

## Standards for practical allergen-specific immunotherapy

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### Foreword

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### Introduction

This paper was produced to establish a common European Standard for Practical Allergen-Specific Immunotherapy that could serve as an overall 'gold standard' to ensure optimum quality for this form of treatment. WHO defines quality of health care as a 'high professional standard', 'effective use of resources', 'minimal patient risk', 'high patient satisfaction' and 'continuity in patient care'. These Standards are minimum requirements for Best Clinical Practice and form the basis for a Quality Assurance Programme. It is intended that the Standards should be an inspiration for local Clinical Guidelines (more comprehensive local guidelines for immunotherapy) that are adapted to National regulations, local conditions and related to the service and the patients. The Clinical Guidelines should be available, known and understood by all staff dealing with allergen-specific immunotherapy.

The greatest problem encountered in trying to provide standards related to practical immunotherapy is the lack of evidence-based information. Consequently, the present standards are based on scientific information as far as possible. The statements of evidence follows the rules of WHO based on Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. *BMJ* 1999;318:593–596. Dosing adjustments and safety procedures are based on evidence (when existing) combined with the authors' long-term experience and systematic attempts to make the treatment as rational as possible, to identify risk-factors and to improve safety balancing time consumption and patient inconvenience and the risk of inducing systemic reactions.

### Immunotherapy glossary

*Allergen* denotes a protein or glycoprotein capable of binding IgE. Most allergens are derived from naturally occurring substances like pollens, animal hair and dander, insects, moulds, foodstuffs etc. Allergenicity is related to the conformational structure of the folded protein recognized by the Fab part of the IgE molecule.

*Allergen product* means a biologic product including allergens or allergen components administered to man for diagnosis, prevention and treatment of allergy and allergic diseases. *Allergen extracts* are solutions of allergens extracted from source materials. *Allergen vaccines* is a term used for therapeutic products in some publications.

*Allergen-specific immunotherapy* is the practice of administering gradually increasing quantities of an allergen product to an individual with IgE-mediated allergic disease in order to ameliorate the symptoms associated with subsequent exposure to the causative allergen. Other terms used in the past include *desensitization*, *hyposensitization*, and *allergy vaccination*.

*Allergic anaphylaxis* is a severe immediate systemic reaction occurring in IgE-sensitized individuals after exposure to an allergen. It is caused by the rapid release of vasoactive mediators from mast cells and basophils. *Anaphylactic shock* implies a drop in blood pressure.

*Cluster immunotherapy* the term for the administration of two or more injections per visit with the aim to achieve the maintenance dose more rapidly than by the conventional 'one-injection-per-week' schedule. Cluster immunotherapy saves time with the cost of a slightly increased frequency of side effects.

*Desensitization* is a previously used term for allergen-specific immunotherapy. Now mostly used in relation to making effector cells less responsive or nonreactive by the (continuous) administration of incremental doses of an allergen or allergenic

substance. Desensitization is most often used for the treatment of allergic reactions to penicillins in patients with an urgent need for penicillin. Desensitization does not induce a long-lasting immunological tolerance as the effect is related to occupying reactive IgE-molecules rather than changing the immune response.

*Immunomodulation* relates to altered immune responses induced by a variety of interventions. Includes changes in specific T and B cells, immune deviation, anergy or tolerance, modification of inflammatory pathways like adhesion, chemotaxis, or signalling within or between immunocompetent cells.

*Immunotherapy* is a general term for the treatment of immunologic diseases. It includes both active and passive immunization for improving a host's defences against microorganisms. A number of diseases are treated by immunotherapy now involving clonal deletion, tolerance and immune deviation. Except for immunotherapy in allergic diseases, the use in other immunologic diseases is immunologically nonspecific (not applying a specific antigen).

*Major allergen* refers to an antigenic determinant (epitope) from a complex allergen binding IgE in >50% of patients sensitive to the allergen, as detected by immunoblot or electrophoresis. For the individual patient a minor allergen (binding <50% of IgE) might clinically represent a 'major' allergen in inducing clinically symptoms.

*Rush immunotherapy* is a form of immunotherapy in which injections are administered at 30- to 60-min intervals implying that the maintenance dose might be reached within hours or days. The technique might be advantageous if rapid protection is needed (like in Hymenoptera venom allergy), or when geographic conditions make the use of conventional or cluster immunotherapy problematic. The risk of systemic side effects is increased and rush immunotherapy should only be performed in hospital in a specialist setting.

## Aim

- To create a quality assured practical daily routine for allergen-specific immunotherapy ensuring a high professional standard and an effective use of resources.
- To ensure that patients and staff are confident and feel secure at initiation and during treatment by describing safety procedures and practical methods to obtain a minimal patient risk, high patient satisfaction and continuity in the course of treatment.

- To supply directions for documentation and follow up of the result of treatment.

## Background

Allergen-specific immunotherapy is a well-documented treatment in allergic diseases (1-3). An important issue is the need for optimal technical performance of immunotherapy. At present this is a limitation for more widespread dissemination of the treatment. Especially for subcutaneous allergen-specific immunotherapy, the clinical outcome and the safety of the treatment necessitate a detailed knowledge of the principles and execution of the treatment. The practical performance of allergen-specific immunotherapy is to a large extent based on empirical experience. These guidelines are based on evidence insofar as this is available (4). The Standards for Practical Allergen-Specific Immunotherapy relate mainly to subcutaneous immunotherapy as this type of treatment involves the greatest risk of anaphylaxis. Noninjective immunotherapy has a better safety profile than subcutaneous treatment and is normally self-administered outside the physician's office.

## Definition of allergen-specific immunotherapy

Allergen-specific immunotherapy is the practice of administering gradually increasing quantities of an allergen product to an allergic subject to ameliorate the symptoms associated with the subsequent exposure to the causative allergen. Allergen-specific immunotherapy induces clinical and immunologic tolerance, has long-term efficacy and may prevent the progression of allergic disease. Allergen-specific immunotherapy also improves the quality of life of allergic patients.

This definition is based on category I evidence.

## Treatment strategy

Available treatments for allergic diseases include allergen avoidance, pharmacotherapy, allergen-specific immunotherapy, and patient education. There are few studies that directly compare the relative advantage of these interventions. However, their optimal combination for each individual patient should improve the clinical outcome. Allergen-avoidance should be considered as a first-line intervention and even when not completely effective, may reduce the need for additional treatment (5). Drug treatment is the next step to reduce disease severity. In patients who need regular pharmacotherapy, it is advantageous to start immunotherapy early while disease remains plastic and when it remains possible to prevent progression of

disease ([1](#), [2](#)). Although many drugs are effective and without significant side-effects, drugs represent a symptomatic treatment, while immunotherapy represents the only treatment that might alter the natural course of the disease ([6-8](#)). Using an appropriate allergen product and a correct indication, immunotherapy can significantly reduce the severity of the allergic disease, reduce the need for anti-allergic drugs, and improve the quality of life for allergic patients ([9](#)).

Since allergen-specific immunotherapy is a disease modifying treatment, it should be initiated early in the course of the disease in order to prevent irreversible damage in mucous membranes of the shock organ.

In summary an optimal strategy for the treatment of allergic patients includes:

- Control of symptoms using an optimal pharmacologic treatment.
- Performing allergy diagnostic procedures (to evaluate the possibilities to institute disease modifying specific treatment).
- Disease modifying treatment.
  - Allergen avoidance (-reduction).
  - Allergen-specific immunotherapy.
- Stepping down the pharmacologic treatment to the lowest possible dose keeping the patient adequately controlled.
- Patients should be followed-up with education and adjustment of the pharmacological treatment until a stable situation is obtained.

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## Allergen products

Allergen product 'means a biologic product, including allergenic extracts and others, that is administered to man for diagnosis, prevention and treatment of allergy and

allergic diseases' (1). The quality of allergen products is a key issue for both diagnosis and therapy. The heterogeneity of allergen extracts and the unknown properties of many of the components of each preparation have made it necessary to develop methodologies to assess their potency and ensure their consistency. In addition, the variable response of each patient to the different allergen components (mainly proteins) may influence the potential clinical outcome and has led to different approaches to allergen standardization.

## Standardization

In a joint effort, authorities, basic researchers, clinical groups and manufactures are trying to define a common platform for the standardization of allergy vaccines (2-8).

*In vivo* standardization methodologies using a representative patient population and dose response studies, based on skin tests, were performed to assign biological activities to reference extracts that were later used as yardsticks to compare production batches (9).

As in-house reference standards (IHRs) are to be developed, European regulations (10) now define specific requirements for the starting materials, production processes and quality control of IHRs. IHRs have to be fully characterized and potency must be assigned by immuno-assays and/or skin prick test in units of biological activity. The references will be used in routine production to assess antigen and allergen composition and thus ensure the consistent quality of each production batch.

In addition, potency should be measured in the last feasible step of the manufacturing process (for modified extracts, this implies just prior to the modification procedure). Guidelines on 'stability tests on active ingredients and finished products' should be followed.

It is likely that recombinant allergens, in the near future, will provide standards for allergen analysis and in consequence, new diagnostic and therapeutic products will be developed.

### Units of biological potency

Skin prick testing provides basic *in vivo* standardization in Europe and units are assigned by comparison to a reference substance such as histamine (usually 10 mg/ml histamine hydrochloride) or by expressing mean wheal areas in a selected population (6).

Treatment doses are adjusted based on clinical experience, using IHRs standardized by the above-mentioned methodologies. Each manufacturer defines specific units and concentrations and, thus, a whole range of not inter-related names for specific units

currently appear on the labels of marketed products (BU, HEP, IR, SE, SQ, STU DPP, SU, UBE, UT etc).

Even when the same methodology is used (e.g. Nordic Guidelines) ([11](#)), extracts from different manufacturers labelled with the same units, e.g. 10 HEP/ml, may not be identical in potency, due to difference in the sensitivity of the selected patient population, the relatively small number of patients tested, and the different methodologies employed.

Major allergen content

The characterization of major allergen components and the development of techniques to quantify them, such as ELISA methodology based on monoclonal antibodies, have led to manufacturers providing information on major allergen content of their extracts ([12](#)). It is recommended that allergen manufacturers in the future state the content of representative major allergens in their products in mass units ( $\mu\text{g/ml}$ ) ([13](#), [14](#)), although comparison between different manufacturers' labelling may not be possible due to differences in assays and methodologies for measurement of the major allergens.

Minor allergens

It is generally accepted that any immunogenic antigen in the allergen source material has allergenic potential. Minor allergens are defined as components within an allergen product, which are recognized by a minority of allergic sera. For patients that do not present the usual allergen recognition pattern, doses of minor allergens are relevant, as they affect the total biological dose and are subject to individual concentration variations. Current standardization methodologies do not fully take into account the contribution of minor allergens to the overall biological potency of allergen products. Electrophoretical methods used for allergen identification only allow qualitative or at best, semiquantitative, assessment of the presence of these components. It is thus desirable to further develop methods to monitor the content of at least some of these components.

## Formulation

Natural allergen products may be subjected to chemical modification during formulation ([15](#), [16](#)) and in addition, may be combined with different adjuvants and slow release formulations ([17](#)). There are intrinsic differences in each approach, in terms of product characteristics and, consequently, safety/efficacy data should be evaluated separately for each therapeutic approach.

Natural allergen products

Allergen products are used directly in a buffered formulation. No adjuvant is used and no chemical modification is performed.



This type of product includes primary lyophilized Hymenoptera venom extracts, inhalant allergen subcutaneous immunotherapy products and some sublingual immunotherapy products.

#### Physically modified allergen products

Different carrier substances are used to adsorb natural allergen products. The most commonly used carriers are aluminium hydroxide, calcium phosphate and tyrosine. The purpose of these formulations is to produce a sustained release of the allergen from the site of injection (depot effect).

#### Chemically modified allergen products

Natural extracts are subjected to chemical modification to reduce their allergenicity and/or to produce high molecular weight aggregates. Products modified with formaldehyde or polymerized and modified with glutaraldehyde are currently available. As in the case of natural products, they can also be adsorbed to different carrier substances.

#### Recombinant allergen products

In recent years, by use of modern molecular biological techniques, the majority of allergens responsible for the common allergic diseases have been cloned and sequenced, such that the production of recombinant allergens is now a reality. In the future it is likely that recombinant allergens will allow a more precise allergy diagnosis of allergic patients, with the potential for tailor-made therapy based on individual patterns of sensitivity. The results of controlled clinical trials are eagerly awaited (18).

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## Subcutaneous immunotherapy

### Efficacy and safety

#### Inhalation allergens

The clinical manifestations of atopic sensitivity to inhalant allergens include rhinitis, conjunctivitis, and asthma. From a clinical point of view, the only parameters that indicate efficacy of a treatment are reductions in symptoms and/or drug intake of a magnitude that significantly reduces morbidity (1). The clinical efficacy of subcutaneous immunotherapy is confirmed by 75 double-blind, placebo-controlled studies published from 1980 to 2005 which demonstrate clinically relevant decreases in symptom-medication scores. Fifteen out of the 75 studies included children.

The category of evidence for clinical efficacy is 'Ia' for asthma and 'Ib' for rhinitis using allergen products from birch, grasses, mountain cedar, cypress, olive, Parietaria, ragweed, cat, *D. pteronyssinus*, *Alternaria*, *Cladosporium*.

Fundamental questions are whether immunotherapy has the potential to provide long-term benefit following its discontinuation and whether immunotherapy may prevent either disease progression and/or the onset of new allergic sensitivities (2). Without long-term reduction in disease severity and disease modifying capability, immunotherapy may not be cost-effective, and consequently not be a real alternative to pharmacologic treatment (3). Some older studies indicate that the treatment may have a long-lasting effect. The study of Durham et al. (4) is the only available controlled study which documents long-term efficacy of immunotherapy following a double-blind, placebo-controlled withdrawal of the treatment (5).

The category of evidence for long-term efficacy and preventive capacity is 'Ib'.

A major limitation for the wider dissemination of allergen-specific immunotherapy is the associated risk of systemic side-effects. The injection of allergens into an IgE-sensitized individual always implies a risk, however small, of inducing anaphylactic side-effects (1, 3, 6). The frequency and severity of systemic reactions vary between studies, depending on the criteria for patient selection, the disease, the allergen product and formulation used, and the type of induction regimen. Evidence suggests that the patients most likely to develop anaphylaxis are those who are highly allergic based on skin tests or specific IgE-tests and patients with more severe disease, particular those with chronic and uncontrolled asthma (7). Systemic side-effects occur more frequently in patients during the induction (up-dosing) phase of treatment when compared to maintenance therapy (8, 9).

#### Hymenoptera venom allergens

Detailed information is available in the position paper on venom allergy of the EAACI task force for insect venom allergy ([10](#)).

The efficacy of venom immunotherapy has been analysed in three controlled ([11-13](#)) and several prospective uncontrolled studies which employed a usual maintenance dose of 100  $\mu\text{g}$  of venom. In these studies, patients were monitored with sting provocation tests during immunotherapy ([14](#)). In all controlled trials analysing patients with either vespid, honey bee or ant venom allergy, comparing venom with either whole-body extract or placebo, a highly significant difference in favour of venom was observed: 75–100% of venom-treated patients tolerated re-sting without allergic symptoms, while 64–75% of whole-body product and 58–72% of placebo-treated patients developed systemic allergic reactions on re-sting challenge. In the prospective uncontrolled studies ([14](#)) only 0–9% of vespid allergic but around 20% of bee venom allergic patients still reacted to the challenge with the respective insect. These studies confirm the superior efficacy for immunotherapy with vespid or ant venom when compared with honey bee venom. In patients who did react following a course of venom immunotherapy, the symptoms were usually mild and less severe than those observed before treatment.

The category of evidence for efficacy is 'Ib'.

The safety of venom immunotherapy is related to the nature of the venom used and the protocol. Definitely more side effects are observed during honey bee venom than vespid venom treatment ([15](#)). In an EAACI multi-centre study ([16](#)) in 840 patients totalling 26 601 injections, 20% of patients developed mostly mild systemic allergic reactions, corresponding to 1.9% of injections during the dose increase phase and 0.5% during the maintenance phase. Rapid dose increase, especially with high cumulative daily doses of 200–500  $\mu\text{g}$  in rush protocols seemed to increase the risk of side effects.

## Indications and contraindications

### Indications

Immunotherapy is indicated for confirmed IgE-mediated disease using standardized products with documented clinical efficacy and safety (grass, birch, ragweed, olive, Parietaria, cypress, cat, house dust mites (*D. pteronyssinus*, *D. farinae*) ([6](#)).

Immunotherapy is indicated as a supplement to allergen avoidance and to pharmacotherapy. Normally subcutaneous immunotherapy is restricted to patients above 5 years of age. Below this age inhalation allergens play a less important role. Furthermore, when subcutaneous allergen-specific immunotherapy is prescribed below 5 years of age, it is critical that the physician responsible for the injections has experience in identifying and treating emerging signs of anaphylaxis in this age group. In addition nurses and other staff administering allergen injections to children must

be especially trained to treat this age group. Except for insect venom allergy subcutaneous immunotherapy is rarely used after the age of 60 years.

Immunotherapy is not indicated for the treatment of food allergy and atopic eczema.

Indications in rhinoconjunctivitis and asthma.

- Patients with symptoms induced predominantly by allergen exposure.
- Patients with clinical symptoms due to a single or few allergens.
- Patients with a prolonged season or with symptoms induced by succeeding pollen seasons.
- Patients with rhinitis and symptoms from the lower airways during peak allergen exposure.
- Patients in whom antihistamines and moderate dose topical glucocorticoids insufficiently control symptoms.
- Patients who do not want to be on constant or long-term pharmacotherapy.
- Patients in whom pharmacotherapy induces undesirable side effects.

It is recommended that the indication follow the guidelines of the EAACI Immunotherapy Position Paper (3). The indication for allergen-specific immunotherapy should be explicitly defined in relation to:

- Disease and disease severity.
- Allergens and the importance of allergen sensitization.
- The need for and the effect of symptomatic treatment.
- The risk of the disease and the treatment.
- Psychological factors.
- The patient's attitude to the disease and treatment.

Indication in Hymenoptera venom allergy.

Venom immunotherapy is indicated in both children and adults with a history of severe systemic allergic reactions including respiratory and/or cardiovascular symptoms and documented sensitization to the respective insect as determined by either skin tests and/or specific serum IgE tests (10, 17). As for systemic nonlife-threatening reactions (urticaria, erythema, pruritus) other factors may influence the decision to initiate venom immunotherapy. These include availability of immediate access to medical care, occupations and/or hobbies where the risk of exposure is

high, concomitant cardiovascular disease, the presence of other pathologies such as mastocytosis and psychological factors arising from anxiety which can seriously impair patient quality of life. Immunotherapy is not recommended for large local reactions or unusual reactions, like non-IgE mediated hypersensitivity reactions such as vasculitis, nephrosis or thrombocytopenia (17).

More detailed information are available from the position paper on venom allergy of the EAACI task force for insect venom allergy (10).

#### Contraindications

The contraindications for subcutaneous allergen-specific immunotherapy with inhalant and *Hymenoptera* venom allergens include (6):

- Absolute contraindications.

- Serious immunological diseases, major cardiovascular disease (except in case of serious insect venom allergies), cancer, chronic infections.
- Severe asthma with persistently reduced lung functions (FEV<sub>1</sub>) below 70% of predicted in spite of optimal pharmacologic treatment.
- Treatment with  $\beta$ -blockers (including topical) (see Hymenoptera below).
- Lack of compliance and severe psychological disorders.

- Relative contraindications.

- Pregnancy (no documentation of teratogenic risk), but a risk of anaphylactic reactions during induction phase and consequent damage of the foetus. It is recommended not to start induction during or in case of planned pregnancy. Uncomplicated maintenance treatment may be continued after careful information and acceptance by the patient. The treatment should be terminated by the slightest patient insecurity or the development of complications of immunotherapy

- Severe atopic eczema

- In contrast to inhalation allergen immunotherapy, immunotherapy for venom allergy is often indicated in elderly patients with coexisting cardiovascular disease, who are at a special risk to develop very severe or even fatal reactions. Such patients are not uncommonly on  $\beta$ -blocker treatment. In this situation the risk of stopping the drug must be carefully balanced against the risk of renouncing venom immunotherapy. In coronary heart disease or severe ventricular arrhythmia the risk of stopping the  $\beta$ -blocker can be unacceptable. If highly exposed to the relevant insect, venom immunotherapy may be carried out in patients with ongoing  $\beta$ -blockade but under careful supervision, including monitoring of blood pressure and electrocardiogram and

with expertise and remedies at hand if severe side effects with resistance to treatment due to the  $\beta$ -blockade should occur (18).

### Preventive and disease modifying capacity

The capacity of subcutaneous immunotherapy to suppress the development of new sensitizations has been investigated in three nonrandomized studies in monosensitized patients (19–21). In an open retrospective study Purello-D'Ambrosio (20) made a follow-up of 7182 monosensitized (to different allergens) patients treated with subcutaneous immunotherapy for 4 years and off immunotherapy for 3 years. The control group consisted of 1214 matched patients followed for 7 years. The development of sensitization to new allergens showed a clinically relevant and statistically significant difference at the 4-year follow-up with figures of 68% in the control group vs 24% in the immunotherapy group and at the 7-year follow-up 78% and 27% respectively. Pajno et al. (21) followed 75 subcutaneous immunotherapy-treated children only sensitized to house dust mites and 63 comparable controls treated pharmacologically for 6 years. In the immunotherapy-treated group 74% continued to be monosensitized vs 33% in the control group. Although these studies are of interest, prospective randomized, controlled studies are needed.

Subcutaneous immunotherapy might prevent the progression of rhinitis into asthma. A multi-centre paediatric study investigated the capacity of immunotherapy in children with allergic rhinitis to down-regulate the development of asthma (22). Children allergic to birch and grass pollen and no symptoms of lower airway hyperreactivity, were randomized to receive either immunotherapy or an optimal pharmacologic treatment. After three years of treatment, the number of children developing clinical asthma was statistically reduced in the immunotherapy group. The development of asthma was 24% in immunotherapy-treated children vs 44% in the drug-treated group, indicating that the high risk of developing symptoms from the lower airways in allergic rhinitic children may be diminished by immunotherapy. Bronchial hyper-responsiveness to methacholine decreased significantly in immunotherapy-treated children, but only two out of 40 children with asthma at inclusion were free of asthma after 3 years indicating that immunotherapy has a greater capacity for preventing than for curing asthma. Further studies are needed to clearly define the preventive capacity of subcutaneous immunotherapy.

### Practical aspects

Organization

Management plan.

It is rational to organize patient management plans based on a quality-assurance programme, e.g. a systematic description of elements and processes related to the diagnosis and treatment of patients offered allergen-specific immunotherapy.

The aim is to describe current 'Best Clinical Practice' in daily clinical work, to define and ensure the chosen level of quality, and to ensure that resources are used in an optimal and rational way.

Competencies.

The physician responsible for management plans involving allergen-specific immunotherapy should optimally be a specialist in allergology (or have equivalent competencies). Special knowledge, education and know-how are demanded for those who treat children.

The indication for allergen-specific immunotherapy should be made by an experienced physician, preferably a paediatrician for children, trained in the evaluation of allergic patients and familiar with the practice of allergen-specific immunotherapy, preferably an allergist.

To ensure safety and efficacy, all staff members involved in allergen-specific immunotherapy should be familiar with common patient scenarios ('high professional standard'). A high degree of professional knowledge encourages cooperation and ensures the most 'effective use of resources'.

Staff.

Physicians, nurses and health care persons must be trained and regularly updated in subcutaneous allergen-specific immunotherapy including the observation and rescue treatment of systemic anaphylactic reactions ('minimal patient risk').

As a minimum requirement, a competent physician must always be present when subcutaneous immunotherapy is carried out and be responsible for the treatment. In addition, one more person should be available for proper management of serious adverse events.

Responsibility and delegation.

The head of the clinic has the overall responsibility for the performance of subcutaneous immunotherapy and the implementation of safety procedures.

When delegating responsibility the head of the clinic must ensure that the staff member in question is educated to deal adequately with the responsibility, and that the staff member accepts to take on the responsibility.

All staff participating actively in subcutaneous immunotherapy should have clearly defined responsibilities, taken into considerations local principles and practice.



Education of staff members.

The clinic should offer a systematic theoretical and practical education of staff members before their active involvement in subcutaneous immunotherapy.

The head of the clinic is responsible for the maintenance of the knowledge of the staff by continuous internal and external education including the recognition and treatment of anaphylaxis.

When new staff-members are introduced to the programme, it is sensible to assign them a mentor who will ensure their education and help them to master the practical aspects of immunotherapy including:

- Evaluation of the patients' condition (in the case that the patient is a child under 15 years of age, parents must be involved in this process) with respect to receiving subcutaneous immunotherapy (clinical state and peak flow measurements).
- Entering data in the individual patient's 'Patient Immunotherapy Record Form' at each visit.
- Injection technique.
- Dose modification.
- Active observation of patients (also children even if they are accompanied by their parents).
- Early recognition of anaphylactic reactions.
- Treatment and monitoring of patients with anaphylactic reactions.
- How to perform scheduled tests and annual assessments.
- Factors determining decision to continue or conclude therapy.

Rescue equipment.

Essential equipment for the treatment and monitoring of systemic anaphylactic reactions must be available, including (6):

- Adrenaline (1 mg/ml) for injection.
- Antihistamine, corticosteroids, and a vasopressor for injection or oral treatment.
- Syringes, needles, tourniquet, and equipment for infusion.
- Saline for infusion.
- Oxygen and suction equipment.

- Silicone mask and equipment for manual ventilation.
- Equipment for measurement of blood pressure.
- Forms for recording the course and treatment of anaphylaxis.

In settings remote from intensive care facilities, equipment for direct laryngoscopy, DC cardioversion, tracheotomy and intracardiac injections may be optional, but the rare situation in which these procedures might be essential does not justify that these procedures are immediately available for subcutaneous immunotherapy.

The responsibility for checking the presence and function of equipment should be delegated to a specified person, and verification should be documented in a logbook.

Communication.

It is rational that all staff members have a mutual responsibility for the treatment and for defined procedures, and feel comfortable with their function. Regular attendance at conferences and educational meetings enhances staff competence.

Deviation from standard operating procedures should be discussed with all staff members involved in relation to correction or definition of new routines.

Patients

Due to the commitment needed from both staff members and patients starting subcutaneous immunotherapy, it is important to individualize and adjust the treatment to the patient's age and social background implying that the patient beside the need for treatment also has a need for communication, continuity and coordination of the course of the treatment. Communication with children in agreement with their age and developmental status is a basic demand.

Cooperation with referring physicians.

With respect to patients referred from general practice, the general practitioner (GP) should receive information on the choice of treatment and the arguments for proposing subcutaneous immunotherapy.

It is recommended that the induction phase be carried out by an experienced allergist as the risk of systemic reactions is highest during this phase. The patient may (in accordance with local regulations) continue maintenance subcutaneous immunotherapy by a GP in close collaboration with the specialist (with the condition that the GP has sufficient training, experience and immediate access to rescue equipment) (see [Rescue equipment](#)).

When patients are referred for maintenance treatment in a primary care setting, the GP should confirm that he/she accepts to take the responsibility for the patient.

Before referral of the patient, the GP should optimally have received training at the referral clinic in order to ensure a high quality of treatment.

Formalized guidelines for the practical performance of subcutaneous immunotherapy and the recording of injections and side effects (Shuttle Case Record Form) should be forwarded to the GP at the time of referral for maintenance treatment. The clinic initiating subcutaneous immunotherapy should preferably follow up all shared care patients annually. A Shuttle Case Record Form could be used as the communication tool. Termination of treatment before the scheduled date for termination should be reported to the master clinic (including reason for termination).

Diagnostic procedures before initiating subcutaneous immunotherapy.

To ensure 'effective use of resources' detailed guidelines for diagnostic procedures (related to disease) to be performed before the start of treatment should be defined.

The IgE-sensitization is assessed by skin testing and/or *in vitro* determination of serum concentrations of allergen-specific IgE antibodies. Allergen challenge tests may occasionally be indicated in case of uncertainty. Immunotherapy should be considered when positive tests correlate with suspected triggers and the patient's known exposures. Immunotherapy should not be given to patients with negative diagnostic tests or those with positive tests that do not correlate with suspected triggers, clinical symptoms, or exposure (the presence of specific IgE antibodies does not necessarily indicate clinical sensitivity). Clinically relevant exposure to allergens like house dust mites and animal dander might need substantiation by quantifying the actual level in mattresses and furniture to which the patient is exposed.

Information.

The patient should be informed in an objective way of the principles of different treatment options, the clinical efficacy including long-term efficacy, symptom reduction vs disease modifying treatment, duration of treatment, side effects, financial costs and commitment. Information should be both verbal and written and be adapted to the patient's capability to receive and comprehend the information.

Patient education.

Before the start of treatment and continuously during treatment it is appropriate to inform and educate the patient in the principles of the treatment and the monitoring of the treatment. The education should ensure a higher dedication to the treatment and consequently a better compliance ('high patient satisfaction'). The active understanding of the nature of the disease and the reaction of the body to the treatment will improve the safety ('minimal patient risk').

Evaluation of treatment.

Guidelines for evaluation of the treatment and a time schedule for the assessments should be defined. The evaluation includes:

- Assessment of efficacy and side effects.
- Criteria for continuing treatment.

Inadequate treatment response, side effects or other conditions resulting in the termination of subcutaneous immunotherapy should be explicitly defined in the Clinical Guidelines.

Practical treatment

Clinical guidelines.

It is recommended to provide clear written instructions for the organization and delegation of competence and responsibility, and all practical procedures:

- How to handle allergen products.
- The technique of deep subcutaneous injection, including aspiration and how to handle the occurrence of aspirating blood.
- Various induction regimens.
- Safety procedures including procedures for checking of rescue equipment.
- Defining actual allergen dose based on the preinjection monitoring of the patient.
- Deciding when to postpone an injection, when to administer a reduced dose or whether not to give increments of the dose.
- How to calculate doses during exacerbations, during allergen seasons and in case of intercurrent infections and other diseases.
- How to diagnose and treat local and systemic reactions.

From a legal point of view, adherence to the Clinical Guidelines will place the responsibility for emergencies in the hands of the head of the office, while on the other hand, deviating from the guidelines places the responsibility on the person performing the injections. The use of Patient Immunotherapy Record Forms is recommended for the documentation of patient's status, preinjection monitoring, dosing, postinjection monitoring and for recording any side-effects.

Allergen product.

Patients with multiple allergic sensitivity may be effectively treated with several individual allergen products according to their individual sensitivities. In general this

approach is limited to two or at most three allergens, which should be injected at 30-min intervals.

Mixtures of related, cross-reacting allergens, such as a mixture of individual grasses are acceptable provided regulatory demands (stability, etc.) are fulfilled. Another appropriate and widely used example is the mixture of *D. pteronyssinus* and *D. farinae* in mite allergen products.

Mixing of unrelated allergens is technically feasible and with the available methodologies, individual allergens can be controlled in the mixture. In view of the potential interactions between enzymatic components, detailed quality control and stability assessments are required (23). A major problem in mixing unrelated allergens is whether optimal doses of individual allergens can be achieved due to the inevitable dilution of individual components. Importantly, the only published controlled immunotherapy trial which evaluated allergen mixtures did not show clinical efficacy. This could have resulted, at least in part, from the failure to reach an optimal dose of individual allergens in the mixture (24).

Transportation, storage and use of allergen products should be in accordance with the recommendations of the manufacturer or alternatively the clinic's own written guidelines. It is recommended to have individualized vials for each patient rather than sharing vials between patients.

The product (allergen, concentration, volume and expiry) date should be double-checked before each injection ('minimal patient risk').

Licensed allergen products with proven safety and efficacy should be used whenever possible. However, these products are rarely available in some countries yet, and standardized allergen products (in term of composition and consistency) should be preferred over nonstandardized products. When changing to a new vial a general safety procedure is to reduce the dose or to fractionate the scheduled dose by administering, e.g. half the dose and postpone the remaining dose for 30 min. If no large immediate local reaction or systemic reaction develops, the remaining dose may be administered (3).

Injection technique.

Guidelines for injection technique and anatomical injection sites should be defined. It is recommended to use the outer aspects of the upper arm. Deep subcutaneous injections should be given using a slow injection (injection of 1 ml should take approximately 60 s and aspirations are performed periodically, e.g. every 0.2 ml). It may be advantageous to fix the needle by two fingers in order to prevent movement of the needle. If blood is aspirated, the injection should be terminated, the blood-contaminated product discarded, and the patient observed intensively for 30 min. If

no signs of a systemic reaction are obvious, the outstanding amount of the dose may be administered using a fresh product.

#### Dosage schedules.

The induction regimen may be conducted as conventional 'one injection per week', or alternatively as a clustered or rush immunotherapy regimen. Dosage schedules and the amount of allergen to be injected are identical for children and adults. The choice depends on the organization of the service, the disease treated and the patient population. It is essential to explain the rationale for selecting a specified induction regimen in terms of efficacy, safety and convenience for the patients. Essentially, the induction regimen represents a compromise between reaching the maintenance dose as fast as possible whilst achieving the highest degree of safety. The schedule is not a fixed proposal and should be adjusted according to the responses of the patient, the time interval between injections, the presence of a co-seasonal allergen exposure etc. The induction regimen will also depend on the choice of either aqueous or depot allergen products.

The maintenance dose is often predefined by the manufacturer, but for some patients it is not possible to reach the recommended top dose (in the range between 5 and 20  $\mu\text{g}$  purified major allergen) (6). The optimal dose is an individualized dose resulting in a high clinical efficacy without any major side effects. In some patients the top dose might be higher than the dose recommended by the manufacturers, based on the clinical response of the patients. Criteria for accepting lower maintenance doses than the standard based on clinical trials should be explicitly defined. For children, in contrast to pharmacotherapy, the doses of allergens for immunotherapy are not necessarily dependent on the age or the weight of the child.

#### Safety procedures.

Safety procedures should be defined and the responsibility for these procedures unequivocally designated ('minimal patient risk'). A logbook for the control of emergency equipment with guidelines for the frequency and degree of control might be appropriate.

Regular training in safety procedures and the treatment and observation of anaphylactic reactions should be implemented.

Safety procedures in relation to injections of allergen products are the responsibility of each individual staff member. Unequivocal guidelines should exist for procedures to be performed, monitoring of the patient and questions to be asked before each injection including:

-Control of adrenaline.

- Identification of the patient and allergen product.
- Evaluation of the patient's clinical state.
- Control of time intervals from the last injection.
- Recording of reactions at the preceding injection.
- Control of the allergen product (appearance and expiry date).

Adequate documentation of safety procedures in the 'Patient Immunotherapy Record Form' is essential, both for individual patient safety and for medico-legal reasons.

The safe delegation of competence to non-physicians in defining allergen doses (dose modification) requires a high level of training and competence and consultation with the responsible physician in any case of doubt.

Guidelines for the observation of patients after injections including the duration of observation should be defined. As a routine, the patients should be under observation for 30 min after each injection (might be extended in case of systemic reactions and after the treatment of systemic reactions). The patient should be informed not to leave the clinic during the observation period and to immediately inform the staff in case of early symptoms of a systemic reaction. Children should be accompanied by an adult.

Before the patient leaves the clinic the response to the injection must be evaluated and recorded.

Clear written guidelines should be given to patients advising how to respond in case of deterioration of allergic symptoms or the delayed occurrence of symptoms after leaving the clinic.

Dose modification.

Detailed guidelines for omitting an injection, repetition of a previous dose or reduction of a dose should be defined ('minimal patient risk') including:

- The patient's clinical state during the last three days preceding the injection.
- Time intervals from the preceding injection.
- Systemic and local reactions following the preceding injection.

Before deciding the dose of allergen, a careful evaluation of the patients' suitability to receive the scheduled dose represents a crucial step to avoid systemic side-effects.

The following guidelines are recommended (6, 25):

- Postpone injections in patients with airway infections or other significant diseases within the last 3 days.
- Postpone injections in patients with deterioration of allergy symptoms or increased need for anti-allergic drugs due to recent allergen exposure within the last 3 days.
- Postpone injections in patients with decreased lung function <80% of personal best value. In asthmatic patients measuring lung function before each injection is mandatory (peak flow is sufficient).
- Reduce the scheduled dose if the interval between injection sessions has been exceeded. The magnitude of reduction depends on the degree exceeded and should be defined in the Clinical Guidelines.
- Reduce the scheduled allergen dose in case of a systemic reaction at the preceding visit. The magnitude of reduction depends on the severity of the reaction and should be defined in the Clinical Guidelines. In case of anaphylactic and other life-threatening reactions the continuation of subcutaneous immunotherapy should be carefully evaluated (except in case of Hymenoptera venom allergy, in which it actually reinforces the indication for immunotherapy).
- Separate allergen injections from other vaccinations for infectious diseases by at least 1 week.
- Traditionally the late local reaction at the injection site has been used to adjust the allergen dosing at the next allergen administration. Several studies have indicated, that the late local reaction at the preceding injection is not related to a risk of developing a systemic reaction at the next injection (25).

Preinjection monitoring of patients also includes a check of any drug intake that may either increase the risk of systemic side-effects or render the treatment of anaphylactic reactions more difficult.  $\beta$ -blockers are the most important example (26). Heavy beer drinking may similarly increase risk due to inhibition of the histamine-converting enzyme diamine oxidase (27).

Dosing during allergen season.

Dose modification and guidelines for injections during allergen seasons should be clearly defined.

It is recommended not to start induction treatment during allergen seasons.

During allergen seasons injections should not be given if the patient has clinical symptoms (3). As a general safety precaution, a routine reduction in allergen dose during allergen seasons is commonly used, but if the patient is symptom-free the dose does not need to be reduced. In symptomatic patients, the injection should be



postponed, symptomatic treatment instituted (intensified), and a reduced allergen dose given when the patient is asymptomatic.

An example of dosage guidelines is given in [Appendix I](#).

Local side effects.

Local swellings commonly occur following injections. In general these swellings are to be expected, are well-tolerated and require no specific therapy.

Subcutaneous nodules are occasionally observed at the location of injections, especially when using aluminium depot products. In most patients they disappear after a period, but in some patient the discomfort necessitates the termination of treatment.

Systemic side effects.

Systemic reactions are any symptoms from organs distant from the location of injection. Systemic side-effects may vary from a few sneezes to fulminate anaphylactic shock and even death. The severity is related to how rapidly the symptoms develop after the injection. Itching in the palms, soles, and on hairy body parts, and rapid onset of erythema and urticaria, rhinitis or asthma occurring within minutes after injection will often progress to anaphylaxis and require treatment without unnecessary delay.

Risk factors for systemic side effects induced by subcutaneous immunotherapy include the presence of asthma, especially uncontrolled asthma (28). The higher frequency of side-effects in asthmatic patients is most likely related to the size of the shock organ (lungs vs upper airways in rhinitics), and a higher degree of airway hyperreactivity. Also the allergen products used most often in asthma are perennial allergens including house-dust mites and pets (cats and dogs), i.e. allergens to which the patient may have recently been exposed before injections. This could induce subclinical asthma which would increase the susceptibility of the patient. Persistent inflammation (29) caused by low grade exposure to perennial allergen might also increase the risk of systemic side-effects.

Systemic reactions are categorized into immediate systemic reactions (occurring within 30 min) and late systemic reactions (debut >30 min after injection). A grading system has been proposed in the EAACI Immunotherapy Position Paper (3). A more operational grading system based on the rate of onset and severity is recommended:

#### Classification of systemic reactions

0 No symptoms or nonspecific symptoms.

I Mild systemic reactions. Symptoms: Localized urticaria, rhinitis or mild asthma (PF < 20% decrease from baseline).

II Moderate systemic reactions. Symptoms: Slow onset (>15 min) of generalized urticaria and/or moderate asthma (PF < 40% decrease from baseline).

III Severe (non-life-threatening) systemic reactions. Symptoms: Rapid onset (<15 min) of generalized urticaria, angioedema, or severe asthma (PF > 40% decrease from baseline).

IV Anaphylactic shock. Symptoms: Immediate evoked reaction of itching, flushing, erythema, generalized urticaria, stridor (angioedema), immediate asthma, hypotension etc.

Classifying the reaction, in addition to type and magnitude of reaction, should also include the time of onset following injection and the rate of subsequent development.

Unequivocal guidelines for the treatment of systemic anaphylactic reactions should exist including recommendations for the hospitalization of patients with anaphylactic reactions for observation. An example of the treatment of systemic side effects is given in [Appendix II](#).

Pharmacologic pre-treatment before injections.

Antihistamine pretreatment during the induction phase has shown to reduce the frequency and severity of systemic side effects (30) (Category of evidence Ib). In a controlled trial of *Hymenoptera* venom immunotherapy involving a small number of patients, antihistamine pretreatment was associated with a better clinical efficacy (31) (category of evidence Ib). Further studies are required. A potential problem is that the use of antihistamine pre-treatment may mask a mild reaction, which would otherwise result in dose modification.

Appropriate guidelines and procedures for checking premedication use are needed.

Documentation.

Guidelines for the recording of the course of the treatment, reactions to injections, side effects and the treatment of side effects should exist. The use of a 'Patient Immunotherapy Record Form' might ensure consistency and quality and improve the opportunities for effective and scientific audit (Appendix III).

Audit of systemic reactions.

In the grading of the severity of symptoms the time factor should be incorporated indicating that prompt treatment with adrenaline of these symptoms (and consequently management of the symptoms) should be graded as a Grad IV reaction (anaphylaxis), even if the patient does not progress to develop manifest shock! The

response to the treatment is also of importance, e.g. late occurring angioedema or generalized urticaria only requiring minimal treatment is classed as a Grad II reaction.

### Paediatric aspects

Indications and contraindications for allergen-specific subcutaneous immunotherapy are the same for children over the age of 5 years as for adults. The specific diagnosis of an IgE-mediated allergic disorder in children, at least in young children, should be performed by a paediatric specialist. Compliance, motivation and co-operation during immunotherapy are especially important when children are treated. Patient education and information is crucial; the language used must fit to the developmental status of the child. The child needs accurate and detailed information about the treatment from the very beginning. It is important to update the child on a regular basis on the progression of treatment. The reason for repeated injections at prolonged intervals during maintenance therapy at times where he/she is asymptomatic should be given. The restrictions on exercise after each injection must be explained and also the reasons for social restriction. It is important to have sufficient time at every visit, so that the child feels safe and relaxed. Compliance with the injection regimen may be affected by age and may be particularly problematic during the adolescent years. Children must always have a parent, guardian or other responsible adult with them at each visit. It is recommended to start immunotherapy as soon as possible in allergic children to modify the natural course of respiratory allergy. Airway remodelling may start early in life, especially in children with severe asthma (32), and ongoing airway inflammation and remodelling in adolescents and young adults may increase the risk of asthma later in life (33). As documented earlier there is evidence that early specific injection immunotherapy reduces the risk of asthma in children with allergic rhinitis (22) and diminishes the risk of new sensitizations in monosensitized children (19, 21).

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## Noninjective immunotherapy

### Efficacy and safety

#### Bronchial immunotherapy

Only two clinical trials have been carried out using this route of administration (1, 2). The results obtained were unimpressive in terms of efficacy and bronchospasm was induced in many of the patients treated. Therefore, this route of administration has been abandoned in view of an unfavourable risk–benefit ratio.

#### Oral immunotherapy

Although a greater number of clinical trials with a suitable design (3) have been carried out using this route of administration, few of them achieved an acceptable level of clinical efficacy (4, 5). In some trials (6, 7), the effect was no better than that of placebo. Furthermore, adverse events including abdominal pain, vomiting and diarrhoea were recorded in some studies (7, 8). Present results do not support the oral route as an effective alternative.

#### Nasal immunotherapy

Twenty-two studies of nasally administered immunotherapy have been evaluated (9). Sixteen used a double-blind, placebo-controlled design. Most of these trials demonstrated significant clinical efficacy in allergic rhinitis. Although the results are encouraging, there are other factors to consider as nasal immunotherapy is a treatment for rhinitis only. Some studies reported local adverse effects (10, 11). The only study addressing long-term efficacy demonstrated no sustained effect following discontinuation of treatment (12). There is no data on the possible preventive capacity.

The category of evidence for clinical efficacy is Ib.

#### Sublingual-swallow immunotherapy

The sublingual route has attracted the greatest interest in recent years, as shown by the number of double-blind, placebo-controlled trials and the fact that sublingual immunotherapy has spread widely in some countries in Europe.

The category of evidence for clinical efficacy is Ia for rhinitis and Ib for asthma.

Further studies are needed to define the most appropriate dosages, the efficacy in paediatric patients, and to evaluate the magnitude of efficacy compared with other available treatments (13–16).

#### Efficacy and safety.

A meta-analysis published by the Cochrane Library (17) of the clinical efficacy of sublingual immunotherapy in patients with rhinitis included 22 double-blind, placebo-controlled clinical trials, and a total of 979 patients. There was significant heterogeneity for most comparisons, most likely due to the use of several alternative scoring systems in the different studies. Results showed a significant reduction in rhinitis symptoms and medication requirements.

The doses of allergen used in the different studies was analysed by Canonica and Passalacqua (9), and ranged from 3–5 to 375 times the cumulative dose of subcutaneous immunotherapy. There was no clear relation between the dose

administered and clinical efficacy, and more dose-response studies are needed to clearly indicate the optimal therapeutic effective dose. A dose-response relationship has been observed for ragweed (18).

The category of evidence for clinical efficacy is 'Ia' for birch, Cipress, grasses, olive, *Parietaria*, *D. farinae*, *D. pteronyssinus*. Out of 22 studies 12 include children (<15 years), four studies were conducted exclusively in children (17).

When introducing a new route of administration, safety is a priority, especially when treatment is self-administrated at home (19). Clinical trials and pharmacosurveillance studies have demonstrated a very low rate of systemic adverse effects and no life-threatening systemic side effects (20, 21).

Local side effects have been described in clinical trials. These include itching and swelling of the lips and under the tongue. These effects are more common in studies involving high dosages. In general, these effects are well tolerated, requiring no medication or dosages modifications, and often resolve with continued treatment.

In a few clinical trials systemic reactions such as urticaria and asthma have been observed, all of them self-limiting. Reactions are dose- and allergen-dependent (17).

Therefore, we can conclude that sublingual immunotherapy is well tolerated in both children and adults. However, despite above findings, patients must be warned about the possibility of major systemic or local reactions because this treatment is administered at home, and patients should be informed how to act in the case of such reactions.

#### Long-term efficacy.

The long-term effect of sublingual immunotherapy was investigated in one open, controlled, observational study included 60 mite sensitive asthmatic children ranging in age from 3 to 17 years (22). Allocation to immunotherapy or pharmacotherapy was based on parental preference. Sublingual immunotherapy was given for 4–5 years and the children followed for 10 years. At 10 years there was a significant reduction in the presence of asthma, use of asthma medication and an increase in PEFr compared with the control group.

#### Sublingual immunotherapy versus subcutaneous immunotherapy.

There have been studies comparing the two routes of administration, one comparing three groups of patients (sublingual, subcutaneous and placebo) (23) and another using an open design (24), they do not provide sufficient information due to insufficient study design (double-blind, double-dummy).

Two studies have had a double-blind, double-dummy design. The first of these studies (25) showed a reduction in the symptom and medication consumption scores in the group of patients treated with sublingual immunotherapy as well as in the group treated with subcutaneous immunotherapy, with no differences between the two routes of administration. This study had a methodologic limitation because it did not include a third placebo-placebo arm and the sample size was small (10 patients per group).

The other double-blind, double-dummy study (16), investigated patients with birch pollen rhinoconjunctivitis, allocated to three groups and efficacy analysed after 1 year of treatment. A significant difference between the two active groups and the placebo group in terms of symptom load and drug intake was found. However, the numbers studied were inadequate to detect a difference between the two active groups, if one existed. More studies with a greater number of patients are needed to evaluate the magnitude of the clinical efficacy and the optimal dosage.

## Indication and contraindications

### Indications

Immunotherapy is only indicated for confirmed IgE-mediated and clinically relevant disease using standardized products with documented clinical efficacy and safety.

- Bronchial and oral immunotherapy are not recommended for clinical use.
- Nasal immunotherapy remains an alternative to the subcutaneous route for adult patients with pollen-induced allergic rhinitis.
- Sublingual-swallow immunotherapy is indicated in:
  - Patients with allergic rhinoconjunctivitis and asthma.
  - Patients sensitive to birch, grasses, cypress, olive, *Parietaria* and house dust mites.
  - Patients insufficiently controlled by antiallergic drugs.
  - Patients with systemic reactions after subcutaneous immunotherapy.
  - Patients refusing injection immunotherapy.

At present, sublingual immunotherapy is restricted to patients above 5 years of age.

### Contraindications

At present contraindications for sublingual immunotherapy should be considered the same as for subcutaneous immunotherapy (3) (see page 6).

## Preventive and disease modifying capacity

A single randomized controlled open sublingual immunotherapy study in children has shown preventive effect on asthma onset (26). In the control group 18 out of 44 developed asthma vs 8 out of 45 in the sublingual group after 3 years of treatment.



Another randomized controlled open study demonstrated the prevention of new sensitizations in a 3-year long trial (27).

The category of evidence for the preventive capacity is Ib.

### Practical aspects

#### Precautions

Because this treatment is given to the patient at home, the following precautions should be taken:

- The patient (for children, their parents) should be given clear, simple written instructions about what to do in the event of an adverse reaction.
- Allergen tablets and drops should be kept in a secure place out of reach of children.

#### Administration management and technique

- Products should be transported, stored, and handled following the instructions of the manufacturer.
- The product is administered sublingually-swallow, placing it directly under the tongue. For solutions measuring out the dose in a teaspoon and depositing the fluid under the tongue can facilitate this manoeuvre.
- Keep the fluid or tablet under the tongue for 2 or 3 min, and then swallow.
- It is preferable to administer the product in fasting conditions and, if possible, at the same time every day.
- Wash hands after using allergen-containing tablets or drops, in order to avoid eye or nasal symptoms due to inadvertent allergen contact.

#### Treatment schedules and dose modification

The scientific documentation for treatment schedules and dose modifications is limited. Neither the optimal induction regimen nor the optimal top dose is defined. For routine treatment following the guidelines from the manufacturers is sensible.

- It is advisable to adjust the dose when systemic adverse effects appear.
- The administration of sublingual immunotherapy must be postponed in the following circumstances:
  - In the presence of oro-pharyngeal infection.

- In the case of major dental surgery.
- Acute gastroenteritis.
- Exacerbation of the asthma.
- PEFR <80% of personal best value.
- Simultaneous administration of viral vaccines.

#### Prevention and treatment of adverse effects

- Local reactions include itching of the oral mucosa, swelling under the tongue, and gastrointestinal symptoms. In general, these reactions are mild and usually remit spontaneously with no need for treatment. If major discomfort occurs, the treatment should be according to the prescribing specialist.
- Systemic reactions should be treated as for subcutaneous immunotherapy.

#### Documentation for patients

Since the treatment is given at home, it is important that the patient has clear, simple instructions on how to proceed if adverse reactions occur. Likewise, the patient should have a logbook to record the administration of treatment, specifying the date of administration, dose administered, and adverse events. This logbook should be evaluated by the specialist at each follow-up visit.

#### Follow-up and withdrawal from treatment

Monitoring and follow-up of patients under treatment with sublingual immunotherapy aim at verifying the efficacy of the treatment and possible adverse effects and their grade.

It is important that the patient be scheduled for follow-up at least three times a year, since compliance is more difficult to supervise than with subcutaneous immunotherapy, due to home administration of treatment.

#### Discontinuation of sublingual immunotherapy

- After a minimum of 3–5 years of administration, the patient is asymptomatic or has mild symptoms for two consecutive years (parallel to subcutaneous).
- Poor compliance with treatment by the patient.
- Appearance of any type of contraindication to immunotherapy.
- Persistent troublesome local side effects.

- Repeated systemic reactions.
- Absence of a clinical response to treatment after 2 years.

#### Paediatric aspects

Sublingual-swallow immunotherapy has been suggested to be a particularly attractive treatment for children where safety is paramount and outpatient, home-based therapy is clearly preferable. However, there are few studies in children, and more are urgently required. Several issues remain unsolved: e.g. optimal doses and duration of treatment in children, the evaluation of quality-of-life in children, compliance with home administration, storage of the allergen product during the time family is out of home, e.g. during holidays, dosing during acute but prolonged gastroenteritis etc. The excellent safety profile of sublingual immunotherapy, and the fact that injections are not required with this method raise the possibility that sublingual immunotherapy could be given to children below the age of 5 years, in an attempt to try to modify the natural course of the allergic disease. However, at present this is speculation and definitive trials are required ([28, 29](#)).

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## Appendix I

Example of dosing guidelines:

### *Dose guidelines subcutaneous immunotherapy induction phase*

Omit injection in case of	(a) infection in airways or other disease during the last 3 days
	(b) deterioration of allergic symptoms or increased needs for drugs during the last 3 days
	(c) peak flow <80% of individual best value
Terminate treatment session	(a) local immediate reaction >5 cm
	(b) systemic reaction
Injection interval	2 weeks → dose escalation according to schedule
	2-4 weeks → repeat preceding dosing
	4-6 weeks → dose reduction 1 step
	6-8 weeks → dose reduction 2 steps
	≥8 weeks → treatment reinstated
Local immediate reaction at preceding injection (30 min)	<5 cm → dose escalation according to schedule
	5-8 cm → repeat preceding dosing
	>8 cm → dose reduction 1 step
Local delayed reaction at preceding injection (1st day)	repeat preceding dose if the reaction has been inconvenient for the patient
Mild systemic reaction at preceding	dose reduction 1-2 steps

injection (mild urticaria, rhinitis, asthma)	
Severe systemic reaction	Conferring on continuous treatment
<i>Dose guidelines maintenance treatment</i>	
Definition of maintenance dose	(a) the optimal dose defined from clinical studies
	(b) the individual optimal dose (based on patient response)
Intervals between injections at shift to maintenance treatment	2 weeks (max. 3 weeks) →→
	4 weeks (max. 5 weeks) →→
	8 weeks (max.10 weeks) maintenance treatment
<i>Dose modifications maintenance treatment</i>	
Omit injection in case of	(a) infection in airways or other disease during the last 3 days
	(b) deteriorations of allergic symptoms or increased need for drugs during the last 3 days
	(c) peak flow <80% of normal value
Injection intervals in maintenance treatment	≤10 weeks →→ unchanged dosing
	10–12 weeks →→ dose reduction 20%
	12–16 weeks →→ - " - 40%
	≥16 weeks →→ treatment reinstated
Local immediate reaction at preceding injection (30 min)	<8 cm →→ unchanged dosing
	>8 cm →→ dose reduction 20%
Local delayed reaction at preceding injection (1st day)	Dose reduction 20% if the reaction has been inconvenient for the patient
Mild systemic reaction	Dose reduction 20–40%
Severe systemic reaction	Conferring on continuous treatment
Dose increases after reduction of maintenance dose	≤20% →→ full dose after 4 weeks and then after 8 weeks
	>20% →→ weekly inj. to maintenance, then 2–4–8 weeks

## Appendix II

Example:

### *Treatment of side effects in adult patients*

Large local reaction (>12 cm after 30 min)	Antihistamine orally
	Observe for minimum 60 min
Rhinitis	Antihistamine orally
	Observe for minimum 60 min and repeat peak flow
Mild urticaria	Antihistamine orally
	Observe for minimum 60 min

Asthma	$\beta$ -2 agonist inhalation
	$\beta$ -2-agonist i.v./s.c.
	Oxygen
	Corticosteroids (Prednisolone 50 mg or Methylprednisolone 40 mg i.v.)
	Consider hospitalization
Systemic reactions	Adrenaline (1 mg/ml) 0.3–0.5 mg deeply i.m.
<i>Generalized urticaria, angioedema</i>	i.v. line (saline)
	Check blood pressure and pulse rates
	Antihistamine clemastine (1 mg/ml) 1–2 ml (1–2 mg) i.m.
	Corticosteroids (prednisolone 50 mg or methylprednisolone 40 mg i.v.)
	Consider hospitalization
Anaphylactic shock	Adrenaline (1 mg/ml) 0.5–0.8 mg deeply i.m.or (diluted 0.1 mg/ml) 0.3–0.5 mg i.v. (slowly in fractionated doses) may be repeated after 10–20 min
	i.v. line (saline)
	Place patient in supine position
	Oxygen 5–10 l/min
	Check blood pressure, pulse rate, and oxygen saturation
	Antihistamine Clemastine (1 mg/ml) 1–2 ml (1–2 mg) i.v.
	Methylprednisolone 80 mg i.v.
	Hospitalization necessary because of the risk of delayed shock
Doses for children	Adrenaline (1 mg/ml) 0.01 mg/kg (0.01 ml/kg) i.m. If needed (diluted 0.1 mg/ml) i.v.
	Antihistamine Clemastine (1 mg/ml) 0.0125–0.025 mg/kg i.m.
	Corticosteroid Methylprednisolone 2 mg/kg i.v.