EAACI food allergy and anaphylaxis guidelines. Primary prevention of food allergy.

Guideline Developer(s)

European Academy of Allergy and Clinical Immunology

Date Released

2014 May

Full Text Guideline

EAACI food allergy and anaphylaxis guidelines. Primary prevention of food allergy.

Evidence Supporting the Recommendations

- References Supporting the Recommendations
  Venter C, Pereira B, Voigt K, Grundy J, Clayton CB, Higgins B, Arshad SH, Dean T. Factors
associated with maternal dietary intake, feeding and weaning practices, and the development of food
cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=19220769)
Heinrich J, Wichmann HE, Bauer CP, Reinhardt D, Berdel D, GINIplus study group. Preventive effect
of hydrolyzed infant formulas persists until age 6 years: long-term results from the German Infant
cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=18539195)
D, German Infant Nutritional Intervention Study Group. The effect of hydrolyzed cow's milk formula for
allergy prevention in the first year of life: the German Infant Nutritional Intervention Study, a
cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12642834)
Zeiger RS, Heller S, Mellon MH, Forsythe AB, O'Connor RD, Hamburger RN, Schatz M. Effect of
combined maternal and infant food-allergen avoidance on development of atopy in early infancy: a
cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=2754147)
Zeiger RS, Heller S, Sampson HA. Genetic and environmental factors affecting the development of
atopy through age 4 in children of atopic parents: a prospective randomized controlled study of food
Zeiger RS, Heller S. The development and prediction of atopy in high-risk children: follow-up at age
seven years in a prospective randomized study of combined maternal and infant food allergen
cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7797786)

Type of Evidence Supporting the Recommendations
The type of supporting evidence is identified and graded for each recommendation (see the "Major
Recommendations" field).

Implementation of the Guideline

Description of Implementation Strategy
Additional supporting information for implementation may be found in the online version of this article
(see the "Availability of Companion Documents" field):

- Table S1. Barriers and facilitators to implementation, audit criteria, and resource implications
  of recommendations.

Implementation Tools
Audit Criteria/Indicators

Benefits/Harms of Implementing the
Guideline Recommendations

Potential Benefits
Food allergy can have a significant effect on people's morbidity and quality of life and can be costly in
terms of medical visits and treatments. Given the morbidity resulting from food allergy, there is
considerable scientific, professional, and lay interest in approaches that may reduce the risk of
developing food allergy.

Potential Harms
Not stated
Grades of Recommendation

**Grade A** Consistent level I studies

**Grade B** Consistent level II or III studies or extrapolations from level I studies

**Grade C** Level IV studies or extrapolations from level II or III studies

**Grade D** Level V evidence or troublingly inconsistent or inconclusive studies at any level

Qualifying Statements

Qualifying Statements
Challenges in Interpreting the Evidence

Food allergy is a complex topic because the symptoms are diverse and allergies can manifest in many different forms. In children, only around one-third of parentally reported food allergy can be confirmed when appropriately investigated. In the population, immunoglobulin E (IgE) sensitization to foods, as detected by skin prick test (SPT) or presence of specific IgE (sIgE), is not always associated with clinical reactions and food allergy. Because the diagnostic accuracy is suboptimal when based solely on history and/or sensitization, if possible a food allergy diagnosis needs to be confirmed by controlled elimination and challenge procedures. Unfortunately, most studies on the prevention of food allergy rely on reported reactions or surrogate markers of food allergy such as sensitization to foods (IgE and/or SPT) and disease outcomes, for example eczema. Moreover, it is important to be aware of the natural course of food allergy, as food allergies develop in the order of exposure to different foods and many children with food allergies, for example cow's milk allergy, develop tolerance during the first years of life. It is therefore important to investigate specific food allergies in the relevant age groups when they experience symptoms suggestive of food allergy and to investigate the specific food allergens that are relevant to that age group and geographic location. Finally, most studies are not sufficiently powered to detect clinically important reductions in the incidence of food allergy.

There are additional ethical and logistical challenges to be considered when interpreting or undertaking food allergy research in young children and infants. For example, it is not ethical to randomize mothers to breastfeeding, and evidence on this topic has therefore been based on high-quality observational studies. However, exclusively breastfed children may not be comparable to others due to self-selection, and these mothers may be more motivated to exclusively breastfeed due to family history of allergic problems or early symptoms in their children. Thus, there is a risk of reverse causation, which is not taken into consideration in most studies.

It is important to note that the quality assessment in the systematic review was, in keeping with standard practice, undertaken on methodological grounds, rather than on the clinical relevance or overall validity of the studies. When extracting the relevant evidence for the guidelines, it is also important to evaluate the scientific quality and clinical relevance of the studies.

Thus, for these recommendations on primary prevention of food allergy, the above-mentioned factors have been considered alongside the formal methodological quality assessment, and experimental studies reporting on confirmed food allergy are ranked highest, whereas studies with self-reported food allergy, atopic symptoms (which may represent food allergy), and sensitization as outcomes were included, but were ascribed less weight. Studies reporting only retrospective data were not included due to their high risk of bias.

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
**Description of Methods Used to Collect/Select the Evidence**

The development of the guideline has been informed by a systematic review of interventions for the primary prevention of food allergy in children and adults (see the “Availability of Companion Documents” field).

**Systematic Review of the Evidence**

The initial full range of questions that were considered important were rationalized through several rounds of iteration to agree to one key overarching question:

- What is the effectiveness of approaches for the primary prevention of food allergy?

**Search Strategy**

The following databases were searched: Cochrane Library, MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), ISI Web of Science, Turning Research into Practice (TRIP) Database, and Clinicaltrials.gov. Experts in the field were contacted for additional studies.

**Inclusion and Exclusion Criteria**

This review focused solely on studies that were primarily concerned with preventing sensitization to food(s) and/or the development of food allergy. Studies seeking to prevent potential manifestations of food allergy such as atopic eczema/dermatitis or asthma, but not including an explicit diagnosis of sensitization to food or food allergy, were not included.

Systematic reviews and meta-analyses, randomized controlled trials, quasi-randomized controlled trials, controlled clinical trials, controlled before-and-after studies, interrupted time series studies, and prospective cohort studies published up until 30 September 2012, were eligible. No language restrictions were applied and, where possible, relevant studies in languages other than English were translated.

**Study Selection**

The titles and abstracts of articles were checked by two independent reviewers and categorized as included, not included, and unsure. Full-text copies of potentially relevant studies were obtained, and their eligibility for inclusion was independently assessed by two reviewers. Any discrepancies were resolved by consensus or discussion with other reviewers.

**Number of Source Documents**

Seventy-four studies were included, comprising 15 systematic reviews (20%), 32 randomized controlled trials (43%), nine nonrandomized comparative studies (12%), and 19 cohort studies (25%).

**Methods Used to Assess the Quality and Strength of the Evidence**

**Weighting According to a Rating Scheme (Scheme Given)**

**Rating Scheme for the Strength of the Evidence**

**Level of Evidence**

- **Level I** Systematic reviews, meta-analysis, randomized controlled trials
- **Level II** Two groups, nonrandomized studies (e.g., cohort, case–control)
- **Level III** One group nonrandomized (e.g., before and after, pretest, and post-test)
- **Level IV** Descriptive studies that include analysis of outcomes (single-subject design, case series)
- **Level V** Case reports and expert opinion that include narrative literature, reviews, and consensus statements

**Methods Used to Analyze the Evidence**

- Review of Published Meta-Analyses
- Systematic Review with Evidence Tables

**Description of the Methods Used to Analyze the Evidence**

The development of the guideline has been informed by a systematic review of interventions for the primary prevention of food allergy in children and adults (see the “Availability of Companion Documents” field).
Risk of Bias Assessment

Risk of bias was independently carried out by two reviewers using adapted versions of the Critical Appraisal Skills Programme (CASP) tool and the Cochrane Effective Practice and Organisation of Care Group (EPOC) Risk of Bias tools. An overall grading of high, medium, or low quality was assigned to each study.

Analysis, Synthesis, and Reporting

Two reviewers independently used a customized data extraction form to obtain data from each study. Discrepancies were resolved by discussion. Experts in the field checked all of the data extraction for accuracy and relevance. Meta-analysis was not appropriate because the studies were heterogeneous in focus, design, target populations, and interventions. Findings were synthesized narratively by grouping studies according to intervention and target population. These syntheses were checked by a group of methodologists and experts to ensure accuracy and relevance.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

This guideline was produced using the Appraisal of Guidelines for Research & Evaluation (AGREE II) approach. This is a structured approach to guideline production that is designed to ensure appropriate representation of the full range of stakeholders, a careful search for and critical appraisal of the relevant literature, a systematic approach to the formulation and presentation of recommendations, and steps to ensure that the risk of bias is minimized at each step of the process. An overview of the approach used is provided below.

Clarifying the Scope and Purpose of the Guideline

This process began in January 2012 with a meeting to discuss the overall approach to guideline development, including detailed discussions on the main aims of the guidelines, the target conditions, clarifying the target populations, to whom the recommendations applied, agreeing the intended end-user group, and ensuring adequate professional and lay representation in the guideline development process.

Ensuring Appropriate Stakeholder Involvement

Participants represented a range of European countries, and disciplinary and clinical backgrounds (including medical secondary care, primary care, and nursing), and patient groups. The Prevention Task Force continued to work together over the ensuing 18 months through email discussions, teleconferences, and face-to-face meetings.

Formulating Recommendations

The authors graded the overall strength and consistency of the evidence to translate the key findings from the systematic review into evidence-linked recommendations. This involved formulating clear recommendations and making clear the strength of evidence underpinning each recommendation. This ranged from consistent evidence derived from systematic reviews of randomized controlled trials through to evidence derived from expert consensus. Experts identified the implications of implementing the recommendations, barriers and facilitators to the implementation of each recommendation, advice on approaches to implementing the recommendations and suggested audit criteria that can help with assessing organizational compliance with each recommendation.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

A draft of this guideline was externally peer-reviewed by experts from a range of organizations, countries, and professional backgrounds. Additionally, the draft guideline was available on the European Academy of Allergy and Clinical Immunology (EAACI) Web site for a 2-week period in June 2013 to allow all stakeholders to comment. All feedback was considered by the Prevention Task Force and, where appropriate, final revisions were made according to the feedback received.
All authors participated in the discussion of the systematic review, the evidence table, recommendations, gaps, and specific sections and approved the final version.

**Identifying Information and Availability**

- **Bibliographic Source(s)**

- **Adaptation**
  Not applicable: The guideline was not adapted from another source.

- **Source(s) of Funding**
  The production of this guideline was funded and supported by the European Academy of Allergy and Clinical Immunology (EAACI). The funders did not have any influence on the guideline production process, its contents, or the decision to publish.

- **Guideline Committee**
  European Academy of Allergy and Clinical Immunology (EAACI) Taskforce on Prevention

- **Composition of Group That Authored the Guideline**
  **Taskforce Members**: A. Muraro, The Referral Centre for Food Allergy Diagnosis and Treatment Veneto Region, Department of Mother and Child Health, University of Padua, Padua, Italy; S. Halken, Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark; S. H. Arshad, Clinical and Experimental Sciences Academic Unit, University of Southampton Faculty of Medicine, Southampton, David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Isle of Wight, NIHR Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust, Southampton, UK; K. Beyer, Clinic for Pediatric Pneumology & Immunology, Charité Universitätsmedizin Berlin, Berlin, Germany; A. E. J. Dubois, Department of Pediatric Pulmonology and Paediatric Allergy, GRIAC Research Institute, University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands; G. Du Toit, Department of Paediatric Allergy, Division of Asthma, Allergy and Lung Biology, MRC & Asthma UK Centre in Allergic Mechanisms of Asthma, King's College London, Guy's and St Thomas' NHS Foundation Trust, London, UK; P. A. Eigenmann, Department of Child and Adolescent, Allergy Unit, University Hospitals of Geneva, Geneva, K. E. C. Grimshaw, Clinical and Experimental Sciences Academic Unit, University of Southampton Faculty of Medicine, Southampton; A. Hoest, Hans Christian Andersen Children's Hospital, Odense University Hospital, Odense, Denmark; G. Lack, Department of Paediatric Allergy, Division of Asthma, Allergy and Lung Biology, MRC & Asthma UK Centre in Allergic Mechanisms of Asthma, King's College London, Guy's and St Thomas' NHS Foundation Trust, London, UK; L. O'Mahony, Swiss Institute of Allergy and Asthma Research, University of Zurich, Zurich, Switzerland; N. G. Papadopoulos, Institute of Human Development, University of Manchester, Manchester, UK, Allergy Department, 2nd Pediatric Clinic, University of Athens, Athens, Greece; S. Panesar, Evidence-Based Health Care Ltd, Edinburgh, UK; S. Prescott, School of Paediatrics and Child Health Research, University of Western Australia, Perth, WA, Australia; G. Roberts, Clinical and Experimental Sciences Academic Unit, University of Southampton Faculty of Medicine, Southampton; D. de Silva, Evidence-Based Health Care Ltd, Edinburgh, UK; C. Venter, David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Isle of Wight, NIHR Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust, Southampton, UK; V. Verhasselt, Hôpital de l'Archet, Université de Nice Sophia-Antipolis EA 6302 "Tolérance Immunitaire", Nice, France; A. C. Akdis, Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland; A. Sheikh, Allergy & Respiratory Research Group, Centre for Population Health Sciences, The University of Edinburgh, Scotland, UK, Division of General Internal Medicine and Primary Care, Brigham and Women's Hospital/Harvard Medical School, Boston, MA, USA

- **Financial Disclosures/Conflicts of Interest**
Conflicts of interest statements were completed by all members of the Task Force, and these were taken into account by Task Force chair as recommendations were formulated.

Conflicts of Interest

Susanne Halken has provided scientific advice for ALK-Abelló. Antonella Muraro has provided scientific advice for Meda. Tony DuBois has provided scientific advice for ALK-Abelló and received funding from ALK-Abelló to support his research activities. Philippe Eigenmann has provided scientific advice for Danone, Novartis, ALK-Abelló, DBV technologies and Stallergenes; he has received funding for research activities from LETI, Nestlé, and ThermoFisher. Arne Høst has provided scientific advice for ALK-Abelló and Danone. Carina Venter has produced educational material for Danone, Mead Johnson, and Nestlé and has received research funding from ThermoFisher, Danone, and Mead Johnson. Debra de Silva, Sukhmeet Panesar, and Aziz Sheikh have received funding for coordinating guideline production and generating the systematic reviews from EAACI. Aziz Sheikh has provided scientific advice to ALK-Abelló, Meda, Lincoln Medical, ThermoFisher, Pfizer, and Stallergenes; he is on the Anaphylaxis Campaign UK’s Scientific Committee, World Allergy Organization's Anaphylaxis Special Committee, UK Resuscitation Council's Anaphylaxis Committee, and the BSACI’s Standard of Care Committee. Gideon Lack has no conflict of interests. Kirsten Beyer has received funding for research activities from the European Union, German Research Foundation, Berliner Sparkasse, BEA-Stiftung, Food Allergy and Anaphylaxis Network, Food Allergy Initiative, Danone, ThermoFisher, DST Diagnostics, Allergopharma and has received honoraria or consultation feed from Danone, MedaPharma, ALK-Abelló, Novartis, Unilever, Allergopharma, MedUpDate, ThermoFisher, HAL. Graham Roberts and Hasan Arshad have provided scientific advice for Danone. Kate Grimshaw has provided scientific advice for Danone. Valérie Verhasselt has received research funding from Nestlé. Liam O’Mahony is a scientific consultant to Alimentary Health Ltd and has received research funding from GSK. George du Toit has received lecture fees from Nutricia and indirectly from the many sponsors of the KCL Allergy Academy. Cesmi A Akdis has received research grants from Allergopharma, Stallergenes, Actelion, and Novartis. Besides, Cesmi A Akdis was President (2011–2013), Past President (2013–2015), and ExCom member in EAACI, which has received financial support from several relevant business entities.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC’s 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the Allergy Journal Web site.

Availability of Companion Documents

The following are available:


Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on November 26, 2014.

Copyright Statement

This NGC summary is based on the original guideline, which is subject to the guideline developer’s copyright restrictions.
Scope

- **Disease/Condition(s)**
  - Food allergy and anaphylaxis

- **Guideline Category**
  - Prevention
  - Risk Assessment

- **Clinical Specialty**
  - Allergy and Immunology
  - Emergency Medicine
  - Family Practice
  - Internal Medicine
  - Nursing
  - Nutrition
  - Obstetrics and Gynecology
  - Pediatrics
  - Preventive Medicine

- **Intended Users**
  - Advanced Practice Nurses
  - Dietitians
  - Health Care Providers
  - Hospitals
  - Nurses
  - Pharmacists

- **Guideline Objective(s)**
  - To provide evidence-based recommendations for the primary prevention of food allergy

- **Target Population**
  - Pregnant women
  - Women who are breastfeeding
  - Infants and children, including infants at high risk for food allergy

- **Interventions and Practices Considered**
  1. Exclusive breastfeeding for the first 4-6 months of age
  2. Hypoallergenic formulas for high-risk infants up to age of 4 months
  3. Standard cow's milk-based formula after age of 4 months
  4. Introduction of complementary food after age of 4 months

  **Note**: The following were considered but not recommended: dietary restrictions during pregnancy and lactation and dietary restrictions after age of 4 months.

- **Major Outcomes Considered**
  - Development of food allergy
  - Food sensitization

**Recommendations**

- **Major Recommendations**
  Definitions of the level of the evidence (I–V) and grades of recommendation (A–D) are provided at the end of the "Major Recommendations" field.

  Refer to Box 5 in the original guideline document for more information on key terms used in this guideline.

  **Recommendations for Primary Prevention of Food Allergy**
Exclusive breastfeeding is recommended for all infants for the first 4–6 months (Evidence level: II–III; Grade: C) (de Silva et al., 2014; Muraro et al., 2004; Kull et al., 2010; Venter et al., 2009; Høst, Husby, & Østerballe, 1988; Lucas et al., 1990).

Dietary restrictions are not recommended for all pregnant or lactating mothers (Evidence level: I–II; Grade: B) (de Silva et al., 2014).

If breastfeeding is insufficient or not possible:

- High-risk infants should receive a hypoallergenic formula with documented preventive effect for the first 4 months. Other infants may receive a standard formula. After the age of 4 months, a standard cow's milk-based formula is recommended according to standard nutrition recommendations, irrespective of atopic heredity (Evidence level: I; Grade: A–B) (de Silva et al., 2014; Muraro et al., 2004; Zeiger et al., 1989; Zeiger, Heller, & Sampson, 1992; Zeiger & Heller, 1995; Odelram et al., 1996; von Berg et al., 2003; von Borg et al., 2008).

- Introduction of complementary foods after the age of 4 months according to normal standard weaning practices and nutrition recommendations, for all children irrespective of atopic heredity (Evidence level: II–III; Grade: C) (de Silva et al., 2014).

- No special dietary restrictions after the age of 4 months for infants with high risk for development of allergic disease. No withholding or encouraging exposure to "highly allergenic" foods such as cow's milk, hen's egg, and peanuts irrespective of atopic heredity, once weaning has commenced (Evidence level: II–III; Grade: C) (de Silva et al., 2014).

Definitions:

Level of Evidence

Level I  Systematic reviews, meta-analysis, randomized controlled trials
Level II  Two groups, nonrandomized studies (e.g., cohort, case-control)
Level III One group nonrandomized (e.g., before and after, pretest, and post-test)
Level IV  Descriptive studies that include analysis of outcomes (single-subject design, case series)
Level V  Case reports and expert opinion that include narrative literature, reviews, and consensus statements

Grades of Recommendation

Grade A  Consistent level I studies
Grade B  Consistent level II or III studies or extrapolations from level I studies
Grade C  Level IV studies or extrapolations from level II or III studies
Grade D  Level V evidence or troublingly inconsistent or inconclusive studies at any level

Clinical Algorithm(s)

None provided

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Staying Healthy

IOM Domain

Effectiveness
Patient-centeredness

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