EAACI Guidelines on Allergen Immunotherapy: allergic rhinoconjunctivitis

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Short title: EAACI Rhinoconjunctivitis Allergen Immunotherapy Guidelines

Key words: allergen immunotherapy, allergy, allergic conjunctivitis, allergic rhinitis, rhinoconjunctivitis

Abbreviations:

AR, allergic rhinoconjunctivitis; AIT, allergen immunotherapy; AGREE II, Appraisal of Guidelines for Research & Evaluation; ARIA, Allergic Rhinitis and its Impact on Asthma; EPIT, epicutaneous immunotherapy; EAACI, European Academy of Allergy and Clinical Immunology; EMA, European Medicines Agency; HDM, house dust mite; ICER, incremental cost-effectiveness ratio; NARES, non-allergic rhinitis with eosinophilia syndrome; QALY, quality-adjusted life years; RCT, randomized controlled trial; SPT, skin prick test; SMD, standardized mean difference; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SmPC, manufacturer’s product information (SmPC), summary or product characteristics.
ABSTRACT

Allergic rhinoconjunctivitis (AR) is an allergic disorder affecting the nose and eyes with a prevalence of about 20% of the general population. Symptoms are frequently controlled with avoidance measures and pharmacotherapy. However, many patients continue to have ongoing symptoms and impaired quality of life. Allergen immunotherapy (AIT) represents an important additional therapeutic option. These Guidelines have been prepared by the European Academy of Allergy and Clinical Immunology’s (EAACI) Taskforce on AIT for AR and are part of the EAACI presidential project ‘AIT Guidelines’. They aim to provide evidence-based clinical recommendations and have been informed by a formal systematic review and meta-analysis. Their generation has followed the Appraisal of Guidelines for Research and Evaluation (AGREE II) approach. The process included representation of the full range of stakeholders. Key sections cover ‘general considerations before initiating AIT for AR’, ‘allergen immunotherapy for AR: evidence-based, clinical recommendations’, ‘other approaches for AIT’, ‘allergen factors that may affect the efficacy of AIT for AR’, ‘patient factors that may affect the efficacy of AIT for AR’, ‘how long should AIT be continued for in AR’, ‘adverse events with ASIT for AR’, ‘preventive effects of AIT for AR’, ‘pharmacoeconomic aspects of AIT versus pharmacotherapy for AR’ and ‘summary, gaps in the evidence and future perspectives’. In general, broad evidence for the clinical efficacy of AIT exists but a product-specific evaluation of evidence is recommended.
SECTION A: INTRODUCTION

Allergic rhinoconjunctivitis (AR) is an allergic disorder affecting the nose and eyes, resulting in chronic, mostly eosinophilic, inflammation of the nasal mucosa and conjunctiva [Eifan 2016; Greiner 2011]. Allergic rhinitis, with or without conjunctivitis, is one of the most prevalent allergic diseases affecting around a fifth of the general population [Singh 2010; Meltzer 2009; Ait-Khaled 2009]. It is associated with considerable loss of productivity and impaired school performance [Walker 2007].

AR can usually be diagnosed from its typical presentation (Figure A). Symptoms include itching, sneezing, watery nasal discharge often nasal congestion [Roberts 2013]. There is often associated eye symptoms (watery, red and/or itchy eyes). Symptoms may be described as seasonal and/or perennial; as intermittent or persistent; or mild, moderate or severe according to its impact on quality of life (Bousquet 2008). Symptoms are related to exposure to the offending allergen as well as to non-specific triggers such as smoke, dust, viral infections, strong odors and cold air [Roberts 2013]. Evidence of allergen-specific IgE sensitization to one or more Aeroallergens suggested by the history supports the diagnosis. AR may co-exist with other forms of rhinitis (Figure A). Additionally, AR may be associated with sinusitis symptoms, auditory dysfunction and asthma [Roberts 2013].

The aims of AR management are to control symptoms and reduce inflammation. Where possible, allergen avoidance can be recommended although effective allergen avoidance is not always feasible [Terreehorst 2003; Sheikh A Cochrane review 2010]. Many patients rely on pharmacotherapy with e.g., oral or topical antihistamines, intranasal corticosteroids, topical cromoglycate or leukotriene receptor antagonists [Roberts 2013]. However, these therapies do not alter the natural history of AR. Additionally, despite medication, a significant number of patients continue to experience symptoms that impair their quality of life. Allergen immunotherapy (AIT) that involves regular subcutaneous (SCIT) or sublingual (SLIT) administration of the culprit allergen(s) may not only desensitize a patient thereby ameliorating symptoms but also modify the underlying natural history of the disease [Pfaar 2014; Jutel 2015; Jutel 2016].

These Guidelines have been prepared by the European Academy of Allergy and Clinical Immunology’s (EAACI) Taskforce on Allergen Immunotherapy (AIT) for Rhinoconjunctivitis and are part of the EAACI AIT Guidelines. These Guidelines aim to provide evidence-based recommendations for the use of AIT for patients with allergic rhinitis with or without conjunctivitis. AR will be used to signify either allergic rhinitis or allergic rhinoconjunctivitis. The primary audience are clinical allergists, although the guidelines are of relevance to other healthcare professionals (e.g. primary care workers, other specialist doctors, nurses and
pharmacists working across a range of clinical settings) dealing with AR. The development of
the Guidelines has been informed by a formal systematic review and meta-analysis of AIT for
AR [Dhami 2017], with systematic review principles being used to identify additional evidence,
where necessary.

Figure A. Differential diagnosis of allergic rhinoconjunctivitis

Adapted from Roberts 2013. Local allergic rhinitis may be seen where there is only evidence
of local nasal allergic sensitization [Campo 2015; Carmen 2010]. There are numerous other
causes of non-allergic, non-infectious rhinitis, examples are non-allergic rhinitis with
eosinophilia syndrome (NARES) and gastro-oesophageal reflux [Roberts 2013]. In individual
patients, symptoms may be driven by more than one trigger. Rhinosinusitis is not included in
the scope of these Guidelines.
### Box 1. Key terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rhinitis</strong></td>
<td>Inflammation of the nasal epithelium resulting in at least two nasal symptoms: rhinorrhea, blockage, sneezing or itching.</td>
</tr>
<tr>
<td><strong>Conjunctivitis</strong></td>
<td>Inflammation of the conjunctiva characterized by watery, itchy, red eyes.</td>
</tr>
<tr>
<td><strong>Sensitization</strong></td>
<td>Detectable allergen specific IgE antibodies, either by means of skin prick test (SPT) or specific IgE antibodies in a blood sample</td>
</tr>
<tr>
<td><strong>Allergen immunotherapy (AIT)</strong></td>
<td>Repeated allergen administration at regular intervals to modulate immune response in order to reduce symptoms and the need of medication for clinical allergies and to prevent the development of new allergies and asthma (adapted from European Medicines Agency (EMA)). This is also sometimes known as allergen specific immunotherapy, desensitization and hypo-sensitization</td>
</tr>
<tr>
<td><strong>Subcutaneous immunotherapy (SCIT)</strong></td>
<td>Form of allergen immunotherapy where the allergen is administered as a series of subcutaneous injections.</td>
</tr>
<tr>
<td><strong>Sublingual immunotherapy (SLIT)</strong></td>
<td>Form of allergen immunotherapy where the allergen is administered under the tongue.</td>
</tr>
<tr>
<td><strong>Short-term efficacy</strong></td>
<td>Clinical benefit to the patient while they are receiving AIT</td>
</tr>
<tr>
<td><strong>Long-term efficacy</strong></td>
<td>Clinical benefit to the patient for at least one year after cessation of the AIT course. This implies that the AIT has altered the natural history of the patient’s allergic disease.</td>
</tr>
</tbody>
</table>
SECTION B: METHODOLOGY

These Guidelines were produced using the Appraisal of Guidelines for Research & Evaluation (AGREE II) approach [Agree Collaboration 2003; Brouwers 2010], 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 regular 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 that assist clinicians in the optimal use of AIT in the management of patients with AR and identifying gaps for further research.

Ensuring appropriate stakeholder involvement

Participants in the EAACI Taskforce on AIT for Allergic Rhinoconjunctivitis represented a range of 16 countries and disciplinary and clinical backgrounds, including allergists, paediatricians, primary care doctors, ophthalmology, ENT, pharmacists, immunologists, nurses and patient representatives. Representatives of immunotherapy product manufactures were given the opportunity to review and comment on the draft guidelines as part of the peer review and public comment process. These comments were considered by the Taskforce and, where appropriate, revisions were made.

Systematic reviews of the evidence

The initial full range of clinical questions that were considered important were rationalized through several rounds of iteration to agree on one key question: what is the effectiveness, cost-effectiveness and safety of AIT in patients with allergic rhinoconjunctivitis. This was then pursued through a formal systematic review of the evidence [Dhami 2016; Dhami 2017].

Formulating recommendations
We graded the strength and consistency of key findings from these systematic reviews (Dhami 2017) to formulate evidence-based recommendations for clinical care [Oxford Centre for Evidence-based Medicine] (Box 2). This involved formulating clear recommendations with the strength of evidence underpinning each recommendation. 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. Recommendations apply to all ages unless otherwise indicated in the tables. 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 (see Supporting Information Tables SX).

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 the 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 are prioritized (see Online supplement).

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 declared at the start of the process and taken into account by the Taskforce Chairs as recommendations were formulated. Final
decisions about strength of evidence for recommendations were checked by the methodologists who had no conflict of interests in this area.

**Updating the guidelines**

EAACI plans to update these guidelines in 2022 unless there are important advances before then.

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**Box 2: Assigning levels of evidence and recommendations [Oxford Centre for Evidence-based Medicine]**

**Level of evidence**

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

**Grades of recommendation**

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

**Strength of recommendations**

- **Strong**: Evidence from studies at low risk of bias / high quality studies
- **Moderate**: Evidence from studies at moderate risk of bias / moderate quality studies
- **Weak**: Evidence from studies at high risk of bias / low quality studies

Recommendations are phrased according to the strength of recommendation: strong: “is recommended”; moderate: “can be recommended”; weak: “may be recommended in specific circumstances”; negative: “cannot be recommended”.

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SECTION C: GENERAL CONSIDERATIONS BEFORE INITIATING AIT FOR AR

General indications
AIT is only indicated in the presence of symptoms strongly suggestive of allergic rhinitis, with or without conjunctivitis (Table 1) [Dhami 2017]. Many patients will also have co-existing asthma. There should be symptoms on aeroallergen exposure and evidence of IgE-sensitization (positive SPT or serum specific-IgE) to one or more clinically relevant allergens [Dhami 2017]. Component resolved diagnostics may have a role in optimizing AIT therapy, but definitive trials to show this approach enhances AIT outcomes are awaited. SPT or specific-IgE results may not identify the important allergens, particularly in polysensitized patients with perennial symptoms. In these circumstances, nasal or conjunctival provocation testing may be helpful, but again there is no definitive evidence that this approach can optimize the selection of the correct allergen for AIT therapy. For AIT to be indicated, a patient should be experiencing moderate-to-severe symptoms (e.g. ARIA categories moderate-to-severe intermittent or persistence [ARIA]), despite avoidance measures and optimal pharmacotherapy, that interfere with their usual daily activities or sleep. AIT may also be considered in less severe AR where a patient wishes to take advantage of its long term effect on rhinitis and potential to prevent asthma [ref prevention guidelines]. Lastly, only AIT products with evidence of efficacy for AR should be used (Pfaar et al. 2014; Bachert et al. 2015). The approach to using AIT for AR across the healthcare system is summarized in Figure B.

Absolute and relative contraindications
Even when AIT is the suitable therapy for a patient with AR, there may be absolute contraindications for its use (Table 2). There are also relative contraindications for conditions/concomitant diseases, where the risks from AIT may outweigh the expected benefits.
### Table 1. General indications for AIT for AR

<table>
<thead>
<tr>
<th>General indications</th>
<th>Key references</th>
<th>Contextual considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIT should be considered when all of these criteria are met:</td>
<td>Dhami 2017</td>
<td>A diagnosis of allergic rhinitis and evidence of IgE-sensitisation were entry criteria for RCTs in the systematic review.</td>
</tr>
<tr>
<td>• has symptoms strongly suggestive of allergic rhinitis, with or without conjunctivitis</td>
<td></td>
<td>AIT has the potential to alter the natural history of disease reducing AR symptoms after cessation of therapy and preventing the development of asthma.</td>
</tr>
<tr>
<td>• there is evidence of IgE-sensitization (positive SPT and / or serum specific-IgE) to one or more clinically relevant allergen</td>
<td></td>
<td>These products have consistent formulations and so different batches are likely to have similar effects.</td>
</tr>
<tr>
<td>• experiencing moderate-to-severe symptoms interfering with their usual daily activities or sleep despite regular and appropriate pharmacotherapy and / or avoidance strategies</td>
<td></td>
<td>However, the systematic review reveals a considerable heterogeneity in effectiveness between products and therefore a product-specific evaluation of efficacy is demanded.</td>
</tr>
<tr>
<td>AIT may also be considered in less severe AR where a patient wishes to take advantage of its long term effect on rhinitis and potential to prevent asthma</td>
<td>ref prevention AIT guidelines</td>
<td></td>
</tr>
<tr>
<td>Standardized AIT products with evidence of efficacy in the clinical documentation should preferably be used</td>
<td>Dhami 2017</td>
<td></td>
</tr>
</tbody>
</table>

Dhami 2017
Table 2. General contraindications for AIT for AR

<table>
<thead>
<tr>
<th>The following are considered to be contraindications:</th>
<th>Key references</th>
<th>Contextual considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncontrolled asthma</td>
<td>Pitsios 2015; Cox 2011; Bousquet 1989; Lockey 2001 Bernstein 2004; CSM 1986; Normansell 2015; Calderon 2012</td>
<td>Weak evidence of risk from case reports or case series of adverse events with AIT. Taskforce considered that these were contraindications to AIT.</td>
</tr>
<tr>
<td>Active, systemic, autoimmune disorders</td>
<td>Cabrera 1993; Sánchez-Morillas 2005; Fiorillo 2011</td>
<td></td>
</tr>
<tr>
<td>Active malignant neoplasia</td>
<td>Wöhrl 2011; Palomares 2010; Larenas-Linnemann 2016</td>
<td></td>
</tr>
<tr>
<td>AIT initiation during pregnancy</td>
<td>Metzger 1978; Chaudhuri 2008]</td>
<td></td>
</tr>
</tbody>
</table>

With the following, AIT should only be used with caution when benefits outweigh potential risks in an individual patient:

<table>
<thead>
<tr>
<th>With the following, AIT should only be used with caution when benefits outweigh potential risks in an individual patient:</th>
<th>Key references</th>
<th>Contextual considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blocker therapy</td>
<td>Hiatt 1985; Matsumura 1976; Cleaveland 1972; Lang 1995</td>
<td>Weak evidence of risk. These may both compromise a patient’s ability to tolerate an episode of anaphylaxis; this must be considered when deciding whether AIT is appropriate.</td>
</tr>
<tr>
<td>Severe cardiovascular diseases, e.g. coronary artery disease</td>
<td>Linneberg 2012; Larenas-Linnemann 2016</td>
<td></td>
</tr>
<tr>
<td>Systemic autoimmune disorders in remission/organ specific (Eg autoimmune thyroiditis)</td>
<td>Pitsios 2015; Cox 2011; Walker 2011; Linneberg 2012; Larenas-Linnemann 2016</td>
<td>Weak evidence of risk from case reports or case series of adverse events with AIT. Taskforce considered that careful consideration and discussion with patient and the treating physician and a case-by-case decision is required before commencing AIT.</td>
</tr>
<tr>
<td>Severe psychiatric disorders</td>
<td>Pitsios 2015</td>
<td></td>
</tr>
<tr>
<td>Poor adherence</td>
<td>Pitsios 2015</td>
<td></td>
</tr>
<tr>
<td>Primary and secondary Immunodeficiencies</td>
<td>Pitsios 2015; Larenas-Linnemann 2016</td>
<td></td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>Epstein 2016</td>
<td></td>
</tr>
</tbody>
</table>
Figure B. Approach to using AIT for allergic rhinoconjunctivitis
Schematic illustration of the approach to using AIT for AR starting with self-medication and management in primary care moving to assessment by an allergist for consideration and initiation of AIT in suitable patients. Structure of healthcare systems differs between countries.
SECTION D: ALLERGEN IMMUNOTHERAPY FOR AR: EVIDENCE-BASED, CLINICAL RECOMMENDATIONS

AIT is recommended for the treatment of AR in selected adults and children who respond inadequately to regular treatment with anti-allergic drugs and/or experience unacceptable side-effects with anti-allergic medication. This is based on pooled data from an EAACI commissioned meta-analysis [Dhami 2017] of 58 studies of SCIT and SLIT which found a standardized mean difference (SMD) of -0.53 (95% confidence intervals (CI) -0.63, -0.42) for symptoms of rhinoconjunctivitis in favor of AIT compared to placebo, consistent with a moderate clinical effect. This finding was also supported by reductions in medication use (45 studies, SMD -0.37 [95%CI -0.49, -0.26] and also in combined symptom-medication scores (15 studies, SMD -0.49 [95%CI -0.69, -0.30]). The high grade of heterogeneity between the trials evaluated underlines the urgent need of an individual product-based evaluation of the evidence for efficacy (Pfaar et al. 2014; Bachert et al. 2015).

However, SCIT immunotherapy is in general recommended for the treatment of AR in adults and children with moderate-to severe disease that is sub-optimally controlled despite optimum pharmacotherapy [Dhami 2017](Table 3). The evidence for short-term benefit is stronger for seasonal rhinitis (Grade A for adults) than for perennial rhinitis (Grade B for adults), where few studies have been performed and results are more heterogeneous (Table 3). SCIT is recommended for seasonal disease whether given continuously or pre- or pre/co-seasonally (Table 3, Grades A or B for adults). Pre/co-seasonal therapy benefits from a shorter course of treatment; the two regimens have not been directly compared in terms of efficacy or adverse events.

SCIT may be administered in aqueous formulation (rarely in Europe) or as a depot adsorbed on aluminum hydroxide or tyroxine. SCIT using either unmodified or modified allergen extracts is recommended for treatment of allergic rhinitis and provides short-term benefit (Table 3, Grade A for adults). This is based on evidence from the systematic review [Dhami 2017] that showed both unmodified allergen extracts (SMD [95%CI]) -0.65 (-0.93, -0.36) and allergoids/polymerized extracts (SMD [95%CI] -0.60 [-0.89, -0.31] to be effective in reducing symptoms compared to placebo, with additional support from reduced medication requirements and combined symptom-medication scores. Although clinical trials of modified allergens involved shorter courses of treatment, there have been no head-to-head comparisons with unmodified preparations evaluating efficacy or adverse events.
Grass pollen SCIT is recommended (Grade A in adults) to be given for a minimum of three years in order to achieve long-term clinical efficacy following discontinuation of treatment (Table 7). This is supported by three RCTs of continuous treatment with the same aluminum hydroxide-adsorbed allergen extract, two in adults [Durham 1999, James 2011] and one in children [Jacobsen L Allergy 2007].

In general, SLIT is recommended for the treatment of seasonal allergic rhinitis in adults and children. SLIT has been shown to provide short term benefit during therapy with moderate-to severe disease that is sub-optimally controlled despite optimum pharmacotherapy (Table 3) [Dhami 2017]. SLIT is recommended to be taken either continuously or pre-/co-seasonally commencing a minimum of two months and ideally four months prior to the start of the pollen season (Grade A for adults).

SLIT may be taken daily either as drops or as tablets that are retained under the tongue for at least one minute and then swallowed. Both are recommended (Grade A or B for adults) based on short-term reductions in symptoms and rescue medication, respectively, for sublingual drops: SMD (95%CI) -0.41 (-0.65, -0.18) and -0.35 (-0.55, -0.14) and for sublingual tablets: -0.56 (-0.80, -0.33) and -0.42 (-0.64, -0.19) [Dhami 2017].

Grass pollen SLIT is recommended (Grade A) to be taken for a minimum of three years in order to provide long-term benefit for at least two years after discontinuation (Table 7). This recommendation is based on four large RCTs [Durham 2012, Didier Clin Trans Allergy 2015, Ott 2009, Valovirta Clin Ther. 2011] (Table 3). This recommendation is further supported by a recent trial that showed that both subcutaneous and sublingual immunotherapy were effective whereas two years treatment was insufficient for long-term clinical efficacy after discontinuation, reinforcing the need for immunotherapy via both routes to be continued for at least 3 years (Scadding GW 2017).

Sublingual house dust mite tablet immunotherapy for at least one year is recommended (Grade A) for the short-term treatment of perennial HDM AR in adults [Didier 2015, Durham 2012, Ott 2009, Bergmann 2014, Mosbech 2015, Demoly 2016] (Table 3). In one trial of one year of sublingual HDM tablet treatment [Bergman 2013], short-term benefit was followed by reduced symptoms assessed at one year after discontinuation.

Where RCTs involving increasing allergen concentrations have been performed there has been clear evidence of a dose-response relationship for both SCIT and SLIT. While higher doses are more effective, they are associated with more side-effects, such that dose selection has been based on a balance of efficacy and side-effects [Didier 2015, Durham 2012, Valovirta 2006, Frew 2006, Jacobsen L Allergy 2007; Calderon 2011].
### Table 3 Recommendations: AIT for treatment of AR: schedules, products, formulations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Adults</th>
<th>Children and adolescents</th>
<th>Strength of recommendation</th>
<th>Other considerations</th>
<th>Key references</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SCIT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scenario</td>
<td>Level</td>
<td>GRADE</td>
<td>Strength</td>
<td>Evidence</td>
<td>Outcome</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
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<td>---------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Continuous grass pollen SCIT is recommended for AR for short and long-term benefit</td>
<td>I</td>
<td>A</td>
<td>I</td>
<td>Strong recommendation for adults based on above evidence plus two high quality long-term studies (Durham 1999, James 2011). Weak recommendation for children as only one low quality (open design) paediatric long-term study (Jacobsen 2007).</td>
<td>A few adult studies and one pediatric study (designed to assess whether SCIT prevents asthma) demonstrating long-term effectiveness.</td>
</tr>
</tbody>
</table>

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Dhami 2017 SR, eg

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Dhami 2017 SR, eg

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Dhami 2017 SR, eg
Adult: Durham 1999, James 2011
Paed: Jacobsen L Allergy 2007 H
<table>
<thead>
<tr>
<th>SLIT</th>
<th>Recommendation</th>
<th>Strength</th>
<th>Evidence</th>
<th>Effect Size</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grass pollen SLIT tablets or solution is recommended for allergic rhinoconjunctivitis for long-term benefit.</td>
<td>I</td>
<td>A</td>
<td>I</td>
<td>B</td>
<td>Strong recommendation for adults based on high quality studies (Durham 2012, Didier Clin Trans Allergy 2015, Ott 2009). One high quality paediatric study with results only available online on EudraCT(Valovirta Clin Ther. 2011)</td>
</tr>
<tr>
<td>HDM SLIT tablet can be recommended for allergic rhinoconjunctivitis for long-term benefit.</td>
<td>I</td>
<td>B</td>
<td>-</td>
<td>C</td>
<td>Moderate recommendation based on one large, high quality (Bergmann 2014). No paediatric data.</td>
</tr>
</tbody>
</table>

SECTION E: Other approaches for AIT

Other approaches aim to improve patient convenience and compliance with shorter courses, whilst improving or maintaining efficacy and reducing the risk of systemic side-effects (Table 4). As such, adjuvants to AIT extracts are possible candidates (Pfaar et al. 2012). For example, TLR-4 agonists (monophosphoryl lipid A) in combination with a grass allergoid has demonstrated effectiveness, although in a phase 3 trial, efficacy was modest and there are no head to head comparisons [Drachenberg 2001]. The TLR-9 agonist (Bacterial DNA oligonucleotides containing a CpG motif) fused to Amb a 1, the major allergen of ragweed showed efficacy in a phase 2 trial [Creticos 2006] although this was not observed in a subsequent phase 3 trial. The combination of anti-IgE injections with conventional and rush AIT with non-modified extracts has been proved to be effective with a marked reduction in systemic side-effects in studies of children [Rolinck-Werninghaus 2004] and adults [Casale 2006], although it is expensive and there is concern when and how to discontinue the anti-IgE when AIT maintenance therapy is achieved [Larenas Linnemann 2014].

Recombinant AIT is attractive as it allows accurate standardization of allergen products and has potential for personalized therapy based on individual allergen sensitivities, and with a hypothetical lower risk of inducing new sensitizations. Subcutaneous recombinant birch (Bet v 1) [Pauli 2008] and a 5- recombinant grass allergen mix [Jutel 2005] have been shown to be efficacious with no safety concerns. A recombinant B cell epitope-based vaccine, comprising a recombinant hybrid grass allergen mix combined with a hepatitis B domain surface Pre-S protein as an immunologic carrier has shown efficacy in a phase 2 trial [Zieglmayer 2016]. T cell peptide immunotherapy for cat allergy using mixtures of short T cell epitopes via the intradermal route, had promising results in environmental chamber phase 2 studies [Patel 2013]; it has been reported that a subsequent phase 3 study did not demonstrate effectiveness. Studies with other allergen peptide approaches are in progress [Ellis 2017; Spertini 2016].

There has been recent interest in the use of alternative modalities of delivery including the epicutaneous, intradermal and intra-lymphatic routes. In RCTs, epicutaneous grass pollen immunotherapy (EPIT) has shown modest benefit [Senti 2012] although accompanied by local eczematous reactions at the patch application site. Intradermal grass pollen immunotherapy inhibited allergen-induced cutaneous late responses although in a subsequent RCT it was ineffective and there was evidence of exacerbation of seasonal outcomes and Th2 inflammation in the skin [Slovick JACI 2017]. The intra-
lymphatic route, using a grass pollen extract and a modified cat allergen extract, showed
efficacy in some trials [Senti 2012, Patterson, A] but not in others [Witten 2013].
Table 4 Recommendations: other approaches for AIT for treatment of AR

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Adults</th>
<th>Children and adolescents</th>
<th>Strength of recommendation</th>
<th>Other considerations</th>
<th>Key references</th>
</tr>
</thead>
<tbody>
<tr>
<td>A combination of the TLR-4 agonist monophosphoryl lipid A with pollen allergoid is recommended for AR</td>
<td>I</td>
<td>B</td>
<td>III</td>
<td>Strong recommendation for adults based on one high quality study (Drachenberg 2001). Weak recommendation for children (Drachenberg 2003). Moderate effect size, limited randomised controlled data. Only one uncontrolled before and after study paediatric study.</td>
<td>Drachenberg 2001, Drachenberg 2003</td>
</tr>
<tr>
<td>Combining anti-IgE injections with AIT for AR is recommended for reducing side-effects</td>
<td>I</td>
<td>A</td>
<td>I</td>
<td>Strong recommendation based on one high quality adult (Casale 2006) and one high quality paediatric (Rolinck-Werninghaus 2004) study. Strong consistent evidence but the required length of co-therapy unclear.</td>
<td>Casale 2006, Rolinck-Werninghaus 2004</td>
</tr>
<tr>
<td>Recombinant AIT may be recommended for birch and grass pollen allergy</td>
<td>I</td>
<td>A</td>
<td>-</td>
<td>Quality of studies unclear (Pauli 2008; Jutel 2005). Some evidence of benefit for adults, no pediatric data.</td>
<td>Pauli 2008; Jutel 2005</td>
</tr>
</tbody>
</table>
SECTION F: ALLERGEN FACTORS THAT MAY AFFECT THE EFFICACY OF AIT for AR

Standardization of allergen extracts

For the common allergens, many companies now provide characterized, standardized, stable preparation for AIT as recommended by European Medicines Agency (EMA) [EMA 2008, regulatory position paper]. For others, such as molds, there are problems with the complexity, variability and stability of the allergens [Coop 2014]. The lack of standardized extracts may hamper the diagnosis of eligible patients for AIT and may impede the effectiveness of AIT [Coop 2014, Twaroch 2015]. Additionally, non-standardized preparations may vary between batches increasing the potential for side effects. Further purification and characterization of such allergens [Twaroch 2015, Lizaso 2006, Slater 2014] may result in better extracts for the future. Where possible, standardized allergen products should be used for AIT. Further discussion is available in a position paper on regulatory aspects of AIT [regulatory position paper].

Formulation of SLIT preparations

In deciding on the appropriate preparation to use for AIT, the formulation should be taken into account. For example, three large studies have showed efficacy for HDM SLIT tablets [Bergmann 2014, Demoly 2016, Mosbech 2014] whereas three HDM SLIT studies with sublingual drops were negative [Bahçeçeler, 2007, Guez, 2000, Hirsch, 1997], and another only demonstrated efficacy in the first and not the second year [Passalacqua 2006]. However, many factors such as differences in allergen content, administered volume, number of participants and statistical power of the study may explain the differences between tablets and drops. We recommend that AIT products with evidence of efficacy in the clinical documentation should preferentially be used.

Allergen mixtures

Both mixtures of grass pollen and mixtures of tree pollen are frequently used in AIT and such an approach is effective [Dharni 2017]. The use of different, non-taxonomically related allergens mixed in one AIT product has been evaluated in a very limited number of studies. One SCIT study showed that a depigmented-polymerized mixed grass/birch pollen extract was effective over placebo [Pfaar 2013]. A small study in children demonstrated efficacy using a mixture of grass pollen and HDM SLIT [Swaney 2012]. One study assessed the efficacy of multi-inhalant allergen subcutaneous AIT (tree, grass
and weed pollen; moulds; cat and dog dander; dust and storage mites), it demonstrated no efficacy over placebo [Radcliffe 2003]. Sublingual immunotherapy that employed a momomeric *Phleum pratense* grass pollen extract was more effective when given alone compared to when given in an equivalent dose as part of a combination with a 9-pollen multi-allergen sublingual extract [Amar 2009].

There are a number of potential drawbacks of mixing allergens including a dilutional effect, potential allergen degradation due to enzymatic activity of some allergens and the difficulties of adequately demonstrating efficacy of a high number of allergen combinations and/or different products. The European Medicines Agency has recommended that only homologous allergens (usually ones that are taxonomically related, for example a mixture of grass pollen extracts [Didier A JACI 2006]) should be mixed and that allergens with enzymatic activity (e.g. HDM) should be never used in a mixture [EMA-AIT GL 2008]. We therefore recommend only homologous allergens to be mixed in AIT preparations until further evidence is available substantiating the efficacy of other mixtures (see Online supplement). Alternatively, extracts should be given separately.

**Specific allergens**

In the recent meta-analysis, there were sufficient SCIT and SLIT studies for subgroup analyses by specific allergens (Dhami 2017). Short-term effectiveness was demonstrated for HDM (symptoms score SMD -0.73; 95%CI -1.37, -0.10), grass pollen (-0.45; -0.54,-0.36); tree pollen (-0.57; -0.92, -0.21) and weed pollen (-0.68; -1.06, -0.30). However, there was lots of heterogeneity for all allergens, particularly molds (-0.56; -2.29, 1.18), suggesting that different preparations may be more or less effective.
Table 5 Recommendations: allergen factors that affect the efficacy of AIT for AR

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Adults</th>
<th>Children and Adolescents</th>
<th>Strength of recommendation</th>
<th>Other considerations</th>
<th>Key references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Either a single allergen or a mixture of well documented homologous allergens from that biological family that covers the major allergens are recommended for patients with AR who are allergic to grass pollens, tree pollens or HDM</td>
<td>I</td>
<td>B</td>
<td>I</td>
<td>B</td>
<td>Strong recommendations on basis of high quality grass pollen (single grass, eg Buße 2009, Dahl 2006a; mixture of grasses, eg Didier 2007, Ott 2009), tree pollen (single tree, eg Bodtger 2002 Charpin 2007; mixture of trees, eg Baida 1998) and house dust mite (single, eg De Bot 2011, Hirsch, 1997; mixture, eg Passalacqua 1998) studies.</td>
</tr>
<tr>
<td>Mixtures of allergens from non-related biological families are not recommended as AIT preparations except for products with supportive published evidence</td>
<td>I</td>
<td>B</td>
<td>-</td>
<td>B</td>
<td>Strong recommendation based on a negative high quality study with multiple allergens (Radcliffe 2003). One positive high quality study combining grass and tree pollens (Pfaar 2013).</td>
</tr>
</tbody>
</table>

Examples of homologous, taxonomically related allergens from the same biological family are the grasses or tree pollens. Also see Table 3.
SECTION G: PATIENT FACTORS THAT EFFECT THE EFFICACY OF AIT FOR AR

Polysensitized patients

Epidemiological data indicate that most patients with AR are polysensitized [Miguereas et al. 2014]. Consequently, consideration needs to be given as to whether patients are (i) clinically mono-allergic (where only one allergen is driving symptoms) and polysensitised or (ii) poly-allergic (with clear cut symptoms on exposure to multiple different allergens) and polysensitised. This may be apparent from the history or may need investigation with component resolved diagnostics or assessment with nasal or conjunctival provocation challenges [Demoly 2016]. Immunotherapy with a single allergen extract is effective in the former while immunotherapy has been shown to be ineffective (Adkinson Jr NEJM) or less effective in the later situation (Amirr/Nelson JACI).

For a poly-sensitized patient who is poly-allergic for homologous (biologically related) allergens (e.g. two grass pollens), a single allergen preparation or a mixture of two homologous allergens is recommended [Demoly 2016]. For polysensitized patients where allergens are not homologous, separate AIT preparations for one or two of the clinically most important allergens are recommended with doses given 30-60 minutes apart at separate locations when two are selected [Demoly 2016; Calderon 2012. This represents a trade-off between efficacy and safety as both are dose-dependent.

Co-existing asthma

Uncontrolled or poorly controlled asthma is considered to be an absolute contraindication to AIT [Pitsios 2015; Cox 2011; Bousquet 1989; Lockey 2001 Bernstein 2004; CSM 1986; Normansell 2015]. Studies that have assessed the impact of co-existing asthma on the efficacy of AIT [Bufo 2004] have reported no effect. Co-existing asthma is seen in many participants in the published AR studies [Dhami 2017]. When controlled, mild-to-moderate asthma does not seem to be a safety issue with AIT [Dhami 2017; Virchow 2016; Asthma AIT guidelines; Pfaar et al. 2014].

Specific pediatric issues

Similarly to adults, AIT should be considered in pediatric patients with AR with evidence of IgE-sensitization to clinically relevant allergens (Table 1, 3).
The evidence for the efficacy of AIT for AR is limited in children younger than five years of age. Some clinical studies have shown the efficacy and safety of both SCIT and SLIT in preschool children (Pajno 2012; Shao 2014; Fiocchi 2005; Agostinis 2005; Roberts 2006), and children were included from four years onward in several of the big SLIT trials (Bufe 2009, Wahn 2009). However, repeated injections of SCIT can be traumatic in small children [Pajno 2013; Arroabarren 2015]. The decision to start the treatment has to be taken on a case by case basis together with the patients and their family. It depends on several factors, such as the severity of the allergic disease, the clear exposure-symptoms pattern supported by allergic sensitisation testing, the impairment of the health related quality of life and the expected acceptance and adherence to the AIT.

There are more data to drive recommendations for school age children and adolescents although major gaps still exist (Table 3). Many of the SCIT trials are now relatively old, many enrolled a few children or do not present pediatric only analyses. Continuous and pre- and pre/co-seasonal SCIT can be recommended (Grade B) for children with seasonal AR (Table 3). Continuous SCIT is also recommended for perennial AR, but with a weaker evidence grade due to the inconsistency in the trial data (Grade C) (Table 3). There are no exclusive pediatric data for allergoid preparations. One open RCT suggests that SCIT for grass pollen driven AR does have a long-term benefit [Jacobsen L Allergy 2007]. For SLIT, there are recent pediatric trial data to support this approach. In general, pre/co-seasonal SLIT is recommended for seasonal AR (Grade A). For continuous SLIT, the results are more heterogeneous, probably because of the products used (Grade B) (Table 3). Both tablet and aqueous formulations are recommended although there is more heterogeneity in results with the latter (Table 3). There is now one unpublished trial supporting the long-term effectiveness for the grass pollen tablet and reduction in asthma symptoms [Valovirta Clin Ther. 2011](Grade B), there are no similar evidence for the aqueous preparations nor the HDM tablet.

**Elderly**

A detailed allergy history is especially important when evaluating older adults suffering with rhinitis as other types of rhinitis that may mimic AR symptoms. There are very few studies specifically evaluating the use of AIT in the elderly but SLIT with grass pollen and HDM has been demonstrated to be effective and safe in two studies [Bozek 2014 and 2016]. AIT elicits responses comparable to studies with younger patients. Another important considerations in
this age group, when contemplating treatment with AIT, is the higher prevalence of comorbidities. Examples are hypertension, coronary artery disease, cerebrovascular disease, and/or cardiac arrhythmias. Also, treatment with medication such as beta-blockers that may impair the treatment of anaphylaxis with adrenaline (epinephrine) (see Box 2).

Pregnancy

There is one prospective study investigating the safety of AIT in pregnancy [Shaikh 2012] and several retrospective studies suggest that there is no greater risk of prematurity, fetal abnormality, or other adverse pregnancy outcome in women who receive AIT during pregnancy [Metzger 1978]. Observations about anaphylaxis in pregnant and breastfeeding women are largely derived from case reports [Chaudhuri 2008] and are generally reassuring [Oykhman 2015]. However, the balance between benefits and potential risks in pregnant patients changes, these should be discussed with the patient. AIT takes months to work, but systemic reactions and their resultant treatment can potentially harm the baby and/or mother. It is therefore recommended that AIT is not initiated during pregnancy but, if already initiated, AIT may be continued during pregnancy or breastfeeding in consultation with the patient’s general practitioner and obstetrician if former AIT treatment has always been tolerated well.

Adherence

There is a great variance between studies (both real life studies and clinical trials) in the criteria used for evaluating compliance and in the rates of compliance [Incorvaria-- Incorvaia 2010; Scurati 2010; Egert-Schmidt 2014; Keil JACI 2013, Vaswani 2015; Leader 2016; Savi 2013]. The range of reported compliance varied from 18% to over 90%, higher in clinical studies than real-life surveys. The main causes for poor adherence are reported to be side effects, inconvenience, lack of efficacy or forgetting to use [Incorvaria-- Incorvaia 2010; Scurati 2010; Egert-Schmidt 2014; Vaswani 2015; Leader 2016; Makatsori M 2014]. A few other factors have been associated with poor adherence, for example age and patient’s educational level. Potential ways to improve adherence are the use of reminder mechanisms (e.g. alarm on mobile phone, internet based tools, service (SMS) electronic reminders, social networks, mobile applications (apps) and monitoring systems – the approach should be tailored to the patient), approaches to improving patient-doctor communication and patient education [Savi 2013; Demoly 2016]. One randomized study suggests that adherence is much better with 3
monthly follow up appointments compared to 6 or 12 monthly follow up [Vita 2010].
Recommendations are summarized in Table 6.
<table>
<thead>
<tr>
<th>Recommendation</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>Polysensitized patients</td>
<td>I</td>
<td>A</td>
<td></td>
<td>Based on expert review of RCT and observational data plus clinical experience.</td>
<td>Demoly 2016, Kim 2006</td>
</tr>
<tr>
<td>Polysensitized patients who are mono-allergic are recommended to receive AIT for the specific allergen that is driving their AR symptoms</td>
<td>II</td>
<td>B</td>
<td></td>
<td>Based on expert review of RCT and observational data plus clinical experience.</td>
<td>Demoly 2016, EMA advice.</td>
</tr>
<tr>
<td>Polysensitized patients who are poly-allergic for taxonomically related homologous allergens can be recommended to receive either a single allergen or a mixture of homologous allergens from that biological family that covers all the major allergens</td>
<td>II</td>
<td>C</td>
<td></td>
<td>Based on expert review of RCT and observational data plus clinical experience.</td>
<td>Demoly 2016, EMA advice; Radcliffe 2003, Kim 2006, Pfaar 2013.</td>
</tr>
<tr>
<td>Patients who are poly-allergic for non-homologous allergens may be recommended to start AIT with either the allergen responsible for most of their allergic rhinoconjunctivitis symptoms or separate treatment with the two clinically most important allergens</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-existing asthma</td>
<td>I</td>
<td>A</td>
<td>Strong recommendation based on high quality studies (asthma AIT SR)</td>
<td>Evidence described in asthma AIT systematic review.</td>
<td>Dhami 2017; Virchow 2016; Asthma AIT SR and asthma AIT guidelines</td>
</tr>
<tr>
<td>Specific pediatric issues</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>---</td>
</tr>
<tr>
<td><strong>In children aged less than 5 years of age, it is recommended that consideration should be given to likely benefits and risks associated with AIT for AR</strong></td>
<td>IV</td>
<td>D</td>
<td>May be more difficult to make a definitive diagnosis of AR in pre-school children. Safety seems to be similar in this age group as per older patients.</td>
<td>Rodriguez-Santos 2008; Rienzo VD 2005</td>
<td></td>
</tr>
<tr>
<td><strong>Elderly</strong></td>
<td>I</td>
<td>A (SCIT), B (SLIT)</td>
<td>Moderate to strong recommendation based on one high quality SCIT study (Bozek 2016) and two SLIT studies of unclear quality (Bozek 2014, Bozek 2012).</td>
<td>Consistent RCT data for SLIT, only one SCIT study. Also see Table 2. A detailed clinical assessment is recommended as other types of rhinitis may mimic allergic rhinitis in older patients.</td>
<td>Bozek 2012, 2014, 2016</td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>V</td>
<td>D</td>
<td>Based on balance of additional risk versus benefits.</td>
<td>Expert opinion</td>
<td></td>
</tr>
<tr>
<td>If patients have not started AIT and are pregnant, it is recommended to wait until after pregnancy to initiate therapy</td>
<td>IV</td>
<td>C</td>
<td>Based on observational data.</td>
<td>Metzger 1978</td>
<td></td>
</tr>
<tr>
<td>If have commenced AIT and still in up-dosing phase, it may be recommended that the current dose is continued and up-dosing is resumed when pregnancy is completed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
If on maintenance AIT, it may be recommended that the current dose is continued | III | C | Weak recommendation based on prospective cohort study [Shaikh 2012] | Expert opinion

### Adherence

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level</th>
<th>Recommendation Type</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is recommended that patients understand how AIT works and the need to take regular doses</td>
<td>II</td>
<td>B</td>
<td>Based on observational data.</td>
</tr>
<tr>
<td>It may be recommended that patients use reminders to maximize adherence with SLIT therapy</td>
<td>V</td>
<td>D</td>
<td>Based on observational data.</td>
</tr>
<tr>
<td>It can be recommended that patients on SLIT are followed up every 3 months to maximize adherence</td>
<td>I</td>
<td>B</td>
<td>Moderate recommendation based on a pseudo-randomized study (Vita 2010).</td>
</tr>
</tbody>
</table>
SECTION H: HOW LONG SHOULD AIT BE CONTINUED FOR IN AR?

Most clinical studies evaluating the efficacy of AIT follow participants for one or two years on therapy. The EMA currently recommends an experimental, randomized, controlled design involving three years of therapy with a two year follow up period off treatment. These studies demonstrate a sustained benefit for SLIT grass pollen therapy for two years off therapy for one tablet [Durham 2010], for one year off for another tablet [Didier 2015] and for one year off drops [Ott 2009]. There are some data to suggest that HDM SLIT drops gives sustained benefit for at least one year after three years of therapy in one RCT [Lin 2016] and another observational one [Stelmach 2012]. There is less evidence on the optimal duration of therapy. In a randomized cessation of therapy study, participants who stopped therapy after 3 or 4 years of grass pollen SCIT did as well three years later as participants who continued therapy [Durham 1999]. Similarly, children randomized to 3 or 5 years HDM SCIT had similar outcomes at five years [Arroabarren 2015] as did adults randomized to 3 years of ragweed SCIT [Naclerio 1997]. A recent study of grass pollen allergic patients showed that two years treatment with either SCIT or SLIT tablets were effective compared to placebo whereas two years was insufficient for long-term efficacy that was measured at 3 years, one year off treatment (Scadding GW 2017). So for patients with AR a minimum of three years of immunotherapy is recommended in order to achieve long-term efficacy after treatment discontinuation (Table 7).
**Table 7. Recommendations: How long should AIT for allergic rhinoconjunctivitis be continued?**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Evidence level</th>
<th>Grade of recommendation</th>
<th>Strength of recommendation</th>
<th>Contextual comments</th>
<th>Key references</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIT is recommended as efficacy is seen from the first year of therapy</td>
<td>I</td>
<td>A</td>
<td>Strong recommendation based on high quality studies (eg Balda 1998, Bergmann 2013, Bousquet 1990, Didier Clin Trans Allergy 2015, Zenner 1997)</td>
<td>Generally consistent data.</td>
<td>Dhami 2017; Bergmann 2013, Didier Clin Trans Allergy 2015</td>
</tr>
</tbody>
</table>
SECTION I: ADVERSE EVENTS WITH AIT FOR AR

SCIT

SCIT is a safe and well-tolerated treatment in selected patients when the injections are
given in a medical setting experienced with this kind of treatment [Alvarez-Cuesta 2006;
Cox 2012; Malling 2000; EAACI SR; Pfaar 2014].

Systemic allergic adverse reactions to SCIT can range between mild to severe adverse
reactions of the skin, upper and lower airways, gastrointestinal tract, or the
cardiovascular system (Table SB in online supplement). In a three year survey that
included over 20 million injection visits, systemic reactions were reported in 0.1% of
injections; there were no fatalities [Epstein 2011] although 4 were reported in the follow
up survey [Epstein 2016]. Fatal, allergic, adverse reactions have though been reported
in earlier surveys [Lockey 2001; Bernstein 2004]. Over 80% of reactions occurred within
30 minutes after injection; very few of the delayed ones were severe. It is therefore
recommended that patients stay in clinic for at least 30 minutes after an injection. There
are a number of possible risk factors for systemic adverse reactions (Table 9).
Interestingly, rush [Brehler 2010] and ultra-rush [Cardona 2012 and Casanovas 2006]
build up schedules with modified allergens are not associated with more adverse events
than conventional ones. When one or more severe adverse reactions occur, the allergist
should re-discuss the benefits and risks of SCIT therapy with the patient and decide
whether or not treatment should be continued.

Redness, itching or swelling represent local reactions at the injection site. These occur
frequently after around half of injections [Dhami 2017]. Local measures (e.g., cooling or
topical glucocorticoids) or oral antihistamines may be helpful for these reactions.
Increased local adverse reactions do not predict an increased individual risk of a
systemic adverse reaction [Kelso 2004]. In case of enlarged local adverse reactions
(redness and/or swelling >10 cm in diameter) occur at the injection site, the
manufacturer's product information (SmPC) leaflet provides adaptions of the dosing-
schemes for the next injection. When local adverse effects occur, pre-medication with
an H1-antihistamine can be used to reduce the frequency and severity of adverse
reactions but this prophylactic treatment does not prevent the onset of systemic adverse
reactions [Nielsen 1996; Reimers 2000]. Alternatively, case series indicate that modified
allergen extracts are associated with less adverse effects [Brehler 2010, Cardona 2012,
Casanovas 2006 & 2007]. For aluminum hydroxide containing SCIT products, rarely
granulomas have been described from a foreign body reaction mainly caused by
incorrect intradermal administration as well as contact allergic reactions, new onset of protein contact dermatitis or a vasculitic inflammatory reactions have been reported [Vogelbruch 2000, Netterlid 2009, Frost et al., Allergy 1985]. If these reactions to SCIT occur, treatment with another aluminum hydroxide-free product is preferred [Pfaar 2014].

SLIT
SLIT is regarded to be a safe and well-tolerated treatment [Radulovic 2010; Canonica 2014; Dhami 2017; Pfaar 2014].

Severe systemic reactions with SLIT are much less likely than with SCIT although the overall rate of any adverse reactions is similar in both SCIT and SLIT [Dhami 2017]. In a review of 66 SLIT studies (over 4000 patients who received over a million doses), there was one systematic reaction for approximately every four years of treatment and only one severe systematic reaction per 384 treatment years [Cox 2006]. There are no new safety concerns in more recent studies [Dhami 2017]. Several severe reactions - in some cases with severe anaphylaxis - are described in the literature occurring within 30 minutes of sublingual administration of allergens in droplet or tablet form [Calderon 2012]. In these cases, SLIT was not administered according to the standards (non-standardized extracts, rush protocols, excessive allergen dose, patients in whom SCIT had previously been interrupted due to severe reactions). As in SCIT, concomitant, poorly controlled asthma has been reported to be associated with severe systemic reactions after SLIT [Calderon 2012]. The majority of adverse events in SLIT develop at home without any medical observations (as after SCIT). Patients should therefore be informed about how to recognize and manage reactions, particularly severe ones. Patients also need education on what to do if a dose is forgotten and when SLIT should be temporarily interrupted (e.g. oropharyngeal lesions [Pfaar 2014]. When one or more severe adverse reactions occur, the allergist should re-discuss the benefits and risks of SLIT with the patient and decide whether or not treatment should be continued.

The frequency of local adverse events during SLIT correlates with the dosage and has been reported to be 40% to 75%, for example temporary local mucosal reactions (oral pruritus or dysesthesia, swelling of the oral mucosa, throat irritation) or abdominal pain [Canonica 2014, Cox 2006; Calderon 2012; Passalacqua 2013]. Most of these reactions occur during the initial phase of the treatment course (commonly in the first three weeks). They are commonly considered to be of mild intensity mild and generally [Canonica 2014]. Nethertheless, these reactions may occasionally lead to cessation of treatment, as observed in 4-8% of cases reported in recent trials of SLIT tablets (Blaiss 2011,
Mosbech 2014, Didier 2007, Dahl 2006). (see section “adherence”). As in SCIT, local adverse reactions may be diminished by the intake of (oral) antihistamines.

Box 3. Risk factors for systemic reactions during AIT

Current allergy symptoms and potential allergen exposure

Current infections

Mast cell disease

Previous systemic reaction to SCIT or SLIT

Hyperthyroidism

Unstable or uncontrolled or severe asthma

A high degree of sensitization

Excess dose escalation during initiation

Beta-blockers use

Poor injection technique

Overdose of allergen extract

Failure to follow manufacturer’s recommendation for dose reduction when change to new production batch

High-intensity physical exercise

Sauna

From Pfaar et al., Allergo J Int., 2014
Table 8. Recommendations: adverse events with AIT for AR

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Evidence level</th>
<th>Grade of recommendation</th>
<th>Strength of recommendation</th>
<th>Contextual comments</th>
<th>Key references</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SCIT or SLIT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For correctly selected patients, SCIT or SLIT is</td>
<td>I</td>
<td>A</td>
<td>Strong recommendation based</td>
<td>Consistent evidence.</td>
<td>Dhami 2017</td>
</tr>
<tr>
<td>recommended as, appropriately administered, it is safe and well tolerated</td>
<td></td>
<td></td>
<td>on high quality RCT studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>and observational studies (Dhami 2017)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>It is recommended that asthma should be</td>
<td>III</td>
<td>C</td>
<td>Strong recommendation</td>
<td>Expert opinion from observational studies</td>
<td>Bernstein 2004; Amin 2006;</td>
</tr>
<tr>
<td>controlled before commencing AIT as</td>
<td></td>
<td></td>
<td>based on high quality</td>
<td></td>
<td>Calderon 2012</td>
</tr>
<tr>
<td>insufficiently controlled asthma is a risk factor</td>
<td></td>
<td></td>
<td>studies (Nielsen 1996,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>for both SCIT and SLIT</td>
<td></td>
<td></td>
<td>Reimers 2000).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premedication with an antihistamine is</td>
<td>I</td>
<td>A</td>
<td>Strong recommendation</td>
<td>Consistent strong evidence from RCT studies</td>
<td>Nielsen 1996; Reimers 2000</td>
</tr>
<tr>
<td>recommended as it reduces the frequency and severity of local and systemic</td>
<td></td>
<td></td>
<td>based on high quality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cutaneous reactions but does not eliminate the risk of other systemic</td>
<td></td>
<td></td>
<td>studies (Nielsen 1996,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>adverse reactions</td>
<td></td>
<td></td>
<td>Reimers 2000).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>When one or more severe adverse reactions</td>
<td>V</td>
<td>D</td>
<td>Expert opinion from</td>
<td>Expert opinion from clinical experience</td>
<td></td>
</tr>
<tr>
<td>occur, it may be recommended that the allergist should re-discuss the</td>
<td></td>
<td></td>
<td>clinical experience</td>
<td></td>
<td></td>
</tr>
<tr>
<td>benefits and risks of AIT therapy with the patient and decide whether or not</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment should be continued</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SCIT
<table>
<thead>
<tr>
<th>It is recommended that patients should wait in the clinic for at least 30 minutes after a SCIT injection</th>
<th>III</th>
<th>C</th>
<th>Consistent observational data</th>
<th>Epstein 2011</th>
</tr>
</thead>
</table>
| If granulomas develop with aluminum hydroxide containing SCIT products, it may be recommended that treatment should be continued with an allergen extract that does not contain aluminum hydroxide | V    | D | Expert opinion | |}

| It is recommended that SCIT should be administered by competent staff with immediate access to resuscitation equipment and a doctor trained in managing anaphylaxis. | I    | C | Consistent observational data | Dhami 2017 |

**SLIT**

<table>
<thead>
<tr>
<th>Where there is concern about the possibility that AIT may cause systemic adverse reactions, SLIT can be recommended as the preferred approach as it is associated with a lower risk of such reactions than SCIT.</th>
<th>II</th>
<th>B</th>
<th>Expert opinion based on consistent observational data</th>
<th>Epstein 2011; Cox 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is recommended that patients should wait in clinic for at least 30 minutes after an initial SLIT dosage</td>
<td>III</td>
<td>C</td>
<td>Expert opinion based on consistent observational data</td>
<td>Calderon 2012</td>
</tr>
<tr>
<td>It is recommended that patients receiving SLIT should be informed about how to recognize and manage reactions, particularly severe ones. Patients also need to know what to do if a SLIT preparation is forgotten and when SLIT should be temporarily interrupted (e.g. oropharyngeal lesions).</td>
<td>V</td>
<td>D</td>
<td>Expert opinion from clinical experience</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>
SECTION J: PREVENTIVE EFFECTS OF AIT FOR AR

A three years course of AIT reduces the likelihood that children and adolescents with allergic rhinitis and pollen allergy go on to develop asthma until at least 2 years posttreatment [EAACI Prevention SR]. There is no documentation for a preventive effect of HDM AIT or for prevention of new sensitivities. It is important to be aware that patients included in these studies had less severe AR than those included in studies on AIT for treatment. This is further discussed in the EAACI AIT Prevention Guidelines [prevention AIT guideline].

SECTION K: PHARMACOECONOMIC ASPECTS OF AIT VERSUS PHARMACOTHERAPY FOR AR

Pharmacoeconomic studies that only analyze costs in monetary units have reported beneficial health care expenditure of AIT in the long-run although savings in the first year are not expected to be economic over symptomatic anti-allergic medications. The majority of pharmacoeconomics studies support the viewpoint that AIT gives value for money, with cost-effectiveness within 6 years of treatment initiation (Meadows 2013). Retrospective and prospective observational studies have shown that SCIT and SLIT positively affects health care expenditure in pharmacotherapy with a reduction between 12% and 80% (Ariano 2006, Berto 2005, Hankin et al. 2008; Hankin et al. 2010; Hankin et al. 2013). A reduction in medical costs in the AIT versus placebo groups have been repeatedly reported, but these savings did not compensate the costs of AIT (Creticos et al. 1996; Berto et al. 2008; Ariano et al. 2006).

In contrast to cost-only studies, cost-effectiveness and cost-utility analysis evaluates the effects of treatment in terms of clinical benefits or health-related quality of life (i.e., quality-adjusted life years [QALYs]). An incremental cost-effectiveness ratio (ICER), which is defined as costs divided by benefits, can be calculated to estimate the costs of a certain gain. Several health economics studies that include cost-effectiveness and cost utility calculations have demonstrated that SCIT and SLIT are economically advantageous (Schadlich et al. 2000; Petersen et al. 2005; Berto et al. 2006; Bachert et al. 2007).

Seven studies based on RCT data conducted from a health system perspective and using QALYS as their outcome measure suggest that SLIT and SCIT would be
considered cost-effective in this patient population in England at the standard National Institute for Health and Care Excellence (NICE) cost-effectiveness threshold of £20,000 (€24616) per QALY (Nasser 2008, Poulsen 2008, Keidig 2007, Ronaldson 2014, Westerhout 2012, Verheggen 2015, Reinhold 2016). ICERs for AIT seemed to vary substantially between different health systems suggesting that straightforward conclusions may not be generalizable even across seemingly similar countries.(Keidig 2007). Finally, the quality of the studies and the general lack of attention to characterizing uncertainty and handling missing data should be taken into account when interpreting these results.

SECTION L: SUMMARY, GAPS IN THE EVIDENCE AND FUTURE PERSPECTIVES

The EAACI Taskforce on AIT for Rhinoconjunctivitis has developed these guidelines as part of the EAACI AIT Guidelines project. The guidelines has been informed by a formal systematic review and meta-analysis of AIT for AR [Dhami 2017], The guidelines provide evidence-based recommendations for the use of AIT for patients with allergic rhinitis with or without allergic conjunctivitis. A summary of the guidelines is provided in Box 3. The recommendations should be of value to all healthcare professionals involved in the management of patients with AR.

There are many areas in these guidelines where there is no high quality evidence, these signify the gaps in the current evidence base. The key ones are highlighted here and in Table 9. There is a major gap in the evidence base for the clinical effectiveness of AIT in children and adolescents with recommendations at least one grade lower than for adults in most areas. As AR usually starts in childhood and AIT changes the natural history of the disease and prevents the development of asthma, this age group has most to benefit. Once safety is established in adult studies, pediatric studies need to be commenced using common outcome measures (Pfaar 2014). There is also little data in the elderly particularly for patients with multi-morbidity. Additionally, more randomized controlled trials need to follow participants post cessation of therapy to establish long-term clinically effectiveness. Agreement about the clinically meaningful effect size of AIT treatment would assist in the interpretation of clinical trial data. Additionally we need data from randomized cost-effectiveness and cost utility studies to use in discussions with healthcare funders. We need biomarkers to predict and quantify the effectiveness of AIT to assist in patient selection (Shamji 2017). The poor adherence associated with SLIT is likely to be impacting on its effectiveness; we need to develop novel approaches to
improve effectiveness in partnership with patients. Finally, to allow better comparison of
safety between approaches, a unified approach to classifying side effects is required.

Despite all these gaps we have clear evidence for the clinical effectiveness of AIT for
moderate-to-severe AR that is otherwise uncontrolled despite optimal pharmacotherapy
with evidence-based recommendations for specific patient groups and specific
approaches. There is now a need to ensure that primary care healthcare professionals
know which patients might benefit from AIT, that national healthcare providers
understand that AIT is cost-effective and that patients and patient support groups are
aware of this approach.
Table 9. Gaps in the evidence

<table>
<thead>
<tr>
<th>Gaps</th>
<th>Plan to address</th>
<th>Priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value of provocation tests in identifying the most appropriate allergen to use in AIT</td>
<td>Prospective controlled studies to assess benefit of provocation testing</td>
<td>Moderate</td>
</tr>
<tr>
<td>Good evidence base for contraindications to AIT</td>
<td>Registries recording patient details, AIT, outcome and adverse effects</td>
<td>Low</td>
</tr>
<tr>
<td>Lack of biomarkers to predict and quantify the effectiveness of AIT</td>
<td>Prospective observational studies to validate potential predictive biomarkers</td>
<td>High</td>
</tr>
<tr>
<td>Agreement about the clinically meaningful effect size of AIT treatment (active versus placebo treated patients)</td>
<td>Consensus discussion</td>
<td>High</td>
</tr>
<tr>
<td>High quality randomized controlled data for children and adolescents</td>
<td>More prospective controlled trials</td>
<td>High</td>
</tr>
<tr>
<td>For some AIT productions there is poor data for clinical effectiveness</td>
<td>Additional prospective controlled trials; use of products with proven effectiveness</td>
<td>Moderate</td>
</tr>
<tr>
<td>Evidence for clinical effectiveness post treatment cessation</td>
<td>More prospective controlled trials with follow up post treatment cessation</td>
<td>High</td>
</tr>
<tr>
<td>Effectiveness of mixtures of homologous allergens from the same, related or different biological families</td>
<td>More prospective controlled trials</td>
<td>Moderate</td>
</tr>
<tr>
<td>Management of AIT in patients who become pregnant on therapy</td>
<td>More prospective observational studies</td>
<td>Moderate</td>
</tr>
<tr>
<td>Standardization of grading of adverse effects of AIT</td>
<td>Future clinical trials should use the WAO systemic reaction grading system</td>
<td>High</td>
</tr>
<tr>
<td>Approaches to minimize adverse effects</td>
<td>More prospective observation and controlled trials</td>
<td>Moderate</td>
</tr>
<tr>
<td>Approaches to improve adherence with SLIT</td>
<td>Working patients to develop to develop novel approaches that can be tested in prospective controlled trials</td>
<td>High</td>
</tr>
<tr>
<td>Lack of standardized AIT preparations for orphan allergens</td>
<td>Multi-centre studies</td>
<td>Low</td>
</tr>
<tr>
<td>Randomized cost-effectiveness and cost utility studies adjusted to socioeconomic differences within and between countries</td>
<td>Additional studies with a health economics focus</td>
<td>High</td>
</tr>
</tbody>
</table>
Box 3. Summary of the EAACI Rhinoconjunctivitis AIT Guidelines

- The EAACI Guidelines on Allergen Immunotherapy (AIT) for allergic rhinitis (AR) aim to provide evidence-based recommendations for the use of AIT for patients with AR.
- Development of the guidelines has been based on a formal systematic review and meta-analysis of AIT for AR.
- AIT should be considered with symptoms strongly suggestive of allergic rhinitis, with or without conjunctivitis; evidence of IgE-sensitization to one or more clinically relevant allergen; and moderate-to-severe symptoms despite regular and appropriate pharmacotherapy and/or avoidance strategies.
- AIT may also be considered in less severe AR where a patient wishes to take advantage of its long term effect on rhinitis and potential to prevent asthma.
- A product based evaluation of evidence is recommended.
- Standardized AIT products with evidence of efficacy in the clinical documentation should preferably be used.
- Key contraindications are uncontrolled asthma; active, systemic autoimmune disorders; active malignant neoplasia. Careful review of benefits and risks are required with beta-blocker or ACE-inhibitor therapy, severe cardiovascular disease, other autoimmune disorders, severe psychiatric disease, poor adherence and immunodeficiency.
- Continuous SCIT is recommended for seasonal (Grade A, B for children) or perennial (Grade B, C for children) AR for short-term benefit in those with moderate-to-severe disease
- Pre- and pre-/co-seasonal SCIT is recommended for seasonal AR for short-term benefit (Grade A, B for children)
- Both modified (allergoids) and unmodified allergen extracts are recommended for AR for short-term benefit (Grade A, B for children)
- Continuous grass pollen SCIT is recommended for AR for short and long-term benefit (Grade A, B for children)
- Pre-/co-seasonal or continuous SLIT is recommended for seasonal ARs for short-term benefit (Grade A, B for continuous in children)
- SLIT with tablets (Grade A) or aqueous solutions (Grade B, A in children) can be recommended for AR for short-term benefit.
- Grass pollen SLIT tablets or solution is recommended for allergic rhinoconjunctivitis for long-term benefit (Grade A, B for children).
- HDM SLIT tablet can be recommended for allergic rhinoconjunctivitis for long-term benefit (Grade B, C for children).
- Polysensitized patients who are poly-allergic for taxonomically related homologous allergens can be recommended to receive either a single allergen or a mixture of homologous allergens from that biological family that covers all the major allergens (Grade B)
- Patients who are poly-allergic for non-homologous allergens may be recommended to start AIT with either the allergen responsible for most of their allergic rhinoconjunctivitis symptoms or separate treatment with the two clinically most important allergens (Grade C).

- In children aged less than 5 years of age, it is recommended that consideration should be given to likely benefits and risks associated with AIT for AR (Grade D).

- AIT can be recommended in otherwise healthy elderly patients with AR whose symptoms cannot be adequately controlled by pharmacotherapy (Grade A for SCIT, B for SLIT)

- If patients have not started AIT and are pregnant, it is recommended to wait until after pregnancy to initiate therapy (Grade D).

- It can be recommended that patients on SLIT are followed up every 3 months to maximize adherence (Grade B).

- To achieve long-term efficacy, it is recommended that a minimum of 3 years of therapy is used (Grade A).

- Premedication with an antihistamine is recommended as it reduces the frequency and severity of local and systemic cutaneous reactions but does not eliminate the risk of other systemic adverse reactions (Grade A).

- It is recommended that patients should wait in the clinic for at least 30 minutes after a SCIT injection (Grade C).

- It is recommended that SCIT should be administered by competent staff with immediate access to resuscitation equipment and a doctor trained in managing anaphylaxis. (Grade C).

- It is recommended that patients should wait in clinic for at least 30 minutes after an initial SLIT dosage (Grade C).

- It is recommended that patients receiving SLIT should be informed about how to recognized and manage reactions, particularly severe ones (Grade D).

- Many gaps in the underpinning evidence have been identified and prioritized.
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1. **General considerations**


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-40.


Patient factors


How long


Adverse events with AIT for allergic rhinoconjunctivitis

SCIT


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Pharmacoeconomic advantage of AIT versus pharmacotherapy


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Gaps


### Homologous allergen groups

Reproduced from Table SA. From Demoly P 2016

<table>
<thead>
<tr>
<th>Homologous groups</th>
<th>No homologous groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tree pollen: 1. Suggested homologous group: birch/fagales</td>
<td></td>
</tr>
</tbody>
</table>
Aesculus hippocastanum = B. pendula = B. alba | Non-grouped species: justification for mixing required  
Alnus glutinosa | European white birch  
Alnus incana | Alder  
Carpinus betulus | Hornbeam  
Corylus avellana | Hazel  
Quercus alba | Oak  
Castanea sativa | Sweet chestnut  
| | |  
2. Suggested homologous group: Oleaceae | |  
Olea europaea | Olive  
Prunus avium | Ash  
Quercus ilex | Holm oak  
| | |  
3. Suggested homologous group: Cupressaceae | |  
Juniperus sp. | Juniper  
Cupressus sp | Cypress  
| Grass and cereal pollen: 4. Suggested homologous group: grass species, the Poaceae (Gramineae) family, Poaceae subfamily | |  
Anthoxanthum odoratum | Sweet vernal grass  
Avena sativa | Oat  
Dactylis glomerata | Orchard grass/cocksfoot  
Festuca rubra | Meadow fescue  
Hakuro nishiki | Velvet grass/yorkshire fog  
Hordeum vulgare | Barley  
Lolium perenne | Perennial ryegrass  
Phleum pratense | Timothy grass  
Poa pratensis | Kentucky bluegrass  
Secale cereale | Cultivated rye  
Triticum aestivum | Cultivated wheat  
| | |  
5. Suggested homologous group: weed pollen species | |  
Ambrosia artemisiifolia, Ambrosia trifida | Ragweed  
Artemisia vulgaris | Mugwort  
| | |  
6. Suggested homologous group: house dust mites of the Dermatophagoides genus | |  
Dermatophagoides farinae | European house dust mite  
Dermatophagoides pteronyssinus | American house dust mite  
| | |  
Non-grouped species: justification for mixing required  
Acarus siro | Flour mite  
Glycyphaga domatia | House dust mite |
Grading systems for adverse reactions

We intended to use the WAO approach to grading adverse reactions. This proved impossible as different authors have used different approaches to classifying these. This means that it is difficult to synthesis the safety data and represents a gap.

Table 2 continued

<table>
<thead>
<tr>
<th>Homologous groups</th>
<th>No homologous groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insect venoms</td>
<td>Lepidophyllus destructor Storage mite</td>
</tr>
<tr>
<td></td>
<td>Tyrophagus domestici Storage mite</td>
</tr>
<tr>
<td></td>
<td>All species</td>
</tr>
<tr>
<td></td>
<td>Non-grouped species justifications for mixing required</td>
</tr>
<tr>
<td>Allergen extracts derived from vertebrates (extracts such as animal epithelia, hair, dander)</td>
<td>Non-grouped species justifications for mixing required</td>
</tr>
<tr>
<td>Moulds</td>
<td>Non-grouped species justifications for mixing required</td>
</tr>
</tbody>
</table>

In case of justification of grouping of mould species, special emphasis on similar stability is necessary.

Table SB 6

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms/signs of one organ system present</td>
<td>Symptoms/signs of more than one organ system present</td>
<td>Lower respiratory</td>
<td>Lower or upper respiratory</td>
<td>Death</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>Lower respiratory</td>
<td>Asthma (e.g., 40% PEF or FEV1 drop not responding to an inhaled bronchodilator)</td>
<td>Respiratory failure with or without loss of consciousness</td>
<td>Respiratory failure with or without loss of consciousness</td>
</tr>
<tr>
<td>Generalized pruritus, urticaria, flushing, or sensation of heat or warmth or Angioedema (not laryngeal, tongue or uvula) or Upper respiratory</td>
<td>Asthma: cough, wheezing, shortness of breath (e.g., less than 40% PEF or FEV1 drop, responding to an inhaled bronchodilator) or Gastrointestinal</td>
<td>Laryngeal, uvular, or tongue edema with or without stridor</td>
<td>Cardiovascular</td>
<td>Death</td>
</tr>
<tr>
<td>Rhinitis (e.g., sneezing, rhinorrhea, nasal pruritus and/or nasal congestion) or</td>
<td>Abdominal cramps, vomiting, or diarrhea or other</td>
<td></td>
<td>Hypertension with or without loss of consciousness</td>
<td></td>
</tr>
<tr>
<td>Throat-clearing (itchy throat) or Cough perceived to originate in the upper airway, not the lung, larynx, or trachea or Conjunctival</td>
<td>Urticaria cramps</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema, pruritus or tearing or other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea, metallic taste, or headache</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients may also have a feeling of impending doom, especially in grades 2, 3, or 4.

Note: Children with anaphylaxis seldom convey a sense of impending doom and their behavior changes may be a sign of anaphylaxis e.g., becoming very quiet or irritable and cranky. Scoring (grade 1-4) includes a suffix (a-d) or (z) that denotes if and when epinephrine is or is not administered in relationship to onset of symptoms/signs of the SIA, ≤5 minutes; b, >5 minutes to ≤10 minutes; c, >10 to 20 minutes; d, >20 minutes; z, epinephrine not administered.

The final grade of the reaction will not be determined until the event is over, regardless of the medication administered. The final report should include the first symptom/sign(s) and the time of onset after the subcutaneous allergen immunotherapy injection and a suffix reflecting if and when epinephrine was or was not administered, e.g., Grade 2a; rhinitic: 10 minutes.

Final Report: Grade a-d, or z

First symptom/sign(s) _____________ Time of onset of first symptom

Comments (on reaction and treatment):

1. This constellation of symptoms may rapidly progress to a more severe reaction.

2. Symptoms occurring within the first minutes after the injection may be a sign of severe anaphylaxis. Mild symptoms may progress rapidly to severe anaphylaxis and death.
Table SC

Grading system for local adverse events in sublingual immunotherapy (SLIT) according to the WAO (modified from [205])

<table>
<thead>
<tr>
<th>Symptom/sign</th>
<th>Grade 1: mild</th>
<th>Grade 2: moderate</th>
<th>Grade 3: severe</th>
<th>unknown severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharynx/swelling of mouth, tongue, or lip; throat irritation; nausea, abdominal pain, vomiting, diarrhea, heartburn, or urticarial edema</td>
<td>not troublesome and no symptomatic treatment required and no discontinuation of SLIT because of local side effects</td>
<td>troublesome and requires symptomatic treatment and no discontinuation of SLIT because of local side effects</td>
<td>Treatment is discontinued; but there is no subjective, objective, or both description of severity from the patient/physician.</td>
<td></td>
</tr>
</tbody>
</table>

Each local adverse event can be early (< 30 minutes) or delayed. *For example, itchy palate, burning or swelling at the throat (added by guideline authors)