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Specific Immunotherapy (hyposensitization) for IgE-mediated allergic diseases*

Guideline of the German Society of Allergy and Clinical Immunology (Deutsche Gesellschaft für Allergologie und Klinische Immunologie; DGAKI), of the Association of German Allergists (Ärzteverband Deutscher Allergologen; ÄDA) and the Society of Pediatric Allergy and Environmental Medicine (Gesellschaft für Pädiatrische Allergologie und Umweltmedizin; GPA), of the Austrian Society of Allergy and Immunology (Österreichische Gesellschaft für Allergologie und Immunologie; ÖGAI) and the Swiss Society of Allergy and Immunology (Schweizerische Gesellschaft für Allergologie und Immunologie; SGAI)

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Specific immunotherapy (hyposensitization) for IgE-mediated allergic diseases

The present guideline on allergen-specific immunotherapy (SIT) was established by German, Austrian and Swiss allergy societies in conjunction with other scientific and medical societies (dermatology, ear-nose-throat, pediatrics, venerology, lung and airway diseases) and a German patient support group according to criteria of the Association of the Scientific Medical Societies in Germany (AWMF). Subcutaneous immunotherapy (SCIT) induces long-term tolerance to the applied allergens after completion due to numerous immunologic effects. Regarding immunologic mechanisms of sublingual immunotherapy (SLIT), no consistent concepts exist. In case of preparations with high doses, though, similar systemic immunologic effects have been observed as with SCIT. Allergen concentrations and products for SCIT or SLIT cannot be compared at present due to their heterogeneous composition and variable assay methods of their active components. Non-modified allergens are used as aqueous or physically coupled (depot) allergen extracts; chemically modified allergens (allergoids) are used as depot extracts for SCIT. Mainly non-modified allergen extracts for SLIT are used as aqueous solutions or tablets. Results from controlled studies differ in extent and in quality, requiring product-specific evaluation of SIT. Systematic reviews demonstrate considerable heterogeneity between study results of SIT, partially explained by different subject groups, the utilized allergen products, the duration of treatment, and the therapeutic dose. Efficacy of SCIT has been demonstrated for pollen and house dust mite allergens in many controlled studies in patients with allergic rhinoconjunctivitis, and for animal dander (cat) and mold allergens (Alternaria, Cladosporium) in few studies. SCIT has been well studied in controlled asthma (according to new GINA guidelines, 2008) and intermittent and mild persistent IgE-mediated allergic asthma (according to former GINA guidelines, 2005) and is recommended as a therapeutic option besides allergen avoidance and pharmacotherapy, particularly in case of concomitant allergic rhinoconjunctivitis. Secondary preventive aspects, especially less novel allergic sensitizations and reduced development of bronchial asthma, are important reasons for an early start of SCIT during childhood and adolescence. Diagnostic allergy work-up, indication and selection of appropriate allergens for SCIT are, in general, made by a physician with allergy training within his/her specialization or carrying a certified (sub)speciality in allergy. SCIT is indicated in patients with IgE-mediated sensitizations and corresponding clinical symptoms to allergens, which do not or insufficiently permit allergen avoidance and which are available as suitable, efficacious extracts. Contraindications have to be considered on an individual basis. Injections of SCIT are administered by a physician experienced in this therapy and who is able to perform emergency treatment in case of an allergic adverse event. A preceding patient's information is mandatory and should be documented. The therapy should last 3 years. Children tolerate the SCIT well and benefit notably from its immunomodulatory effects. Severe, potentially life-threatening systemic adverse events can occur after SCIT, but are very rare in case of complete adherence to safety standards. Most adverse events are mild to moderate and easily treatable. Risk factors for and results of adverse systemic effects can effectively be minimized by training the staff members involved, adhering to safety standards and immediate emergency treatment. In case of systemic reactions due to hymenoptera (bee, wasp) venom hypersensitivity, SCIT has excellent efficacy and should be continued for at least 3 – 5 years. An extended, sometimes lifelong SCIT is necessary in some patients. Efficacy of SLIT in grass pollen-induced allergic rhinoconjunctivitis has been proven in several large-scale, controlled clinical studies. Applying other allergen sources (house dust mites, animal dander, molds), less and in part methodologically insufficient studies with contradictory results exist so far. Efficacy of SLIT in allergic bronchial asthma has not enough evidence until now. SLIT with efficacious products is an option for adults with allergic rhinoconjunctivitis due to pollen allergens, particularly if SCIT is not suitable. In case of house dust mite allergy or symptoms due to other allergen sources and allergic asthma due to inhalants, SLIT does not substitute SCIT. SLIT can be indicated in children and adolescents, if SCIT is not an option, using a preparation with proven clinical efficacy in this age group. SLIT is started by a physician experienced in the therapy of allergic diseases (see guideline wording) and who is able to perform emergency treatment in case of an allergic adverse event. According to the leaflet of the product manufacturer, the patient should be informed about the therapy, usually lasting 3 years as pre- and coseasonal or perennial regimen. During this course consultations should take place at least every 3 months. Apart from very frequently to frequently occurring dose-dependent adverse local oral and pharyngeal symptoms, systemic reactions, mostly of mild nature, have rarely been described after SLIT. With regard to anaphylactic and other severe systemic reactions SLIT demonstrates a superior safety profile compared to SCIT. Additional research fields such as allergen characteriza-

Abbreviations

AMG	German Medicines Act
DBPC	double-blind and placebo-controlled
FEV_1	forced expiratory volume in the first second
GCP	good clinical practice
GMP	good manufacturing practice
Ig	immunoglobulin
IL	interleukin
CI	confidence interval
OAS	oral allergy syndrom
PEI	Paul-Ehrlich-Institut
SCIT	subcutaneous immunotherapy
SIT	specific immunotherapy
SLIT	sublingual immunotherapy
SMD	standardized mean difference
TGF	transforming growth factor

tion, routes of application, adjuvants, updosing regimen and preventive aspects demonstrate new developments in SIT are currently being examined for clinical efficacy.

1. Objectives and development of the guidelines

This guideline for specific immunotherapy with allergens (SIT, hyposensitization) reflects the development that has taken place in the past decades and in which safety and efficacy of SIT have been documented in numerous controlled studies (summary in [1, 24, 38, 129, 168]). The immunologic mechanisms are being better understood [3, 57, 92]. At present subcutaneous immunotherapy (SCIT) is considered to be the only treatment with a positive causal influence on the course of allergic diseases by impairing the development of bronchial asthma [76] and by possibly preventing novel allergic sensitizations in some patients with allergic rhinoconjunctivitis [127, 148].

This guideline was produced on behalf of and financed by the following allergy societies: German Society of Allergy and Clinical Immunology (Deutsche Gesellschaft für Allergologie und klinische Immunologie; DGAKI), Association of German Allergists (Ärzteverband Deutscher Allergologen; ÄDA) and Society of Pediatric Allergy and Environmental Medicine (Gesellschaft für Pädiatrische Allergologie und Umweltmedizin; GPA). It replaces the S2 guideline published in 2006 [86]. For the first time the Austrian Society of Allergy and Immunology (Österreichische Gesellschaft für Allergologie und Immunologie; ÖGAI) and the Swiss Society of Allergy and Immunology (Schweizerische Gesellschaft für Allergologie und Immunologie; SGAI) were directly involved in the development of the guideline. When developing the guideline, international (World Health Organization (WHO)), European (European Academy of Allergology and Clinical Immunology (EAACI)) and existing recommendations for sublingual immunotherapy (SLIT) were taken into account [85].

The SIT guideline was developed according to the methodic requirements for the development of guidelines for diagnostic work-up and therapy defined by the Association of Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften; AWMF) and corresponds, according to the AWMF's three-step concept, to a S2 guideline, supplemented by stages of recommendation and evidence (Table 1) as well as by clinical algorithms (for explanation see Figure 1) for diagnostic work-up and indication. Statements in the guideline were completed by stages of recommendation and evidence established by meta-analyses, clinical trials and other scientific investigations.

It is essential to establish a consensus in order to create acceptance for a guideline even if evidence is low in order to support its dissemination and implementation. To obtain consensus we used a combination of nominal group process and delphi technique involving authorized representatives from scientific and medical societies: Wolfgang Wehrmann, Münster, Professional Association of German Dermatologists (Berufsverband der Deutschen Dermatologen; BVDD), Frank Friedrichs, German Association of Pediatricians (Berufsverband der Kinder- und Jugendärzte; BVKJ), Thomas Hering, Berlin, German Federal Association of Pneumologists (Bundesverband der Pneumologen; BDP), Andrea Koch, Köln, and Horst Müsken, Bad Lippspringe, German Society of Pneumology (Deutsche Gesellschaft für Pneumologie, DGP), Heinrich Lenders, Schwäbisch Hall, and Sylvia Schnitzer, Grevesmühlen, German Professional Association of Ear, Nose and Throat Doctors (Deutscher Berufsverband der Hals-Nasen-Ohrenärzte; BVHNO), Boris A. Stuck, Mannheim, German Society for Ear, Nose and Throat Medicine, Head and Neck Surgery (Deutsche Gesellschaft für Hals-Nasen-Ohren-Heilkunde, Kopf- und Hals-Chirurgie; DGHNOKHC), Joachim Saloga and Bettina Wedi, German Society of Dermatology, (Deutsche Dermatologische Gesellschaft, DDG), Ingrid Voigtmann, Mönchengladbach, German Allergy and Asthma Association/Patient Organization (Deutscher Allergie- und Asthmabund; DAAB). The fol-

Table 1. Levels of recommendation and evidence for MW guidelines (according to Centre for Evidence-Based Medicine Oxford) [8].

Level of recommendation	Level of evidence	Evidence by
A	1a	systematic review of RCTs
	1b	well-planned randomized controlled trial
	1c	all or none principle
B	2a	systematic review of well-planned cohort studies
	2b	well-planned cohort study, RCT with moderate follow-up
	2c	outcome research studies
	3a	systematic review of case control studies
	3b	individual case control study
C	4	case series (and poor quality cohort and case control studies
D	5	expert opinion without explicit critical appraisal, or based on physiology, laboratory research or "first principles"

RCT = randomized controlled study.

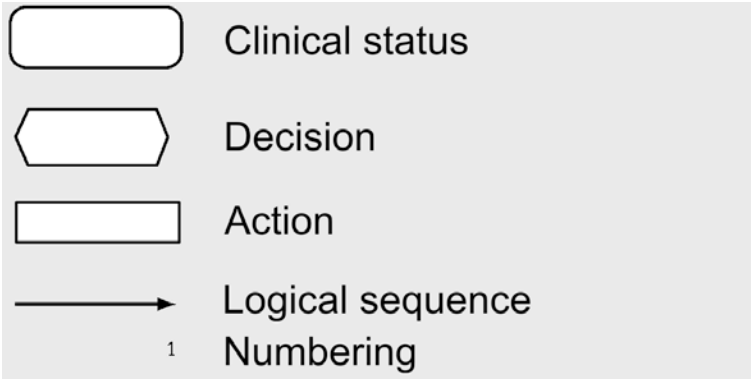

Figure 1. Standardized terminology for clinical algorithms: A clinical algorithm is a procedure formulated in a finite number of steps which solves a clinical problem using conditional logical statements (if-then-logic). It is usually presented as a graphic using the nomenclature recommended by the Society for Medical Decision Making. Status, action and decision nodes are used. Status and action nodes have one exit each, decision nodes have exactly 2 exits (yes and no).

lowing persons accompanied the consensus conference and the guideline process as neutral observers: Susanne Kaul, Langen, Paul-Ehrlich-Institut (PEI), Department of Allergology, Burkhard Luther, Oberursel, Medical Review Board of the Health Care Providers (Medizinischer Dienst der Krankenversicherung; MDK) Hessen, and Anja Schwalfenberg, Mönchengladbach, DAAB. Following the consensus procedure the guideline was presented to all responsible committees for annotation and recommended for acceptance.

The guideline is addressed to all physicians who treat allergic patients and shall be updated by the authors of the allergy societies three years after publication; the first author is responsible for this. The guideline is published and distributed by the allergy societies in their associated organs of publication (Allergo Journal, Pädiatrische Allergologie in Klinik und Praxis) and in the AWMF guideline collection. The guideline is recommended to be accepted by other involved societies and is made available for reprint for interested journals with allergologic content.

2. Immunologic mechanisms

Most immunologic effects in the context of SIT have first been described for SCIT. According to the current state of knowledge immunotherapy causes alterations on the level of antigen representation, T cell response and antibody response, influencing the effector cells [92]. Current data support several models of the immunologic efficacy of immunotherapy:

- SCIT modifies the function of allergen T cells by activating regulatory $CD4^+$ T cells that produce interleukin-(IL-)10 and transforming growth factor-(TGF-)β and mediate tolerance [2, 3, 13, 57, 58, 78, 123] (Figure 2). Th2 cells become anergic and their reactivity reduces with decreasing cytokine production and proliferation after stimulation by the T cell receptor [54, 102, 113].
- SCIT causes a shift of the dominant Th2 response (e.g., IL-4, IL-5, IL-13) in favor of a more pronounced Th1 response (Interferon-γ) [13, 79, 158] (Figure 2).
- SCIT, like vaccinations, induces a new allergen-specific immune response characterized by a more pronounced production of allergen-specific IgG antibodies [56, 121, 162], particularly of IgG_1- and IgG_4 antibodies [131] which are able to inhibit allergen-specific mast cell degranulation, T cell activation and allergen-induced boost of the IgE production [23, 62, 112].
- The functions of effector cells, like mast cells and basophil granulocytes or eosinophil granulocytes, are inhibited [137, 142].

Thus, SCIT interferes in the basic immunologic mechanisms of all allergic (atopic) disease patterns. This means that SCIT is a causal form of therapy and thus of particular importance in the therapy of allergic diseases. However, the immunologic effects do not always correlate with the clinical efficacy.

To date there is no common agreement upon the mechanisms involved in SLIT; in

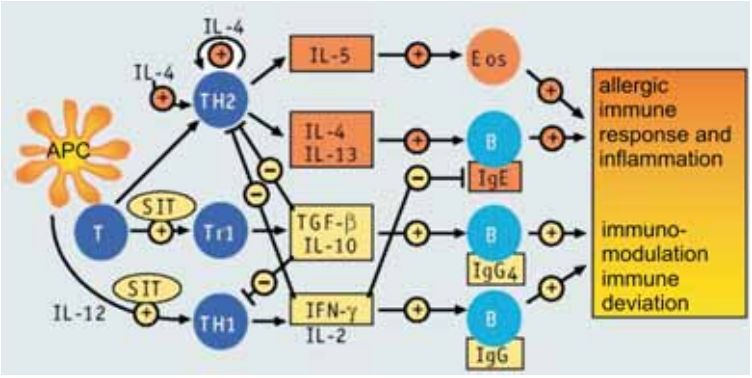

Figure 2. Allergic immune response and mechanisms of SCIT: By interleukin (IL-)5 production Type 2 T-helper (Th2-) cells induce an allergic inflammation characterized by eosinophil granulocytes (Eos); by IL-4 and IL-13 they induce immunoglobulin E (IgE-) synthesis of B-lymphocytes (B). Subcutaneous specific immunotherapy (SCIT) inhibits the function of Th cells by and increased release of TGF-β (transforming growth factor beta) and IL-10 cytokines from regulatory Tr1-like cells (immunomodulation). Furthermore, a regulatory Th1 immune response is induced (immune deviation): IL-12 from antigen-presenting cells (APC) stimulates the production of interferon (IFN-)γ by TH1 cells and thereby inhibits formation of IgE and differentiation of Th2 cells. For SLIT, similar mechanisms have been suggested and partially shown for certain products with high allergen contents. Figure characteristics: Circle containing +: induced; circle containing –: inhibited; red coding: increased allergic immune response (immediate-type allergy); yellow coding: reduced allergic immune response.

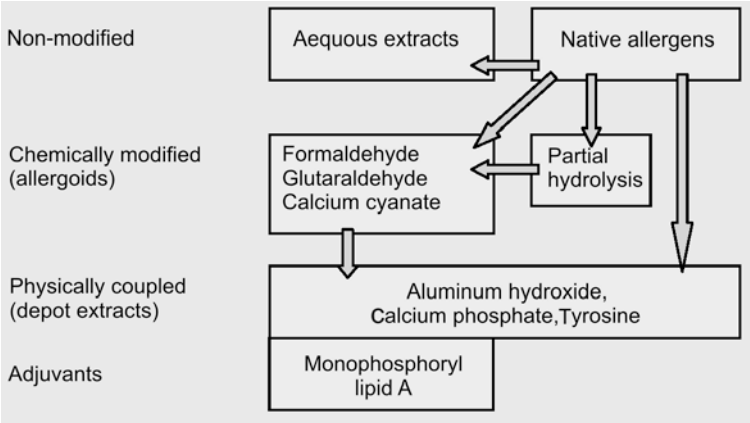

Figure 3. Allergen extracts available for SCIT (for explanation see Section 3.).

cases of successful SLIT a local anti-inflammatory immune response in terms of production of local cytokines, primarily of IL-10 from regulatory T cells, was found [20]. In current studies the increase of factors that inhibit the binding of IgE to allergens was observed [41, 109]. Under SLIT the increase in allergen-specific IgG-antibodies and IgG_4-antibodies can differ [48, 134]. In SLIT with a grass pollen extract in tablet form the allergen-specific IgE-antibodies were significantly increased above the value observed with natural pollen concentrations ("boost") [48]. The clinical relevance of this increase remains unclear.

Conclusion: Subcutaneous immunotherapy (SCIT) induces long-term tolerance to the applied allergens after completion as defined by numerous immunologic effects. Regarding immunologic mechanisms of sublingual immunotherapy (SLIT), no consistent concepts exist. In case of preparations with high doses, though, similar systemic immunologic effects have been observed as with SCIT.

3. Allergen extracts, their evaluation and marketing authorization

3.1. Production and composition of allergen extracts

Due to manufacturer-specific processing the produced allergen extracts differ concerning composition and allergen activity and thus are not comparable even if the same allergen sources are used. The total activity of the extracts is evaluated by in vitro methods and is biologically standardized using skin tests. For the production of allergen preparations for SIT preferably standardized allergen extracts should be used, because non-standardized extracts vary significantly in terms of biologic activity [94]. The determination of dominant single allergens (e.g., major allergens) using standardized validated methods is recommended by international guidelines and, if available, will be used more frequently for important allergen sources [143]. At the moment, however, it is impossible to compare allergen concentrations of different preparations, as until now the manufacturers use different references and measuring methods to determine the major allergens.

For SCIT non-modified ("native") extracts with unchanged allergen conformation and chemically modified (polymerized) extracts (so-called allergoids) can be used. It is assumed that allergoids possess less reactive B cell epitopes and thus a reduced IgE binding, while their T cell epitopes and their immunogenic effect remain unchanged. Besides aqueous extracts, which are common for induction therapy in insect venom allergy,

Text box 1. Important terms of the German Medicines Act (AMG).

Finished medicinal product
Section 4 Sub-section 1 AMG [10]: "Finished medicinal products are medicinal products which are manufactured beforehand and placed on the market in packaging intended for distribution to the consumer or other medicinal products intended for distribution to the consumer, in the preparation of which ... an industrial process is used or medicinal products which are produced commercially."

Marketing authorization
Section 21 Sub-section 1 AMG: Finished medicinal products which are medicinal products as defined in Section 2 sub-section 1 or sub-section 2 no. 1, may only be placed on the market within the purview of the present Act, if they have been authorized by the competent higher federal authority..."

Individual formulations
Section 21 Sub-section 2 AMG: "A marketing authorization shall not be required for medicinal products which ... 1b: ... are prepared on prescription in the form of therapy allergens for individual persons …"

mainly depot extracts, in which native or modified allergens are physically coupled to a carrier (e.g., aluminum hydroxide, tyrosine or calcium phosphate), are used in Europe, depot extracts, in which native or modified allergens are physically coupled to a carrier (e.g., aluminum hydroxide, tyrosine or calcium phosphate), are most commonly used with the exception of insect venom allergy, where aqueous extracts are applied for induction therapy (Figure 3).

Preparations for SLIT are available with allergens in unmodified conformation or as modified extracts in the form of aqueous solutions or tablets. There are preparations that have to be stored in the refrigerator and others that can be stored at room temperature.

Conclusion: Allergen concentrations and products for SCIT or SLIT cannot be compared at present due to their heterogeneous composition and variable assay methods of their active components. Non-modified allergens are used as aqueous or physically coupled (depot) allergen extracts; chemically modified allergens (allergoids) are used as depot extracts for SCIT. Mainly non-modified allergen extracts for SLIT are used as aqueous solutions or tablets.

3.2. Criteria for evaluation of specific immunotherapy in subcutaneous or sublingual application

SIT was evaluated by controlled studies in which efficacy, tolerability and additional effects were examined. For this purpose symptoms and drug use were analyzed using previously defined score-based systems that also reflect the patient's individual disease management: For example pronounced symptoms in association with low drug use or less pronounced symptoms in association with high drug use. Symptom and medication scores, indicated either as separate scores or as a combined symptom/medication score, are linked to each other. Until now, they have not been validated regarding weighting, distribution and (quantitative) interdependence. They have, however, prospectively been fixed in the study protocols for double-blind, placebo-controlled (DBPC) trials.

As a result, the outcomes of SIT studies are hardly comparable due to differences in score systems, patient cohorts and study designs. As preparations (dose, allergen composition, modifications) and routes of application (up-dosing regimen, frequency of application and duration of therapy) also differ significantly, a general evaluation is difficult. Thus, instead of providing generalized statements concerning SIT, SCIT or SLIT, this guideline is aiming at making product-specific assumptions of successful placebo-controlled studies and at evaluating the clinical relevance of the results.

This gives a high significance to the scope and accuracy of the pre-clinical and clinical documentation for a preparation and to its marketing authorization, in order to evaluate certain products and procedures for SIT. For allergen preparations the reverse is not imperatively true, i.e., preparations without controlled studies are not necessarily ineffective, their clinical efficacy is just not documented.

3.3. Significance of the marketing authorization of allergen preparations

Preparations of native or modified allergen extracts are available as authorized drugs or as individual formulations. According to the 14th novel of the German Medicines Act (AMG) authorized therapy allergens as well as individual formulations are ready-to-use medicinal products (Text box 1). In principle, all ready-to-use medicinal products have to be authorized. However, the AMG allows exceptions for some drugs, with individual formulations for therapy allergens belonging to this group (Text box 1). Thus, the term ready-to-use medicinal product is no longer appropriate to distinguish between authorized therapy allergens and individual formulations. Basically, both types of products are prescribable and negotiable. Until the Regulation on Therapy Allergens "Regulation on the

Text box 2. List of therapy allergens for which market authorization is required*.

- Species of the family poacea except Poa mays (true grasses except maize)
- Betula sp. (species of genus birch)
- Alnus sp. (species of genus alder)
- Corylus sp. (species of genus hazel)
- Dermatophagoides sp. (species of the genus house dust mite)
- Bee venom
- Wasp venom

*List of therapy allergens that have to obtain a marketing authorization according to the regulation on therapy allergens [163] and that in the future may not be marketed – neither as single preparations nor as mixtures – without permission.

Text box 3. Procedure* for marketing authorization of drugs in Germany.

- National procedure by which the medicinal product is authorized for Germany only.
- Mutual recognition procedure, if the preparation has already obtained authorization in one EU member state and the marketing authorization is supposed to be extended to other EU member states.
- Decentralized procedure, if the medicinal product has not obtained national marketing authorization yet and is supposed to be subject to parallel authorization in several EU member states.
- Central procedure (parallel marketing authorization in all EU member states) for medicinal products that are named in the appendix of the EC regulation 726/2004 (e.g., medicinal products that have been produced using biotechnologic procedures); under certain circumstances this procedure can also be used for other medicinal products.

*All procedures that result in marketing authorization in several or all EU states are coordinated by the European Medicines Agency (EMEA).

expansion of specifications of the marketing authorization of drugs based on therapy allergens prepared on the basis of individual formulations for certain persons and regulation on the process control for governmental batch testing (Therapieallergen-Verordnung)" came into effect on November 14, 2008 only authorized allergen preparations were subject to governmental batch tests in Germany. In these authorized preparations the batch testing is carried out in the end product and/or in the inter-stage products. Depending on the size of the primary packaging, they can be identified by the batch number (Ch.-B.) on the label or, in any case, by the authorization number (Zul.-Nr.) and the batch designation on the outer package. These characteristics make them distinguishable from individual formulations that are not certified by the Paul-Ehrlich-Institut (PEI).

The Regulation on Therapy Allergens stipulates that – with certain transitional regulations – therapy allergens that contain at least one extract of an allergen source that frequently causes diseases (Text box 2) have to be authorized. Individual formulations have to be reported to the PEI if they contain those kinds of allergens and an application for authorization is to be made. The same is the case if no marketing authorization is intended, but a therapy that had been started is supposed to be continued for a maximum of 3 years. After a transitional time until final marketing authorization or until their negotiability ends, all reported preparations stay negotiable and are subject to batch tests carried out by the PEI. These batch tests are not carried out in the final product but in the respective parent extracts (parent extract batch testing). All further therapy allergens produced as individual formulations (those which do not contain allergens listed in the appendix of the Regulation on Therapy Allergens) continue to be exempted and are not subject to governmental batch testing. For reasons of pharmacovigilance and drug safety, authorized and unauthorized preparations for SCIT are distributed in a patient-related form directly by the manufacturer and not via the wholesale.

In Germany the Paul-Ehrlich-Institut (PEI) is responsible for the marketing authorization of allergen preparations (Text box 3) for therapy and diagnosis. In Austria these affairs are regulated by the Bundesamt für Sicherheit im Gesundheitswesen (Federal Office for the Safety in the Public Health Sector) which refers to the Österreichische Agentur für Gesundheit und Ernährung (Austrian Agency for Health and Nutrition; AGES-PharmMed). In Switzerland the marketing authorization of allergens is supervised by the Swiss medicine institute Swissmedic. Thus, the above-mentioned regulations do not apply for Austria and Switzerland.

Together with the authorization documents, information on the production process of the drug and on its quality control as well as the results of all pre-clinical and clinical studies and of further medical testing has to be provided to the PEI. The documents for current and recent marketing authorizations have to comply with the requirements stated in the guidelines for good manufacturing practice (GMP) and in the guidelines for good clinical practice (GCP), with the European pharmacopoeia as well as with the respective EMEA guidelines (European Medicines Agency; www.emea.europa.eu/pdfs/human/bwp/30483107enfin.pdf, http://www.emea.europa.eu/pdfs/human/ewp/1850406enfin.pdf). The preparations are only authorized for those indications and patient groups for which safety and efficacy have been proven in clinical trials. Apart from bee and wasp venom preparations, since 1993 marketing authorization is only being granted if at least one double-blind, placebo-controlled study was carried out successfully. For hymenoptera venom preparations placebo control is not required due to ethical reasons. In these cases

the new preparation is usually tested by comparing it to an established comparator product. Formerly, sometimes also open-label studies were accepted as evidence for efficacy – corresponding to the standard of knowledge at that time. Since the GCP regulation came into effect in August 2004 clinical examinations have to be approved by the responsible authority beforehand. All GCP criteria have to be met. This has led to a significant improvement in the quality of data obtained in clinical studies and of the evidence for safety and efficacy of preparations authorized on the basis of these studies. Thus, authorized preparations (www.pei.de > Ärzte und Apotheker > Arzneimittel > Liste zugelassener Arzneimittel > Allergene) [81] have been examined in terms of quality, efficacy and tolerability in correspondence with the respective standard of knowledge at the time of marketing authorization.

This means that those preparations which were produced as individual formulations (named patient products) and therapy allergens that did not require authorization (Text box 1) were not officially controlled concerning quality, efficacy and tolerability and they were not subject to governmental batch testing. Due to the Regulation on Therapy Allergens most individual formulations are subject to governmental batch testing in the parent solutions after a transitional period. An official examination of safety and efficacy is only available with the final marketing authorization.

For all other individual formulations (single or in mixtures) that do not contain ingredients listed in the allergen list (Text box 2) still no marketing authorization is necessary and they continue not to be subject to any official control. Nevertheless, according to the manufacturers, the parent extracts used for the formulations are produced in accordance with the GMP criteria and are examined on the basis of internal specifications.

It is estimated that a total of more than 50% of therapy preparations of both application forms (SCIT, SLIT) are available as individual formulations [104] and thus are not examined by the PEI. Individual formulations are frequently evaluated in uncontrolled studies – if they are examined at all. This is the reason why hardly any solid data concerning efficacy and tolerability and only sparse data concerning tolerability are available. In some cases data might already correspond to the current state of knowledge; these preparations will probably easily be authorized according to the Regulation on Therapy Allergens. As a result of Regulation on Therapy Allergens data will be collected for further individual formulations in the near future.

In our opinion, authorized allergen preparations with documented safety and efficacy should be preferred as long as the patient's sensitization spectrum allows for it (D, 5). The manufacturer can present the efficacy results from respective studies in the technical information of the leaflet under Article 5.1. The quality of these studies, however, can significantly vary because of the differences in requirements from 1990 until today. In the case of authorized preparations these presentations are also officially examined. For current marketing authorizations the manufacturers use this possibility and make information on the respective preparation available for the physician as part of the leaflet.

As authorized finished medicinal products cannot cover the whole spectrum of allergen extracts that have to be used for SIT, individual formulations (named patient products) are still necessary in cases where the extract must be tailored to the allergologic problem of an individual patient (D, 5) [104].

4. Efficacy in clinical studies

4.1. Systematic reviews and meta-analyses for evaluation of specific immunotherapy

Systematic reviews and meta-analyses are used for a global evaluation of therapies, because they provide the opportunity to carry out a summarized conclusion by "global" statistics. Individual studies examining small numbers of cases, have shown trends without statistic significance and have used different study designs or heterogenous products (e.g., allergen preparations) and differing subject groups.

A systematic review of 22 SLIT studies published until September 2002 showed a significant weak-to-moderate clinical effect of verum vs. placebo therapy in the treatment of allergic (exclusively pollen-induced) rhinitis in adults. This applies to the reduction of symptoms (standardized mean difference (SMD) –0.42; 95% confidence interval (CI) –0.69 to –0.15; $p = 0.002$) and to the use of rescue medication (SMD –0.43; 95% CI –0.63 to –0.23; $p = 0.00003$) after SLIT [168]. In contrast, no sufficient effects were found for perennial rhinoconjunctivitis, allergic bronchial asthma in adults and allergic respiratory diseases in childhood [168]. The comprehensive studies concerning SLIT that had been published in the meantime were not yet taken into account in the review published by the Cochrane Collaboration in 2003.

A systematic review published in 2007 by the Cochrane Collaboration reporting on 15

Text box 4. Defintions of SCIT with allergens.

Short-term therapy
Limited number of 4 – 7 injections before the seasonal symptoms start.

Preseasonal therapy
Start of treatment in sufficient time before the start of pollen season; weekly injections during dose-increase period and monthly injection with the maintenance dose until the start of pollen season.

Perennial therapy
Start of therapy with up to 16 weekly injections during the dose-increase period and monthly injections with the maintenance dose; in case of seasonal allergen sources, a reduction of the maintenance dose during the symptom season according to the manufacturer's information is possible.

studies on SCIT that had been published until February 2006 shows significant moderate-to-strong effects of verum vs. placebo in the therapy of seasonal allergic rhinoconjunctivitis. The improvement was related to the reduction of symptoms (SMD –0.73; 95% CI –0.97 to –0.50; $p < 0.00001$) and to the reduced rescue medication use (SMD –0.57; 95% CI –0.82 to –0.33; $p < 0.00001$) [38]. On the other hand there was a considerable positive impact of few studies with low numbers of cases on this effect on symptom and medication scores [38].

Meta-analyses [1, 38, 132, 133, 168] depend on the quality of the single studies taken into account, on their mathematically determined heterogeneity [1, 38, 168] and on the possible publication bias. The publication of systematic reviews and meta-analyses in the Cochrane Library [1, 38, 168] is superior to the publication in expert journals [132, 149], because in the former transparent and stringent evaluation criteria are used.

Conclusion: Systematic reviews demonstrate considerable heterogeneity between study results of SIT, partially explained by different subject groups, the utilized allergen products, the duration of treatment, and the therapeutic dose.

4.2. Efficacy of SCIT

4.2.1. Efficacy of SCIT in allergic rhinoconjunctivitis

The documentation of the clinical efficacy of SCIT in allergic rhinoconjunctivitis is based on numerous placebo-controlled double-blind studies that vary in size and quality and that have been summarized for seasonal allergen sources in a systematic review with meta-analysis [38]. In these studies a median reduction of symptoms/drug use of 45 – 60% was described for the comparison verum vs. placebo [38].

The majority of analyzed studies evaluate the efficacy of specific SCIT in pollen allergies. Most of these studies were carried out for grass pollen allergies using chemically unmodified allergen extracts; however, not all available preparations were tested. In almost all studies a reduction in symptoms and/or drug use of at least 30% in the treatment group vs. the placebo group was observed (A, 1a) [38].

Efficacy studies for birch pollen allergies showed a reduction in symptoms and/or drug use of an average of 45% (A, 1b) [9, 12, 19, 120].

The evaluation of efficacy of SCIT in rhinoconjunctivitis caused by house dust mite is based on several studies. All studies show a reduction in symptoms and/or drug use of at least 30% in the treatment group vs. the placebo group (A, 1b) [17, 24, 55, 105, 106, 135, 136].

In animal dander allergens efficacy was only shown with cat allergen extracts. For other animals only few reports exist. In the case of mold allergies the evidence of clinical efficacy is limited to only a few studies (Alternaria, Cladosporium; B, 2b) [46, 74, 101].

Most SCIT studies that show positive effects were carried out in adults (75%). Only six studies involved children. Thus, the evidence for a positive effect of SCIT is not completely secured for this age group.

Short-term SCIT is carried out with allergoids (with or without adjuvant) and with non-modified allergens. The manufacturers recommend 4 – 8 injections, depending on the used extract. Nevertheless, modifications are possible according to the patient's tolerability.

Efficacy of short-term SCIT in cases of seasonal allergic rhinoconjunctivitis was not only documented in older controlled studies (with or without placebo control [39, 107, 130]) but also in more recent publications [12, 40, 45, 161, 172].

Immunologic changes (see 2.) can be verified similarly in short-term SCIT [40, 71, 88, 139, 172]. In view of the lower cumulative dose, short-term therapy should only be carried out if its clinical efficacy can be demonstrated in DBPC studies and if the patient is not able to ensure patience for a preseasonal or perennial SCIT (for explanation see Text box 4) in which a higher number of injections of the maximum dose is required or if there is only little time left before the pollen season starts (D, 5). Preventive effects, long-term efficacy, efficacy in children or in bronchial asthma proven by randomized placebo-controlled studies have not been published until now. Short-term therapy should be carried out until the start of pollen season (D, 5).

Conclusion: Efficacy of SCIT has been demonstrated for pollen and house dust mite allergens in many controlled studies in patients with allergic rhinoconjunctivitis, but for animal dander (cat) and mold allergens (Alternaria, Cladosporium) in few studies. Results from controlled studies differ in extent and in quality, requiring product-specific evaluation of SIT.

4.2.2. Efficacy of SCIT in allergic bronchial asthma

In order to be able to take into account the asthma criteria used in older studies, the severity of asthma is given in terms of the old (2005) [34, 63] as well as in terms of the new (2008) GINA recommendations [64] .

In contrast to the application of SCIT in allergic rhinoconjunctivitis its efficacy in allergic bronchial asthma is still discussed controversially [14, 61]. SCIT cannot replace an adequate anti-asthma therapy. On the basis of numerous studies SCIT can be recommended for intermittent (Stage I) and mild persistent bronchial asthma (Stage II) (B, 2a-c) [14, 22, 24, 61]. The justification for this is a repeatedly updated meta-analysis of the Cochrane Library consisting of 75 controlled, however methodologically heterogeneous studies: after SCIT asthma symptoms, drug use and degree of specific and non-specific hyperreactivity were reduced compared to placebo, whereas lung function parameters were not improved (A, 1a) [1, 26]. In patients with perennial allergic asthma and house dust mite allergy SCIT with mite extracts resulted in a reduction of symptoms [5, 60, 166], drug use [5, 18, 60] and allergen-specific bronchial hyperreactivity [5, 60] as well as in an improved quality of life [5, 60] compared to treatment with placebo.

Mainly young patients with allergic rhinoconjunctivitis, mono- or oligosensitization and a clear association between asthma symptoms and allergen exposure proven by patient history or by provocation can benefit from SCIT. In contrast, older patients with a long-lasting course of asthma, allergen-independent complaints and minor improvement after anti-asthma therapy hardly benefit from SCIT (B, 2a) [22, 26], but carry a high risk for adverse events instead (B, 2a) [25].

Conclusion: SCIT has been well studied in controlled asthma (according to new GINA guidelines, 2008) and intermittent and mild persisting IgE-mediated allergic asthma (according to former GINA guidelines, 2005) and is recommended as a therapeutic option in addition to allergen avoidance and pharmacotherapy, particularly in case of concomitant allergic rhinoconjunctivitis.

4.2.3. Efficacy of SCIT in other indications

Data concerning efficacy of SCIT with pollen allergens in the therapy of oral allergy syndrome (OAS) are scarce [103] so that further studies have to be carried out before a final assessment can be made. At present, SCIT for OAS without respiratory symptoms caused by pollen allergens is not indicated (D, 5).

Current studies show clinical effects of SCIT in patients with allergic atopic dermatitis and corresponding, probably clinically relevant, Type I sensitization (e.g., eczemas triggered by airborne allergens; review in [37, 124]). Atopic eczema is not a contraindication for SCIT in cases of allergic respiratory symptoms requiring treatment (D, 5). Currently further studies are investigating whether atopic dermatitis can be a sole indication for SCIT [167].

4.3. Efficacy of SLIT

4.3.1. Efficacy of SLIT in allergic rhinoconjunctivitis

New controlled studies with higher patient numbers have contributed to provide more data concerning SLIT.

For SLIT the amount of clinical documentation varies considerably depending on the product. While for some products no randomized controlled studies have been published so far, for some preparations and allergen sources (e.g., grass pollen extract) substantial data from several studies are available that have led to the European marketing authorization as a finished medicinal product for a lyophilized orodispersible tablet of a timothy pollen extract for the treatment of seasonal allergic rhinoconjunctivitis in adults (A, 1b). The lyophilized orodispersible tablet is used for SLIT perennially without dose-increase period (review in [108]) and showed a decrease in symptoms of 30% (mean) and of 38% (mean) in medication use compared to the placebo group in a study with more than 600 participants. For this preparation efficacy data from several pollen seasons are available [43]. A similar tablet product based on lactose, which is also authorized in Germany, containing a mixed pollen extract of 5 vernal grasses is used, after a short dose-increase period, approximately 4 months prior to the start of pollen season for pre- and coseasonal SLIT in adults: In a study with more than 600 participants for higher doses a reduction in symptoms of 37% (median) and in drug use (46%, median) compared to the placebo group could be shown (A, 1b) [44].

A high-dosed liquid single-dose preparation with a mixed pollen extract from 6 grasses is used, after a 30-minute titration phase, for at least 3 months before the pollen season starts for perennial as well as for pre- and coseasonal SLIT in adults. In a study with 185 participants the combined symptom and medication score of the 104 analyzed subjects was reduced by 46% (mean) compared to the placebo group (A, 1b) [134, 169].

Studies involving children with allergic rhinoconjunctivitis caused by grass pollen allergens showed a similar efficacy similar efficacy as in the adult study for the period of one season: Using the lyophilized orodispersible tablet a reduction in symptoms of 24% (median) and a reduction in drug use of 34% (median) [32] was achieved. The use of the product based on lactose resulted in a reduction in symptoms of 28% (mean) and in a reduction in medication use of 24% (mean) compared to placebo [165]. In Germany, both preparations are authorized for children of 5 years and older. Until now, only efficacy data for the period of one pollen season are available for these grass pollen tablets when used in childhood and adolescence.

For other preparations heterogeneous data are available (review in [42, 99, 168]), probably because of the dose and composition of these preparations as well as for methodological reasons.

Studies comparing SLIT and SCIT in adults [118, 141] only show the clinical efficacy of both therapies and are methodologically deficient [100]. Due to the small number of cases in the only existing study comparing both forms of SIT [83], it is impossible to make a statement on the differences of SLIT and SCIT with regard to efficacy. However, in the case of SLIT, contrary to SCIT, no adverse systemic reactions were observed. In contrast to SCIT [47], long-term effects [145] and preventive effects with regard to lower airway involvement (development of asthma) [125] of SLIT are less well documented due to methodological deficiencies. SLIT with a liquid pollen extract from 5 vernal grasses, using an identical composition and dose as the product based on lactose, showed a trend of sustained efficacy ("carry-over" effect in the combined symptom/medication score with significantly less symptoms) compared to placebo during the pollen season after a 3-year period of coseasonal treatment [126]. SLIT continues to be examined with regards to these open questions and will represent a further option for treating allergic diseases. Nevertheless, some questions (Text box 10) have to be answered for numerous preparations before SLIT can be considered as an adequate alternative for SCIT.

Conclusion: Efficacy of SLIT in grass pollen-induced allergic rhinoconjunctivitis has been proven in several large-scale, controlled clinical studies. Applying other allergen sources (house dust mites, animal dander, molds), less and in part methodologically insufficient studies with contradictory results exist so far.

4.3.2. Efficacy of SLIT in allergic bronchial asthma

For the use of SLIT in cases of allergic bronchial asthma less data are available as for allergic rhinoconjunctivitis [93, 168]. There was hardly any investigation on the efficacy of SLIT in bronchial asthma. The results are inconsistent so that SCIT should not be routinely used for treatment of allergic bronchial asthma (D).

Conclusion: Efficacy of SLIT in allergic asthma does not currently have enough evidence to suggest its use.

4.4. Prevention of asthma and novel allergic sensitization

Studies in children and adolescents show the prophylactic value of SCIT for certain preparations (A, 1b). In cases of allergic rhinoconjunctivitis the risk of the development of asthma symptoms and bronchial hyperreactivity can be reduced in the long term (A, 1b) [110, 122]. These effects are still verifiable 7 years after SCIT completion compared to the untreated control group [76], which led to an extension of the indication for this preparation by the regulatory authorities. In cases of mono- and oligosensitizations the frequency of novel allergic sensitizations can be reduced (B, 2c) [51, 127, 140, 148]. Until 12 years after completion of SCIT with a modified allergen preparation there was evidence for this and other secondary preventive effects compared to an untreated control group [50].

So far, no evidence for a reduction in sensitization rate was found for the sublingual route of application [125, 145]. In one study a reduction of primary asthma diagnosis was described, nevertheless the high rate of discontinuations and significant inter-center differences limit the result of this study [125].

Conclusion: Secondary preventive aspects, especially the reduction in novel allergic sensitizations and reduced development of bronchial asthma, are important reasons for an early start of SCIT during childhood and adolescence.

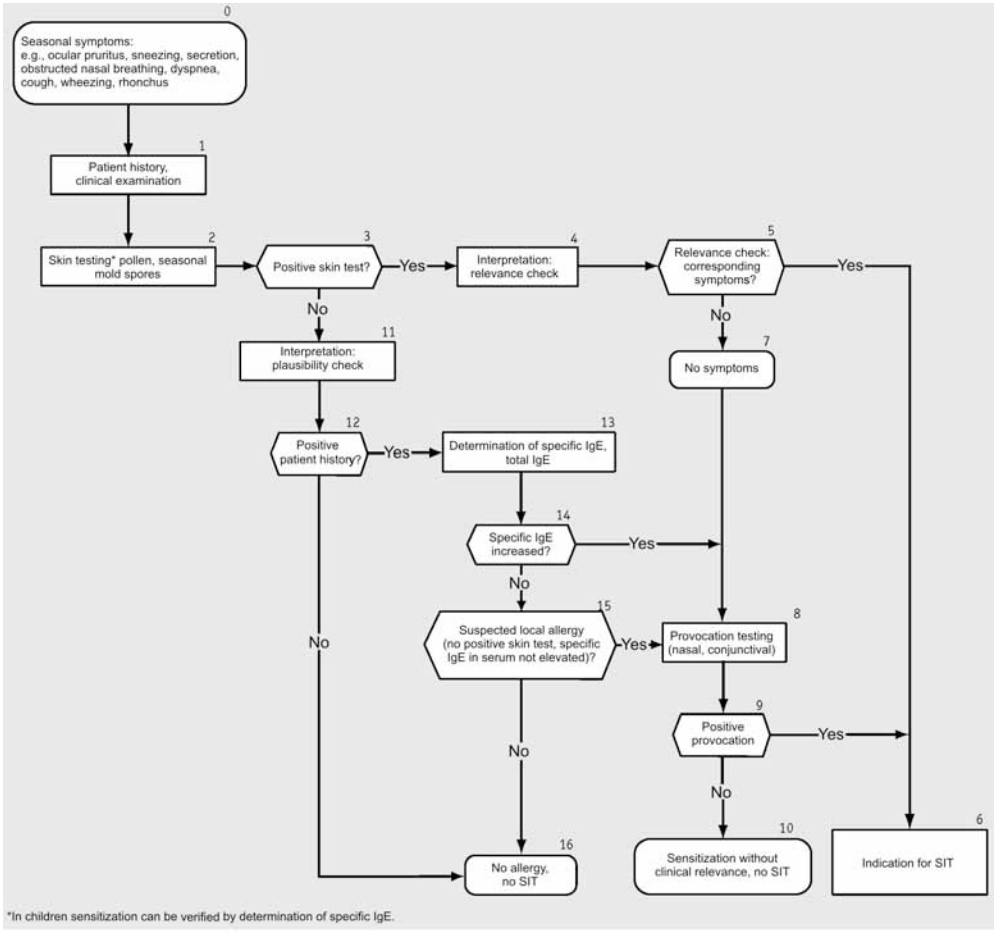

Figure 4. Diagnostic work-up for SIT with seasonal allergens (clinical algorithm).

5. Indications and contraindications

Diagnostic work-up, indication (Figure 4) and the selection of appropriate allergens should, in general, be carried out independently of the route of application (subcutaneous or sublingual) by a physician with allergy training within his/her specialization (dermatology, otorhinolaryngology, pediatrics, pulmonology or internal medicine with focus on pneumology) or carrying a certified (sub) speciality in allergy.

In Austria the indication for immunotherapy can only be made by specialized allergy centers (allergologic outpatient clinics) or by physicians specialized in dermatology, otorhinolaryngology, pediatrics or pulmonology. Accordingly, the package "initial treatment" can only be prescribed by these specialists; "continuation treatment" can also be prescribed by a general practitioner.

In Switzerland initial treatment may only be carried out after prior allergologic work-up; otherwise, the health insurances can refuse to meet the costs. The SGAI recommends that a physician or specialist with allergy training (dermatology, otorhinolaryngology, pediatrics, pulmonology) should carry out the evaluation and indication. Continuation treatment can also be prescribed by a general practitioner.

For the indication of SIT other therapeutic measures have to be taken into account (allergen avoidance, pharmacotherapy and education of patients). SCIT is indicated in patients with proven clinically relevant IgE-mediated sensitization against immediate-type allergens when exposure to or provocation with these allergens causes clinical symptoms (allergic rhinoconjunctivitis, bronchial asthma) and allergen avoidance is not possible or not sufficiently effective (Text box 6) (A, 1a; A, 1b) [1, 24, 38]. The same indication is also valid for SLIT (Text box 8) (B, 1a; B, 1b); there are, however, limitations concerning the selection of allergens and patients (see 5.2.). When seasonal allergic symptoms newly develop, the following season should be followed before SIT is indicated on the basis of at least two anamnestically secured observa-

Text box 5. Success predictors* of SCIT.

- Dominating pollen allergy
- No sensitization against perennial allergen sources
- Narrow allergen spectrum
- Short duration of disease
- Minor involvement of the lower airways
- Young age
- Perennial treatment

*The more of these predictors apply, the higher the probability for a reduction of symptoms and medication use as well as for the prevention of disease progression including the development of bronchial asthma and a broadening of the allergen spectrum (D).

Text box 6. Indications for SCIT with allergens.

- Verification of IgE-mediated sensitization (preferably* using skin test and**/or*** in vitro diagnosis) and unambiguous relation to clinical symptoms (if applicable, provocation testing).
- Availability of standardized or high-quality allergen extracts.
- Proof of efficacy of the planned SCIT for the respective indication.
- Allergen avoidance impossible or insufficient.

*In Switzerland, verification of sensitization preferably by skin testing; **"and" refers to rare allergens or diagnostically doubtful results. ***"or" refers to diagnostic work-up in children.

Text box 7. Contraindications* for SCIT with allergens.

- Partially controlled or uncontrolled bronchial asthma (classification according to the current GINA recommendations 2008) as well as a moderate or severe persisting bronchial asthma (classification according to the older GINA recommendations 2005) with a FEV_1 of less than 70% of the predicted value despite adequate pharmacotherapy.
- Cardiovascular disease with increased risk of side effects after epinephrine administration (except insect venom allergy).
- Treatment with β-blockers (local, systemic)**.
- Severe autoimmune diseases, immunodeficiencies.
- Malignant neoplastic diseases with current disease relevance.
- Insufficient compliance.

*In justified individual cases specific immunotherapy is possible despite existence of contraindications. **In Germany ACE inhibitor therapies are also suggested as contraindication for insect venom SCIT.

tional periods. In patients with minor complaints who only sporadically require antiallergic therapy the benefit of SIT has to be thoroughly weighed against its costs.

Sensitizations without clinical symptoms are no indication for SIT.

Conclusion: Diagnostic allergy work-up, indication and selection of appropriate allergens for SCIT are, in general, made by a physician with allergy training within his/her specialization or carrying a certified (sub)speciality in allergy.

5.1. Indications and contraindications of SCIT

Several variables are suspected to influence the success of SCIT and thus should be considered when a therapy is planned (Text box 5).

Broken down into allergen sources the indications given in Text box 6 are valid without limitation for SCIT with pollen allergens (A, 1b). In cases of confirmed house dust mite allergy SCIT can be carried out if measures for mite avoidance (mite allergen-proof mattress encasings, washable blankets and further measures for reduction of house dust mite allergens) are not sufficient (Figure 5) and if symptoms do not improve after 3 months of mite avoidance (D, 5). A meta-analysis published in 2008 questions the efficacy of control measures against mites [70]. In evaluated studies only 17 of 47 showed a significant reduction of house dust mites. In the investigated studies the interventional measures were very heterogeneous and no subgroup analysis of children was carried out. Due to methodological deficiencies of this meta-analysis the authors' conclusion is not comprehensible. Thus, the above-mentioned interventional measures are primarily indicated in patients with clinically relevant allergy against house dust mites [90, 155]. In cases of allergies against animal dander allergen avoidance is the treatment of choice (D, 5). If allergen avoidance is not possible, SCIT with animal dander allergens might be considered in some cases (especially cat dander) (D, 5) (Figure 5). In cases of mold allergy total allergen avoidance is only possible in exceptional cases. Obvious allergen sources, like mold contaminations in living or working areas, should be removed. SCIT with perennial mold allergens is only rarely carried out. If a seasonal mold allergy and the corresponding indication are present and if well-characterized extracts (Alternaria, Cladosporium) are available, a therapy with mold allergens can be considered (B, 1b) [46, 74].

The effectiveness of SIT depends on the optimal therapeutic dose of each clinically relevant allergen. The knowledge concerning efficacy and immunologic effects of SIT is mainly based on studies in which monotherapy with an allergen extract was carried out. Thus, as few different allergen groups as possible should be mixed in an allergen preparation used for therapy. In general, seasonal and perennial allergens are not mixed together in one extract. One reason for this is to avoid an unnecessary reduction of the fraction of perennial allergens during pollen season [17, 24, 55, 106]. Due to enzymatic reactions, mite and animal dander, mite and mold

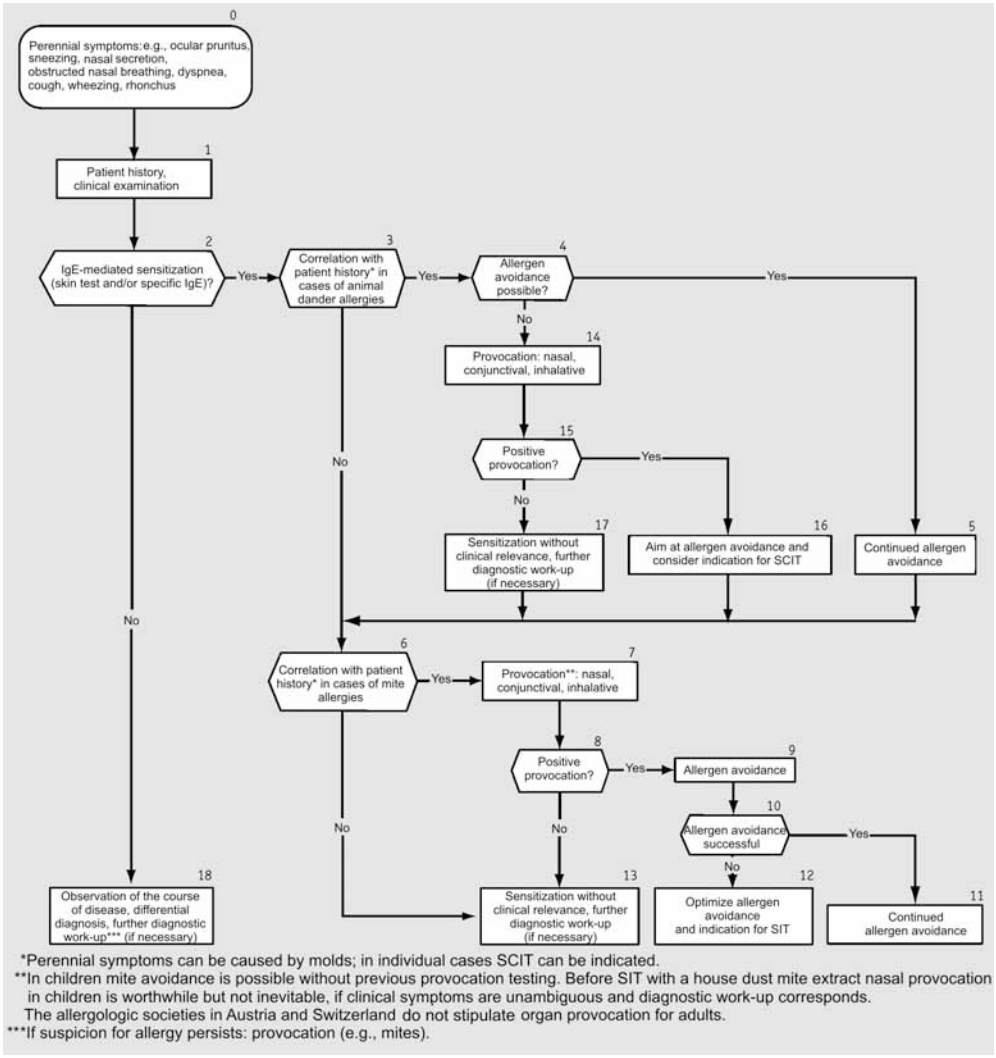

Figure 5. Diagnostic work-up for the indication of SCIT with perennial allergens.

allergens, or extracts with pollen and mold allergens (C, 5) should not be combined in one preparation.

In order to be able to make a decision for SCIT some contraindications have to be considered (Text box 7). For safety reasons, a partially controlled or uncontrolled bronchial asthma (classification according to the current GINA recommendations 2008 [64]) as well as a moderate (forced expiratory volume in the first second (FEV_1) < 80% until > 60% of the expected value, Stage III) or severe (FEV_1 < 60% of the expected value, Stage IV) persisting bronchial asthma (classification according to the older GINA recommendations 2005 [34, 63]) are contraindications for SCIT, specifically SCIT should not be used, if the FEV_1 is lower than 70% of the expected value (B, 2a) [25].

Although pregnancy is considered to be a contraindication for the start of SCIT, a continuation of SCIT in cases of life-threatening allergies against insect venom (bee, wasp) is recommendable if the therapy is well tolerated by the patient; SCIT with airborne allergens is possible when the dose is significantly reduced (e.g., 1/10) (D, 5). For safety reasons SCIT should not be started during pregnancy (only exception: life-threatening indication).

Clinical experience shows that the formerly used age limit is no longer justified; an age of 50 years and older is no longer a contraindication for SIT (D, 5). The use of β blockers (also locally applied, like ophthalmics) under SCIT increases the risk of adverse airway reactions (bronchial obstruction) and carries the danger that an adrenalin therapy that might me necessary in a case of an emergency is less effective. The decision whether it is necessary to continue the therapy with these substances has to be made on an individual basis.

Conclusion: SCIT is indicated in patients with IgE-mediated sensitizations and

Text box 8. Indications for SLIT with allergens.

- Verification of IgE-mediated sensitization (preferably* using skin test and**/or*** in vitro diagnosis) and unambiguous relation to clinical symptoms (if applicable, provocation testing), particularly if treatment with SCIT is not applicable.
- Availability of standardized and high-quality allergen extracts.
- Proof of efficacy of the planned SLIT for the respective indication
- Age of patients with grass pollen allergy ≥ 5 years.
- Age of patients preferably ≥ 18 years****.

*In Switzerland, verification of sensitization preferably by skin testing; **"and" refers to rare allergens or diagnostically doubtful results; ***"or" refers to conditions that impede skin testing and to diagnosis in children; ****better/more studies available for adults than for children and adolescents.

Text box 9. Contraindication* for SLIT with allergens.

- Partially controlled or uncontrolled bronchial asthma (classification according to the current GINA recommendations 2008) as well as a moderate or severe persisting bronchial asthma (classification according to the older GINA recommendations 2005) with a FEV_1 of less than 70% of the predicted value despite adequate pharmacotherapy.
- Severe autoimmune diseases, immunodeficiencies, immunosuppression.
- Malignant neoplastic diseases with current disease relevance.
- Insufficient compliance.
- Inflammations of the oral cavity with severe symptoms.

*In justified individual cases specific immunotherapy is possible despite existence of contraindications.

corresponding clinical symptoms to allergens, which do not or insufficiently permit allergen avoidance and which are available as suitable, efficacious extracts. Diagnostic allergy work-up, indication and selection of appropriate allergens should only be made by a physician with allergy training within his/her specialization or carrying a certified (sub)speciality in allergy (according to the text of the guidelines). Contraindications have to be considered on an individual basis.

5.2. Indications and contraindications of SLIT

In cases of allergic rhinoconjunctivitis with seasonal allergen basis using preparations for which clinical efficacy was proven in DBPC studies SLIT can be used in adults (B, 1a) (Text box 8). Particularly when SCIT is not a treatment option, SLIT can be considered. Reasons would, for example, be phobia of syringes, general refusal of subcutaneous injections, fear of (rare) systemic anaphylactic reactions or lacking time for the repeated injections.

When perennial symptoms caused by house dust mite allergens were present, SLIT showed heterogenous results so that it should only be used cautiously for this indication (D). In Switzerland all physicians are allowed to prescribe SLIT by grass tablets or solutions as long as the requirements presented in Section 5 are fulfilled.

Patients with chronic diseases of the oral mucosa are not suitable for SLIT. Furthermore, apart from the use of β blockers, contraindications (Text box 9) are similar to those for SCIT . The application of SLIT in children and adolescents is presented in Section 7.2.

Conclusion: SLIT with efficacious products is an option for adults with allergic rhinoconjunctivitis due to pollen allergens, particularly if SCIT is not suitable. In case of house dust mite allergy or symptoms due to other allergen sources and allergic asthma due to inhalants, SLIT cannot substitute SCIT.

6. Procedure of specific immunotherapy

SIT should only be carried out by a physician with allergy training within his/her specialization, carrying a certified (sub)speciality in allergy or who is skilled in these kinds of therapy and able to deal with adverse drug reactions (systemic allergic reactions up to anaphylactic shock, severe asthma attacks) (D, 5) [11, 24]. Before starting SIT patients have to be informed about method and duration of treatment, expected effects, possible risks and existing therapy options. This information should be documented (D, 5) [157].

If SIT is carried out or continued after the indication was set by another physician, a close cooperation is essential in order to warrant a consistent and low-risk implementation of SIT. This applies in particular to the occurrence of adverse events; if necessary, the patient has to be referred back to the same physician who originally decided on the indication for SIT. Changing preparations during the course of therapy must be avoided.

If the treatment is not successful after a maximum of 2 years, it has to be critically investigated and, if necessary, discontinued. For allergens like house dust mites the patient's environment has to be organized in a way that warrants the least possible allergen exposure.

6.1. SCIT

Before injection the patient has to be interviewed for current allergic or other rele-

vant symptoms (fever, general condition), tolerability of the last injection, current infections, new or modified medication and vaccinations, and the interval from the last injection has to be checked. Confusing preparations should be avoided by all means, e.g., by reading the allergen preparation and the patient's name aloud to the patient.

For injection, which is the physician's task and should not be delegated, a 1 ml syringe with graduation intervals of 0.01 ml with an injection needle (size No. 14 – 18, short bevel) is used. The injections are carried out strictly subcutaneously into a lifted skin fold after previous or, depending on the injection volume, repeated aspiration, preferably six inches above the olecranon on the extensor side of the upper arms and are documented indicating injection site and dose. The patient has to stay under medical control for at least 30 minutes after injection. The patient should be advised to communicate all symptoms pointing to an allergic reaction to the staff. If a strong local reaction develops, it has to be controlled and documented by the physician, because a dose adjustment might be necessary for the following injection (see Section 9.2.).

Shortly before and on the rest of the day of injection augmenting factors for allergic reactions (e.g., physical exercise, sauna, alcohol etc.) should be avoided (D, 5). The time interval between an SCIT injection and a vaccination that can be planned should be 1 week at least. Thus, vaccinations should be carried out during the SCIT maintenance phase and administered between two SCIT injections which are applied in a 4-week interval. Vaccinations that have to be given immediately (e.g., tetanus after injuries) can be carried out at any time. Afterwards, SCIT can be continued according to the product insert or 2 weeks after vaccination with the previously administered dose.

6.2. SCIT with inhalant allergens

This therapy is mainly carried out on an outpatient basis. For high risk patients (strong systemic reactions, relative contraindications) an inpatient start of SCIT should be considered.

Allergen extracts for SCIT are mainly applied as depot solutions. During the escalation period (frequently doubling of the previous dose) the therapy intervals are between 3 – 7 days for aqueous solutions and 1 – 2 weeks for depot solutions. If cluster or rush escalations schedules are applied, several injections are administered depending on the day of treatment. After the maximum tolerated dose is reached, the injection intervals can be increased to 4 – 8 weeks, if the product insert permits this. In cases of seasonal aero allergens therapy is started before the allergen season and continued for 2 further years preseasonally. It can also be continued perennially. In this case it can be reduced during allergen season on an individual basis or depending on the extract (C, 4). For one preparation intraseasonal updosing with a grass pollen extract up to 10,000 SQ-U with a 1- to 3-day injection interval was authorized by the PEI for Germany. After the end of pollen season the dose can be further increased to the maximum dose of 100,000 SQ-U with an injection interval of 7 (– 14) days. An intraseasonal start of SIT in pollen allergy cannot be recommended because no scientific findings concerning safety and efficacy of such procedure have been published until now. Coseasonal SCIT (continuation during the respective season) without dose reduction is possible, if the product insert permits it, if no allergic symptoms are present and if clinical documentation is carefully carried out.

Only half of the scheduled dose should be applied for continuation treatment when a new lot is used (according to the product insert) because the biologic activity can differ. When the injection interval was exceeded, the dose has to be reduced according to the product insert. The longer the time was, the more the dose has to be reduced. In cases of airway allergies the duration of SCIT should at least be 3 years. Although controlled studies concerning parallel immunotherapy with two different allergen extracts administered at the same time are lacking, clinical experience shows that it is beneficial to have a time interval of at least 15 minutes between the injections (D, 5). After the last injection, the prevailing observation period of 30 minutes has to be kept.

In patients receiving SCIT due to allergic bronchial asthma the peak flow should be measured before and 30 minutes after each injection. Furthermore, it is recommended to record the peak flow measurements during the complete duration of therapy and to carry out regular lung function measurements.

Conclusion: Injections of SCIT are administered by a physician experienced in this therapy and who is able to perform emergency treatment in case of an allergic adverse event. Preceding information of the patients is mandatory and should be documented. The therapy should last 3 years.

6.3. SLIT with inhalant allergens

SLIT is carried out on an outpatient basis according to the product inserts enclosed by

the manufacturer. These recommendations developed by the manufacturer should be carefully adhered to, because there are several variants concerning galenics, storage and application of products as well as handling them in particular situations.

Depending on the preparation used, on the manufacturers' instructions and on the evaluation of the patient's individual tolerability, the application of the first dose should be observed by a physician with experience in allergology (for definition see 5.). The drops or tablets are administered at the same time of day to the fasted patient and applied under the tongue where they should be kept for 2 – 3 minutes before the saliva is swallowed. When preparations with direct allergen contact are used it can be useful to wash hands after application in order to avoid ophthalmic or nasal symptoms by indirect carry-over of allergens [4]. During the first 5 minutes after application the patient should not drink or brush teeth.

If recommended by the manufacturer, the introduction period with e.g. doubling of the dose is between 1 and 14 days. After this, the drops or tablets are applied daily or every second day. Depending on the manufacturer's recommendations no or only short introduction periods exist, culminating in ultra rush titration where the maximum dose is reached on the first day after several dose increases in 20-minute intervals. When lyophilized allergen tablets are used, an immediate administration of the maximum dose is possible so that no dose escalation period is necessary.

After the tolerated or recommended maximum dose has been reached the intervals of administration are kept in the original frequency. When febrile diseases, especially airway infections, occur, the administration has to be stopped and afterwards the dose has to be increased again to the maximum dose according to the product insert. Depending on the product insert the allergen extract for SLIT should also not be administered in the following cases: acute inflammations or injuries of the oral or pharyngeal mucosa, surgical interventions in the oral cavity, acute gastroenteritis, asthma exacerbations, reduction of peak flow below 70% or 80% of the personal optimum values, simultaneous vaccination with an antiviral vaccine [4]. When vaccinations and SLIT are carried out on different days, it is easier to allocate side effects to the respective application. When new impairing oropharyngeal symptoms occur, the therapy can be discontinued or reduced, depending on the extract used. The same is true for products with seasonal allergen sources that, if necessary, can be reduced during season on an individual basis and depending on the preparation (C, 4). Coseasonal SCIT (continuation during the respective season) without dose reduction is possible, if the product insert permits it, if no allergic symptoms are present and if clinical documentation is carefully carried out. When the administration was discontinued for more than 7 – 14 days, the dose has to be reduced according to the product insert. The longer the time was, the more the dose has to be reduced.

Based on the experience with SCIT for airway allergens the duration of SLIT should be at least 3 years (D). The reasons for a premature discontinuation of SLIT can be: bad compliance, newly developing contraindications, persisting inacceptable local side effects, repeated systemic reactions and missing clinical reactions after 2 years [4]. Parallel immunotherapy with two different allergen extracts should be applied at different times of day (e.g., one in the morning, the other one in the evening) (D). Based on current data SLIT can only be recommended for adults when preparations with proven efficacy are used. When treatment is continued in another medical practice, there should be close cooperation with the physician who originally made the indication, especially regarding safety and efficacy.

Conclusion: SLIT is started by a physician experienced in the therapy of allergic diseases (see guideline wording) and who is able to perform emergency treatment in case of an allergic adverse event. According to the leaflet of the product manufacturer, the patient should be informed about the therapy, usually lasting 3 years as pre- and coseasonal or perennial regimen. During this course consultations should take place at least every 3 months.

7. Characteristics of specific immunotherapy in children

7.1. SCIT in children

There are several reasons that support the indication of specific SCIT in children (C, 4):

- Frequently, the disease has not yet led to secondary alterations.
- The risk for the progression of the disease is reduced.
- The risk for possible further sensitizations is reduced.

Basically, indication in children is not different from that in adults. However, preventive aspects should be considered as well. These consist of the possible prevention of a progression of the disease (development of bronchial asthma when rhinoconjunctivitis is present; A, 1b) as well as to the positive ef-

fects on the development of new sensitizations (B, 2b; see 4.4.). There is no generally recommended lower age limit: while there is in principle no age limitation in cases of potentially life-threatening insect venom allergy, SCIT against inhalants is better tolerated when the child is at least approximately 6 years old – this is due to psychological factors rather than to immunologic reasons (D, 5). Furthermore, indication for SCIT is normally more reliable when a child is older than approximately 6 years. When an appropriate indication is present, the risks of SCIT in children can be considered as low. The rate of systemic reactions is below 0.1% of injections (B, 2b) [36].

Conclusion: Children tolerate the SCIT well and benefit notably from its immunomodulatory effects.

7.2. SLIT in children

Recent studies on SLIT in children show less methodologic deficiencies and included higher numbers of children [32, 33, 75, 128, 151, 165]. Despite weak partial effects in subgroups, some of these studies did not show clinically relevant efficacy of SLIT in children with the respective preparations when selectively evaluated clinical criteria were applied or when certain time points were compared.

Two recent independent studies on tablet products (lyophilized orodispersible tablet, tablet based on lactose; see above) for the treatment of rhinoconjunctivitis with concurrent asthma have shown clinically relevant improvement: After 4-months treatment with grass pollen allergens symptoms and drug use in children were significantly reduced [32, 165].

The long-term effects of SLIT were not placebo-controlled [145] and the preventive effects with regard to asthma development were only investigated in an open study [125].

Based on current data, an application of SLIT in children and adolescents can only be recommended if efficacy is proved and if SCIT is not possible (B, 1b). The final recommendation on SLIT in children and adolescents is postponed until further study results are available.

One parent should stay near the child during the intake of the preparation and shortly after. As the rate of side effects is relatively high in the beginning of SLIT, particularly in children low compliance has to be suspected. It is recommended to inform the patient about the risk of side effects and to follow them up more closely.

Conclusion: SLIT can be indicated in children and adolescents, if SCIT is not an option, using a preparation with proven clinical efficacy in this age group.

8. Subcutaneous immunotherapy with insect venom allergens

8.1. Efficacy

Between 0.8% and 5% of people are affected by systemic hypersensitivity reactions after hymenoptera stings (e.g., bee, wasp) (C, 2b) [69, 156]. In children these reactions are rare and mainly mild, while in beekeepers they occur more frequently [7, 15, 66]. Almost all of these cases are IgE-mediated with symptoms of an immediate-type allergy. The reactions can be classified according to their degree of severity [147] that has to be considered for the indication of SIT: skin symptoms only (systemic skin reactions exceeding increased local reactions; Stage I), skin symptoms and/or airway symptoms and/or drop in blood pressure and tachycardia (Stage II), bronchospasm, unconsciousness, shock (Stage III), respiratory and cardiac arrest (Stage IV). Allergies against bee and wasp venom can occur independently from each other.

Between 30% and 60% of patients with a history of general reaction after an insect sting again develop a systemic hypersensitivity reaction after the next sting (B, 3b) [21, 66]. In patients with severe reactions the risk of recurrence is higher. Adulthood, repeated stings in short time intervals, severe previous reactions and comorbidity are considered to be risk factors [15].

SCIT is a highly effective treatment for hymenoptera venom allergies (C, 4; B, 3b) [68, 111, 115, 138] and is more effective than SCIT in allergies against inhalants. Its efficacy is better for wasp venom than for bee venom allergies (C, 4) [114, 115]. With the standard maintenance dose of 100 µg efficacy is approximately 75 – 95%; with an increased dose (in most cases 200 µg are sufficient) efficacy is almost 100% (C, 4) [154]. Long-term efficacy after completion of SCIT was proven particularly in children (A, 1b) [67].

8.2. Indication

Indication for SCIT is based on patient history, skin tests and in vitro examinations. Positive skin testing or specific IgE against insect venom without a history of systemic reactions (e.g., exclusive occurrence of an in-

creased local reaction) is not an indication for SCIT (C, 4) [69, 156]. When severe systemic reactions occur, the indication for hyposensitization treatment with insect venom is obligatory (Stage III – IV; C, 2b) [15, 21, 117, 138]. When systemic reactions are not life-threatening (Stage I – II) further factors like potential masking of more pronounced symptoms by early therapy, high exposure (e.g., beekeepers), increased risk of severe anaphylaxis (e.g., mastocytosis, increased serum tryptase), concomitant cardiovascular diseases or psychologic factors (fear, quality of life) have to be considered for the indication [15, 21, 117, 138]. In Germany SCIT with insect venom is already indicated in Stage II, independently from concomitant factors.

In children with a systemic reaction that is limited to the skin (Stage I) hyposensitization is only recommended in exceptional cases, because severe symptoms after a new sting are rare (C, 2b) [67, 138]. In older adults systemic reactions are more often severe so that SCIT with insect venom is frequently indicated in those persons [15, 138].

Titrated skin tests are carried out with commercially available bee and wasp venom extracts in the form of prick and/or intracutaneous testing. In case of doubt (systemic reaction despite missing skin test reaction and negative specific IgE) diagnosis can be completed by basophil allergen stimulation test (histamine release, leukotriene production, activation marker CD63 or CD203c) for indirect (cellular) IgE detection (C, 4). IgE antibodies against cross-reactive carbohydrate determinants (CCD) that are responsible for 80% of cross-reactions with unclear clinical relevance can make diagnosis difficult, especially in atopics, due to nonspecific IgE reactivity against insect venom (D, 5) [15, 77]. Double-sensitizations can be clarified using the reciprocal IgE inhibition test. In some cases diagnostic work-up with recombinant allergens can be useful [116].

At least in the case of severe reactions to stings mast cell tryptase should be analyzed, because the risk is particularly high and life-long SCIT is recommended when serum tryptase levels are increased (> 11.4 µg/l) and/or mastocytosis is present (D, 5) [97, 138].

In addition and taking into account contraindications, the patient should be provided an "emergency kit" for self-medication with epinephrine in an autoinjector. If respiratory symptoms have to be expected, the patient should further have an inhalable β_2-sympathomimetic preparation, a glucocorticoid and a H1-antihistamine (in solution or in a rapidly soluble form) that can be taken orally [146].

8.3. Procedure

Therapy can be started either on an inpatient or on an outpatient basis. For the former the patient should stay in hospital for several days; therapy is started with aqueous commercial extracts using different dose increase recommendations (C, 4) [16]. In the latter case therapy is initially carried out in weekly intervals. The so-called conventional rush SCIT, which is the prevailing method in Germany, in which the maximum dose is reached after several days or one week (C, 4) [159] and ultra rush methods in which the maximum dose is reached within 2 – 3 days (C, 4) [28, 29, 49] have to be started on an inpatient basis and have the advantage that the maintenance dose is reached early having a corresponding protective effect which is especially beneficial during the insect season and in cases with severe reactions.

Subsequently, therapy is continued with an (authorized) aqueous or depot preparation applying a maintenance dose of 100 µg of insect venom extract, the injection intervals are increased to 4 weeks (C, 4) [138]. In cases of bee and wasp venom allergy in which the patient is highly exposed to the allergens or is subject to an increased risk for severe anaphylaxis a maintenance dose of 200 µg is recommended (B, 2b) [138].

Furthermore, in Switzerland ultra rush procedures with a duration of approximately 4 hours are carried out to start therapy [80, 144, 152] either on an inpatient or on an outpatient basis. The subsequent after-treatment with the maintenance dose is carried out according to the usual schedules in 4- to 6-week intervals.

8.4. Duration of therapy, tolerability and monitoring

SCIT with insect venoms is carried out for at least 3 or ideally 5 years (A, 1b) [65, 138, 153]. If a high exposure or an increased individual risk for severe reactions (guideline on insect venom allergy [138]) is present, it should be carried out even longer. In patients with extremely high risks (e.g., mastocytosis) a longer and sometimes even life-long SCIT are recommended (D, 5) [65, 138]. Discontinuation of SCIT with insect venoms should be decided on an individual basis; details have been presented extensively [21, 117, 138].

For SCIT with bee venom systemic side effects have been observed more frequently than for SCIT with wasp venom (D, 5) [27, 171].

Therapy failure can be demonstrated by a controlled sting under clinical conditions. For

Text box 10. Open questions concerning SLIT* (modified according to [168]).

- Optimal single or cumulative dose**? Frequency of application** and duration of treatment? Identical for all allergens – seasonal or perennial?
- Magnitude of symptomatic improvement compared to SCIT?
- Modified immune response by SLIT? Long-lasting, persisting effect of treatment? Course after withdrawal of active treatment?
- Safety profile for routine practice?
- Influence of co-factors on safety (e.g., application of β-blockers)?
- Compliance in controlled trials comparable to compliance in routine application at home over a period of 3 years?
- Reasons for less convincing proof of efficacy in children**?

*Some of these questions are also applicable for SCIT products. **For certain products (grass pollen allergen tablets) these questions cannot be applied or have already been answered in controlled studies.

Text box 11. Risk factors for SCIT.

- Current allergy symptoms and potential allergen exposure.
- Unstable or insufficiently treated asthma (FEV_1 less than 70% of the predicted value).
- High degree of sensitization.
- Inadequate dose increase during induction therapy.
- Drug use (β-blockers).
- Inadequate circulatory stress, physical exercise, sauna (shortly before and for the rest of the day of injection augmenting factors should be avoided).
- Inadequate technique of injection.
- Allergen extract overdose.
- Manufacturer's recommendation for dose reduction in case of changing to a new package (production batch) was overlooked.

sting provocation, ideally carried out 6 – 12 months after start of treatment, individual risk factors have to be considered, because a missing protection would result in an increased risk when the patient is stung by an insect in the future. Apart from sting provocation there are generally no accepted parameters for evaluating therapeutic success at the moment. Concerning this topic we refer to the current DGAKI guideline [138].

If no adequate protection can be obtained under 100 µg of insect venom, the maintenance dose should be increased from 100 µg to 200 µg (A, 1b) [153]. Also for patients with bee venom allergy and high exposure (e.g., beekeepers) or increased risk for severe anaphylaxis (e.g., mastocytosis) an increased dose is recommended (D, 5) [138, 153]. If after treatment there is again a systemic reaction after an insect sting, SCIT should be started again [138].

Conclusion: In case of systemic reactions due to hymenoptera (bee, wasp) venom hypersensitivity, SCIT has excellent efficacy and should be continued for at least 3 – 5 years. An extended, sometimes lifelong SCIT is necessary in some patients.

9. Safety, risk factors and adverse events

9.1. Safety and risk factors in SCIT

Severe, life-threatening systemic reactions are very rare, i.e., they occur in less than 1 of 10.000 cases (classification according to guideline "Summary of Product Characteristics (SPC)": very frequent ≥ 10%, frequent ≥ 1% to < 10%, occasional ≥ 0.1% to < 1%, rare ≥ 0.01% to < 0,1%, very rare < 0.01%; A, 1a) [98]. On the basis of data provided by the PEI (1991 – 2000) an incidence of 0.002 – 0.0076% (of injections) for non-modified allergen extracts and of 0.0005 – 0.01% for chemically modified allergen extracts (allergoids) was calculated (C, 4) [96]. Data obtained in the context of authorization extensions between 2001 and 2005 do not indicate changes in the incidence of severe adverse events as compared to data published in 2001 [Lüderitz-Püchel, PEI, personal communication]. When risk factors are considered (A, 1a) [98] severe reactions are sometimes foreseeable and avoidable by caution and prophylaxis (Text box 11) (D, 5). If severe reactions develop, they mainly occur as severe bronchial obstruction and only rarely as anaphylactic shock (A, 1a) [98]. In particular, severe reactions can occur in cases of asthma exacerbation, simultaneous administration of β-blockers, inappropriate dose increase (e.g., despite adverse events when the previous injection was administered), non-observance of the 30-minute waiting period or subsequent circulatory stress (Text box 11) (A, 1a) [25, 98]. In cases of repeated insufficient compliance (e.g., patient does not stay long enough in the doctor's office, interval is exceeded, inappropriate physical strain or avoidable allergen contact shortly before or after injection) the treatment should be discontinued.

When adverse reactions occur premedication with an antihistamine is possible (B, 2b) [30, 144]. Nevertheless, systemic reactions cannot be excluded.

9.2. Side effects of SCIT

When increased local reactions (redness and/or swelling > 10 cm in diameter) at the in-

jection site occur, it is recommended not to increase the dose or to go back – according to the product insert – to a dose that was already tolerated before it is increased again (D, 5). Delayed (6 – 12 hours) increased local reactions do not represent an increased individual risk for systemic reactions [82].

When systemic reactions occur, the decision for continuation or discontinuation of the therapy should be made by an allergologist taking into consideration the risks of continuation, the urgency of indication and treatment alternatives. For this purpose the patient has to be referred to the physician who initially made the indication for SCIT if necessary. Possible reasons for the systemic reaction (e.g., additional allergen exposure, drug intake, infections, physical strain, other stress situations or diseases) should be analyzed and avoided for future allergen injections. If the therapy is continued the dose should necessarily be significantly reduced by at least 2 – 3 stages (when the dose was doubled before) or to 1/4 – 1/8 of the last dose taking into consideration the product insert of the respective preparation (D, 5).

Circulating immune complexes can develop during the course of SCIT; their clinical relevance, however, remains unclear (C, 4). The frequency of granulomas depends on the extract or on the method of application (e.g., not deep enough subcutaneously) (B, 2c) [164, 171] and can rather be attributed to foreign body reactions (C, 4) [59].

Conclusion: Severe, potentially life-threatening systemic adverse events can occur after SCIT, being very rare in case of complete adherence to safety standards. Most adverse events are mild to moderate and easily treatable.

9.3. Safety, risk factors and side effects in SLIT

Side effects in SLIT depend on the dose and appear, depending on the preparation, as temporary local mucosal reactions (pruritus or dysesthesia in the oral cavity, swelling of the oral mucosa, throat irritation) in 30 – 70% of affected patients. These side effects are mainly mild and diminish in a period of 1 – 3 weeks after start of therapy. Nevertheless, due to their anatomic localization pronounced local reactions can be potentially life-threatening (e.g., uvular or laryngeal edema).

Based on present experience the risk for severe adverse events in SLIT is lower than in SCIT [96]. While for SCIT there is a very low risk for anaphylactic potentially life-threatening reactions (0.0004% per injection; data of 1981 – 2000 [96]), this was not assumed accordingly for SLIT, and the frequency of severe non-life-threatening reactions was indicated with 0.0011% of intakes, this number summing up several studies [6].

An analysis of severe adverse events during SLIT showed 1 reaction in 285 patients (0.35%) or 1.4 reactions in 100,000 administrations (0.0014%), respectively. Very few case reports, with varying documentation quality, on systemic or anaphylactic reactions during SLIT have been published. It has to be taken into account that in most of these cases polysensitized patients with allergic bronchial asthma were affected. Furthermore, gastrointestinal symptoms during SLIT can occur in up to 30% of patients [6]. Postmarketing observations for a grass pollen product (lyophilized orodispersible tablet) show that severe adverse events are rare (4 severe adverse events in 4,500 sold packings) and occur mainly in the form of swellings of the tongue or asthma exacerbation (ALK-Abelló, drug safety; data on file). Premedication with non-sedating antihistamines is potentially apt to reduce the degree of local reactions (D, 5). It must, however, be considered that allergen intake is carried out without supervision by a physician and thus side effects cannot be treated immediately. Therefore, the patient should receive simple, easily understandable instructions on how to behave in the case of adverse events and be urged to call a physician as soon as possible when systemic reactions occur.

Based on present data the risk factors for severe allergic reactions during SLIT are the same as for SCIT: uncontrolled allergic asthma and polysensitization. It remains to be analyzed to which extent augmentation factors for anaphylaxis, like physical strain, excessive alcohol consumption, infections and β-blockers, are also relevant in SLIT. If severe reactions develop, they mainly occur as bronchial obstruction.

Conclusion: Apart from very frequently to frequently occurring dose-dependent unwanted local oral and pharyngeal symptoms, systemic reactions, mostly of mild nature, have rarely been described after SLIT. With regard to anaphylactic and other severe systemic reactions SLIT demonstrates a superior safety profile compared to SCIT.

10. Emergency therapy

Systemic reactions after SIT occur mainly within the first 30 minutes after allergen application. Therefore, in the case of SCIT, patients have to be monitored under medical responsibility for at least 30 minutes after injection and should report any symptom that

could point to an allergic reaction. Systemic reactions can begin within a few minutes after injection. Due to the risk of rapid aggravation they must be treated immediately (D, 5) [146]. Thus, the responsible staff has to be familiar with the handling of obligatory drugs (D, 5) [87] and equipment for an allergologic emergency (D, 5) [146]. First measures involve the adequate positioning of the patient, epinephrine (i.m.), an infusion therapy via a large-bore intravenous access site and the administration of O2. Attending physician and practice team have to be trained in cardiopulmonary resuscitation. Epinephrine is especially useful for the therapy of anaphylactic reactions so that an early administration should be considered. If applicable, autoinjectors for i.m. injection can be used.

Systemic reactions have to be recognized early and treated immediately. The signals for life-threatening side effects involve burning sensation and pruritus of palms and soles, sneezing attacks, generalized pruritus of the skin and generalized urticaria, swelling of tongue and larynx/pharynx, dyspnea, tachycardia, bradycardia, nausea and hypotonia. Mainly skin symptoms and pruritus are the first symptoms that occur. Symptoms can develop consecutively. Occasionally, biphasic courses have been observed.

Due to ethical reasons hardly any controlled studies concerning therapeutic recommendations for the emergency treatment are available. Clinical experience and considerations based on pathophysiologic relations have led to the guideline for the acute therapy of anaphylactic reactions [146] which was revised by the respective scientific medical societies and which is also valid for the acute therapy of a SIT emergency.

These recommendations are also valid for anaphylactic reactions occurring during SLIT.

When Stage IV anaphylactic reactions occur, the recommendations for cardiopulmonary resuscitation published by the German Medical Association (www.aerzte blatt.de/v4/archiv/artikel.asp?src=suche&id=50906 oder www.inm-online.de/pdf/Wis sen/Reanimation/deutsches_aerzteblatt.pdf) based on the German translation [53] of the international guideline published by the European Resuscitation Council (ERC; www.erc.edu) [52] and available via the German Interdisciplinary Organization for Intensive Care and Emergency Medicine (DIVI) (www.divi-org.de/Leitlinien-des-European-Resusc.49.0.html) are valid.

Conclusion: Risk factors for and results of unwanted systemic effects can effectively be minimized by training the staff members involved, adhering to safety standards and immediate emergency treatment.

11. Future prospects

Despite the success achieved, innovations and advancements are desirable in order to increase the efficacy of SIT, particularly for special, complex allergen sources, to lower the rate of side effects and to raise patients' compliance. Some approaches seem to be of particular interest and thus, several of them are clinically tested (Phase I/II):

- Diagnostic work-up and monitoring: recombinant allergens, so-called marker allergens, could turn out to be valuable instruments for facilitating patient selection for SIT and permitting documentation of the immune response to the administered preparation (immune monitoring).
- Optimization of application without injections: development of mucosal tolerance by higher allergen doses, improved galenics or addition of specific adjuvants seems to be possible. This opens up new perspectives for oral or local routes of application.
- Accelerated dose increase: like in SCIT with insect venom allergens, the dose can also be increased more quickly in case of inhalants. Some SLIT protocols already start with the maximum dose. Allergen modification e.g. by formaldehyde or glutaraldehyde (allergoidization) allows for a quick dose increase.
- Allergen characterization: the use of purified or biotechnologically manufactured and molecularly characterized allergens would allow for the composition of optimized allergen preparations containing the allergens that are most important for the respective therapy. Particularly in the case of complex allergen mixtures, like molds or food, it is possible to manufacture preparations that could not be produced by extraction only. In addition, it is easier to maintain the same quality standards.
- Improved efficacy: by identifying the molecular mechanisms of SIT new opportunities for therapy optimization by combination of allergens and allergen extracts with newly identified immune modulators will open up. These molecules frequently are of microbial origin and interact at the interface between native and acquired immunity; they are either toll-like receptor agonists or so-called nonspecific immune modulators.
- Less side effects: the combination of allergens with other molecules like in the case of the additional use of anti-IgE or the development of allergen fragments, folding variants or multimeres from allergens opens up new therapy options with potentially less side effects. Combining subcu-

taneous allergen application with anti-IgE (omalizumab) can possibly increase the safety and efficacy of SCIT in allergic rhinoconjunctivitis. Due to economic considerations, this combination would only be taken into account for individual cases (D, 2b) [89, 91, 150], particularly since anti-IgE is not authorized for this purpose at the moment. The scientific evaluation of this combination seems to be interesting in cases of allergic bronchial asthma.

– Use of SCIT or SLIT for allergy prevention: studies have proven that SIT prevents further sensitization and the development of asthma. Further analyses, also involving other preparations, have to be carried out to prove this potentially interesting indication.

Conclusion: Various research fields like allergen characterization, routes of application, adjuvants, updosing regimen and preventive aspects demonstrate new developments in SIT being currently examined for clinical efficacy.

References

1] *Abramson MJ, Puy RM, Weiner JM.* Allergen immunotherapy for asthma. Cochrane Database Syst Rev. 2003; *4:* CD001186.

[2] *Akdis CA, Blesken T, Akdis M, Wüthrich B, Blaser K.* Role of interleukin 10 in specific immunotherapy. J Clin Invest. 1998; *102*: 98-106.

[3] *Akdis M, Akdis CA.* Mechanisms of allergen-specific immunotherapy. J Allergy Clin Immunol. 2007; *119:* 780-791.

[4] *Alvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Malling HJ, Valovirta E.* Standards for practical allergen-specific immunotherapy. Allergy. 2006; *61 (Suppl 82):* 1-20.

[5] *Ameal A, Vega-Chicote JM, Fernandez S, Miranda A, Carmona MJ, Rondon MC, Reina E, Garcia-Gonzalez JJ.* Double-blind and placebo-controlled study to assess efficacy and safety of a modified allergen extract of Dermatophagoides pteronyssinus in allergic asthma. Allergy. 2005; *60:* 1178-1183.

[6] *André C, Vatrinet C, Galvain S, Carat F, Sicard H.* Safety of sublingual-swallow immunotherapy in children and adults. Int Arch Allergy Immunol. 2000; *121:* 229-234.

[7] *Annila IT, Karjalainen ES, Annila PA, Kuusisto PA.* Bee and wasp sting reactions in current beekeepers. Ann Allergy Asthma Immunol. 1996; *77:* 423-427.

[8] *Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF).* Das Leitlinien-Manual von AWMF und ÄZQ. Z Ärztl Fortbild Qual Sich. 2001; *95:* 1-84.

[9] *Arvidsson MB, Lowhagen O, Rak S.* Effect of 2-year placebo-controlled immunotherapy on airway symptoms and medication in patients with birch pollen allergy. J Allergy Clin Immunol. 2002; *109:* 777-783.

[10] *Arzneimittelgesetz AMG.* 14. Gesetz zur Änderung des Arzneimittelgesetzes. Bundesgesetzblatt. 2005; *Teil I, Nr. 54*.

[11] *Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ).* Stellungnahme der AkdÄ zur allergenspezifischen Immuntherapie. Dtsch Ärztebl. 2007; *104:* A3355-3357.

[12] *Balda BR, Wolf H, Baumgarten C, Klimek L, Rasp G, Kunkel G, Müller S, Mann W, Hauswald B, Heppt W, Przybilla B, Amon U, Bischoff R, Becher G, Hummel S, Frosch PJ, Rustemeyer T, Jäger L, Brehler R, Luger T.* Tree-pollen allergy is efficiently treated by short-term immunotherapy (STI) with seven preseasonal injections of molecular standardized allergens. Allergy. 1998; *53:* 740-748.

[13] *Bellinghausen I, Metz G, Enk AH, Christmann S, Knop J, Saloga J.* Insect venom immunotherapy induces interleukin-10 production and a Th2- to Th1-shift, and changes surface marker expression in venom-allergic subjects. Eur J Immunol. 1997; *27:* 1131-1139.

[14] *Bergmann K-C.* Spezifische Immuntherapie bei allergischem Asthma bronchiale. Pneumologie. 2003; *57:* 84-90.

[15] *Bilo BM, Ruëff F, Mosbech H, Bonifazi F, Oude-Elberink JN.* Diagnosis of Hymenoptera venom allergy. Allergy. 2005; *60:* 1339-1349.

[16] *Birnbaum J, Charpin D, Vervloet D.* Rapid Hymenoptera venom immunotherapy: comparative safety of three protocols. Clin Exp Allergy. 1993; *23:* 226-230.

[17] *Blainey AD, Philips MJ, Ollier RJ, Davies RJ.* Hyposensitization with a tyrosine adsorbed extract of Dermatophagoides pteronyssinus in adults with perennial rhinitis. Allergy. 1984; *39:* 521-528.

[18] *Blumberga G, Groes L, Haugaard L, Dahl R.* Steroid-sparing effect of subcutaneous SQ-standardised specific immunotherapy in moderate and severe house dust mite allergic asthmatics. Allergy. 2006; *61:* 843-848.

[19] *Bodtger U, Poulsen LK, Jacobi HH, Malling HJ.* The safety and efficacy of subcutaneous birch pollen immunotherapy – a one-year, randomised, double-blind, placebo-controlled study. Allergy. 2002; *57:* 297-305.

[20] *Bohle B, Kinaciyan T, Gerstmayr M, Radakovics A, Jahn-Schmid B, Ebner C.* Sublingual immunotherapy induces IL-10-producing T regulatory cells, allergen-specific T-cell tolerance, and immune deviation. J Allergy Clin Immunol. 2007; *120:* 707-713.

[21] *Bonifazi F, Jutel M, Bilo BM, Birnbaum J, Müller U.* Prevention and treatment of Hymenoptera venom allergy: guidelines for clinical practice. Allergy. 2005; *60:* 1459-1470.

[22] *Bousquet J.* Specific immunotherapy in asthma. Allergy. 1999; *54 (Suppl 56):* 37-38.

[23] *Bousquet J, Braquemond P, Feinberg J, Guerin B, Maasch H, Michel FB.* Specific IgE response before and after rush immunotherapy with a standardized allergen or allergoid in grass pollen allergy. Ann Allergy. 1986; *56:* 456-459.

[24] *Bousquet J, Lockey RF, Malling H-J.* Allergen immunotherapy: therapeutic vaccines for allergic

diseases. WHO position paper. Allergy. 1998; *53: (Suppl 44):* 1-42.

[25] *Bousquet J, Michel FB.* Safety considerations in assessing the role of immunotherapy in allergic disorders. Drug Saf. 1994; *10:* 5-17.

[26] *Bousquet J, Michel FB, Malling HJ.* Is allergen immunotherapy effective in asthma? A meta-analysis of randomized clinical trials. Am J Respir Crit Care Med. 1995; *152:* 1737-1738.

[27] *Bousquet J, Müller UR, Dreborg S.* Immunotherapy with Hymenoptera venoms. Position paper of the Working Group on Immunotherapy of the European Academy of Allergy and Clinical Immunology. Allergy. 1987; *42:* 401-413.

[28] *Brehler R, Wolf H, Kutting B, Schnitker J, Luger T.* Safety of a two-day ultrarush insect venom immunotherapy protocol in comparison with protocols of longer duration and involving a larger number of injections. J Allergy Clin Immunol. 2000; *105:* 1231-1235.

[29] *Brehler R, Wolf H, Luger T.* Development of a three-day-protocol for the desensitization with insect venom. J Allergy Clin Immunol. 1999; *103:* S181.

[30] *Brockow K, Kiehn M, Riethmüller C, Vieluf D, Berger J, Ring J.* Efficacy of antihistamine pretreatment in the prevention of adverse reactions to Hymenoptera immunotherapy: a prospective, randomized, placebo-controlled trial. J Allergy Clin Immunol. 1997; *100:* 458-463.

[31] *Bucur J, Dreborg S, Einarsson R.* Immunotherapy with dog and cat allergen preparations in dog-sensitive and cat-sensitive asthmatics. Ann Allergy. 1989; *62:* 355-361.

[32] *Bufe A, Eberle P, Franke-Beckmann E, Funck J, Kimmig M, Klimek L, Knecht R, Stephan V, Tholstrup B, Weisshaar C, Kaiser F.* Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. J Allergy Clin Immunol. 2009; *123:* 167-173.

[33] *Bufe A, Ziegler-Kirbach E, Stoeckmann E, Heidemann P, Gehlhar K, Holland-Letz T, Braun W.* Efficacy of sublingual swallow immunotherapy in children with severe grass pollen allergic symptoms: a double-blind placebo-controlled study. Allergy. 2004; *59:* 498-504.

[34] *Buhl R, Berdel D, Criée CP, Gillissen A, Kardos P, Kroegel C, Leupold W, Lindemann H, Magnussen H, Nowak D, Pfeiffer-Kascha D, Rabe K, Rolke M, Schultze-Werninghaus G, Sitter H, Ukena D, Vogelmeier C, Welte T, Wettengel R, Worth H.* Leitlinie zur Diagnostik und Therapie von Patienten mit Asthma. Pneumologie. 2006; *60:* 139-183.

[35] *Bundesärztekammer.* Eckpunkte der Bundesärztekammer für die Reanimation 2006. Dtsch Ärztebl. 2006; *103:* A961-962.

[36] *Businco L, Zannino L, Cantani A, Corrias A, Fiocchi A, La Rosa M.* Systemic reactions to specific immunotherapy in children with respiratory allergy: a prospective study. Pediatr Allergy Immunol. 1995; *6:* 44-47.

[37] *Bussmann C, Bockenhoff A, Henke H, Werfel T, Novak N.* Does allergen-specific immunotherapy represent a therapeutic option for patients with atopic dermatitis? J Allergy Clin Immunol. 2006; *118:* 1292-1298.

[38] *Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S.* Allergen injection immunotherapy for seasonal allergic rhinitis. Cochrane Database Syst Rev. 2007; *1:* CD001936.

[39] *Cockcroft DW, Cuff MT, Tarlo SM, Dolovich J, Hargreave FE.* Allergen injection therapy with glutaraldehyde-modified ragweed pollen-tyrosine adsorbate. A double-blind trial. J Allergy Clin Immunol. 1977; *60:* 56-62.

[40] *Corrigan CJ, Kettner J, Doemer C, Cromwell O, Narkus A.* Efficacy and safety of preseasonal-specific immunotherapy with an aluminium-adsorbed six-grass pollen allergoid. Allergy. 2005; *60:* 801-807.

[41] *Cosmi L, Santarlasci V, Angeli R, Liotta F, Maggi L, Frosali F, Rossi O, Falagiani P, Riva G, Romagnani S, Annunziato F, Maggi E.* Sublingual immunotherapy with Dermatophagoides monomeric allergoid down-regulates allergen-specific immunoglobulin E and increases both interferon-gamma- and interleukin-10-production. Clin Exp Allergy. 2006; *36:* 261-272.

[42] *Cox LS, Linnemann DL, Nolte H, Weldon D, Finegold I, Nelson HS.* Sublingual immunotherapy: a comprehensive review. J Allergy Clin Immunol. 2006; *117:* 1021-1035.

[43] *Dahl R, Kapp A, Colombo G, de Monchy JG, Rak S, Emminger W, Riis B, Gronager PM, Durham SR.* Sublingual grass allergen tablet immunotherapy provides sustained clinical benefit with progressive immunologic changes over 2 years. J Allergy Clin Immunol. 2008; *121:* 512-518.

[44] *Didier A, Malling HJ, Worm M, Horak F, Jäger S, Montagut A, André C, de Beaumont O, Melac M.* Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. J Allergy Clin Immunol. 2007; *120:* 1338-1345.

[45] *Drachenberg KJ, Wheeler AW, Stuebner P, Horak F.* A well-tolerated grass pollen-specific allergy vaccine containing a novel adjuvant, monophosphoryl lipid A, reduces allergic symptoms after only four preseasonal injections. Allergy. 2001; *56:* 498-505.

[46] *Dreborg S, Agrell B, Foucard T, Kjellman NI, Koivikko A, Nilsson S.* A double-blind, multicenter immunotherapy trial in children, using a purified and standardized Cladosporium herbarum preparation. I. Clinical results. Allergy. 1986; *41:* 131-140.

[47] *Durham SR, Walker SM, Varga EM, Jacobson MR, OBrien F, Noble W, Till SJ, Hamid QA, Nouri-Aria KT.* Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med. 1999; *341:* 468-475.

[48] *Durham SR, Yang WH, Pedersen MR, Johansen N, Rak S.* Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2006; *117:* 802-809.

[49] *Elsner J, Sack A, Petering H, Schäfer T, Korner M, Kapp A.* Ultrarush SIT in venom allergy. Allergy. 2000; *55:* 582-583.

[50] *Eng PA, Borer-Reinhold M, Heijnen IA, Gnehm HP.* Twelve-year follow-up after discontinuation of preseasonal grass pollen immunotherapy in childhood. Allergy. 2006; *61:* 198-201.

[51] *Eng PA, Reinhold M, Gnehm HP.* Long-term efficacy of preseasonal grass pollen immunotherapy in children. Allergy. 2002; *57:* 306-312.

[52] *European Resuscitation Council.* European Resuscitation Council Guidelines for Resuscitation 2005. Resuscitation. 2005; *67 (Suppl):* S1-189.

[53] *European Resuscitation Council.* Leitlinien des European Resuscitation Council 2005 zur Reanimation (Übersetzung). Notfall Rettungsmed. 2006; *9:* 4-170.

[54] *Evans R, Pence H, Kaplan H, Rocklin RE.* The effect of immunotherapy on humoral and cellular responses in ragweed hayfever. J Clin Invest. 1976; *57:* 1378-1385.

[55] *Ewan PW, Alexander MM, Snape C, Ind PW, Agrell B, Dreborg S.* Effective hyposensitization in allergic rhinitis using a potent partially purified extract of house dust mite. Clin Allergy. 1988; *18:* 501-508.

[56] *Flicker S, Valenta R.* Renaissance of the blocking antibody concept in type I allergy. Int Arch Allergy Immunol. 2003; *132:* 13-24.

[57] *Francis JN, James LK, Paraskevopoulos G, Wong C, Calderon MA, Durham SR, Till SJ.* Grass pollen immunotherapy: IL-10 induction and suppression of late responses precedes IgG_4 inhibitory antibody activity. J Allergy Clin Immunol. 2008; *121:* 1120-1125.

[58] *Francis JN, Till SJ, Durham SR.* Induction of $IL\text{-}10^{+}CD4^{+}CD25^{+}$ T cells by grass pollen immunotherapy. J Allergy Clin Immunol. 2003; *111:* 1255-1261.

[59] *Garcia-Patos V, Pujol RM, Alomar A, Cistero A, Curell R, Fernandez-Figueras MT, de Moragas JM.* Persistent subcutaneous nodules in patients hyposensitized with aluminum-containing allergen extracts. Arch Dermatol. 1995; *131:* 1421-1424.

[60] *Garcia-Robaina JC, Sanchez I, de la Torre F, Fernandez-Caldas E, Casanovas M.* Successful management of mite-allergic asthma with modified extracts of Dermatophagoides pteronyssinus and Dermatophagoides farinae in a double-blind, placebo-controlled study. J Allergy Clin Immunol. 2006; *118:* 1026-1032.

[61] *Gillissen A, Bergmann K-C, Kleine-Tebbe J, Schultze-Werninghaus G, Virchow JC, Wahn U, Graf von der Schulenburg JM.* Die spezifische Immuntherapie bei allergischem Asthma. Dtsch Med Wochenschr. 2003; *128:* 204-209.

[62] *Gleich GJ, Zimmermann EM, Henderson LL, Yunginger JW.* Effect of immunotherapy on immunoglobulin E and immunoglobulin G antibodies to ragweed antigens: a six-year prospective study. J Allergy Clin Immunol. 1982; *70:* 261-271.

[63] *Global Initiative for Asthma (GINA).* Global Strategy for Asthma Management and Prevention (updated 2005). GINA. 2005 (www.ginasthma.org).

[64] *Global Initiative for Asthma (GINA).* Global Strategy for Asthma Management and Prevention (updated 2008). GINA. 2009 (www.ginasthma.org).

[65] *Golden DB.* Discontinuing venom immunotherapy. Curr Opin Allergy Clin Immunol. 2001; *1:* 353-356.

[66] *Golden DB.* Insect allergy in children. Curr Opin Allergy Clin Immunol. 2006; *6:* 289-293.

[67] *Golden DB, Kagey-Sobotka A, Norman PS, Hamilton RG, Lichtenstein LM.* Outcomes of allergy to insect stings in children, with and without venom immunotherapy. N Engl J Med. 2004; *351:* 668-674.

[68] *Golden DB, Kagey-Sobotka A, Valentine MD, Lichtenstein LM.* Dose dependence of Hymenoptera venom immunotherapy. J Allergy Clin Immunol. 1981; *67:* 370-374.

[69] *Golden DB, Valentine MD.* Insect sting allergy. Ann Allergy. 1984; *53:* 444-449.

[70] *Götzsche PC, Johansen HK.* House dust mite control measures for asthma: systematic review. Allergy. 2008; *63:* 646-659.

[71] *Hauser U, Wagenmann M, Rudack C, Cromwell O, Ganzer U.* Specific immunotherapy suppresses IL-1b and IL-8 levels in nasal secretions: a possible explanation for the inhibition of inflammatory cell migration. Otorhinolaryngol Nova. 1997; *7:* 31-39.

[72] *Hedlin G, Graff-Lonnevig V, Heilborn H, Lilja G, Norrlind K, Pegelow K, Sundin B, Løwenstein H.* Immunotherapy with cat- and dog-dander extracts. V. Effects of 3 years of treatment. J Allergy Clin Immunol. 1991; *87:* 955-964.

[73] *Hedlin G, Heilborn H, Lilja G, Norrlind K, Pegelow KO, Schou C, Løwenstein H.* Long-term follow-up of patients treated with a three-year course of cat or dog immunotherapy. J Allergy Clin Immunol. 1995; *96:* 879-885.

[74] *Horst M, Hejjaoui A, Horst V, Michel F-B, Bousquet J.* Double-blind, placebo-controlled rush immunotherapy with a standardized Alternaria extract. J Allergy Clin Immunol. 1990; *85:* 460-472.

[75] *Ippoliti F, De Santis W, Volterrani A, Lenti L, Canitano N, Lucarelli S, Frediani T.* Immunomodulation during sublingual therapy in allergic children. Pediatr Allergy Immunol. 2003; *14:* 216-221.

[76] *Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Host A, Koivikko A, Norberg LA, Valovirta E, Wahn U, Möller C.* Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. Allergy. 2007; *62:* 943-948.

[77] *Jappe U, Raulf-Heimsoth M, Hoffmann M, Burow G, Hübsch-Müller C, Enk A.* In vitro Hymenoptera venom allergy diagnosis: improved by screening for cross-reactive carbohydrate determinants and reciprocal inhibition. Allergy. 2006; *61:* 1220-1229.

[78] *Jutel M, Akdis M, Budak F, Aebischer-Casaulta C, Wrzyszcz M, Blaser K, Akdis CA.* IL-10 and TGF-beta cooperate in the regulatory T cell response to mucosal allergens in normal immunity and specific immunotherapy. Eur J Immunol. 2003; *33:* 1205-1214.

[79] *Jutel M, Pichler WJ, Skrbic D, Urwyler A, Dahinden C, Müller UR.* Bee venom immunotherapy results in decrease of IL-4 and IL-5 and increase of IFN-gamma secretion in specific allergen-stimulated T cell cultures. J Immunol. 1995; *154:* 4187-4194.

[80] *Jutel M, Skrbic D, Pichler WJ, Müller UR.* Ultra rush bee venom immunotherapy does not reduce cutaneous weal responses to bee venom and codeine phosphate. Clin Exp Allergy. 1995; *25:* 1205-1210.

[81] *Kaul S, Jappe U, Vieths S, May S.* Überwachung von Allergenextrakten zur spezifischen Immuntherapie: Rechtliche Grundlagen und Verfahren. Allergo J. 2008; *17:* 385-393.

[82] *Kelso JM.* The rate of systemic reactions to immunotherapy injections is the same whether or not the dose is reduced after a local reaction. Ann Allergy Asthma Immunol. 2004; *92:* 225-227.

[83] *Khinchi MS, Poulsen LK, Carat F, André C, Hansen AB, Malling HJ.* Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: a randomized, placebo-controlled, double-blind, double-dummy study. Allergy. 2004; *59:* 45-53.

[84] *Kleine-Tebbe J.* A bright future for sublingual immunotherapy – contra. Frankfurt am Main: Arb Paul Ehrlich Inst Bundesamt Sera Impfstoffe; 2006, 242-250, discussion 250-252.

[85] *Kleine-Tebbe J, Bachert C, Bergmann K-C, Bieber T, Brehler R, Friedrichs F, Fuchs T, Klimek L, Kopp MV, Lepp U, Przybilla B, Rebien W, Saloga J, Simon J, Wedi B, Werfel T, Worm M, Virchow JC.* Aktueller Stellenwert der sublingualen Immuntherapie bei allergischen Krankheiten. Allergo J. 2007; *16:* 492-500.

[86] *Kleine-Tebbe J, Bergmann K-C, Friedrichs F, Fuchs T, Jung K, Klimek L, Kühr J, Lässig W, Lepp U, Niggemann B, Rakoski J, Rebien W, Renz H, Saloga J, Simon J, Sitter H, Virchow J-C, Worm M.* Die spezifische Immuntherapie (Hyposensibilisierung) bei IgE-vermittelten allergischen Erkrankungen. Allergo J. 2006; *15:* 56-74 und Pädiatr Allergol. 2006; *1:* 12-25.

[87] *Kleine-Tebbe J, Fuchs T, Klimek L, Kühr J, Lepp U, Niggemann B, Rakoski J, Renz H, Saloga J, Simon J.* Die spezifische Immuntherapie (Hyposensibilisierung) mit Allergenen. Positionspapier der DGAI, inhaltlich abgestimmt mit dem ÄDA. Allergo J. 2000; *9:* 317-324.

[88] *Klimek L, Wolf H, Mewes T, Dormann D, Reske-Kunz A, Schnitker J, Mann W.* The effect of short-term immunotherapy with molecular standardized grass and rye allergens on eosinophil cationic protein and tryptase in nasal secretions. J Allergy Clin Immunol. 1999; *103:* 47-53.

[89] *Kopp MV, Hamelmann E, Zielen S, Kamin W, Bergmann KC, Sieder C, Stenglein S, Seyfried S, Wahn U.* Combination of omalizumab and specific immunotherapy is superior to immunotherapy in patients with seasonal allergic rhinoconjunctivitis and co-morbid seasonal allergic asthma. Clin Exp Allergy. 2009; *39:* 271-279.

[90] *Kopp MV, Niggemann B, Forster J.* House dust mite allergy: complete removal of the provoking allergen is a primary therapeutic approach. Allergy. 2009; *64:* 187-188, author reply 190.

[91] *Kühr J, Brauburger J, Zielen S, Schauer U, Kamin W, von Berg A, Leupold W, Bergmann KC, Rolinck-Werninghaus C, Grave M, Hultsch T, Wahn U.* Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. J Allergy Clin Immunol. 2002; *109:* 274-280.

[92] *Larché M, Akdis CA, Valenta R.* Immunological mechanisms of allergen-specific immunotherapy. Nat Rev Immunol. 2006; *6:* 761-771.

[93] *Larenas-Linnemann DE, Cox LS.* Sublingual immunotherapy for asthma: need for high quality meta-analyses to prove the concept. Allergy. 2007; *62:* 704-705.

[94] *Li JT, Lockey RF, Bernstein I, Portnoy JM, Nicklas RA.* Allergen immunotherapy: a practice parameter. American Academy of Allergy, Asthma and Immunology. American College of Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol. 2003; *90:* 1-40.

[95] *Löwer J, Becker W-M, Vieths S.* Regulatory control and standardization of allergenic extracts. 10th International Paul-Ehrlich-Seminar, October 2002, Lübeck, Germany. Arbeiten aus dem Paul-Ehrlich-Institut, Band 94. Frankfurt/Main: Druck- und Verlagshaus Sperlich; 2003.

[96] *Lüderitz-Püchel U, Keller-Stanislawski B, Haustein D.* Neubewertung des Risikos von Test- und Therapieallergenen. Eine Analyse der UAW-Meldungen von 1991 bis 2000. Bundesgesundheitsbl Gesundheitsforsch Gesundheitsschutz. 2001; *44:* 709-718.

[97] *Ludolph-Hauser D, Ruëff F, Fries C, Schöpf P, Przybilla B.* Constitutively raised serum concentrations of mast-cell tryptase and severe anaphylactic reactions to Hymenoptera stings. Lancet. 2001; *357:* 361-362.

[98] *Malling HJ.* Minimising the risks of allergen-specific injection immunotherapy. Drug Saf. 2000; *23:* 323-332.

[99] *Malling HJ.* Is sublingual immunotherapy clinically effective? Curr Opin Allergy Clin Immunol. 2002; *2:* 523-531.

[100] *Malling HJ.* Comparison of the clinical efficacy and safety of subcutaneous and sublingual immunotherapy: methodological approaches and experimental results. Curr Opin Allergy Clin Immunol. 2004; *4:* 539-542.

[101] *Malling HJ, Dreborg S, Weeke B.* Diagnosis and immunotherapy of mould allergy. V. Clinical efficacy and side effects of immunotherapy with Cladosporium herbarum. Allergy. 1986; *41:* 507-519.

[102] *Marcotte GV, Braun CM, Norman PS, Nicodemus CF, Kagey-Sobotka A, Lichtenstein LM, Essayan DM.* Effects of peptide therapy on ex vivo T-cell responses. J Allergy Clin Immunol. 1998; *101:* 506-513.

[103] *Mari A, Ballmer-Weber BK, Vieths S.* The oral allergy syndrome: improved diagnostic and treatment methods. Curr Opin Allergy Clin Immunol. 2005; *5:* 267-273.

[104] *May S, Haustein D.* Die individuelle Rezeptur in der spezifischen Immuntherapie. Notwendigkeit und Fehlerquellen. Bundesgesundheitsbl Gesundheitsforsch Gesundheitsschutz. 2001; *44:* 719-723.

[105] *McHugh SM, Ewan PW.* Reduction of increased serum neutrophil chemotactic activity following effective hyposensitization in house dust mite allergy. Clin Exp Allergy. 1989; *19:* 327-334.

[106] *McHugh SM, Lavelle B, Kemeny DM, Patel S, Ewan PW.* A placebo-controlled trial of immunotherapy with two extracts of Dermatophagoides pteronyssinus in allergic rhinitis, comparing clinical outcome with changes in antigen-specific IgE, IgG, and IgG subclasses. J Allergy Clin Immunol. 1990; *86:* 521-531.

[107] *Metzger WJ, Dorminey HC, Richerson HB, Weiler JM, Donnelly A, Moran D.* Clinical and immunologic evaluation of glutaraldehyde-modified tyrosine-adsorbed short ragweed extract: a double-

blind, placebo-controlled trial. J Allergy Clin Immunol. 1981; *68:* 442-448.

[108] *Möhrenschlager M, Kapp A, Kleine-Tebbe J, Bachert C, Ring J, Wüstenberg E.* Lyophylisierte Graspollentablette zur sublingualen Immuntherapie bei Graspollenallergie: aktueller Wissensstand und Ergebnisse des Entwicklungsprogramms eines neuen Präparats. Allergologie. 2008; *31:* 23-35.

[109] *Moingeon P, Batard T, Fadel R, Frati F, Sieber J, Van Overtvelt L.* Immune mechanisms of allergen-specific sublingual immunotherapy. Allergy. 2006; *61:* 151-165.

[110] *Möller C, Dreborg S, Ferdousi HA, Halken S, Host A, Jacobsen L, Koivikko A, Koller DY, Niggemann B, Norberg LA, Urbanek R, Valovirta E, Wahn U.* Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol. 2002; *109:* 251-256.

[111] *Mosbech H, Malling HJ, Biering I, Böwadt H, Søborg M, Weeke B, Løwenstein H.* Immunotherapy with yellow jacket venom. A comparative study including three different extracts, one adsorbed to aluminium hydroxide and two unmodified. Allergy. 1986; *41:* 95-103.

[112] *Mothes N, Heinzkill M, Drachenberg KJ, Sperr WR, Krauth MT, Majlesi Y, Semper H, Valent P, Niederberger V, Kraft D, Valenta R.* Allergen-specific immunotherapy with a monophosphoryl lipid A-adjuvanted vaccine: reduced seasonally boosted immunoglobulin E production and inhibition of basophil histamine release by therapy-induced blocking antibodies. Clin Exp Allergy. 2003; *33:* 1198-1208.

[113] *Müller U, Akdis CA, Fricker M, Akdis M, Blesken T, Bettens F, Blaser K.* Successful immunotherapy with T-cell epitope peptides of bee venom phospholipase A_2 induces specific T-cell anergy in patients allergic to bee venom. J Allergy Clin Immunol. 1998; *101:* 747-754.

[114] *Müller U, Berchtold E, Helbling A.* Honeybee venom allergy: results of a sting challenge 1 year after stopping successful venom immunotherapy in 86 patients. J Allergy Clin Immunol. 1991; *87:* 702-709.

[115] *Müller U, Helbling A, Berchtold E.* Immunotherapy with honeybee venom and yellow jacket venom is different regarding efficacy and safety. J Allergy Clin Immunol. 1992; *89:* 529-535.

[116] *Müller UR.* Recent developments and future strategies for immunotherapy of insect venom allergy. Curr Opin Allergy Clin Immunol. 2003; *3:* 299-303.

[117] *Müller UR, Mosbech H.* Immunotherapy with Hymenoptera venoms. Position paper. Allergy. 1993; *48 (Suppl):* 37-46.

[118] *Mungan D, Misirligil Z, Gurbuz L.* Comparison of the efficacy of subcutaneous and sublingual immunotherapy in mite-sensitive patients with rhinitis and asthma – a placebo controlled study. Ann Allergy Asthma Immunol. 1999; *82:* 485-490.

[119] *Nanda A, OConnor M, Anand M, Dreskin SC, Zhang L, Hines B, Lane D, Wheat W, Routes JM, Sawyer R, Rosenwasser LJ, Nelson HS.* Dose dependence and time course of the immunologic response to administration of standardized cat allergen extract. J Allergy Clin Immunol. 2004; *114:* 1339-1344.

[120] *van Neerven RJ, Arvidsson M, Ipsen H, Sparholt SH, Rak S, Wurtzen PA.* A double-blind, placebo-controlled birch allergy vaccination study: inhibition of CD23-mediated serum-immunoglobulin E-facilitated allergen presentation. Clin Exp Allergy. 2004; *34:* 420-428.

[121] *van Neerven RJ, Wikborg T, Lund G, Jacobsen B, Brinch-Nielsen A, Arnved J, Ipsen H.* Blocking antibodies induced by specific allergy vaccination prevent the activation of $CD4^+$ T cells by inhibiting serum-IgE-facilitated allergen presentation. J Immunol. 1999; *163:* 2944-2952.

[122] *Niggemann B, Jacobsen L, Dreborg S, Ferdousi HA, Halken S, Host A, Koivikko A, Koller D, Norberg LA, Urbanek R, Valovirta E, Wahn U, Möller C.* Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. Allergy. 2006; *61:* 855-859.

[123] *Nouri-Aria KT, Wachholz PA, Francis JN, Jacobson MR, Walker SM, Wilcock LK, Staple SQ, Aalberse RC, Till SJ, Durham SR.* Grass pollen immunotherapy induces mucosal and peripheral IL-10 responses and blocking IgG activity. J Immunol. 2004; *172:* 3252-3259.

[124] *Novak N.* Allergen specific immunotherapy for atopic dermatitis. Curr Opin Allergy Clin Immunol. 2007; *7:* 542-546.

[125] *Novembre E, Galli E, Landi F, Caffarelli C, Pifferi M, De Marco E, Burastero SE, Calori G, Benetti L, Bonazza P, Puccinelli P, Parmiani S, Bernardini R, Vierucci A.* Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2004; *114:* 851-857.

[126] *Ott H, Sieber J, Brehler R, Fölster-Holst R, Kapp A, Klimek L, Pfaar O, Merk H.* Efficacy of grass pollen sublingual immunotherapy for three consecutive seasons and after cessation of treatment: the ECRIT study. Allergy. 2009; *64:* 179-186.

[127] *Pajno GB, Barberio G, De Luca F, Morabito L, Parmiani S.* Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. Clin Exp Allergy. 2001; *31:* 1392-1397.

[128] *Pajno GB, Vita D, Parmiani S, Caminiti L, La Grutta S, Barberio G.* Impact of sublingual immunotherapy on seasonal asthma and skin reactivity in children allergic to Parietaria pollen treated with inhaled fluticasone propionate. Clin Exp Allergy. 2003; *33:* 1641-1647.

[129] *Passalacqua G, Durham SR.* Allergic rhinitis and its impact on asthma update: allergen immunotherapy. J Allergy Clin Immunol. 2007; *119:* 881-891.

[130] *Pastorello E, Pravettoni V, Mambretti M, Franck E, Wahl R, Zanussi C.* Clinical and immunological effects of immunotherapy with alum-absorbed grass allergoid in grass-pollen-induced hay fever. Allergy. 1992; *47:* 281-290.

[131] *Pauli G, Larsen TH, Rak S, Horak F, Pastorello E, Valenta R, Purohit A, Arvidsson M, Kavina A, Schroeder JW, Mothes N, Spitzauer S, Montagut A, Galvain S, Melac M, André C, Poulsen LK, Malling HJ.* Efficacy of recombinant birch pollen vaccine for the treatment of birch-allergic rhino-

conjunctivitis. J Allergy Clin Immunol. 2008; *122:* 951-960.

[132] *Penagos M, Compalati E, Tarantini F, Baena-Cagnani R, Huerta J, Passalacqua G, Canonica GW.* Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in pediatric patients 3 to 18 years of age: a meta-analysis of randomized, placebo-controlled, double-blind trials. Ann Allergy Asthma Immunol. 2006; *97:* 141-148.

[133] *Penagos M, Passalacqua G, Compalati E, Baena-Cagnani CE, Orozco S, Pedroza A, Canonica GW.* Metaanalysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age. Chest. 2008; *133:* 599-609.

[134] *Pfaar O, Klimek L.* Efficacy and safety of specific immunotherapy with a high-dose sublingual grass pollen preparation: a double-blind, placebo-controlled trial. Ann Allergy Asthma Immunol. 2008; *100:* 256-263.

[135] *Pichler CE, Helbling A, Pichler WJ.* Three years of specific immunotherapy with house dust mite extracts in patients with rhinitis and asthma: significant improvement of allergen-specific parameters and of non-specific bronchial hyperreactivity. Allergy. 2001; *56:* 301-306.

[136] *Pichler CE, Marquardsen A, Sparholt S, Løwenstein H, Bircher A, Bischof M, Pichler WJ.* Specific immunotherapy with Dermatophagoides pteronyssinus and D. farinae results in decreased bronchial hyperreactivity. Allergy. 1997; *52:* 274-283.

[137] *Pierkes M, Bellinghausen I, Hultsch T, Metz G, Knop J, Saloga J.* Decreased release of histamine and sulfidoleukotrienes by human peripheral blood leukocytes after wasp venom immunotherapy is partially due to induction of IL-10 and IFN-gamma production of T cells. J Allergy Clin Immunol. 1999; *103:* 326-332.

[138] *Przybilla B, Ruëff F, Fuchs T, Pfeiffer C, Rakoski J, Stolz W, Vieluf D.* Insektengiftallergie – Leitlinie der Deutschen Gesellschaft für Allergologie und klinische Immunologie (DGAI). Allergo J. 2004; *13:* 186-190.

[139] *Puggioni F, Durham SR, Francis JN.* Monophosphoryl lipid A (MPL) promotes allergen-induced immune deviation in favour of Th1 responses. Allergy. 2005; *60:* 678-684.

[140] *Purello-DAmbrosio F, Gangemi S, Merendino RA, Isola S, Puccinelli P, Parmiani S, Ricciardi L.* Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not. A retrospective study. Clin Exp Allergy. 2001; *31:* 1295-1302.

[141] *Quirino T, Iemoli E, Siciliani E, Parmiani S, Milazzo F.* Sublingual versus injective immunotherapy in grass pollen allergic patients: a double blind (double dummy) study. Clin Exp Allergy. 1996; *26:* 1253-1261.

[142] *Rak S, Lowhagen O, Venge P.* The effect of immunotherapy on bronchial hyperresponsiveness and eosinophil cationic protein in pollen-allergic patients. J Allergy Clin Immunol. 1988; *82:* 470-480.

[143] *van Ree R, Chapman MD, Ferreira F, Vieths S, Bryan D, Cromwell O, Villalba M, Durham SR, Becker WM, Aalbers M, André C, Barber D, Cistero Bahima A, Custovic A, Didierlaurent A, Dolman C, Dorpema JW, Di Felice G, Eberhardt F, Fernandez Caldas E.* The CREATE project: development of certified reference materials for allergenic products and validation of methods for their quantification. Allergy. 2008; *63:* 310-326.

[144] *Reimers A, Hari Y, Müller U.* Reduction of side-effects from ultrarush immunotherapy with honeybee venom by pretreatment with fexofenadine: a double-blind, placebo-controlled trial. Allergy. 2000; *55:* 484-488.

[145] *Di Rienzo V, Marcucci F, Puccinelli P, Parmiani S, Frati F, Sensi L, Canonica GW, Passalacqua G.* Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study. Clin Exp Allergy. 2003; *33:* 206-210.

[146] *Ring J, Brockow K, Duda D, Eschenhagen T, Fuchs T, Huttegger I, Kapp A, Klimek L, Müller U, Niggemann B, Pfaar O, Przybilla B, Rebien W, Rietschel E, Ruëff F, Schnadt S, Tryba M, Worm M, Sitter H, Schultze-Werninghaus G.* Akuttherapie anaphylaktischer Reaktionen. Leitlinie der Deutschen Gesellschaft für Allergologie und klinische Immunologie (DGAKI), des Ärzteverbandes Deutscher Allergologen (ÄDA), der Gesellschaft für Pädiatrische Allergologie und Umweltmedizin (GPA) und der Deutschen Akademie für Allergologie und Umweltmedizin (DAAU). Allergo J. 2007; *16:* 420-434.

[147] *Ring J, Messmer K.* Incidence and severity of anaphylactoid reactions to colloid volume substitutes. Lancet. 1977; *1:* 466-469.

[148] *Des Roches A, Paradis L, Menardo JL, Bouges S, Daures JP, Bousquet J.* Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. J Allergy Clin Immunol. 1997; *99:* 450-453.

[149] *Röder E, Berger MY, de Groot H, van Wijk RG.* Immunotherapy in children and adolescents with allergic rhinoconjunctivitis: a systematic review. Pediatr Allergy Immunol. 2008; *19:* 197-207.

[150] *Rolinck-Werninghaus C, Hamelmann E, Keil T, Kulig M, Koetz K, Gerstner B, Kuehr J, Zielen S, Schauer U, Kamin W, von Berg A, Hammermann J, Weinkauf B, Weidinger G, Stenglein S, Wahn U.* The co-seasonal application of anti-IgE after preseasonal specific immunotherapy decreases ocular and nasal symptom scores and rescue medication use in grass pollen allergic children. Allergy. 2004; *59:* 973-979.

[151] *Rolinck-Werninghaus C, Wolf H, Liebke C, Baars JC, Lange J, Kopp MV, Hammermann J, Leupold W, Bartels P, Gruebl A, Bauer CP, Schnitker J, Wahn U, Niggemann B.* A prospective, randomized, double-blind, placebo-controlled multi-centre study on the efficacy and safety of sublingual immunotherapy (SLIT) in children with seasonal allergic rhinoconjunctivitis to grass pollen. Allergy. 2004; *59:* 1285-1293.

[152] *Roll A, Hofbauer G, Ballmer-Weber BK, Schmid-Grendelmeier P.* Safety of specific immunotherapy using a four-hour ultra-rush induction scheme in bee and wasp allergy. J Investig Allergol Clin Immunol. 2006; *16:* 79-85.

[153] *Ruëff F, Przybilla B.* Venom immunotherapy: adverse reactions and treatment failure. Curr Opin Allergy Clin Immunol. 2004; *4:* 307-311.

[154] *Ruëff F, Przybilla B, Müller U, Mosbech H.* The sting challenge test in Hymenoptera venom al-

lergy. Position paper of the Subcommittee on Insect Venom Allergy of the European Academy of Allergology and Clinical Immunology. Allergy. 1996; *51:* 216-225.

[155] *Schäfer T.* Allergieprävention – evidenzbasierte und konsentierte Leitlinie. Allergo J. 2009; *18:* 332-341.

[156] *Schäfer T, Przybilla B.* IgE antibodies to Hymenoptera venoms in the serum are common in the general population and are related to indications of atopy. Allergy. 1996; *51:* 372-377.

[157] *Schultze-Werninghaus G.* Aufklärung bei allergischen Erkrankungen. Leserforum. Allergo J. 1993; *2:* 10-11.

[158] *Secrist H, Chelen CJ, Wen Y, Marshall JD, Umetsu DT.* Allergen immunotherapy decreases interleukin 4 production in $CD4^+$ T cells from allergic individuals. J Exp Med. 1993; *178:* 2123-2130.

[159] *Sturm G, Kranke B, Rudolph C, Aberer W.* Rush Hymenoptera venom immunotherapy: a safe and practical protocol for high-risk patients. J Allergy Clin Immunol. 2002; *110:* 928-933.

[160] *Sundin B, Lilja G, Graff-Lonnevig V, Hedlin G, Heilborn H, Norrlind K, Pegelow KO, Løwenstein H.* Immunotherapy with partially purified and standardized animal dander extracts. I. Clinical results from a double-blind study on patients with animal dander asthma. J Allergy Clin Immunol. 1986; *77:* 478-487.

[161] *Tari MG, Mancino M, Ghezzi E, Frank E, Cromwell O.* Immunotherapy with an alum-adsorbed Parietaria-pollen allergoid: a 2-year, double-blind, placebo-controlled study. Allergy. 1997; *52:* 65-74.

[162] *Valenta R, Ball T, Focke M, Linhart B, Mothes N, Niederberger V, Spitzauer S, Swoboda I, Vrtala S, Westritschnig K, Kraft D.* Immunotherapy of allergic disease. Adv Immunol. 2004; *82:* 105-153.

[163] Verordnung über die Ausdehnung der Vorschriften über die Zulassung der Arzneimittel auf Therapieallergene, die für einzelne Personen aufgrund einer Rezeptur hergestellt werden, sowie über Verfahrensregelungen der staatlichen Chargenprüfung (Therapieallergene-Verordnung). Bundesgesetzblatt. 2008; Teil I, Nr. *51:* 2177-2178.

[164] *Vogelbruch M, Nuss B, Korner M, Kapp A, Kiehl P, Bohm W.* Aluminium-induced granulomas after inaccurate intradermal hyposensitization injections of aluminium-adsorbed depot preparations. Allergy. 2000; *55:* 883-887.

[165] *Wahn U, Tabar A, Kuna P, Halken S, Montagut A, Beaumont O de, Le Gall M.* Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2009; *123:* 160-166.

[166] *Wang H, Lin X, Hao C, Zhang C, Sun B, Zheng J, Chen P, Sheng J, Wu A, Zhong N.* A double-blind, placebo-controlled study of house dust mite immunotherapy in Chinese asthmatic patients. Allergy. 2006; *61:* 191-197.

[167] *Werfel T, Breuer K, Ruëff F, Przybilla B, Worm M, Grewe M, Ruzicka T, Brehler R, Wolf H, Schnitker J, Kapp A.* Usefulness of specific immunotherapy in patients with atopic dermatitis and allergic sensitization to house dust mites: a multi-centre, randomized, dose-response study. Allergy. 2006; *61:* 202-205.

[168] *Wilson DR, Torres LI, Durham SR.* Sublingual immunotherapy for allergic rhinitis. Cochrane Database Syst Rev. 2003; *2:* CD002893.

[169] *Worm M.* Efficacy and tolerability of high dose sublingual immunotherapy in patients with rhinoconjunctivitis. Allerg Immunol (Paris). 2006; *38:* 355-360.

[170] *Wüthrich B, Gumowski PL, Fah J, Hurlimann A, Deluze C, André C, Fadel R, Carat F.* Safety and efficacy of specific immunotherapy with standardized allergenic extracts adsorbed on aluminium hydroxide. J Investig Allergol Clin Immunol. 2001; *11:* 149-156.

[171] *Yunginger JW, Paull BR, Jones RT, Santrach RJ.* Rush venom immunotherapy program for honeybee sting sensitivity. J Allergy Clin Immunol. 1979; *63:* 340-347.

[172] *Zenner HP, Baumgarten C, Rasp G, Fuchs T, Kunkel G, Hauswald B, Ring J, Effendy I, Behrendt W, Frosch PJ, Przybilla B, Brunner FX, Merk HF, Kapp A, Schnitker J, Wolf H.* Short-term immunotherapy: a prospective, randomized, double-blind, placebo-controlled multicenter study of molecular standardized grass and rye allergens in patients with grass pollen-induced allergic rhinitis. J Allergy Clin Immunol. 1997; *100:* 23-29.

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