General

Guideline Title

EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy.

Bibliographic Source(s)


Guideline Status

This is the current release of the guideline.

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

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 the original guideline document for more information on key terms used in this guideline (Table 1) and food-induced allergic disorders (classified based on the underlying immunopathology) (Table 2).

European Academy of Allergy and Clinical Immunology (EAACI) Recommendation on the Diagnosis of Food Allergy

Patient's Clinical History

- Detailed clinical history is essential for the diagnosis of food allergy (Evidence level IV; Grade: D) (Expert opinion).
- When taking a clinical history eliciting allergens, timing and chronicity, symptoms, severity and signs, reproducibility, known risk (co)factors, family history, coexisting medical problems including other allergic diseases should be addressed (Evidence level V; Grade: D) (Expert opinion).
- The use of structured questions on symptoms, foods, and other background information is recommended (Evidence level V; Grade: D) (Expert opinion).

Determination of Sensitization to Food
Where available, standardized tests and procedures should be used (Evidence level: IV; Grade: D) (Expert opinion).

Immunoglobulin E (IgE) sensitization does not always predict clinically relevant food allergy, so specific allergy testing should be directed by case history (Evidence level: IV; Grade: C) (Soares-Weiser et al., 2014).

Either skin prick test (SPT) or specific IgE (sIgE) can be the test of choice for sensitization depending on local availability and absolute and relative contraindications to SPT (Evidence level: IV; Grade: C) (Soares-Weiser et al., 2014).

Evidence of IgE sensitization to common food and appropriate aeroallergens can support a diagnosis of food allergy in conjunction with clinical history and/or food challenge (Evidence level: I–III*; Grade: A–C) (Soares-Weiser et al., 2014).

In the presence of a suggestive history, a negative SPT or sIgE needs to be interpreted with caution particularly as these are expected in non-IgE-mediated food allergy (Evidence level: IV; Grade: C) (Soares-Weiser et al., 2014).

Where SPT and sIgE tests are inconclusive, component-resolved diagnostic test (if available) may provide additional diagnostic information (Evidence level: I–IV*; Grade: A–C*) (Soares-Weiser et al., 2014; Glaumann et al., 2012; Eller & Bindslev-Jensen, 2013; Morita et al., 2009).

If clinical history with SPT and/or sIgE results is not highly predictive (see Figure 1 in the original guideline document), an oral food challenge (OFC) is required (Evidence level: IV; Grade: D) (Expert opinion).

Determination of total IgE is particularly useful in patients with severe eczema; a very high total IgE level suggests that positive sIgE results should be interpreted with care as they may represent asymptomatic sensitization (Evidence level: IV; Grade: D) (Expert opinion).

Elimination Diets for Diagnostic Purposes

Determining which foods to be avoided should be based on the allergy-focused diet history, clinical history, and allergy testing (SPTs and/or sIgE) (Evidence level: V; Grade: D) (Expert opinion).

For each individually avoided food, the results of the diagnostic elimination diet should be carefully monitored and evaluated over 2–4 weeks of avoidance (Evidence level: V; Grade: D) (Expert opinion).

Where the elimination diet leads to a significant relief of symptoms, it should be continued until the provocation test is performed (Evidence level: V; Grade: D) (Expert opinion).

Where the elimination diet does not lead to a significant relief of symptoms, food allergy to the eliminated foods is highly unlikely (Evidence level: V; Grade: D) (Expert opinion).

Oral Food Challenge (OFC)

The OFC (particularly the double-blind placebo-controlled food challenge [DBPCFC]) is the gold standard investigation for the objective diagnosis of IgE- and non-IgE-mediated food allergy (Evidence level: IV; Grade: D) (Expert opinion).

OFCs should be used to demonstrate allergy or tolerance and in so doing facilitate safe dietary expansion or appropriate allergen avoidance (Evidence level: IV; Grade: D) (Expert opinion).

The DBPCFC should be performed when symptoms are subjective, with delayed or atypical symptoms, where patients and/or caregivers are anxious, and considered in all research settings (Evidence level: IV; Grade: D) (Bindslev-Jensen et al., 2004; Sampson et al., 2012).

A negative DBPCFC should end with an open or cumulative ingestion of the food based on a normal age-appropriate portion to confirm oral tolerance (Evidence level: IV; Grade: D) (Expert opinion).

OFC must be performed in a specialist setting with emergency support immediately available; where there is a moderate-to-high risk of a severe reaction, intensive care support must be immediately available (Evidence level: IV; Grade: D) (Expert opinion).

Diagnosis of Eosinophilic Esophagitis (EoE)

Every patient with EoE should be referred to an allergist/immunologist for workup (Evidence level: IV; Grade: D) (Straumann et al., 2012).

EoE is diagnosed by an upper endoscopy with 2–4 biopsies from both the proximal and distal esophageal biopsies. Biopsies should be performed when the patient has been treated for at least 6 weeks with double-dose proton-pump inhibitors to rule out esophageal eosinophilia caused by gastroesophageal reflux disease and to exclude proton-pump inhibitor-responsive esophageal eosinophilia (Evidence level: IV; Grade: D) (Straumann et al., 2012; Dellon et al., 2013).

The clinical utility of measuring serum food sIgE and SPT results to generate a successful elimination diet needs further investigation. Future studies should clearly document a clinical and histologic benefit from dietary interventions guided by results from serum IgE levels, skin prick testing, or atopy patch testing (Evidence level: IV; Grade: D) (Straumann et al., 2012).

Unconventional Tests, Including Specific Immunoglobulin G (IgG) Testing

There are no unconventional tests which can be recommended as an alternative or complementary diagnostic tool in the workup of suspected food allergy, and their use should be discouraged (Evidence level: III; Grade: C) (Stapel et al., 2008).
**EAACI Recommendation on the Management of Food Allergy**

**Acute Management**

- The patient at risk of severe reactions should be properly and timely identified (Evidence level: IV; Grade: D) (Expert opinion).

**Antihistamines and Mast Cell Stabilizers**

- There is evidence to support the benefits of antihistamines for children and adults with acute non-life-threatening symptoms from food allergy (Evidence level: III; Grade: C) (de Silva et al., 2014).
- The prophylactic application of antihistamines is not recommended (Evidence level: V; Grade: D) (Expert opinion).
- Mast cell stabilizers are not recommended for the prophylactic treatment of food allergy (Evidence level: III; Grade: C) (de Silva et al., 2014).

**Long-Term Management Strategies**

**Elimination Diet**

- A sufficient elimination diet should be based on a formal allergy diagnosis identifying the food allergen(s) responsible of the patient's symptoms/reactions. The indications should be re-evaluated at appropriate intervals (Evidence level: IV; Grade: D) (Agata et al., 1993; Alonso et al., 1994; Chen & Bahna, 2011).
- Appropriate dietary avoidance is the key treatment in the management of food allergy (Evidence level: IV; Grade: D) (Expert opinion).
- Patients with food allergy who are on long-term elimination diets should have access to appropriate dietetic counseling, ideally by a dietitian with competencies in food allergy, and regular monitoring of growth (in children) (Evidence level: IV; Grade: D) (Expert opinion).
- Extensively hydrolyzed cow's milk formulas with documented hypoallergenicity can be recommended as first choice for the treatment of cow's milk allergy, especially in infants and young children. Amino acid formulas can also be recommended especially for the subgroup of patients with more severe symptoms (Evidence level: I; Grade: A) (Hill et al., 2007; Koletzko et al., 2012; Muraro et al., 2004; Niggemann et al., 2001).
- Soy formulas should not be recommended before 6 months of age and at any age in the presence of gastrointestinal symptoms. From 6 to 12 months, it can be considered on a case-by-case basis (Evidence level: I; Grade: B) (de Silva et al., 2014).
- Currently, probiotic supplements cannot be recommended for the management of food allergy (Evidence level: I; Grade: D) (de Silva et al., 2014; Hol et al., 2008).

**Education and Risk Assessment**

- Patients and caregivers need to be informed about the foods that should be avoided and practical advice given on avoidance measures, how to recognize a further reaction and the self-management of these reactions (Evidence level: V; Grade: D) (Expert opinion).
- The diagnosis of food allergy should, with permission, be communicated to all relevant caregivers (Evidence level: V; Grade: D) (Expert opinion).
- Patients/carers should be encouraged to join an appropriate patient support organization (Evidence level: V; Grade: D) (Expert opinion).
- All patients with food allergy require a management plan with appropriate education for the patient, caregiver including school (Evidence level: V; Grade: D) (Expert opinion).
- Education should cover allergen avoidance, symptom recognition, and indication for specific treatment and administration of specific medication (Evidence level: V; Grade: D) (Expert opinion).
- Absolute indications with adrenaline autoinjector include previous anaphylaxis to any food, food allergy associated with persistent or severe asthma, and exercise-induced food-dependent anaphylaxis (Evidence level: IV; Grade: D) (Expert opinion; see the National Guideline Clearinghouse [NGC] summary of the EAACI guideline *Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology*).
- Relative indications for adrenaline autoinjector with food allergy include (i) food allergies that are likely to be persistent; (ii) mild-to-moderate allergic reaction to peanut and/or tree nut; (iii) mild-to-moderate reaction to very small amounts of food; and (iv) specific high-risk groups, e.g., adolescents, young adults, children, poor access to medical care (Evidence level: IV–V*; Grade: C–D*) (Expert opinion; see the NGC summary of the EAACI guideline *Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology*).
- Adrenaline should be immediately administered for cardiovascular symptoms and/or respiratory symptoms such as altered voice, stridor, or bronchospasm that are thought to be induced by food allergy (Evidence level: IV; Grade: C) (see the NGC summary of the EAACI guideline *Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology*).
- Short-acting beta agonists should be included in the management plan for all patients with coexisting asthma and should be administered for
bronchospasm after adrenaline has been administered (Evidence level: V; Grade: D) (Expert opinion; see the NGC summary of the EAACI guideline Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology).

- Patient held glucocorticosteroids may be given with reactions to possibly prevent late-phase respiratory symptoms (self-administered if traveling far from medical care, otherwise in emergency center) (Evidence level: V; Grade: D) (Expert opinion; see the NGC summary of the EAACI guideline Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology).

- Any patient who has received adrenaline should be reviewed in an emergency department (Evidence level: IV; Grade: D) (Expert opinion; see the NGC summary of the EAACI guideline Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology).

### Specific Immunotherapy

- Food allergen-specific immunotherapy for primary food allergy is a promising immunomodulatory treatment approach (Evidence level: I), but it is associated with risk of adverse reactions, including anaphylaxis (Evidence level: I); it is therefore not currently recommended for routine clinical use (Evidence level: III; Grade: C) (de Silva et al., 2014).

- For patients with respiratory or other allergy symptoms to inhalant allergens that may also cause cross-reactive food allergy, specific immunotherapy is only recommended for the treatment of the respiratory symptoms, not for cross-reactive food allergy (Evidence level: IV; Grade: D) (Expert opinion).

### Anti-IgE

- The use of anti-IgE alone or in combination with specific immunotherapy is currently not recommended for the treatment of food allergy although it represents a promising treatment modality (Evidence level: IV; Grade: D) (de Silva et al., 2014).

### Challenges at Regular Intervals to Assess Achievements of Tolerance

- OFC should be performed at regularly at intervals, as appropriate for the specific food and patient's history, in order to assess achievement of tolerance (Evidence level: V; Grade: D) (Expert opinion).

- Specific IgE testing (in vitro and SPT) has limited value in guiding adequately the timing of OFCs for the development of tolerance (Evidence level: V; Grade: D) (Expert opinion).

### Cofactors

- In food allergy reactions, the potential augmenting role of cofactors (e.g., exercise, nonsteroidal anti-inflammatory drug [NSAID], omeprazole, alcohol intake) should be assessed in a structured history (Evidence level: III–IV**; Grade: D) (Expert opinion).

- In allergic reactions occurring after exercise, NSAID or alcohol intake, an underlying allergy to foods consumed in the previous hours should be assessed (especially gliadin sensitization or lipid-transfer proteins in southern Europe) (Evidence level: IV; Grade: D) (Morita et al., 2009; Cardona et al., 2012; Romano et al., 2012).

*Range of levels of evidence and grades are due to range of indications.

**Range of levels of evidence and grades are due to range of different cofactors.

### Definitions:

#### Level of Evidence for Establishing Diagnostic Test Accuracy

<table>
<thead>
<tr>
<th>Level</th>
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<td>A study of test accuracy with an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation</td>
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<tr>
<td>Level III-1*</td>
<td>A study of test accuracy with an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation</td>
</tr>
<tr>
<td>Level III-2*</td>
<td>A comparison with reference standard that does not meet the criteria required for level II and III-1 evidence</td>
</tr>
<tr>
<td>Level III-3*</td>
<td>Diagnostic case-control study</td>
</tr>
<tr>
<td>Level IV</td>
<td>Study of diagnostic yield (no reference standard)</td>
</tr>
<tr>
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<td>Case reports and expert opinion that include narrative literature, reviews and consensus statements</td>
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*For consistency with the Anaphylaxis guidelines, level III-1 – level III-3 for establishing diagnostic test accuracy were summarised as level III in this document.

Level of Evidence for Assessing Effectiveness of Interventions

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<td>One group nonrandomized (e.g., before and after, pretest, and post-test)</td>
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<tr>
<td>Level IV</td>
<td>Descriptive studies that include analysis of outcomes (single-subject design, case series)</td>
</tr>
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Grades of Recommendation

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<tr>
<td>Grade A</td>
<td>Consistent level I studies</td>
</tr>
<tr>
<td>Grade B</td>
<td>Consistent level II or III studies or extrapolations from level I studies</td>
</tr>
<tr>
<td>Grade C</td>
<td>Level IV studies or extrapolations from level II or III studies</td>
</tr>
<tr>
<td>Grade D</td>
<td>Level V evidence or troublingly inconsistent or inconclusive studies at any level</td>
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Clinical Algorithm(s)

The following algorithms are provided in the original guideline document:

- Algorithm for the diagnosis of food allergy
- Algorithm for oral food challenge

Scope

Disease/Condition(s)

Food allergy and anaphylaxis

Guideline Category

Counseling
Diagnosis
Evaluation
Management
Prevention
Risk Assessment
Treatment

Clinical Specialty

Allergy and Immunology
Critical Care
Intended Users

Advanced Practice Nurses
Emergency Medical Technicians/Paramedics
Health Care Providers
Hospitals
Nurses
Pharmacists
Physician Assistants
Physicians

Guideline Objective(s)

To provide evidence-based recommendations for the diagnosis and management of patients of any age with suspected or confirmed food allergy

Target Population

Patients of any age with suspected or confirmed food allergy

Interventions and Practices Considered

Diagnosis/Evaluation

1. Detailed clinical history including use of structured questions on symptoms, foods, and other background information
2. Determination of sensitization to food: skin prick test (SPT), specific immunoglobulin E (sIgE), component-resolved diagnostic test, determination of total IgE
3. Elimination diet
4. Diagnostic oral food challenge (OFC), including the double-blind placebo-controlled food challenge (DBPCFC)
5. Diagnosis of eosinophilic esophagitis (EoE): upper endoscopy and biopsies after proton-pump inhibitor treatment

Management/Treatment

1. Acute management
   - Timely management
   - Antihistamines
2. Elimination diet
   - Appropriate dietary avoidance
- Dietetic counseling
- Use of extensively hydrolyzed cow's milk formula
- Amino acid formulas
- Soy formulas

3. Education and risk assessment
   - Patient and caregiver education and counseling
   - Use of adrenaline autoinjector
   - Short-acting beta agonists
   - Glucocorticosteroids
   - Emergency department review

4. Specific immunotherapy (not recommended routinely)

5. OFCs at regular intervals to assess achievements of tolerance

6. Assessment of potential augmenting role of cofactors in food allergy reactions

Note: The following were considered but not recommended: unconventional tests including specific immunoglobulin G (IgG) testing, mast cell stabilizers, probiotic supplements, anti-IgE.

Major Outcomes Considered

- Frequency, risk factors, and outcomes of food allergy in Europe
- Diagnostic accuracy of tests aimed at supporting the clinical diagnosis of food allergy
- Effectiveness of pharmacological and nonpharmacological interventions for the management of acute, non-life-threatening food-allergic reactions
- Effectiveness of pharmacological and nonpharmacological interventions for the longer-term management of food allergy

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
Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

In developing these guidelines, three recent systematic reviews on the epidemiology, diagnosis, and management of food allergy were conducted (see the "Availability of Companion Documents" field).

Key questions addressed in the supporting systematic reviews: diagnosis and management:

- What is the epidemiology (i.e., frequency, risk factors, and outcomes) of food allergy in Europe and how does this vary by time, place, and person?
- What is the diagnostic accuracy of tests aimed at supporting the clinical diagnosis of food allergy?
- What is the effectiveness of pharmacological and nonpharmacological interventions for the management of acute, non-life-threatening food-allergic reactions?
- What is the effectiveness of pharmacological and nonpharmacological interventions for the longer-term management of food allergy?

The Epidemiology of Food Allergy in Europe: a Systematic Review

Search Strategy
Articles were retrieved using a highly sensitive search strategy implemented in four electronic databases (OVID MEDLINE, OVID EMBASE, CINAHL, and ISI Web of Science). The search strategy was devised on OVID MEDLINE and then adapted for the other databases (see Box 1 in the systematic review supplemental information [see the "Availability of Companion Documents" field]). Systematic reviews were retrieved by using the systematic review filter developed at McMaster University Health Information Research Unit (HIRU) (http://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx#Reviews). We also adapted the search filter from York University Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/intertasc/epidemiological_studies.html) to retrieve the characteristics describing the epidemiology of food allergy (FA). The McMaster filter (http://hiru.mcmaster.ca/hiru/HIRU_Hedges_EMBASE_Strategies.aspx#Prognosis) was applied for retrieving studies on prognostic factors. Additional references were located by hand search. Unpublished work and research in progress were searched through discussion with experts in the field. There were no language restrictions, and where possible the literature in languages other than English was translated. The literature that the reviewers were unable to translate is shown in the PRISMA flow diagram (see Figure 1 in the systematic review supplemental information [see the "Availability of Companion Documents" field]).

Inclusion and Exclusion Criteria

The following study designs were included: systematic reviews and meta-analyses, cohort studies, cross-sectional studies, case–control studies, and routine healthcare studies published in Europe between 1 January 2000 and 30 September 2012. These were chosen to ensure that the highest levels of European evidence were pooled based on the aims of the review. Reviews, discussion papers, nonresearch letters and editorials, case studies, and case series plus animal studies and all randomized controlled trials were excluded. See the systematic review supporting information (see the "Availability of Companion Documents" field) for more information.

Study Selection

The titles of retrieved articles were checked by two independent consultant reviewers according to the selection criteria and categorized as included, not included, and unsure. The abstracts of papers in the unsure category were retrieved and recategorized as above after further discussion. 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 a third reviewer arbitrated.

The Diagnosis of Food Allergy: a Systematic Review and Meta-analysis

Search Strategy

Articles were retrieved using a highly sensitive search strategy implemented in the following databases: Cochrane Library including Cochrane Database of Systematic Reviews, Database of Reviews of Effectiveness (DARE), Cochrane Central Register of Controlled Trials (CENTRAL) (Trials), Methods Studies, Health Technology Assessments (HTA), Economic Evaluations Database (EED), MEDLINE (OVID), EMBASE (OVID), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (Ebscohost), ISI Web of Science (Thomson Web of Knowledge), Turning Research into Practice (TRIP) Database, and Clinicaltrials.gov National Institutes of Health ([NIH] web).

The search strategies were supplemented by contacting an international panel of experts for potential studies. There were no language restrictions, and where possible, non-English language papers were translated.

Inclusion and Exclusion Criteria

Prospective or retrospective, cross-sectional or case–control studies that evaluated atopy patch test (APT), skin prick test (SPT), specific immunoglobulin Es (IgEs), and component-specific IgE in children or adults presenting with suspected food allergy caused by cow's milk, hen's egg, wheat, soy, peanut, tree nut, fish, or shellfish were included. The reference standard was double-blind placebo-controlled food challenge (DBPCFC) used in at least 50% of the participants. Studies in which participants were selected based on having a positive food allergy test result (index test or reference standard) or for which no 2 X 2 data could be extracted were excluded.

Study Selection

Two reviewers independently checked titles and abstracts identified by the search, followed by review of the full text for assessment of eligibility.

Acute and Long-term Management of Food Allergy: Systematic Review

Search Strategy

The following databases were searched: Cochrane Library, MEDLINE, EMBASE, CINAHL, ISI Web of Science, TRIP Database and Clinicaltrials.gov. Experts in the field were contacted for additional studies. Specific search strategies are included in the online supplement for this review (see the "Availability of Companion Documents" field).
Inclusion and Exclusion Criteria

Studies of children or adults diagnosed with food allergy or reporting that they had food allergy were included. This included allergy where food was the primary sensitizer and pollen-associated food allergy if there was a direct diagnosis of food allergy. Studies of interventions for life-threatening manifestations were excluded because they were the focus of another review in this series. Systematic reviews and meta-analyses, randomized controlled trials, quasi-randomized controlled trials, controlled clinical trials, controlled before-and-after studies, and interrupted time series studies published up until September 30, 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 a third reviewer.

Number of Source Documents

The Epidemiology of Anaphylaxis in Europe: a Systematic Review

The authors identified 4053 articles through database searching and 9 through other sources. One hundred and nine articles were assessed for eligibility, and 75 (based on 56 primary studies) were included in the narrative synthesis and 30 studies in the meta-analysis.

The Diagnosis of Food Allergy: a Systematic Review and Meta-analysis

The authors identified 6260 studies (excluding duplicates) and 312 were eligible for full-text review. Twenty-four studies (33 references) with a total of 2831 participants were included in the quantitative analyses.

Acute and Long-term Management of Food Allergy: Systematic Review

Eighty-four studies were included, comprising 12 systematic reviews (15%), 54 randomized controlled trials (64%), and 18 nonrandomized comparative or controlled cross-over studies (21%).

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 for Establishing Diagnostic Test Accuracy

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Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

In developing these guidelines, three recent systematic reviews on the epidemiology, diagnosis, and management of food allergy were conducted (see the "Availability of Companion Documents" field).

The Epidemiology of Anaphylaxis in Europe: a Systematic Review

Risk of Bias Assessment

Risk of bias in the studies was independently carried out by two reviewers using adapted relevant versions of the Critical Appraisal Skills Programme (CASP) tool (http://www.casp-uk.net/). An overall grading was assigned to each study based on the grading obtained from the various components of the study (i.e., the appropriateness of the study design for the research question, the risk of selection bias, exposure, and outcome assessment). Discrepancies were resolved by consensus or a third reviewer arbitrated.

Analysis, Synthesis, and Reporting

A customized data extraction form was developed and independently used to obtain relevant data from each study by two reviewers. Discrepancies were resolved by discussion or arbitration by a third reviewer. Reviewers recalculated all the frequency estimates of any food allergy (FA) occurrence if adequate data were provided by authors by using minimal measured events rather than extrapolated ones. The 95% confidence intervals (95% CI) of recalculations were computed by the Wilson score method without continuity correction. A random-effects meta-analysis was performed for clinically and methodologically comparable studies to estimate the frequency of FA. Reviewers calculated the age-stratified pooled estimates for the age group 0–17 years (children) and 18 years and over (adults). The pooled estimates were also stratified by geographical region in Europe. Statistical analysis was undertaken using STATA 11 (Stata Corp, College Station, TX). See Supporting Information for this systematic review for further details (see the "Availability of Companion Documents" field).

The Diagnosis of Food Allergy: a Systematic Review and Meta-analysis

Data Extraction

Two reviewers extracted data using a customized form and assessed risk of bias using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool. Any discrepancies were resolved by consensus and, where necessary, a senior reviewer was consulted. Reviewers collected study characteristics and recorded the number of true positives, true negatives, false positives, and false negatives for constructing a 2 × 2 table for each study. In cases where 2 × 2 data were not available, where possible, reviewers derived them from reported summary statistics such as sensitivity, specificity, and/or likelihood ratios.

Data Analysis, Synthesis, and Reporting

For each test, diagnostic accuracy was assessed according to target food. Preliminary exploratory analyses were conducted for each test by plotting pairs of sensitivity and specificity from each study on forest plots and in receiver operating characteristic (ROC) space. Hierarchical summary ROC models were used to summarize the accuracy of each test and to compare the accuracy of two or more tests. Where studies used
a common or similar cutoff, parameter estimates from the models were used to compute summary sensitivities and specificities with 95% confidence regions. Analyses were performed in Review Manager 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2012), and SAS software (version 9.2; SAS Institute, Cary, NC, USA).

Acute and Long-term Management of Food Allergy: Systematic Review

Risk of Bias Assessment

Risk of bias was independently carried out by two reviewers using adapted versions of the CASP tool and the Cochrane Effective Practice and Organization 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

A customized data extraction form was used to abstract data from each study, this process being independently undertaken by two reviewers. Discrepancies were resolved by discussion. Three 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 topic, design, quality, and outcomes. The narrative synthesis was checked by a group of methodologists and subject experts to ensure accuracy and relevance.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

These Guidelines were produced using the Appraisal of Guidelines for Research & Evaluation (AGREE II) approach. This is a structured approach for the production of guidelines designed to ensure appropriate representation of the full range of stakeholders, a careful search and appraisal of the relevant literature and a systematic approach to the formulation and presentation of recommendations. In order to ensure that the risk of bias is minimized at each step of the process, interim consensus meetings were organised. An overview of the approach is provided below.

Clarifying the Scope and Purpose of the Guidelines

The scope of these European Academy of Allergy and Clinical Immunology (EAACI) guidelines is multi-faceted providing statements that assist clinicians in the management of food allergy in daily practice; harmonizing the approach to this disease among stakeholders across Europe; and advocating for further research.

Ensuring Appropriate Stakeholder Involvement

Participants and Experts in the Food Allergy Diagnosis and Management Taskforce represented a range of 12 European countries, and disciplinary and clinical backgrounds, i.e., gastroenterologists, primary care, dietitians, and patient groups.

Systematic Reviews of the Evidence

The initial full range of questions that were considered important were rationalized through several rounds of iteration into key questions that were then pursued through formal systematic reviews of the evidence.

Formulating Recommendations

The Taskforce graded the strength and consistency of key findings from these systematic reviews to formulate evidence-linked recommendations for care. This involved formulation of clear recommendations and the strength of evidence underpinning each recommendation. Experts identified barriers and facilitators to the implementation of each recommendation and included advice how to implement and listed audit criteria that may facilitate organizational compliance.

Rating Scheme for the Strength of the Recommendations

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 |

**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**

Peer Review and Public Comment

A draft of these guidelines was externally peer-reviewed by invited experts from a range of organizations, countries and professional backgrounds. Additionally, the draft guideline was made available on the European Academy of Allergy and Clinical Immunology (EAACI) website for a 3 week period (June 2013) to allow all stakeholders to comment. All feedback was considered by the Food Allergy Diagnosis and Management Taskforce and, where appropriate, revisions were made.

**Evidence Supporting the Recommendations**

**References Supporting the Recommendations**


Type of Evidence Supporting the Recommendations

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

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate diagnosis and management of food allergy

Potential Harms

- For skin prick tests (SPTs), the use of good-quality food allergen extracts, characterized by the demonstration of clinical efficacy and the presence of relevant allergens, is strongly recommended when available. Due to a possible under-representation of minor allergens or instability of the allergenic proteins, false-negative reactions can occur. Whenever these types of extracts are not available and/or minor or instable allergens are relevant for the sensitization (i.e., most fruits and vegetables), fresh foods should be used. Only trained healthcare professionals, able to interpret results and manage possible adverse reactions, should perform SPTs.
- SPT and specific immunoglobulin E (sIgE) (and probably component-resolved diagnosis [CRD]) offer high sensitivity in relation to a range of allergens implicated in IgE-mediated food allergy. Direct comparisons among the tests are difficult given the limited body of evidence in which these tests have been compared in the same population. There is greater variation in the specificity of these tests, because they indicate sensitization that may not be of clinical relevance, with sIgE tending to have a higher rate of false-positive results.
- Oral food challenge must be performed in a specialist setting with emergency support immediately available; where there is a moderate-to-high risk of a severe reaction, intensive care support must be immediately available.
- Food allergen-specific immunotherapy for primary food allergy is a promising immunomodulatory treatment approach, but it is associated with risk of adverse reactions, including anaphylaxis. For oral immunotherapy, two systematic reviews, eight randomized trials, and three nonrandomized comparisons found that oral immunotherapy with food allergens was associated with improved tolerance and reduced symptoms for children and adults with various food allergies. However, around 90% of participants have side-effects although these were usually not severe. Oral immunotherapy was more efficacious for desensitization to cow’s milk than sublingual immunotherapy but was accompanied by more systemic side-effects in one study. One randomized trial found no benefit. The two systematic reviews found mixed evidence and suggested that oral immunotherapy should not currently be recommended as routine treatment. In light of its potential benefit, it should be performed only in highly specialized centers, with expert staff and adequate equipment, and in accordance with clinical protocols approved by local ethics committees.

Implementation of the Guideline

Description of Implementation Strategy

Education is a key feature in the management of food allergy and should be heavily promoted to patients, families, and caregivers as well as to healthcare professionals. Developing and validating educational tools will further the establishment of vertical and horizontal networks between Centres of Excellence, allergy specialists, and primary care practitioners. Implementation at the community level should be in partnership with the patient organizations. Adequate reimbursement from national healthcare systems and insurance bodies for diagnostic procedures and the management strategies, including education, should be available.

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

Table S2. Food allergy diagnosis: barriers and facilitators to implementation of recommendations
Table S4. Management of food allergy: barriers and facilitators to implementation of recommendations
Implementation Tools

Clinical Algorithm

For information about availability, see the Availability of Companion Documents and Patient Resources fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Safety

Timeliness

Identifying Information and Availability

Bibliographic Source(s)


Adaptation

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

Date Released

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Guideline Developer(s)

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European Academy of Allergy and Clinical Immunology (EAACI)

Guideline Committee

European Academy of Allergy and Clinical Immunology (EAACI) Food Allergy Diagnosis and Management Taskforce

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Financial Disclosures/Conflicts of Interest

Antonella Muraro has provided scientific advice for Meda. Graham Roberts has provided scientific advice for Danone and ALK-Abelló; Thomas Werfel has provided scientific advice for Meda and Novartis. Caroline Nilsson and Susanne Halcken have provided scientific advice for ALK-Abelló. Barbara Ballmer-Weber has provided scientific advice for Thermo Fisher Scientific. Thermo Fisher and ALK-Abelló have provided consumables for his research activities. Tony DuBois has provided scientific advice for ALK-Abelló and received funding from ALK-Abelló to support his research activities. Margitta Worm has provided scientific advice for ALK-Abelló, Meda, Novartis, and Stallergenes.Montserrat Fernández Rivas has provided scientific advice to GSK and has received funding from the European Union, the Spanish Ministry of Science, and
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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