

Review Up-date

Dietary prevention of allergic diseases in infants and small children

Amendment to previous published articles in *Pediatric Allergy and Immunology* 2004, by an expert group set up by the Section on Pediatrics, European Academy of Allergology and Clinical Immunology

Høst A, Halcken S, Muraro A, Dreborg S, Niggemann B, Aalberse R, Arshad SH, von Berg A, Carlsen KH, Duschén K, Eigenmann PA, Hill D, Jones C, Mellon M, Oldeus G, Oranje A, Pascual C, Prescott S, Sampson H, Svartengren M, Wahn U, Warner JA, Warner JO, Vandenplas Y, Wickman M, Zeiger RS. Dietary prevention of allergic diseases in infants and small children.

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Because of scientific fraud four trials have been excluded from the original Cochrane meta-analysis on formulas containing hydrolyzed protein for prevention of allergy and food intolerance in infants. Unlike the conclusions of the revised Cochrane review the expert group set up by the Section on Paediatrics, European Academy of Allergology and Clinical Immunology (SP-EAACI) do not find that the exclusion of the four trials demands a change of the previous recommendations regarding primary dietary prevention of allergic diseases. Ideally, recommendations on primary dietary prevention should be based only on the results of randomized and quasi-randomized trials (selection criteria in the Cochrane review). However, regarding breastfeeding randomization is unethical. Therefore, in the development of recommendations on dietary primary prevention, high-quality systematic reviews of high-quality cohort studies should be included in the evidence base. The study type combined with assessment of the methodological quality determines the level of evidence. In view of some methodological concerns in the Cochrane meta-analysis, particularly regarding definitions and diagnostic criteria for outcome measures and inclusion of non peer-reviewed studies/reports, a revision of the Cochrane analysis may seem warranted. Based on analysis of published peer-reviewed observational and interventional studies the results still indicate that breastfeeding is highly recommended for all infants irrespective of atopic heredity. A dietary regimen is effective in the prevention of allergic diseases in high-risk infants, particularly in early infancy regarding food allergy and eczema. The most effective dietary regimen is exclusively breastfeeding for at least 4–6 months or, in absence of breast milk, formulas with documented reduced allergenicity for at least the first 4 months, combined with avoidance of solid food and cow's milk for the first 4 months.

Arne Høst¹, Susanne Halcken¹, Antonella Muraro², Sten Dreborg³, Bodo Niggemann⁴, Rob Aalberse⁵, Syed H. Arshad⁶, Andrea von Berg⁷, Kai-Håkon Carlsen⁸, Karel Duschén⁹, Philippe A. Eigenmann¹⁰, David Hill¹¹, Catherine Jones¹², Michael Mellon¹³, Göran Oldeus¹⁴, Arnold Oranje¹⁵, Cristina Pascual¹⁶, Susan Prescott¹⁷, Hugh Sampson¹⁸, Magnus Svartengren¹⁹, Ulrich Wahn²⁰, Jill A. Warner¹², John O. Warner¹², Yvan Vandenplas²⁰, Magnus Wickman²¹ and Robert S. Zeiger¹³

¹Department of Pediatrics, Odense University Hospital, Odense, Denmark, ²Department of Pediatrics, University of Padua, Padua, Italy, ³ESPACI Past President, Lerum, Sweden, ⁴Department of Pneumology and Immunology, University Children's Hospital Charité, Humboldt University, Berlin, Germany, ⁵Department of Allergy CLB, Amsterdam, The Netherlands, ⁶Clinical Allergy Research Unit, St Mary's Hospital, Newport, Isle of Wight, UK, ⁷Abt. für Kinderheilkunde, Marien-Hospital, Wesel, Germany, ⁸Voksentoppen National Centre of Asthma, Allergy and Chronic, Lung Diseases in Children, Oslo, Norway, ⁹Department of Paediatrics, University Hospital Linköping, Linköping, Sweden, ¹⁰Allergologie/Pediatrie, University of Geneva, Geneva, Switzerland, ¹¹Department of Allergy, Royal Children's Hospital, North Melbourne, Victoria, Australia, ¹²Child Health, Level G (803) Centre Block, Southampton General Hospital, Southampton, UK, ¹³Kaiser Permanente San Diego, San Diego, CA, USA, ¹⁴Department of Paediatrics, County Hospital Ryhov, Jönköping, Sweden, ¹⁵Department of Dermatology and Venerology Pediatric Dermatology Unit, ErasmusMC-University Medical Center, Sophia Children's Hospital Rotterdam, Rotterdam, The Netherlands, ¹⁶Servicio de Alergia, Hospital Infantil Universitario La Paz, Madrid, Espana, ¹⁷Department of Paediatrics, University of Western Australia, Subiaco, Western Australia, ¹⁸Department of Pediatrics, Division of Allergy and Immunology, Mount Sinai School of Medicine, New York, NY, USA, ¹⁹Department of Public Health Sciences, Division of

Occupational Medicine, Karolinska Hospital, Stockholm, Sweden, ²⁰A.Z.- Kinderen, Free University of Brussels, Brussels, Belgium, ²¹Department of Environmental Health, Karolinska Hospital, Stockholm, Sweden

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Antonella Muraro, Department of Pediatrics, University of Padua, Via Giustiniani 3 35128, Padua, Italy
Tel.: +39 049 8213505, 06 + 39 049 8212538
Fax: +39 049 8213509
E-mail: muraro@pediatria.unipd.it

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The role of primary prevention of allergic diseases has been a matter of debate for the last 40 yr. In order to shed some light on this issue, a group of experts from the Section on Pediatrics, EAACI (SP-EAACI) reviewed critically the existing literature on Dietary Primary Prevention of Allergic Diseases in Infancy and Early Childhood. Based on this review, three articles were published (1–3).

Since the publication of this review, the first author (Chandra RK) of four of the papers included in part III has been accused of scientific fraud (4, 5). Based on an investigation at the University of Saskatchewan, it has been concluded that the published data in the papers by Chandra (6–9) cannot be verified. (The National, January 30, January 31 and February 1, 2006: <http://www.cbc.ca/national/news/chandra>).

Three attempts were made by the SP-EAACI and the authors of another review on hydrolyzed infant formulae (10), to solicit information from the University of St. John where Chandra was based but without success. Inevitably, the original Cochrane meta-analysis on formulas containing hydrolyzed protein for prevention of allergy and food intolerance in infants was revised excluding the Chandra studies (11).

The exclusion of these trials and inclusion of a new, large trial have resulted in changes to the Cochrane review conclusions (11). In contrast to the earlier Cochrane meta-analysis, the authors now conclude that: *in high-risk infants who are unable to be completely breast-fed, there is limited evidence that prolonged feeding with a hydrolysed formula compared to a cow's milk formula reduces infant and childhood allergy and infant cow's-milk allergy*. In view of methodological concerns and inconsistency of findings, further large, well-designed trials comparing formulas containing partially hydrolysed whey, or extensively hydro-

lysed casein to cow's milk formulas are needed. As emphasized by the expert group of SP-EAACI (1), evaluation of hypoallergenic formula should be made per brand of hydrolyzed formula and not by source of protein (casein or whey) because the amount of residual protein may vary considerably between different hydrolyzed products, casein as well as whey hydrolysates, depending on the degree of hydrolysis.

Unlike the previous Cochrane review on this issue (2003/2004), the members of the expert group of the SP-EAACI were guarded in their evaluation of the quality of the studies on primary dietary prevention by Chandra [see (3)]. However, we do not find that the exclusion of the two sets of trials by Chandra (6–9) demands a change of the recommendations regarding primary dietary prevention of allergic diseases (particularly food allergy/cow's-milk allergy) in high-risk infants (3).

We recognize the need to conduct a comprehensive systematic review using Cochrane methodology (11). Ideally, recommendations on primary dietary prevention should be based only on the results of randomized and quasi-randomized trials that compare the use of hydrolyzed infant formula to standard cow's-milk formula (selection criteria in the Cochrane review). However, no sensible paediatrician would even contemplate attempting a randomized comparison with human milk as it would be totally unethical. Despite this, the authors of the Cochrane review (11) in their discussion appear to be suggesting that such trials are required. We should all accept that milk formulae will never be preferred to breast-feeding as considerations extend way beyond allergy.

In our opinion, mothers who are able to breast-feed should breast-feed, and there is no reason to supplement with formula-feeding when

breast-feeding is sufficient. When developing recommendations on dietary primary prevention, high-quality systematic reviews of high-quality cohort studies should be included in the evidence base (3). The study type combined with assessment of the methodological quality determines the levels of evidence (12). It can be recommended to follow the recommendations on evaluation of methods in allergy prevention studies and definitions and diagnostic criteria of allergic diseases in the position paper by the SP-EAACI (2). This review includes description of target group for dietary prevention, and methods and diagnostic criteria of atopic dermatitis, asthma and food allergy for prevention studies.

In the Cochrane review, the primary outcomes were 'any allergy' including asthma, atopic dermatitis, allergic rhinitis or food allergy. In many of the included studies, the diagnosis of allergy/allergic disease was based on questionnaires. That is highly questionable. The authors seem to use the term *food intolerance*, which has been abandoned. Regarding updated definitions on allergy/atopy/allergic diseases – see recent guidelines (13). An important point regarding the diagnosis of food allergy is that many food allergies may be overlooked if the infants/children are not investigated at the time of onset of symptoms but only investigated at fixed time points. A diagnosis of food allergy cannot be made based on parental reports of symptoms and positive specific immunoglobulin E (IgE) or skin prick tests. It can only be based on controlled elimination and challenge procedures, in young children not necessarily DBPCFC [see (2, 14)]. Studies without use of strict diagnostic criteria and well-defined and verified outcome measures (apparent in more of the studies included in the Cochrane review) may confound the findings and make studies non-conclusive. Important factors regarding methodological quality are emphasized in the Cochrane review, such as adequate method of randomization, allocation concealment and blinding of treatment and blinding of measurement and evaluation of allergy. However, even studies meeting these demands on methodological quality may be misleading and non-conclusive if adequate definitions, diagnostic criteria and outcome measures have not been used and followed.

The authors of the Cochrane review have excluded studies where losses to follow-up are greater than 20%. This may raise the question whether this is correct. There are well-conducted studies with losses greater than 20% due to a careful description of drop-outs and reasons for drop-out. One study (15) has been excluded due

to excess losses >20%, which is not correct according to data presented in the paper.

The authors seem to be in favour of intention to treat analysis. However, this may not be the correct method in studies where the effect of a specific diet is evaluated. The reason for non-compliance to a diet may, for example, be due to parental refusal (e.g. due to unpalatability of a product) and not related to whether or not the infant tolerated the feeding with the product in question. Therefore, careful per-protocol analysis may be justified as well.

Regarding randomization, the term quasi-randomization has been used for randomization according to date of birth and this form for randomization has been classified as not adequate. Presumably, the children or parents or doctors will not be able to influence this kind of randomization. In at least two studies (15, 16), allocation concealment was questioned in the Cochrane review though it has been described adequately in the papers.

The review performed by the expert group of the SP-EAACI (3) only included studies published in peer-reviewed scientific journals in contrast to the recent Cochrane review (11), which also included a study published in an internal company report (Nestlé Internal Report 1992) (17), and another large study (18) published as a supplement to a scientific journal, which according to the publisher was not peer-reviewed. The reason for inclusion of such studies seems questionable.

Possible effects of primary dietary prevention

Due to the well-known clinical course of allergic diseases in early childhood (the allergy march), the greatest possible impact of primary dietary allergy prevention may be on development of food allergy, particularly cow's-milk allergy, and eczema (atopic dermatitis). Later in childhood, allergies to inhalant allergens typically occur and increases in asthma and rhinoconjunctivitis develop. Food allergy and eczema related to allergy to food may be IgE-mediated or non-IgE mediated (13) and eczema may be IgE-associated (atopic eczema) or non-atopic. In many studies, the immunological type of allergic disease has not been investigated and in most of the studies where eczema has been registered as an outcome parameter, the infants/children have not been investigated appropriately for food allergy by elimination and challenge procedures. That makes the evaluation of a possible preventive effect difficult. Thus, in a recent large prospective, randomized intervention study, it was found

that certain hydrolyzed formulas (particularly an extensively hydrolyzed casein formula) reduced the incidence of atopic dermatitis at 3 yr in high-risk infants (19). However, it was not reported whether atopic dermatitis was related to allergy (food allergy) (19). In future studies and reviews/meta-analyses, recommendations to ensure methodological quality should be followed [see (2)].

Present recommendations

Breast-feeding is highly recommended for all infants irrespective of atopic heredity. Although the number of high-quality observational and interventional studies is limited, the following evidence-based recommendations should be followed:

- (i) A dietary regimen is effective for prevention of allergy to the avoided food, in *high-risk infants*, particularly in early infancy regarding food allergy (cow's-milk allergy) and eczema (atopic or non-atopic). Evidence that such avoidance affects the later allergic manifestations such as asthma and rhinitis is lacking. The most effective dietary regimen is exclusively breast-feeding for at least 4–6 months or, in case of lack of breast milk, formulas with documented reduced allergenicity for at least 4 months, combined with avoidance of solid food and cow's milk for the same period may be considered.
- (ii) No conclusive evidence for protective effect of maternal exclusion diet during pregnancy or lactation has been documented.

There is no evidence for preventive effect of dietary restrictions after the age of 4–6 months. Besides, there is insufficient evidence to make any recommendations on weaning strategies.

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