EAACI guidelines on allergen immunotherapy: IgE mediated Food Allergy

Draft 0.14; 12th May 2017

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Short title: EAACI Food Allergy Immunotherapy Guidelines

Key words: adolescent, adult, allergen immunotherapy, allergy, food, paediatric

Words: 4831

Abbreviations: AGREE II, Appraisal of Guidelines for Research & Evaluation; AIT, Allergen immunotherapy; BAT, basophil activation test; CCT, controlled clinical trial; CI, confidence
interval; CM, cow’s milk; CRD, component-resolved diagnosis; DBPCFC, double-blind, placebo-controlled food challenge; EAACI, European Academy of Allergy and Clinical Immunology; EMA, European Medicines Agency; EPIT, Epicutaneous immunotherapy; EoE, eosinophilic esophagitis; FA, food allergy; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HE, hen’s egg; IgE, immunoglobulin E; IgG, immunoglobulin G; IgG4, immunoglobulin G4; OFC, oral food challenge; OIT, oral immunotherapy; QoL, quality of life; RCT, randomized controlled trial; RR, risk ratio; sIgE, specific IgE; SCIT subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SPT, skin prick test; SR, systematic review; WAO, World Allergy Organization.
ABSTRACT

Food allergy can have significant effects on morbidity and quality of life and can be costly in terms of medical visits and treatments. There is therefore considerable interest in generating efficient and new active therapeutic approaches that represent a novel strategy for the treatment of food allergies. In this field, current clinical research focuses on food allergen-specific immunotherapy through oral (OIT), sublingual (SLIT) or epicutaneous (EPIT) routes. These Guidelines have been prepared by the European Academy of Allergy and Clinical Immunology (EAACI) Task Force on Allergen Immunotherapy for IgE mediated food allergy and are part of the EAACI Guidelines for Allergen Immunotherapy – AIT guidelines for clinical practice. They aim to provide evidence based recommendations for active treatment of IgE mediated food allergy with food allergen immunotherapy (AIT).

Immunotherapy relies on the delivery of gradually increasing doses of specific allergen to increase threshold of reaction while on therapy (e.g. desensitization) in patients with persistent food allergy and ultimately, to achieve post-discontinuation effectiveness (e.g. tolerance). The most frequent route of administration for AIT for food allergy is the oral route, where the allergen is either immediately swallowed (OIT) or held under the tongue for an interval (SLIT). Epicutaneous (EPIT) route is also under investigation, it consists of the application of patches containing food allergen onto the skin. Overall, the studies revealed a substantial benefit for the patients undergoing either OIT or SLIT with respect to efficacy during treatment. Regarding post-discontinuation effectiveness a benefit for the patient trough allergen immunotherapy was suggested but could not be confirmed. Adverse events during AIT had been frequently reported. However, few subjects had to discontinue immunotherapy. Based on this evidence, patients and their families can be provided with evidence based advice about AIT for IgE mediated food allergy. The advice includes that there is more evidence of efficacy of AIT in children in comparison with adults, and for cow’s milk, hen’s egg and peanut allergies than for other food allergies. Taking into account both currently issues and gaps, AIT could be performed in research centers or in specialized clinical centers for food allergy immunotherapy.
§1. Introduction

Food allergy (FA) has emerged as a significant medical problem in recent decades. With FA affecting up to 8% of children and 5% of adults in westernized countries, development of therapies for this potentially life-threatening condition has become a public health priority (1-3). The key terms and clinical presentation of food allergy are summarized in Boxes 1 and 2A.

The current approach to managing FA focuses on avoidance of the trigger foods and availability and training in the use of rescue medication in the event of an allergic reaction developing. Allergen immunotherapy (AIT) is potentially a curative therapy. AIT has the potential to increase the amount of food that the patient can tolerate, preventing allergic symptoms and reducing the risk of potentially life-threatening allergic reactions. The first case of AIT was described in 1908 to hen’s egg (4) and the principles underlying the therapy have remained the same i.e. therapy consists of the administration of gradually increasing doses of food allergens via an oral (OIT), sublingual (SLIT), subcutaneous (SCIT) route (2). A fixed dose of allergen can be administered through an epicutaneous route (EPIT) (2).

The ultimate goal of AIT for FA is to achieve post-discontinuation effectiveness so ideally a patient can eat a normal serving of the trigger food without symptoms. This is also known as “tolerance” or “sustained unresponsiveness”. These all imply that the food allergen can be ingested without the appearance of allergic symptoms despite a period of absence of exposure. The time period required to establish true post-discontinuation effectiveness is not yet defined. Based on current evidence, a more attainable target is effectiveness during treatment (typically referred to as “desensitization”) which concerns a reversible or partially reversible clinical response that is dependent on ongoing allergen exposure. If the administration of the allergen is discontinued, the previous level of clinical reactivity frequently returns (5).

The primary outcome of efficacy of AIT for FA is a change in the threshold of reactivity, which is ideally determined by an oral food challenge (OFC) and where possible, a double-blind, placebo-controlled food challenge (DBPCFC). There is great variability described in the change in threshold between different studies and for different food (6,7). Additional parameters have been included in the monitoring of AIT for FA: SPTs (8), sIgE, IgG and IgG₄ levels in serum (9). Few studies looked at basophil activation test (BAT) (10), cytokines...
(e.g. IL-10, IL-5 and IFN-\(\gamma\)) (11-12), or regulatory T-cells (13).

The most frequent route of administration of AIT for FA is the oral route, where the allergen is either immediately swallowed (oral immunotherapy, OIT) or held under the tongue for an interval (sublingual immunotherapy (SLIT)) (3). There are currently ongoing studies with the subcutaneous route (SCIT) for peanut and fish allergies (14-16). Epicutaneous immunotherapy (EPIT) is also under investigation for peanut and milk; it involves application of patches containing food allergen onto the skin (17). There is no consistent formulation of the food used for FA-AIT in studies conducted to date (18). Dilution of unprocessed products, crude extracts and flours have been used (18). In addition, some studies have been carried out with powered or lyophilized products, prepared by pharmaceutical companies or hospital pharmacies (19).

These guidelines have been prepared by the European Academy of Allergy and Clinical Immunology (EAACI) Task Force on Allergen Immunotherapy for IgE-mediated Food Allergy and are part of the EAACI allergen specific immunotherapy (AIT) guidelines for clinical practice. The guidelines aim to provide evidence based recommendations for the use of AIT in patients with diagnosed IgE-mediated FA. The primary audience is hospital-based clinical allergists or pediatric allergists. However, these guidelines are also likely to be of relevance to other healthcare professionals (e.g. doctors, nurses, dieticians, psychologists and paramedics) who are involved in the management of allergic patients and their families in any setting. The development of these Guidelines has been informed by the systematic review (SR) and meta-analysis on AIT for FA (18).
### Box 1. Key terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allergen immunotherapy</strong></td>
<td>Repeated allergen exposure at regular intervals to modulate immune response to reduce symptoms and the need for medication for clinical allergies and to prevent the development of new allergies [adapted from EMA]. This is also known as allergen specific immunotherapy.</td>
</tr>
<tr>
<td><strong>Effectiveness during treatment</strong></td>
<td>The ability to safely consume foods containing the culprit allergen while on allergen immunotherapy. This clinical response is dependent on ongoing allergen exposure. If the administration of the allergen is discontinued, the previous level of clinical reactivity frequently returns. It is also referred to as “desensitization”.</td>
</tr>
<tr>
<td><strong>Food</strong></td>
<td>Any substance, whether processed, semi-processed, or raw, which is intended for human consumption, and includes drink, chewing gum, and any substance which has been used in the manufacture, preparation, or treatment of ‘food’ but does not include cosmetics or tobacco or substances used only as drugs [Codex Alimentarius]. Food is eaten, drunk or otherwise taken to the body to provide energy and nutritional support, maintain life, or stimulate growth.</td>
</tr>
<tr>
<td><strong>Food allergy</strong></td>
<td>An adverse reaction to food mediated by an immunologic mechanism, involving specific IgE (IgE-mediated), cell-mediated mechanisms (non-IgE-mediated) or both IgE- and cell-mediated mechanisms (mixed IgE- and non-IgE-mediated) [from EAACI Food Allergy and Anaphylaxis Guidelines (3)].</td>
</tr>
<tr>
<td><strong>Post-discontinuation effectiveness</strong></td>
<td>The ability to safely consume a normal serving of foods containing the trigger allergen despite a period of absence of exposure. This is also known as “tolerance” or “sustained unresponsiveness”.</td>
</tr>
<tr>
<td><strong>Sensitization</strong></td>
<td>Detectable IgE antibodies, either by means of skin prick test or determination of serum specific IgE antibodies.</td>
</tr>
</tbody>
</table>
**Box 2A. Clinical presentations of IgE-mediated food allergy**

<table>
<thead>
<tr>
<th>Systems</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cutaneous</strong></td>
<td>pruritus, erythema/flushing, urticaria, angioedema, contact urticaria</td>
</tr>
<tr>
<td><strong>Ocular</strong></td>
<td>itching, redness, tearing, periorbital edema</td>
</tr>
<tr>
<td><strong>Nasal</strong></td>
<td>nasal congestion, nasal pruritus, rhinorrhea, sneezing</td>
</tr>
<tr>
<td><strong>Oropharynx</strong></td>
<td>itching, dryness/discomfort, swelling of the oral cavity, lips, tongue and/or pharynx</td>
</tr>
<tr>
<td><strong>Lower Respiratory tract</strong></td>
<td>hoarseness, laryngeal edema, dysphonia, shortness of breath, cough, wheezing, chest tightness/pain</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>abdominal pain, nausea, emesis, diarrhea</td>
</tr>
<tr>
<td><strong>Cardiovascular/Neurological</strong></td>
<td>tachycardia, hypotension, dizziness, loss of consciousness/fainting, seizures, incontinence</td>
</tr>
<tr>
<td><strong>Multi-organ</strong></td>
<td>anaphylaxis</td>
</tr>
<tr>
<td><strong>Miscellaneous:</strong></td>
<td>sense of impending doom, uterine cramping/contractions</td>
</tr>
</tbody>
</table>
§2. Methodology

These Guidelines were produced using the Appraisal of Guidelines for Research & Evaluation (AGREE II) framework (20,21), which is a structured approach to guideline production. This 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. The process started in April 2015 beginning with detailed face-to-face discussions agreeing the process and the key clinical areas to address, followed by face-to-face meetings and web-conferences in which professional and lay representatives participated.

Clarifying the scope and purpose of the guidelines

The scope of these EAACI Guidelines is multifaceted providing statements to assist qualified clinicians in the optimal use of AIT in the management of patients with IgE-mediated FA and identifying gaps for further research.

Ensuring appropriate stakeholder involvement

Participants in the EAACI Taskforce on FA-AIT represented a range of 13 countries, and different disciplinary and clinical backgrounds, such as allergists, pediatricians, primary care physicians, and patient group representatives. Additionally, producers of AIT products were given the opportunity to review and comment on the draft guidelines to allow suggestions for new product research. These comments were considered by the Taskforce and, where appropriate, revisions were made.

Systematic reviews of the evidence

The initial full range of questions that were considered important were rationalized through several rounds of iteration to agree one key question: what is the effectiveness, changes in disease specific quality of life, cost-effectiveness and safety of AIT in patients with IgE mediated FA. This was then pursued through a formal systematic review of the evidence (18) (see Box 3).
Box 3. Summary of the aims and outcomes of the supporting systematic review (18)

Aims: To provide a systematic review of the evidence on the effectiveness, safety and cost-effectiveness of AIT for food allergy.

Study outcomes:

Primary

➢ Effectiveness during the treatment (i.e. the ability to safely consume foods containing the allergen in question while on AIT) or post-discontinuation effectiveness (the ability to consume foods containing the allergen in question after discontinuing AIT) at food challenge.
➢ Assessment of changes in disease specific quality of life (QoL) using a validated instrument.

Secondary

➢ Secondary outcome measures of interest were safety as assessed by local and systemic reactions in accordance with the World Allergy Organization’s (WAO) grading system of side-effects
➢ Health economic analysis from the perspective of the health system/payer as reported in studies.

Formulating recommendations

We graded the strength and consistency of key findings from the SR to formulate evidence-based recommendations for clinical care (Oxford Centre for Evidence-based Medicine) (Box 4) (22). This involved formulating clear recommendations with the strength of evidence underpinning each recommendation made clear. Where the systematic review did not cover the clinical area, we took a hierarchical approach reviewing other evidence until we could formulate a recommendation, i.e.: (i) other systematic reviews on the subject to see if these provided any clarity on the topic; (ii) randomized controlled trials (RCTS) within these systematic reviews; (iii) other RCTs known to Taskforce members; and (iv) a consensus-based approach. Experts identified the resource 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.

**Box 4.** Assigning levels of evidence and recommendations (Oxford Centre for Evidence-based Medicine) (22)

<table>
<thead>
<tr>
<th>Levels of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level I</strong> Systematic reviews, meta-analysis, randomized controlled trials</td>
</tr>
<tr>
<td><strong>Level II</strong> Two groups, nonrandomized studies (e.g., cohort, case–control)</td>
</tr>
<tr>
<td><strong>Level III</strong> One group nonrandomized (e.g., before and after, pre-test, and post-test)</td>
</tr>
<tr>
<td><strong>Level IV</strong> Descriptive studies that include analysis of outcomes (single-subject design, case series)</td>
</tr>
<tr>
<td><strong>Level V</strong> Case reports and expert opinion that include narrative literature, reviews, and consensus statements</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grades of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade A</strong> Consistent level I studies</td>
</tr>
<tr>
<td><strong>Grade B</strong> Consistent level II or III studies or extrapolations from level I studies</td>
</tr>
<tr>
<td><strong>Grade C</strong> Level IV studies or extrapolations from level II or III studies</td>
</tr>
<tr>
<td><strong>Grade D</strong> Level V evidence or troublingly inconsistent or inconclusive studies at any level</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strength of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strong</strong> Evidence from studies at low risk of bias/high quality studies</td>
</tr>
<tr>
<td><strong>Moderate</strong> Evidence from studies at moderate risk of bias/ moderate quality studies</td>
</tr>
<tr>
<td><strong>Weak</strong> Evidence from studies at low risk of bias/high quality studies</td>
</tr>
</tbody>
</table>

Recommendation are phrased according to the strength of recommendation: strong, “is recommended”; moderate, “can be recommended”; weak, “may be recommended in specific circumstances”; negative, “can not be recommended”.
**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 guidelines were made available on the EAACI Website for a 3-week period in May 2017 to allow a broader array of stakeholders to comment. All feedback was considered by the Taskforce and, where appropriate, final revisions were made in light of the feedback received. We will be pleased to continue to receive feedback on these Guidelines, which should be addressed to the corresponding author.

**Identification of evidence gaps**

The process of developing these Guidelines has identified a number of evidence gaps which we have prioritized.

**Editorial independence and managing conflict of interests**

The production of these Guidelines was funded and supported by EAACI. The funder did not have any influence on the guideline production process, on its contents, or on the decision to publish. Taskforce members’ conflict of interests were taken into account by the Taskforce Chairs as recommendations were formulated. Final decisions about strength of evidence for recommendations were reviewed by methodologists who had no conflict of interests in this area.

**Updating the guidelines**

We plan to update these guidelines in 2021 unless there are important advances before then.
§3. General considerations before initiating AIT for IgE-mediated food allergy

AIT is indicated for patients with evidence of an IgE-mediated FA and in whom avoidance measures are ineffective, undesirable or cause severe limitations to a patient’s quality of life. Prior to initiating AIT, a diagnosis of IgE-mediated FA is critical. This requires a clear clinical history of an acute reaction(s) after consumption of the triggering food. The presence of sIgE to the triggering food should be established with SPT and/or sIgE. To complete the diagnosis of food allergy a food challenge may be required (Box 5).

<table>
<thead>
<tr>
<th>Box 5. Diagnosis of IgE-mediated food allergy before initiating AIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ Detailed medical history to establish current clinical reactivity to the food (recent reactions)</td>
</tr>
<tr>
<td>➢ Allergy testing (skin prick tests (SPT) with food allergen extracts or fresh foods) and/or specific IgE (sIgE) to food allergen extract(s) or component(s) (component resolved diagnosis, CRD)</td>
</tr>
<tr>
<td>➢ Oral food challenge (OFC)</td>
</tr>
</tbody>
</table>

Current studies have enrolled patients with heterogeneous ages and clinical presentations (18). Although studies have included infants and pre-school children who have tolerated AIT safely (23,24), the limited ability of young children to report early symptoms of allergic reactions should be considered. Furthermore, young children have a high likelihood of developing spontaneous tolerance, particularly to cow’s milk (CM), hen’s egg (HE), wheat and soy (25-31). Therefore, for these allergens it may be more appropriate to commence AIT only if spontaneous tolerance is not apparent during early childhood.

Lastly, AIT for FA is logistically demanding, time-consuming and most patients are affected by frequent side effects. Only patients and families who understand the aim of the intervention and its risks, and are motivated and adherent should be considered for FA-AIT. Therefore, there are many variables to be considered and discussed with the patient and family before commencing FA-AIT (Box 6). AIT for FA should only be undertaken in centres with professional training in FA care with the expertise, competencies and full resuscitation facilities to safely deliver this therapy and manage any complications, including anaphylaxis (Box 7).
Box 6. General considerations before initiating AIT for food allergy

1. Confirmed, persistent, moderate to severe systemic IgE-mediated FA.
2. Consider the likelihood of spontaneous resolution of the specific FA (e.g. CM and HE allergies)
3. Patients and their families should be motivated, adherent and capable of administering emergency treatment (including intramuscular adrenaline) in case of adverse effects.
4. Clinical centres undertaking AIT for FA should have the expertise and facilities to safely deliver this therapy.

*These considerations are based on expert opinion.*

Box 7. Personnel and equipment required to perform AIT for food allergy

<table>
<thead>
<tr>
<th>Personnel</th>
<th>Medical doctor and nurse trained and experienced in the diagnosis of food allergy including oral challenges, and trained and experienced in the treatment of allergic reactions including anaphylaxis. Hospital personnel should be able to provide at least 12h of observation in case of adverse reactions related to AIT. Minimum: 1 medical doctor, 1 nurse. #Anesthesiology team or equivalent team particularly trained in resuscitation on call, at hand within 5 minutes.</th>
</tr>
</thead>
</table>
| Equipment | Phonendoscope  
Sphygmomanometer  
Pulse oximeter  
Oxygen  
Spirometer, peak flow meter  
Laryngoscope(s), intubation tube(s), ventilation bag(s)  
Heart defibrillator (knowledge and experience how to use it)  
#Crash trolley |
| Medication | Adrenaline (epinephrine), antihistamine (oral and parenteral), inhaled beta₂-agonist, corticosteroids (oral, parenteral).  
IV lines and IV fluids |

# According to the local facilities and organization of assistance to patients experiencing a severe anaphylaxis.
§4. General contraindications

Given the long-treatment duration and common adverse reactions, any medical or social condition that impedes the ability for frequent clinical visits, awareness of side effects and adherence to treatment represent an absolute contraindication. Uncontrolled asthma is an absolute contraindication as it is associated with an increased risk of life-threatening systemic reactions (32). Well-controlled asthma is not a contraindication for AIT for FA. Whilst a history of anaphylaxis to a food may be associated with more side effects, it is not a contraindication, these patients should be more closely supervised. Uncontrolled, severe atopic dermatitis/eczema and uncontrolled urticaria are relative contraindications given the risk of acute exacerbation while on AIT; these should be controlled before AIT is initiated. Patients on therapy for eosinophilic esophagitis (EOS) should not be treated with OIT because of the high risk of an exacerbation. There is a lack of available data on the risks associated with AIT for FA and autoimmune diseases. Similarly, given the lack of data and the theoretical risk of disease exacerbation, malignant neoplasias and autoimmune diseases unresponsive to treatment are considered an absolute contraindication. Medications such as beta-blockers or severe medical conditions such as cardiovascular diseases that impede efficacy of adrenaline (epinephrine) to treat anaphylaxis or increase its side effects, respectively, are all relative contraindications (Box 8). The final decision on starting AIT is therefore to be established on an individual basis in discussion with the patient and/or family.
Box 8. General contraindications to allergen immunotherapy for food allergy

1. ABSOLUTE:
   a. inability to adhere to the protocol, e.g. unable to regularly attending clinic
   b. uncontrolled asthma
   c. active malignant neoplasia(s)
   d. autoimmune diseases unresponsive to treatment

2. RELATIVE
   a. eosinophilic esophagitis (EoE) and other eosinophilic gastrointestinal disorders
   b. severe systemic illness or severe medical conditions such as cardiovascular diseases
   c. uncontrolled, severe atopic dermatitis/eczema
   d. uncontrolled urticaria
   e. beta-blockers

§5. Efficacy of different approaches to AIT for IgE-mediated food allergy

The efficacy of FA-AIT has to be assessed in regard to the timing of AIT, the culprit food and route of administration.

Efficacy of oral immunotherapy (OIT)

A recently performed meta-analysis identified 23 controlled trials, including eight which were placebo-controlled, plus 17 studies that employed clinical outcome(s) and immunological parameters for the assessment of efficacy of OIT in regard to efficacy during treatment (18). Overall, the studies revealed a substantial benefit for the patients undergoing OIT with respect to efficacy during treatment (18). There were a few studies that assessed post-discontinuation effectiveness, of which only 4 trials could be included in the meta-analysis (18). A benefit for the patient post-discontinuation of OIT was suggested, but could not be confirmed (18).. Only one RCT reported disease-specific QoL scores for patients and their families but no comparative results between the OIT group and the control group were reported (5).
Regimens for OIT varied widely from rush protocols to slow up-dosing regimens with or without an initial dose escalation day (34). There seems to be no striking difference in regard to efficacy during treatment between the different protocols with all showing a substantial risk reduction (18). The data published to date do not allow the ideal treatment regimen concerning doses and intervals to be determined. Recommendations for FA-OIT are shown in Boxes 9-12 according to the food allergen and age of patients.
<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Evidence level</th>
<th>Grade of recommendation</th>
<th>Strength of recommendation</th>
<th>Other considerations</th>
<th>Key references</th>
</tr>
</thead>
<tbody>
<tr>
<td>OIT is recommended as a treatment option to increase threshold of reaction while on treatment in children with persistent cow’s milk allergy</td>
<td>I</td>
<td>A</td>
<td>Strong recommendation based on convincing evidence for effect from systematic review and meta analyses including high quality RCTs</td>
<td>Risk of adverse reactions to be considered</td>
<td>Nurmatov, 2017 (18); Longo 2008 (7); Skripak 2008 (35)</td>
</tr>
<tr>
<td>OIT may be recommended to achieve post discontinuation effectiveness in children with persistent cow’s milk allergy</td>
<td>I</td>
<td>A</td>
<td>Weak recommendation based on one low quality RCT</td>
<td>Risk of adverse reactions to be considered</td>
<td>Staden 2007 (33)</td>
</tr>
</tbody>
</table>
**Box 9b. Recommendations on efficacy of OIT in adults with cow’s milk allergy**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Evidence level</th>
<th>Grade of recommendation</th>
<th>Strength of recommendation</th>
<th>Other considerations</th>
<th>Key references</th>
</tr>
</thead>
<tbody>
<tr>
<td>OIT may be recommended as a treatment option to increase the threshold of reaction while on treatment in adults with persistent cow’s milk allergy</td>
<td>I</td>
<td>A</td>
<td>Weak recommendation based on one study including mixed populations</td>
<td>Risk of adverse reactions to be considered</td>
<td>Skripak 2008 (35)</td>
</tr>
<tr>
<td>No recommendation can be made about OIT as a treatment option in adults with persistent cow’s milk allergy with the goal of post discontinuation effectiveness</td>
<td>V</td>
<td>D</td>
<td>No recommendation due to lack of evidence</td>
<td></td>
<td>Nurmatov, 2017 (18)</td>
</tr>
</tbody>
</table>
### Box 10a. Recommendation on efficacy of OIT in children with hen’s egg allergy

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Evidence level</th>
<th>Grade of recommendation</th>
<th>Strength of recommendation</th>
<th>Other considerations</th>
<th>Key references</th>
</tr>
</thead>
<tbody>
<tr>
<td>OIT is recommended as a treatment option to increase the threshold of reaction while on OIT in children with persistent hen’s egg allergy</td>
<td>I</td>
<td>A</td>
<td>Strong recommendation based on convincing evidence for effect from systematic review and meta analyses including high quality RCTs</td>
<td>Risk of adverse reactions to be considered</td>
<td>Nurmatov, 2017 (18); Caminiti 2015 (36); Burks, 2012 (8)</td>
</tr>
<tr>
<td>OIT may be recommended as a treatment option to achieve post-discontinuation effectiveness in children with persistent hen’s egg allergy</td>
<td>I</td>
<td>A</td>
<td>Moderate/weak recommendation based on one RCT</td>
<td>Risk of adverse reactions to be considered</td>
<td>Escudero 2015 (37)</td>
</tr>
</tbody>
</table>
Box 10b. Recommendations on efficacy of OIT in adults with hen’s egg allergy

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Evidence level</th>
<th>Grade of recommendation</th>
<th>Strength of recommendation</th>
<th>Other considerations</th>
<th>Key references</th>
</tr>
</thead>
<tbody>
<tr>
<td>No recommendation can be made about OIT as a treatment option in adults with persistent hen’s egg allergy</td>
<td>V</td>
<td>D</td>
<td>No recommendation due to lack of evidence</td>
<td>Nurmatov, 2017 (18)</td>
<td></td>
</tr>
</tbody>
</table>
**Box 11a. Recommendations on efficacy of OIT in children with peanut allergy**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Evidence level</th>
<th>Grade of recommendation</th>
<th>Strength of recommendation</th>
<th>Other considerations</th>
<th>Key references</th>
</tr>
</thead>
<tbody>
<tr>
<td>OIT is recommended as a treatment option to increase the threshold of reaction while on treatment in children with peanut allergy</td>
<td>I</td>
<td>A</td>
<td>Strong recommendation based on convincing evidence for effect from high quality RCTs</td>
<td>Risk of adverse reactions to be considered</td>
<td>Tang, 2015 (38); Varshey 2011 (39); Narisety 2014 (40),</td>
</tr>
<tr>
<td>OIT may be recommended as a treatment option to achieve post discontinuation effectiveness in children with peanut allergy</td>
<td>I</td>
<td>A</td>
<td>Moderate/weak recommendation based on one RCT with small sample size (only children) and one CCT including mixed populations</td>
<td></td>
<td>Narisety 2014 (40), Syed, 2014 (41)</td>
</tr>
</tbody>
</table>
1 **Box 11b.** Recommendations on efficacy of OIT in adults with peanut allergy

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Evidence level</th>
<th>Grade of recommendation</th>
<th>Strength of recommendation</th>
<th>Other considerations</th>
<th>Key references</th>
</tr>
</thead>
<tbody>
<tr>
<td>No recommendation can be made about OIT as a treatment option in adults with peanut allergy</td>
<td>II</td>
<td>B</td>
<td>No recommendation due to lack of evidence. One CCT including mixed populations</td>
<td></td>
<td>Nurmatov, 2017 (18); Syed, 2014 (41)</td>
</tr>
</tbody>
</table>
**Box 12a. Recommendations on efficacy of OIT in children with allergies to other foods**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Evidence level</th>
<th>Grade of recommendation</th>
<th>Strength of recommendation</th>
<th>Other considerations</th>
<th>Key references</th>
</tr>
</thead>
<tbody>
<tr>
<td>OIT may be recommended as a treatment option to increase the threshold of reaction while on treatment in children allergic to other foods (e.g. fish, wheat, peach)</td>
<td>II</td>
<td>B</td>
<td>Low recommendation based on a few cases reported in one RCT at high risk of bias and one CCT at moderate risk of bias</td>
<td>Risk of adverse reactions to be considered</td>
<td>Patriarca, 1998 (42), Patriarca, 2003 (43); Patriarca, 2007 (44)</td>
</tr>
<tr>
<td>No recommendation can be made about OIT as a treatment option to achieve post-discontinuation effectiveness in children allergic to other foods</td>
<td>V</td>
<td>D</td>
<td>No recommendation due to lack of evidence.</td>
<td></td>
<td>Nurmatov, 2017 (18)</td>
</tr>
</tbody>
</table>
### Box 12b. Recommendations on efficacy of OIT in adults with allergies to other foods

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Evidence level</th>
<th>Grade of recommendation</th>
<th>Strength of recommendation</th>
<th>Other considerations</th>
<th>Key references</th>
</tr>
</thead>
<tbody>
<tr>
<td>No recommendation can be made about OIT as a treatment option in adults allergic to other foods (e.g. fish, wheat, peach,…)</td>
<td>V</td>
<td>D</td>
<td>No recommendation due to lack of evidence.</td>
<td></td>
<td>Nurmatov, 2017 (18)</td>
</tr>
</tbody>
</table>
Efficacy of sublingual immunotherapy (SLIT)

There are few published studies which have assessed the effectiveness of SLIT. A recent meta-analysis identified four placebo-controlled RCTS and one CCT for the assessment of efficacy of SLIT while on therapy (18), and overall, SLIT revealed substantial benefits for the patients in regard to desensitization (18). However, an open follow-up of a peanut SLIT trial in children and adults found only 11% of patients achieving tolerance after 3 years on SLIT and post-discontinuation of the AIT for 4-6 weeks (45).

Head to head trials of OIT versus SLIT

Two trials directly compared the efficacy of OIT and SLIT, the first focused on cow’s milk and the second on peanut allergy (40,46). The first trial randomized 30 children with CM allergy to SLIT alone or SLIT followed by OIT (40). The trial clearly showed that OIT was more efficacious for desensitization and sustained unresponsiveness after 6 weeks off therapy to CM than SLIT alone (46). The second trial was a double-blind study involving 21 children with peanut allergy who were randomized to receive either active SLIT/placebo OIT or active OIT/placebo SLIT. Similarly, as in the CM trial OIT appeared far more effective than SLIT for the treatment of peanut allergy as the increased threshold was significantly greater in the active OIT group while on therapy (40). At present, OIT would seem to be a better therapeutic option than SLIT, but it is associated with significantly more adverse reactions as discussed below.

Other immunotherapies under investigation

In addition to OIT and SLIT, the epicutaneous route (EPIT) with unmodified allergens is currently under investigation for peanut and milk. Efficacy results of one placebo controlled RCT with peanut EPIT in 74 subjects aged 4 to 25 years have shown an increase in the threshold of reaction while on therapy. This effect was higher in patients below 11 years of age (17). Moreover, SCIT with modified allergens is also under development (15, 16). Two SCIT trials are currently ongoing, one using a chemically modified peanut extract (15) and another one using hypoallergenic recombinant parvalbumin for fish allergy (16). And last, a phase 1 trial with modified peanut allergens administered by the rectal route has been conducted but showed significant side effects, which led to early termination of the trial (47).
§6. Safety of AIT

Besides efficacy, safety is pivotal to a treatment. In AIT, safety is particularly important, as potential adverse events are mostly immediate onset, food-induced IgE-mediated reactions, which can lead to anaphylaxis. Events related to safety have been highlighted in the studies addressed by our systematic review (18). Seven publication were included in the analysis.

Patients in the active arm had a 9% higher risk of systemic reaction than those in the placebo groups (risk ratio, RR of not experiencing a systemic reaction in controls: 1.09, 95% CI 1.00 – 1.19), only observed in patients on OIT (RR: 1.16, 95% CI 1.03 – 1.30) but not in those on SLIT (RR 0.98, 95% CI 0.84 – 1.13). Local reactions were also reported, with pooled meta-analysis from nine publications. AIT was associated with an increased risk of adverse reactions (RR of not experiencing a reaction in controls 2.12, 95% CI 1.50, 3.00), with a higher risk for OIT than for SLIT (RR: 2.14, 95% CI 1.47 – 3.12)(18).

In summary, the meta-analyses highlighted that in AIT to foods, patients receiving the active preparation experienced significantly more reactions, both systemic and local, than those who received placebo. (18). Recommendations on safety of AIT are shown in Box 13.
### Box 13. Recommendations on safety of FA-AIT

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Evidence level</th>
<th>Grade of recommendation</th>
<th>Strength of recommendation</th>
<th>Other considerations</th>
<th>Key references</th>
</tr>
</thead>
<tbody>
<tr>
<td>A careful evaluation and explanation to the patient and his/her caregiver(s) of the risk of reactions during FA-AIT is recommended before starting AIT</td>
<td>V</td>
<td>D</td>
<td>Strong recommendation based on the risk identified in the systematic reviews and meta analyses including high quality RCTs</td>
<td></td>
<td>Nurmatov, 2017 (18); Longo 2008 (7); Skripak 2008 (35)</td>
</tr>
<tr>
<td>A careful evaluation of levels of sIgE, specific SPT and concomitant asthma is recommended before starting FA-AIT as high levels of sIgE and skin reactivity and asthma have been found as risk factors for adverse events.</td>
<td>II</td>
<td>B</td>
<td>Moderate recommendation based on non-randomized studies</td>
<td>Individual predictors of severe reactions still need to be identified</td>
<td>Vazquez-Ortiz, 2014 (48); Vazquez-Ortiz, 2013 (49); Martinez-Botas (50) Varshney, 2009 (51) Narisety 2009 (52)</td>
</tr>
<tr>
<td>Before starting FA-AIT it is recommended to explain to the patient and his/her caregiver(s) that</td>
<td>I</td>
<td>A</td>
<td>Strong recommendation based on systematic</td>
<td></td>
<td>Nurmatov, 2017 (18)</td>
</tr>
<tr>
<td>adverse events are usually more frequent during up-dosing but can also be seen following maintenance doses previously tolerated.</td>
<td>reviews and meta analyses including high quality RCTs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**OIT**
OIT to foods is associated with a large number of local reactions (itching of the oropharynx, perioral rash, and gastrointestinal symptoms) that can be bothersome when they occur repeatedly. Local reactions may evolve into more severe systemic reactions. Known risk factors include exercise, infection, medication use and menses which may increase the risk of reactions (53) especially during the maintenance phase(s) of OIT, when patients continue treatment at home. However, in OIT studies most adverse reactions have been reported in the absence of these risk factors. With OIT, individual patients will take several hundred doses of foods, and although they have a statistically low risk to react to a given intake, they have a high risk of experiencing a significant reaction during the course of the OIT.

**SLIT**
SLIT is associated with a lower risk of significant adverse events than OIT. In randomized placebo controlled trials of SLIT systemic reactions are uncommon (<0.5-2.3% of doses) and generally mild, and do not differ from those observed in the placebo treated patients (11,12,45,54,55). The most common adverse events are mild local reactions in the oropharyngeal area (7-40% of patients), which can be observed during up-dosing and home maintenance. Other types of symptoms are uncommon.

**SCIT and EPIT**
SCIT and EPIT to foods has not been included in the systematic review due to the low number of studies available. The experience with SCIT using whole peanut allergen extracts has been limited, mostly due to the high number of severe adverse events (including severe anaphylaxis) (56,57). SCIT studies are currently underway with hypoallergenic recombinant parvalbumin and chemically modified peanut extract. These modified allergens have a reduced allergenicity but the safety profiles have not been yet reported (15,16). A single prospective RCT of EPIT with peanut suggests a favorable safety profile (17).

**Dosing in patients with repeated adverse events**
In food AIT trials, dose adaptations are made according to the severity of the reactions. In mild reactions, doses can remain the same according to the protocol. However, with repeated mild reactions, particularly when bothersome to the patient, dose progression may be stopped, or doses may even be reduced. With systemic reactions, doses are usually...
reduced, although it is not established if a reduction is necessary in all patients, particularly when co-factors are involved. We recommend a case-by-case evaluation of dose adaptation, and a thoroughly revision of any underlying condition. The treatment of any allergic disease, and especially asthma has to be optimal. Safety should remain the priority and after most significant adverse events, the dose will need to be reduced.

Patients with higher serum specific IgE levels (>8.85 kU/L to ovomucoid in HE-OIT, and >50 kU/L to CM in CM-OIT), higher skin tests (>9 mm to milk in CM-OIT), low threshold of reactivity and/or severe reactions in the entry food challenge or upon accidental exposure, and underlying asthma have been identified as risks factors for repeated reactions and early failure (48). In these patients individualized schedules with a longer and slower up-dosing phase, and premedication (antihistamines, chromones, or even omalizumab) should be considered (48).

Two studies performed in children allergic to CM have shown that IgE recognition of peptides of CM proteins are biomarkers that predict safety and efficacy of CM- AIT (40,45).

Local or systemic reactions have occurred with previously tolerated doses in the occasions of exercise (58), viral illness, or suboptimal controlled asthma (50). The amount of food should be decreased if a viral illness interferes.

**The clinical setting for food allergy AIT**

The setting for FA-AIT needs to be adapted to manage patients with the whole spectrum of FA severity. In particular, administration of initial doses and regular increments requires the presence of a staff trained for treatment of potentially severe allergic reactions. Doses tolerated in the clinical setting are subsequently taken at home. Patients need thorough instructions on how to detect an allergic reaction and its appropriate treatment. They also need to have on-hand adequate medications including an adrenaline auto-injector. All dose increments have to be performed in the hospital setting, and once desensitization has been assessed the dose can be taken at home.

**When to stop AIT after adverse reactions?**

With repeated local adverse reactions or systemic adverse events, discontinuation of AIT should be discussed with the patient and/or family.
Long term safety

Long term safety is overall not addressed in trials with most focusing on efficacy and short term safety. Some patients receiving OIT have been reported to have developed EoE (52,59,60).

§7. Allergen factors that affect efficacy and safety of AIT

In the systematic review on FA-AIT, the majority of trials were on CM (n=16), HE (n=11) and peanut (n=7), with only 1-3 studies for each of the other foods (18). AIT for CM, HE and peanut had similar efficacies with RR of 0.12 (95%CI 0.06–0.25), 0.22 (95%CI 0.11–0.45) and 0.11 (95%CI 0.04–0.31) respectively. Of note, in these pooled analyses, the majority of the studies were OIT, but a few were SLIT. Often the utilized products differed (e.g. peanut meal for OIT versus a peanut extract for SLIT). Regarding safety, data from only seven trials on different foods (3 CM, 1 HE, 1 peanut, and two others; the latter dealing with SLIT) could be pooled for analysis regarding occurrence of systemic reactions. A slightly increased risk was observed with AIT with a RR of not experiencing a reaction in controls 1.09 (95%CI 1.00–1.19). Data from two SLIT studies (1 hazelnut and 1 peach) showed no difference between arms (RR of not experiencing a reaction in controls=0.98, 95%CI 0.85, 1.14). Regarding safety, only the trial for milk could be used for analysis about occurrence of systemic reactions: a slightly increased risk was observed with AIT with a RR of not experiencing a reaction in controls of 1.19 (95%CI 1.03–1.37). For local reactions milk seems more prone to cause side effects than egg, although no statistical significant differences were found between them ( milk RR 2.70; 95%CI 1.33–5.47; egg RR 1.55 ; 95%CI 1.09–2.22) In conclusion, there is no evidence that the efficacy and safety are affected by the type and nature of the food allergen used in AIT.
§8. Patient factors that affect the efficacy and safety of AIT

Different patient factors have been suspected to affect the outcomes of FA-AIT, both in terms of efficacy and safety. Concerning patient age, the systematic review and meta-analysis on FA-AIT has found that FA-AIT is effective in reducing food allergy in children and a population of mixed ages with IgE-mediated food allergy to a range of foods both whilst receiving (i.e. desensitization) and after discontinuing treatment (RR = 0.16; 95%CI 0.09 - 0.27). It is still unclear if AIT is effective for adults. There are no studies of OIT performed exclusively in adults and in those performed with mixed (children and adults) populations efficacy could not be analysed separately according to age (18). The only studies focused on adults used SLIT, dealt with hazelnut and peach, and showed an increase in threshold while on therapy (11, 54).

In the systematic review and meta-analysis on FA-AIT, there were not sufficient data to analyze the role of other patient factors such as the number of culprit foods of clinical relevance, co-existence of asthma or other severe allergic disorders on the FA-AIT outcomes (18). However, some studies have shown that those patients with a higher sensitisation, lower threshold/higher severity and associated asthma are those with a higher frequency of adverse events (53).

In several studies, smaller SPT wheal sizes and lower sIgE levels have been associated with an increased likelihood of achieving desensitization and tolerance (61,62). However, other studies did not find a significant correlation between pre-FA-AIT SPT/ sIgE score and treatment success (40, 55). Furthermore, some FA-AIT studies included children with severe FAs or anaphylaxis with elevated sIgE who were successfully treated with FA-AIT (7,9).

§9. Adherence with AIT

Adherence with treatment is pivotal for both efficacy and safety of FA-AIT. Given that the procedure of FA-AIT is time-consuming and burdened by potential side effects, patients and their families must be extremely adherent, reliable and committed to the treatment. Considering all these premises, a careful selection of patients and respective families committed to AIT is mandatory and a poor adherence to the treatment has to be considered an absolute contraindication. Therefore, a clear and detailed explanation about the FA-AIT
procedure (timing, setting), the related outcomes and risk of side effects, together with getting information on patients’ and/or families’ opinions and expectations are preliminary to the inclusion in the treatment protocol. Nevertheless, patients and their families need to be supported during the entire treatment. An informed consent should be signed by patients or their parents or caregivers, according to local ethical requirements.

§10. Summary, gaps in the evidence and future perspectives

FA-AIT represents the active treatment of IgE-mediated FA instead of avoidance and rescue management. The usual management of FA demands changes in eating habits with serious repercussions on QoL, potential risk of nutritional deficiencies especially in children and severe adverse reaction in case of accidental exposure to the culprit food.

The recent systematic review and meta-analysis on FA-AIT (18) clearly demonstrated that FA-AIT is effective in reducing the likelihood of reacting to foods. In a sub-group of pediatric patients with FA to a CM and peanut data suggests that OIT is more effective than SLIT (40,55). There is an increased risk of local (the most frequent) reactions with both OIT and SLIT, but only OIT showed a significant higher risk of systemic reactions. Because of the length of the protocol and safety issues, patients and their families must be extremely adherent, reliable and committed to the treatment. FA-AIT may improve quality of life scores, particularly with regard to social limitations, accidental exposure and anxiety (5).

Many children with CM allergy or HE allergy develop tolerance spontaneously. For these children, avoiding the allergen, waiting for the natural history of their allergies may represent a better option than FA-AIT. Therefore, FA-AIT cannot be recommended as a routine practice, but must be limited only to carefully selected patients treated inside specialized clinical settings, by trained personnel Boxes 14 & 15)
**Box 14. Summary of the management**

1. Provision of individualized schedule, clearly written in a simple non-medical language. It should include personal identification data (name, address, contact details of the parents, guardian, a next of kin, family doctor).
2. Copy of schedule should be kept by the patients or his/her caregiver(s), and family doctor.
3. Clear identification of food allergen to be administered during FA-AIT.
4. Clear explanation that FA-AIT escalation dose(s) has to be administered in clinical specialized setting under strict medical supervision properly equipped for treatment of potentially severe allergic reactions.
5. The risk of reaction caused by FA-AIT should be explained to the patient and his/her caregiver before starting FA-AIT.
6. Provision of emergency kit with copy of anaphylaxis emergency action plan and medications for self-treatment e.g. adrenaline auto-injector where appropriate.
7. Regarding sublingual route (SLIT), patients should be well informed of the possible limited efficacy of the procedure.
8. Regarding the oral route (OIT) patients should be well informed of the higher risk of systemic reactions during treatment.

**Box 15. Practical recommendations**

1. Take dose daily
2. Do not take dose on an empty stomach
3. Do not go to the bed in the hour following a dose
4. Do not exercise in the 2-3 hours following a dose
5. Reduce the dose with infections, stress, asthma exacerbations, gastrointestinal diseases or menses.

The duration of FA-AIT may be burdensome for patients and their families. After completion of therapy, patients are likely to need to frequently consume the allergen to maintain tolerance. It may be easier to achieve the post-discontinuation effectiveness (e.g. tolerance or sustained unresponsiveness) for allergens that are typically outgrown in childhood e.g. milk and egg compared to what it is for allergens such as peanut, where probably lifelong
ingestion may be required after therapy. In addition, efficacy during the treatment with CM can be maintained with a twice weekly regimen. We await maintenance follow-up studies to assess whether more flexible regimens are possible with other foods (63).

The quality of allergen preparations is critical for both diagnosis and treatment. Standardized allergen preparations of known potency and shelf life should be used (Box 16). Currently, the allergens containing food protein and those prepared by pharmaceutical companies or hospital pharmacies are not available as standardized products. The allergens in such products should be well characterized as it is known that different formulation of a product may have significant variations in allergen load. Both the bacteriological load and biological activity of these products are still undetermined. Therefore, the use of fresh material or native foods for FA-AIT is advisable to achieve the goal of desensitization. Different disciplinary and clinical background including medical care, patient groups, allergen manufacturers and regulators should be involved in the process of producing new data on standardized allergen preparations for the active treatment of FA.

Novel therapeutic approaches are being developed to improve FA-AIT, most of them in pre-clinical or early clinical trials. In particular, humanized monoclonal anti-IgE (omalizumab) seems to markedly reduce adverse reactions due to OIT compared to placebo (64-66). Furthermore, as bacteria are potent stimulants of Th1 immune responses, modified bacterial products are under investigation as adjuvants for FA-AIT (47).

Clinical studies carried out with FA-AIT have some limitations, such as the heterogeneity in protocols between centres. It is yet unclear what duration and frequency of ingestion of the allergic food(s) is required to maintain desensitization. Furthermore, we are lacking criteria with which to evaluate and diagnose permanent tolerance. In AIT trials and in clinical practice, safety is of the paramount importance: strategies for improving safety during either up-dosing protocol or maintenance regimen need to be standardized. Managing these pivotal issues is mandatory for use of OIT/SLIT outside research settings or specialized clinical centers for FA-AIT.
**Box 16. Current gaps in FA AIT therapy**

<table>
<thead>
<tr>
<th>Gaps in the evidence of FA AIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Standardized products</td>
</tr>
<tr>
<td>2. Establish validated protocols with optimal dosing and duration of therapy</td>
</tr>
<tr>
<td>3. Updated nomenclature according to clinical needs, newly developing treatments and mechanisms</td>
</tr>
<tr>
<td>4. Improve post-discontinuation treatment effectiveness</td>
</tr>
<tr>
<td>5. Improve safety of FA-AIT undergoing up-dosing regimen and maintenance phase</td>
</tr>
<tr>
<td>6. Effect of concomitant administration of anti-IgE on safety and efficacy and length of treatment</td>
</tr>
<tr>
<td>7. Effect of concomitant administration of probiotics on safety and efficacy</td>
</tr>
<tr>
<td>8. Deep insight in the mechanisms of action</td>
</tr>
<tr>
<td>9. Identify markers of response</td>
</tr>
<tr>
<td>10. Identify the most suitable candidates (personalized care)</td>
</tr>
<tr>
<td>11. Impact on QoL (disease-related outcomes)</td>
</tr>
<tr>
<td>12. Cost-effectiveness</td>
</tr>
<tr>
<td>13. Position of the different alternative routes</td>
</tr>
<tr>
<td>14. Common registry of systemic adverse events</td>
</tr>
<tr>
<td>15. “Precision medicine” algorithms for treatments tailored on individual patients</td>
</tr>
</tbody>
</table>
References


