IgE to cow's milk protein (CMP), and Isolauri and Turjanmaa[19] reported that approximately 50% of the children whom they studied were skin prick test–positive to CMP, whereas the other 50% reacted only to atopy patch tests—ie, patch tests with common food or inhalant allergens. Later, Niggemann et al[20] found that older children with AEDS and CMA, as proven by DBPCFC, all had positive atopy patch test results but negative skin prick test results. It would have been useful to know whether or not the AEDS symptoms reported were related to IgE and whether they were caused by CMP.

Finally, there is the question of when follow-up should be reported. In the present trial, mothers were advised to breast-feed for 4 or (better) 6 months. If the mother had no breast milk, supplementation was given in the form of CMF, pHF, or either of 2 eHFs until 6 months of age. Solid foods were avoided until the age of 6 months. Follow-up was for 1 year. It would be more appropriate to report on CMA as measured by DBPCFC if and when symptoms appeared up until the age of 6 months, the time for blinded intervention with formulas and the start of introduction of solid foods. Certainly, follow-up at 1 year of age would be of some value.

No definite conclusion can be drawn from the data presented as to whether pHFs (or eHFs) are able to prevent the development of allergy in high-risk infants. Obviously, the eHF based on casein reduced the number of children with AEDS. However, the claim that the pHF also prevented the disease must be questioned. The *P* value of .048 was probably obtained by chance, inasmuch as too many comparisons were made to allow the use of $P < .05$ as significant. To me, it seems, this might be an instance of "significance-fishing." Actually, I would advise that the design used in drug trials be used in future prospective food intervention trials—ie, only 1 major question should be addressed in each trial; all other findings should be used only for the generation of a hypothesis.

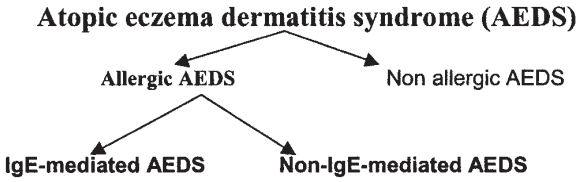


**FIG 2.** The nomenclature of AEDS (AD), according to the nomenclature proposed by EAACI.[4]

As an example of how extra data are sometimes generated from a trial with a single research question and used to respond to another interesting question, the same authors[21] recently published data on 2 subgroups of children—breast-fed and cow's milk–fed infants—from the present trial.[2] They conclude that breast-feeding protects from the development of AEDS, but just as in the present article[2] they do not diagnose CMA.

Having discussed the nomenclature and noted that AEDS is caused by at least 2 mechanisms—via IgE and mast cells and via T cells—I must admit that there have been discussions of the fact that the high-affinity receptor for IgE, FcεR1, is present on the surface of dendritic cells and IgE might also play a role in AEDS without immediate reaction.[22] Despite this fact, however, and especially given that the mechanisms of AEDS are under discussion, it is of great importance to use strict definitions and diagnostic procedures.

Because the outcome parameters in the study of von Berg et al[2] are not sufficiently well defined, further trials are needed to address a number of specific questions. Among them are the following: Does HF—especially pHF—reduce the risk for CMA, and is this CMA IgE-associated or non–IgE-associated? Does solid food avoidance for 6 months or even 1 year reduce the risk of developing allergies to the avoided allergens? Does avoidance of 1 or several allergens during infancy reduce the risk of developing other specific allergies or allergic diseases later in life? It is of utmost importance that in these future investigations strict rules be set and followed.

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