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# Guidelines for practice of Allergen Immunotherapy in India

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**Abstract**

**The guidelines for practice of immunotherapy (IT) in India have been prepared consulting the literature and inputs from experts belonging to Indian College of Allergy, Asthma and Applied Immunology and other organizations. Most of the studies/clinical trials suggest significant improvement in allergic asthma and rhinitis or rhino-conjunctivitis patients post IT (1-5 years) than baseline or placebo. However, IT should be practiced by trained allergy physicians in properly selected cases with appropriate vaccines. Also the benefit to risk ratio should be assessed prior to start or during the course of immunotherapy in individual patient.**

**Key words:** Allergen immunotherapy, Allergic asthma, Rhino- conjunctivitis, Allergic rhinitis, Guidelines

## INTRODUCTION

Allergen specific immunotherapy is a method of treatment for IgE mediated allergic diseases to control the symptoms and decrease the sensitivity toward allergen(s) by giving sequentially increasing dose of antigen(s) inducing a shift of the immunological response from TH2 to TH1. Allergen immunotherapy has several names like desensitization, hyposensitization, allergy vaccine etc. Guidelines for immunotherapy are available in western/ developed countries, but a separate Guideline focusing on India is necessitated due to, (1) variations in the soil characteristics and the environment of India from western world, (2) difference in the type of allergens, as in India outdoor allergens are more common than indoor allergens, which are more common in western countries, (3) keeping pets is not very common in India but cattle are commonly inhabitated in the residential campus in villages, (4) having various types of food items, and thus exposure to many possible allergens, (5) most of Indian population is agro-based, (6) and the financial capability may be limited with respect to costly investigations, like specific IgE.

Following the International regulations, which are also relevant for India, the practice of allergy skin testing and immunotherapy should be **allowed only to those Physicians who have obtained specialized training in Allergy and Immunotherapy, and to be practiced at a place where facilities of managing anaphylaxis are available.**

## TRAINING OF PHYSICIANS IN ALLERGY AND IMMUNOTHERAPY

1) The physicians ( belonging to Internal Medicine/ Respiratory Medicine/Pulmonary Medicine/Chest

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Diseases/Pediatrics) (MD/DNB/ DTCD) or ENT Surgeons (MS/DLO) are relevant and to be trained in Allergy and Immunotherapy.

2) Training is provided at places identified by the ICAAAI (Indian College of Allergy, Asthma and Applied Immunology). This training is provided by V.P. Chest Institute, Delhi since the last several years.

3) Training comprises didactic lectures/ practical demonstrations on various aspects of respiratory allergy diagnosis and management including pharmacotherapy, immunotherapy as well as management of anaphylaxis.

4) Practising allergist is required to have knowledge of the flora and fauna of the area. He may take the help of pollen calendar or the relevant published literature on aeroallergens.

## SELECTION OF ALLERGEN

The local flora / airborne pollens changes approximately every 200 km distance in India. The soil conditions along with environment of the place affect the protein content as well as the antigenicity of the allergens. The urban and rural set up as well as the coastal or hilly climate affects the type or antigenicity of the atmospheric pollens in our country. Hence, it is essential to select the antigens for testing in patient based on the above points and confirming the history of exposure. Besides, it is important to have the knowledge about the geographic habitat, occupation/residence of the patient and also the precipitating factors for his/her allergic symptoms.

A document on aeroallergens (pollens) in different part of the country has been published[1]and can be consulted to frame the testing kit for patients residing in respective area. Physicians/Allergologists are also required to consult local aerobiological studies [2-9] published in relevant journals for the prevalence of airborne pollens, fungi, insects and mite allergens. They can consult the researchers at their nearest botany, plant pathology and entomology departments or attend training courses in identification of allergens. Approximately 40-45 pollen and 15-20 fungi and insect allergens are included in Indian allergen manufacturer's list that are mostly common throughout the country. Two house dust mite species namely *Dermatophagoides pteronyssinus* and *D. ferinae* are predominant in regions with high humidity, especially in coastal areas. In some patients, new antigens for testing may be required decided on individual basis after surveying patient's environment.

## QUALITY CONTROL OF ALLERGEN EXTRACTS

Several allergen vaccines (extracts) are available commercially in the country, standardized using certain parameters. It is recommended that allergen manufacturers should supply vaccines tested for consistency relative to an in-house reference standard. There has been significant progress in allergen standardization in recent years, and a large number of standardized allergen extracts are marketed in US.

In recent years, a lot of knowledge has been generated in India on characterization of major/ minor allergen of pollen, fungi, food and insect sources[9-17]. However, the purified proteins (major allergens) and monoclonal/polyclonal antibodies are not available for characterization based on major allergen content. Under these circumstances, allergen extracts are standardized based on weight/volume and protein estimation by modified Lowry's, bicinchoninic acid assay or microkjeldahl method[18]. Researches have shown that allergen source material processed by freeze drying gives better quality extracts[12-14]. The pollen contents in the samples/raw materials should be >90% for grasses/weeds and >95% in case of trees.

Most of the allergenic proteins (>80%) comes in the solution within first few minutes of extraction. Recent studies have shown that 4-8 hours extraction in phosphate buffer saline (pH 7.4) or ammonium bicarbonate (pH 8.0) yields extracts with optimum allergenic potency[13-15]. The extraction buffer should contain phenyl methyl sulphonyl floride and EDTA as protease inhibitors.

Fifty percent glycerol is a good stabilizer of proteins in skin prick test solutions. However, same concentration can not be used for therapeutic extracts and the lower concentrations are not effective[19]. Recently sucrose or epsilon-amino caproic acid (EACA) has been used successfully for stabilizing

grass pollen[14] and cockroach extracts[19]. Cool gel packs or cold chain should be used/developed for transporting the extracts throughout the country.

Allergen extract(s) vary from one manufacturer to another, hence it is suggested that diagnostic and therapeutic allergen extracts should be procured from the same allergen manufacturer.

Drug controller of India / state unit(s) regulates the allergen manufacture in the country. Currently the emphasis is on good manufacture practice (GMP) to be implemented in these drug antigen units. However, the coordinated efforts of experts from Indian College of Allergy, Asthma and Applied Immunology, Antigen Units and Drug regulatory Authorities are required to upgrade the quality control of allergen extracts following standard WHO/IUIS protocols. In fact there is need to develop allergen certification centre in the country like Food and Drug Administration (FDA) and Centre for Biologics Evaluation and Research, (CBER) USA.

The methods for antigen preparation and quality control of extracts/vaccine are summarized below for reference:

1) Allergy units recommended for defining potency of extracts vary across different countries. Hence at present w/v (weight/volume), protein estimation (PNU in µg/ml) and SDS-PAGE protein profile should be followed for maintaining the quality of antigen in different batches.
2) Source material for antigen extraction should be freeze dried, fungal culture (extracts) of 10-20 days be taken and phosphate buffered saline (PBS) of 0.1 M, pH 7.2 has been found most suitable for antigen extraction.
3) For stability of aqueous extracts, addition of sucrose or EACA is recommended.[19]
4) Allergen extracts should be free of contaminants including of aflatoxins and endotoxins.
5) Sterility test is required for each batch of antigen extracts.
6) Storage of antigen-
    a) The allergen extracts/ vaccines should be stored at 4-8$^{o}$C, in a refrigerator.
    b) In case of withdrawl of more antigen from the vaccine vial, it should not be injected back in vial to avoid contamination.
    c) In case of electricity failure for more than 2 hours, keep vaccine in a ice box or any other cooling device/pack.
    d) Transportation of antigen should be done using a cooling device.

## SELECTION OF PATIENTS

The success of immunotherapy (IT) depends on proper selection of patients, allergens, doses, quality of allergens, and compliance to the treatment. Immunotherapy results may reflect failure, if done by a untrained person, in a very young (<5 years) or elderly persons (>65 years). Unnecessary testing, wrong prescription of IT and taking advantage of psychology of patient can lead to adverse reputation in Immunotherapy practice.

Immunotherapy has proved useful in patients with IgE mediated diseases like allergic rhinitis, asthma, and insect sting hypersensitivity. Immunotherapy should be considered in patient who had history of systemic anaphylaxis reaction after an insect sting and have documented IgE sensitivity to specific venom, and there is a likelihood of future exposure to the insect. IT can be life saving in such cases with appropriate antigen.

Patients of allergic rhinitis, and asthma, with history of symptoms after natural exposure to the allergen and demonstrated specific IgE antibodies against the offending allergens. The allergy is assessed by clinical history, skin tests and RAST or ELISA. Immunotherapy is primarily useful in patients between 12 years to 45 years age group, with severe symptoms interfering with their routine work or school performance, causing sleep disturbances, and quality of life. Patients who failed to avoid allergen exposure in spite of all efforts or had no response to allergen avoidance, had poor response to drugs or tired of taking drugs or developed adverse reactions to medicines are most suitable candidates for immunotherapy.

The patients selected must assure long term compliance for the therapy and should not have contra-

indications for IT, like malignancy, coronary artery disease, recent myocardial infarction or arrhythmia, severe psychological disorder, compromised lung functions etc.

The patients taking beta blockers or having history of severe reactions to previous IT, should not be considered for immunotherapy.

## DIAGNOSTIC TESTS FOR DETECTING SENSITIZING ALLERGEN(S)

For immunotherapy of patients with IgE mediated respiratory allergic disorders, identification of specific causative allergens is of paramount importance. The following *in vivo* and *in vitro* diagnostic tests are recommended[20-22] and commonly used:

*In vivo tests*

(i) Skin tests (Intradermal, Prick, Scratch tests)[23-25]

(ii) Mucosal challenge tests (Bronchial[26] and Nasal[27] challenge, Double blind placebo controlled food challenge[15])

*In vitro tests*

(I) For quantification of total serum IgE/ allergen-specific IgE levels

  i) Radio allergosorbent test (RAST)[28,29] and Enzyme linked allergosorbent test (EAST)

  ii) Radio- and Enzyme immunoassays[22]

  ii) Multi-allergen screening assays

*In vivo tests*

Skin tests with inhalant allergens are simple and effective method for identification of causative allergens. Intradermal and prick tests vary in sensitivity and specificity, which depends on multiple factors like criteria of grading, concentration and quality of allergen solution. For grading the cutaneous response, size of wheal (weal) and/or erythema is taken into consideration. Skin tests are graded as negative, and 1+ to 4+ depending on the diameter/area of allergen induced wheal and/or erythema as compared to the reaction induced by negative or positive controls (buffered saline and histamine)[20,21,23]. However, in Indian patients only wheal diameter is measured, because erythema is not always intense or visible to form an important parameter[25,] mainly due to dark skin colour.

In western countries, allergen extract solutions for intradermal tests have been recommended to be 100-fold or 1000-fold dilution of the concentration used for prick test. However, in India 25 to 50 fold dilution of the concentration used for prick tests (1:10/1:20 w/v) i.e. 1:500 w/v has been found suitable for intradermal tests[23,25].

A positive control (Histamine diphosphate) is always used to ensure i) that the patient is suitable for performance of skin tests and ii) is not taking any medication(s) which may suppress the cutaneous response to injected allergen extracts. In United States, the recommended concentration of histamine base for prick and intradermal tests is 1 mg/ml and 10 µg/ml, respectively (2.7 mg/ml and 27 µg/ml of histamine phosphate equivalent to 5.43 mmol/L and 0.0543 mmol/L)[24]. However, in Indian patients these concentrations were found to be inadequate for inducing proper skin response. **The histamine base concentrations of 5 mg/ml and 100 µg/ml were found suitable for prick and intradermal tests, respectively.** This variation in skin reactivity to histamine may be due to the fact that Indian population has been exposed to tropical sun for centuries[25].

Similarly, test with the diluent used to prepare/ preserve the allergen extracts is also performed as negative control to rule out the possibility of getting false positive skin response due to dermographism or traumatic reactivity induced by skin test device. The position papers on skin tests by European Academy of Allergy and Clinical Immunology and US Joint Council of Allergy, Asthma and Immunology state that, properly performed, prick test is a most convenient for better clinical correlation and is a least expensive in vivo diagnostic test[24].

Mucosal challenge tests with allergen extracts, both, bronchial challenge and nasal provocation tests, are of limited clinical value[26,27]. These tests are mostly used for research purposes as they do not give any significant clinical information, in addition to that provided by properly taken clinical history and carefully performed and graded skin tests. The methods are summarized below for reference:

1) There are various methods mentioned in literature for allergy testing in *vivo*, e.g. conjunctival test, Prausnitz Kutsner test, Intradermal test, prick test, patch test, and provocation test. The first two tests are not recommended/preferred now due to risk involved.

2) Provocation tests with allergen are recommended only at the Institution level and are mainly done for research purposes.

3) Intradermal or prick tests are followed commonly for allergy diagnosis with allergen extracts.

4) Long acting antihistamines like cetrizine, and loratadine are discontinued for 4 weeks prior to skin test. Short acting antihistamines are discontinued for 72 hours. Bronchodilators, adrenaline and steroids do not affect the sensitivity of skin test with allergen extract, hence a gap of 12 hours is sufficient.

5) Patient having skin diseases like eczema, leukoderma, dermographism, severe dermatitis and any other chronic skin disease is not fit for skin testing and in case of fever, the test is postponed till patient becomes normal.

6) Antigens are administered in the volar aspect of the arm or on the back of the patient with a distance of 5 cm (Intrademal) or 3 cm (Prick) in between the two tests.

7) Grading of skin reaction is done after 15-20 minutes in comparison with negative control (Phosphate buffer saline) and positive control (Histamine diphosphate).

8) In **Intradermal test,** antigens are injected intradermaly in 1:500 w/v dilution and in **Prick test,** the antigens are tested in 1:10 or 1:20 w/v dilution.

9) Skin test reaction equal or larger than positive control is considered as markedly positive reaction (significant) for that antigen.

10) Physician should be available at the time of skin testing to take care of any adverse reaction.

11) In case of high sensitivity (history), skin tests are performed with diluted antigen extracts.

12) In case of doubtful reaction, a repeat skin test is performed to confirm the reaction.

13) Skin testing for food items is not recommended until it is suspected of producing anaphylaxis or having a strong history. Rather a diet provocation test is more definite for the diagnosis of food allergy.

13) For grading of allergic reaction (skin tests), the criteria given in Table 1 or 2 can be followed[23,25].

**Table 1.** Grading for Intradermal test[30]:

| | | |
|---|---|---|
| < 6 mm | = | Negative (phosphate buffer saline = PBS) = Negative control (C) |
| 2 x C | = | 1 + |
| 3 x C | = | 2 + = Positive control (Histamine) |
| 4 x C | = | 3 +, with 1-2 pseudopodia |
| >4 x C | = | 4 +, with >2 pseudopodia |

**Table 2.** Grading for Prick test[23,29]

| | | |
|---|---|---|
| 0 mm | = | Negative (phosphate buffer saline = PBS) = Negative control (C) |
| <3 mm | = | 1+ |
| 3-5 mm | = | 2+ = Positive control (Histamine) |
| <5-7 mm | = | 3 + |
| <7-9 mm | = | 4 + |

*In vitro tests*

Most commonly used in vitro diagnostic tests[29] for estimation of total IgE and allergen specific IgE levels in the sera of allergic patients are radio / enzyme immunoassays. The basic principle remains the same in which a solid phase allergen/ antibody binds with primary antibody which is further detected using a radio / enzyme labeled secondary antibody. The binding signal is converted to a quantitative measurement of concentration using a standard curve in which one reactant is added in known amounts.

To establish atopic status of the patient, total serum IgE levels are measured.[22] However, the measurement

of total serum IgE levels has limited value because raised IgE levels are also found in some non atopic individuals and in patients suffering with various non allergic diseases[29].

Measurement of allergen specific IgE levels gives reliable information about patients' clinical sensitivity to various aeroallergens. For this purpose, kits based on immunoenzymetric techniques commercially available can be used. Multiallergen screens are useful to support a more extensive clinical and immunologic investigation for allergic diseases[29].

Quality assurance is very important for all these in vitro diagnostic tests. In USA, external proficiency surveys are conducted in selected laboratories for checking uniformity of results using reference samples. In India, there is an urgent need to conduct such surveys to establish indigenous quality control standards for measurement of allergen specific IgE levels. Use of imported kits for this purpose may have limited significance, since profiles of allergenic proteins of the extracts of a given pollen collected from different places varies quantitatively as well as qualitatively. Also most of such kits do not contain pollens (solid phase) relevant to patient's exposure in India. Thus, generation of indigenous test reagents is the first and foremost requirement.

## TYPES OF IMMUNOTHERAPY

*Rush Immunotherapy*

The advantage of rush schedule is that patients can attain the maintenance dose more quickly. Schedule for rush Immunotherapy entail administering multiple injection in a row preferably in a hospital set up. Schedules using eight injections over 3 days or 8 injections in a single day have been published[31]. But these protocols need further investigation in terms of risk and benefit ratio to patient.

*Subcutaneous Perennial Immunotherapy*

In most of the cases, immunotherapy is started with 1:5000 w/v diluted antigen and the injections are given two times a week starting from and increased by 0.1 ml in every injections. The injections are given subcutaneously or intradermally with graduated syringe or insulin syringe. The idea is to achieve the highest maintenance dose i.e. 1:50 – one time a month, 1.0 ml. usually the maintenance dose is between 0.5ml to 1.0 ml of 1:50 dilution.

In cases showing high skin sensitivity with local/ systemic reaction after initiation (1;5000 w/v) of immunotherapy, IT is rescheduled/started with higher dilution i.e. 1: 50000 w/v or even higher dilution and the first injection is administred in the hospital/clinic having facilities to manage anaphylaxis.

*Cluster Immunotherapy*

The starting dose is similar to those of perennial immunotherapy regimen. Here weekly visits are necessary, because, at each visit more than one injection is given at a small interval between injections, varying from 30 minutes to 2 hours. After the maintenance dose is reached in approximately 2 months, interval between visits is increased. The cluster regimen is advantageous to the patients who reside at a significant distance from the physician. There are similar efficacy and immunological changes in Cluster regimen as observed with the perennial IT in various studies. [32] However, the initial doses are required to be given in a hospital set up able to manage emergencies associated with this form of therapy.

*Bronchial Immunotherapy*

Only two clinical trials have been carried out using this route of administration [33,34]. The results obtained were unimpressive in terms of efficacy and the bronchospasm was induced in many of the patients treated. Therefore, this route of administration has been abandoned in view of an unfavorable risk–benefit ratio.

*Oral Immunotherapy*

Although a greater number of clinical trials with a suitable design[35] have been carried out using this route of administration, few of them achieved an acceptable level of clinical efficacy[36,37]. In some trials[38,39], the effect was no better than that of placebo. Furthermore, adverse events including abdominal pain, vomiting and diarrhoea were recorded in some studies[39,40]. Present results do not support the oral route as an effective alternative.

*Nasal Immunotherapy*

Twenty-two studies of intranasal administered immunotherapy have been evaluated [41]. Sixteen used a double-blind, placebo-controlled design. Most of these trials demonstrated significant clinical efficacy in allergic rhinitis. The results are encouraging, but nasal immunotherapy seems to be a treatment for allergic rhinitis only. Some studies also reported local adverse effects[42,43]. The only study addressing long-term efficacy demonstrated no sustained effect following discontinuation of the treatment[44]. There is no data on the possible preventive capacity. The category of evidence for clinical efficacy of nasal IT is Ib.

## SUBLINGUAL-SWALLOW IMMUNOTHERAPY (SLIT)

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 swallow immunotherapy has spread widely in some countries in Europe. The category of evidence for clinical efficacy is Ia for rhinitis and Ib for asthma.

However, further studies are needed to define the most appropriate dosage, the efficacy in pediatric patients, and to evaluate the magnitude of efficacy compared to other available treatments[45-48].

## MECHANISM OF IMMUNOTHERAPY

Initially it was presumed that by giving low doses of same antigen, the immune system produces IgG antibodies (Blocking antibodies) instead of IgE antibodies and thus consumes the antigens, resulting in less number of IgE molecules available to produce allergic reaction. However, the changes in clinical parameters post IT did not always correlate with the changes in IgG or IgE levels. There is now strong evidence that immunotherapy produces a shift of TH2 response towards TH1 and down regulates IL-4. This brings about the reduction in release of inflammatory mediators, specific IgE levels, allergen specific airway hyper-responsiveness apart from producing clinical improvement. There is an increase in specific IgG levels after immunotherapy. But initial increase in IgG4 level after immunotherapy indicates poor prognosis but that of IgG1 means a better prognosis. Specific immunotherapy (SIT) induces a decrease in IL-4 and IL-5 production by CD4+ TH2 cells and a shift towards increased IFN-γ production by TH1 cells. Activation of TH1 subset is associated with the development of cell mediated immunity, essential for protective immune response against the development of allergy/asthma. IT acts by modifying TH4+ T cell responses either by immune deviation, T cell anergy or both. Further, a subtype of T cells with immunosuppressive function and cytokines profiles distinct from their TH1 and TH2 cells, termed regulation/suppressor T cell have been described. T regulatory cells producing IL-10 and possibly TGF-β, CD4+ CD25+ T cells (possibly TGF-β) and TH3 cells (also TGF-β) play a major role in the inhibition of allergic disorders.

## STANDARD PRESCRIPTION (PROTOCOL) FOR PERENNIAL SUBCUTANEOUS IMMUNOTHERAPY

1) The antigens are decided after correlating with history, evidence of exposure, precipitation of symptoms after exposure and skin test positivity. If possible RAST / ELISA correlation can be done for specific IgE.
2) In cases of rhinitis and sinusitis, it is important to exclude mechanical causes like gross DNS.
3) The antigens should be presents in the patient environment e.g. a person skin test positive to ragweed staying in India, does not require Immunotherapy with ragweed, (because it is present mainly in USA).
4) Number of antigens in an IT prescription should no exceed 4-5. As per WHO criterion upto 4 antigen are permitted in IT vaccines.
5) Amount of individual antigen should be decided depending upon their skin test positivity. More is the positivity, more is the amount of that antigen to be included in vaccine.
6) Antigens of same group show cross positivity, hence the most potent and relevant antigen should be selected from the group.
7) Antigens mixing in vaccines should be done with precaution as certain antigens have proteolytic enzymes and thus reduce the potency of other

antigen. Hence it is recommended not to mix house dust mite or fungal antigens with any other antigen and prescribe these in separate vials.

8) Immunotherapy injections should be prescribed ONLY BY TRAINED PHYSICIAN and administred in his presence in a place having facility of managing anaphylaxis.

9) Immunotherapy is started usually with 1:5000 w/v diluted antigen and the injections are given two times a week starting from 0.1 ml and increased in every injection by 0.1 ml. The injections are given subcutaneously or intradermally with graduated syringe or insulin syringe. The further schedule is as follows:

1:5000 – Two times a week, from 0.1 ml to 0.9 ml

1:500 – Two times a week, from 0.1 ml to 0.9 ml

1:50 – one time a week, from 0.1 ml to 0.5 ml

1:50 – one time in 2 weeks, 0.6 ml

1:50 – one time in 3 weeks, 0.7 ml

1:50 – one time a month, 0.8 ml

1:50 – one time a month, 0.9 ml

1:50 – one time a month, 1.0 ml – Highest maintenance dose

In cases showing high skin sensitivity or IT with single antigen showing local/systemic reaction at initiation of immunotherapy, higher dilution i.e. 1: 50000 w/v can be selected and the first injection should be given in the hospital/clinic.

10) Usually the maintenance dose is between 0.5ml to 1.0 ml of 1:50 dilution in different patients.

11) The duration of immunotherapy is usually 5 years but in India, where it is not possible to avoid the presence of antigens (mostly pollens, dusts, and insects), the decision has to be individualized.

12) Immunotherapy will not be effective when response is not there even upto 1:50 w/v, 0.8 ml dose, once a month, hence it should be discontinued or the case should be reassessed.

13) Response of immunotherapy starts very slowly and usually takes more than 6 months. Hence, a relief within 3-6 months of initiation of immunotherapy is mainly psychological.

14) In case of default – upto 1 month – no change in schedule; 1-2 months – continue with last lower dose; 2-4 months – continue with last dilution and >4 months – re assess the case a fresh.

15) Antigen for skin testing and for immunotherapy should be procured from the same manufacturer, to avoid difference in potency of the allergen. The difference in potency of extracts among different manufacturers has been reported world over.

## EFFICACY AND SAFETY

*Subcutaneous Immunotherapy (SCIT)*

The clinical manifestations of allergy to inhalant allergens include rhinitis, conjunctivitis, and asthma. The parameters that indicate clinical efficacy of a treatment are reduction in symptoms and/or drug intake of a magnitude that significantly reduces morbidity[49]. The clinical efficacy of subcutaneous immunotherapy has been validated by 75 double-blind, placebo-controlled studies from 1980 to 2005 which demonstrate clinically relevant decreases in symptom-medication scores. Fifteen of the 75 studies included children also.

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, *Dermatophagoides pteronyssinus*, *Alternaria* and *Cladosporium*.

Fundamental questions on immunotherapy are (1) whether it has potential to provide long-term benefit following its discontinuation and, (2) whether it can prevent either disease progression or the onset of new allergic sensitivities[50]. 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[51]. Previous studies on IT indicate that the treatment may have a long-lasting effect. A controlled study by Durham *et al*.[52] has documented the long-term efficacy of immunotherapy after withdrawal of the treatment following a double-blind, placebo-controlled trial[53]. The category of evidence for long-term efficacy and preventive

capacity of IT 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[35,49,51]. 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 injection regimen. Evidence suggests that the patients most likely to develop anaphylaxis are those who are highly sensitive as determined by skin tests or specific IgE-tests and patients with more severe disease, in particular with chronic and uncontrolled asthma[54]. Systemic side-effects occur more frequently in patients during the induction (up-dosing) phase of treatment compared to maintenance therapy[55,56].

## VENOM IMMUNOTHERAPY

The efficacy of venom immunotherapy has been analyzed in three controlled[57-59] and several prospective uncontrolled studies which employed a usual maintenance dose of 100 μg of venom. In these studies, patients were monitored with sting provocation tests during immunotherapy[60]. In all controlled trials with vespid, honey bee or ant venom allergy, comparing venom with either whole-body extract or placebo, a highly significant difference was observed in favour of venom IT. Here, 75–100% of venom-treated patients tolerated re-sting without any 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, only 0–9% of vespid allergic and around 20% of bee venom allergic patients reacted to the challenge with the respective insect. These studies suggest the superior efficacy for immunotherapy with vespid or ant venom compared to honey bee venom. The patients who reacted following a course of venom immunotherapy, had mild symptoms than those observed before the treatment. The category of evidence for efficacy of venom IT is 'Ib'.

The safety of venom immunotherapy is related to the nature of the venom used and the protocol. More side effects were observed during IT with honey bee venom than vespid venom[61]. In an EAACI multi-centre study[62] of 840 patients totalling 26601 injections, 20% of patients developed 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 μg in rush protocols may increase the risk of side effects.

## PREVENTIVE AND DISEASE MODIFYING CAPACITY

The capacity of subcutaneous immunotherapy to prevent the development of new sensitizations has been investigated in three nonrandomized studies in mono-sensitized patients[63-65]. In an open retrospective study, Purello-D'Ambrosio[64] made a follow-up of 7182 mono-sensitized (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.[65] followed 75 subcutaneous immunotherapy-treated children mono-sensitized to house dust mites and 63 comparable controls treated pharmacologically for 6 years. In the immunotherapy group, 74% continued to be mono-sensitized *vs* 33% in the control group. Although these studies are of interest, prospective randomized, controlled studies are needed. In India, a double blind placebo controlled study showed significant improvement in clinico-immunologic parameters in asthma and rhinitis patients after 1 year of immunotherapy with whole body mosquito extract[66]. A placebo controlled study demonstrated early relapse of symptoms after discontinuation of treatment in patients receiving pharmacotherapy, whereas it was 3-5 years in immunotherapy group patients[67].

Subcutaneous immunotherapy might prevent the progression of rhinitis into asthma. A multi-centre pediatric study investigated the capacity of immunotherapy in children with allergic rhinitis to down-regulate the development of asthma[68]. 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 in 24% children in immunotherapy group *vs* 44% in the drug-treated group, indicating high risk of developing asthmatic symptoms in allergic rhinitis children is diminished by immunotherapy. Bronchial hyper-responsiveness to methacholine decreased significantly in immunotherapy-treated children, but only 2 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.

## DURATION OF IMMUNOTHERAPY

Allergen immunotherapy is generally administered for 3-5 years and duration of immunotherapy and decision to discontinue immunotherapy must be individualized. Some patients may require longer periods of treatment to maintain relief of their allergic symptoms. It is difficult to predict, that how long patients will experience symptomatic relief following discontinuation of immunotherapy. The experts advocate repeat skin tests for evaluating the benefit or decision to stop the allergy shots. However, IT should not be empirically discontinued after a prescribed period (3-5 years) of time. Studies have shown that allergen immunotherapy inhibits allergen-driven TH2 response, so the cytokines typical for TH1 Vs TH2 responses could be used as markers to judge the response of allergen immunotherapy. The immunological markers such as Treg. cells with increase in IL-10 (Interleukin-10) and IgG4 blocking antibody) correlate well with reduction in immediate skin test response and decrease in LPR (Late phase response), which may be used to assess the response of specific immunotherapy and to decide when to stop immunotherapy[69].

## IMMUNOTHERAPY TRIALS INCLUDING COCHRANE DATABASE ANALYSIS

*As per WHO and AAAAI Recommendations[53]*

At present Allergen avoidance and IT are the only treatment that modifies the course of an allergic disease either by preventing the development of new sensitivity or by altering the natural history of disease or disease progression.

*Bronchial asthma*

Allergen immunotherapy (SCIT or SLIT) - is effective for treatment of stinging insect hypersensitivity, allergic rhinitis, allergic conjunctivitis and allergic asthma. Many double blind placebo controlled trials are available demonstrating improvement in one or more clinico-immunologic parameters such as symptoms, lung function, nonspecific airway reactivity and other relevant serological tests in rhinitis[70-72], asthma[73-77] and stinging insect hypersensitivity[78,79]. It has been found effective both in adults and children[80,81]. A meta analysis of 75 immunotherapy trials concluded that there is a significant reduction in asthma symptoms and drug requirement as well as in bronchial hyper-reactivity with immunotherapy[75]. Allergen immuno-therapy has been found to maintain a persistent improvement after discontinuation of immunotherapy[52,82-84] and also reduces the risk of future development of asthma in rhinitis cases[52,69,83-87]. Successful IT prevents development of new allergen sensitivities in mono-sensitized individuals[63-65].

Seventy-five trials were included (52 of 54 previous trials and 23 new trials) with a total of 3,506 participants (3,188 with asthma) for data analysis[75]. There were 36 trials of immunotherapy for house dust mite allergy, 20 pollen allergy, 10 animal dander allergy, 2 *Cladosporium* mold allergy, 1 latex and 6 for multiple allergens. Concealment of allocation was assessed as clearly adequate in only 15 of these trials. Significant heterogeneity was present in a number of comparisons. Overall, there was a significant reduction in asthma symptoms and medication and improvement in bronchial hyper-reactivity following immun-otherapy. Also a significant improvement was there in asthma symptom scores (standardized mean difference -0.72, 95% confidence interval -0.99 to -0.33) and it would have been necessary to treat 4 (95% CI 3 to 5) patients with immunotherapy to avoid one deterioration in increased medication. Allergen immunotherapy significantly reduced allergen specific

bronchial hyper-reactivity, with some reduction in non-specific bronchial hyper-reactivity as well. However, there was no consistent effect on lung function.

*Allergic rhinitis*

Allergen immunotherapy alters allergic disease through a series of injections of clinically relevant allergens and has been recognized as the only therapeutic option known to alter the natural history of allergic rhinitis[88]. According to the American Academy of Allergy, Asthma and Immunology (AAAAI)[89], allergen immunotherapy is successful in 90% of patients with seasonal allergic rhinitis and in 80% of patients suffering with perennial allergic rhinitis. Hence, **subcutaneous allergen immunotherapy** was approved for management of allergic rhinitis and / or allergic asthma. However, immunotherapy is currently indicated as a supplement to allergen avoidance and to pharmacotherapy[90]. Its efficacy in prevention of the allergic march and the development of asthma among patients with allergic rhinitis has been demonstrated[70]. Data were extracted from 16 studies showing clinical effectiveness of subcutaneous immunotherapy (SCIT) in the treatment of allergic rhinitis, involving 759 patients (546 adults, 53 children, 160 all ages). In 15 (94%) of the studies, SCIT led to significant improvement in both symptoms and medication scores[69]. Its efficacy has been validated in many trials, using grass, ragweed, and birch pollen extracts[50]. Importantly, SCIT has been shown effective even in patients with severe seasonal rhinitis that is resistant to conventional drug therapy. There was a highly significant decrease versus median placebo (95% confidence interval for difference between medians) in total symptom scores (p=0.001), total drug use (p=0.002) and visual analogue symptom scores (p=0.02), 2.2 v 5.5 [-4.8 to -0.5]. Provocation tests after allergen IT showed a greater than 10-fold reduction in immediate conjunctival allergen sensitivity (p=0.001), a 40% decrease in early phase response (p=0.02), and a 57% decrease in the late phase (p=0.001) cutaneous response after intradermal allergen challenge[53].

A recent Cochrane review,[91] on the meta-analysis of 51 randomized double blind placebo controlled trials involving 2871 subjects with seasonal allergic rhinitis or controls has shown that immunotherapy results in significant improvement in overall symptoms, medication use and quality of life. The benefits of SIT for perennial rhinitis are less than for seasonal rhinitis. In part, this reflects the difficulty in determining the extent to which allergy is responsible for perennial symptoms. Nevertheless, clinical trials have shown a definite benefit in appropriately selected subjects[92]. Clearer evidence has been obtained in perennial rhinitis due to pet allergy. Several studies have shown a marked improvement in tolerance of cat exposure after SIT, validated both on challenge tests and simulated natural exposure[93].

*IT studies (SCIT) in India*

A limited number of studies are available on allergen immunotherapy from our country[66,67,94-96]. Immunotherapy for 1 year in cases of asthma and/or rhinitis has demonstrated >50% improvement in clinical parameters (symptoms)[94]. A placebo-controlled study[95] on IT for 6-12 months with *Cocos nucifera* pollen extract showed significant clinical improvement (symptom-medication score), reduction in IgE and elevation of specific IgG in post-therapeutic patients' sera than placebo. An open comparative study[67] of immunotherapy vs budesonide inhalation, has reported almost equal improvement in asthma patients in both the groups. But the decline in benefit was rapid in drug treatment group than IT after cessation of treatment. A recent double blind placebo controlled study[66] on IT with mosquito extract in asthma and allergic rhinitis patients has demonstrated significant clinical improvement, supported with changes in airway reactivity and immunologic parameters (IgE, IgG1, IgG4 and IFN-γ) from the baseline and placebo. Further, IT with two to three mix extracts[96] from the same allergen group is effective for insect hypersensitivity. All these studies show substantial evidence in favor of allergen IT, however more studies are required involving long term clinical trials from the country.

***Studies on Sublingual Immunotherapy****:* A meta-analysis published by the Cochrane Library[97] on 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, likely due to the use of several alternative scoring systems in different studies. However, results showed a significant reduction in rhinitis symptoms and medication requirements.

The doses of allergen used in different studies were analyzed by Canonica and Passalacqua[41], that ranged from 3–5 to 375 times the cumulative dose of subcutaneous immunotherapy. There was no clear relation ship between the dose administered and clinical efficacy, hence more dose-response studies are needed to clearly indicate the optimal therapeutic dose. A dose–response relationship has been analyzed for ragweed extract[98].

The category of evidence for clinical efficacy is 'Ia' for birch, cypress, grasses, olive, *Parietaria*, *D. farinae*, *D. pteronyssinus*. Out of 22 studies, 12 included children <15 years whereas four studies were conducted exclusively in children[97]. 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, more studies in children, are urgently required, because several issues remain unsolved: e.g. optimal doses and duration of treatment in children, the evaluation of quality-of-life and compliance with administration, of vaccine at home. Besides, storage of the allergen product during the time family is out of home, e.g. during holidays and dosing during acute but prolonged gastroenteritis also required to be investigated. The excellent safety profile of sublingual immunotherapy, and the fact that injections are not required with this approach raise the possibility that sublingual immunotherapy could be given to children below the age of 5 years, in an attempt to modify the natural course of the allergic disease. However, definitive trials are required[99,100] to achieve this objective.

When introducing a new route of administration, safety is a priority, especially when treatment is self-administrated at home[50]. Clinical trials and pharmacosurveillance studies have demonstrated a very low rate of systemic adverse effects and no life-threatening systemic side effects[101,102] with SLIT,

Local side effects include itching and swelling of the lips and under the tongue in SLIT. These effects are more common in studies involving high dosages. In general, these effects are well tolerated, requiring no medication or dosage modifications, and often resolve with continued treatment. In a few clinical trials, systemic reactions such as urticaria and asthma have been observed, but all of them were self-limiting. The reactions were dose- and allergen-dependent [97].

A single randomized controlled open sublingual immunotherapy study in children has shown preventive effect on asthma onset[103]. In control group, 18 of 44 developed asthma *vs* 8 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[104]. The category of evidence for the preventive capacity is Ib.

The long-term effect of sublingual immunotherapy was investigated in an open, controlled, study including 60 mite sensitive asthmatic children aged 3 to 17 years[105]. Allocation to immunotherapy or pharmacotherapy group 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 onset of asthma, use of asthma medication and an increase in peak expiratory flow rate (PEFR) compared to control group.

***Studies comparing sublingual and subcutaneous immunotherapy*:** There have been studies comparing the two routes of antigen administration, one consisting three groups of patients (sublingual, subcutaneous and placebo) and another using an open design[106]. However, they do not provide sufficient information due to insufficient study design (double-blind, double-dummy).

Two studies were conducted using a double-blind, double-dummy design. The first of these studies[107] showed a reduction in the symptom and medication scores in patients treated with sublingual immunotherapy as well as in patients treated with subcutaneous immunotherapy, with no difference between the two routes of administration. However, 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[48], investigated efficacy after 1 year of treatment in

patients with birch pollen rhinoconjunctivitis, allocated to three groups. 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.

*SLIT : Allergic rhinitis – (Cochrane Library 11 Feb., 2003)*[108]

Twenty-two trials involving 979 patients were included. There were six trials of SLIT for house dust mite allergy, five for grass pollen, five for *Parietaria*, two for olive and one each for ragweed, cat, tree and *Cupressus*. Five studies enrolled exclusively children. Seventeen studies administered the allergen by sublingual drops subsequently swallowed, three by drops subsequently spat out and two by sublingual tablets. Eight studies involved treatment for less than six months, 10 studies for 6 to 12 months and 4 studies for more than 12 months. All these studies were double-blind placebo-controlled trials of parallel group design. Concealment of treatment allocation was considered adequate in all studies and the use of identical placebo preparations were almost universal. There was significant heterogeneity, most likely due to widely differing scoring systems between studies, for most comparisons.

Overall there was a significant reduction in both symptoms (SMD -0.42, 95% confidence interval -0.69 to -0.15; p = 0.002) and medication requirements (SMD -0.43 [-0.63, -0.23]; p = 0.00003) following immunotherapy. Subgroup analyses failed to identify a disproportionate benefit of treatment according to the allergen administered. There was no significant reduction in symptoms and medication scores in those studies involving only children, and the total numbers of participants were too small to make this a reliable conclusion. Increasing duration of treatment does not clearly increase efficacy. The total dose of allergen administered may be important but insufficient data are available to analyse this factor.

*Assessment of response of immunotherapy*

The assessment of the response of immunotherapy is made by symptoms, repeat skin test, repeat bronchial hyperresponsiveness test, assessment of quality of life, and immunological parameters such as specific IgE, IgG, IgG4, IFN-γ or regulatory cytokine IL-10. However, these parameters may not always correlate with improvement in allergic disease status of patients. Measurement of total IgE has no value for such assessment.

*Complications during skin test or immunotherapy*

1) Systemic reactions (anaphylaxis) are generally rare, but facilities for its management should be available at the place of skin testing and immunotherapy. 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[51]. But a more operational grading system based on the rate of onset and severity is recommended:
2) Important symptoms of anaphylaxis include – change in voice, frequent change in posture, itching in eye and skin, redness in eye, appearance of symptoms-such as rhinitis, asthma and urticaria, fall in blood pressure and feeble pulse, mental confusion, sinking sensation and loosing consciousness.
3) Sequential increase in the size of swelling at the site of injection is suggestive of impending anaphylaxis.
4) Other complications may include vasovagal attack.

*Precautions for skin test and IT during pregnancy*

1) Do not perform skin testing in a pregnant lady.
2) Do not start immunotherapy in a pregnant lady.
3) Skin testing and immunotherapy is to be avoided upto 6 months after delivery or earlier, if lactation is discontinued before.
4) Do not discontinue immunotherapy, if person is already on immunotherapy started much before pregnancy and receiving benefit from the therapy.

*Anaphylaxis and its management*

Systemic reaction(s) (anaphylaxis) may occur in patients while skin testing with some antigens or

during injections for immunotherapy (mainly in initiation phase). Anaphylaxis refers to severe allergic reaction in which prominent dermal and systemic signs including symptoms manifest. The full-blown syndrome includes urticaria (hives) and/or angioedema with hypotension and bronchospasm. The classic form, described in 1902, involved prior sensitization to an allergen with later re-exposure, producing symptoms via an immunologic mechanism. An anaphylactoid reaction produces a very similar clinical syndrome but is not immune-mediated.

Pathophysiology of anaphylaxis is characterized by **r**apid onset of increased secretion from mucous membrane, increased bronchial smooth muscle tone, decreased vascular smooth muscle tone, and increased capillary permeability after exposure to an inciting substance. These effects are produced by the release of mediators, such as histamine, leukotriene C4, prostaglandin D2, and tryptase. The release of these mediators are immune mediated involving type I allergic reaction that occurs when the antigen (allergen) binds to antigen-specific immunoglobulin E (IgE) attached to previously sensitized basophils and mast cells. The mediators are released almost immediately when the antigen binds.

The most common inciting agents in anaphylaxis are parenteral antibiotics (especially penicillins), intravenous contrast materials, hymenoptera stings, and certain foods (most notably, peanuts). Oral medications and many other types of exposures also have been implicated in anaphylaxis. Anaphylaxis may sometimes be idiopathic.

Anaphylactic reaction is clinically manifested by respiratory distress, laryngeal edema, and/or intense bronchospasm, often followed by vascular collapse or by shock without antecedent respiratory difficulty. Cutaneous manifestations exemplified by pruritus and urticaria with or without angioedema are characteristic of such systemic anaphylactic reactions. Gastrointestinal manifestations include nausea, vomiting, crampy abdominal pain, and diarrhoea.

Pre-hospital interventions include high-flow oxygen, cardiac monitoring, and facility for intravenous line. Active airway intervention is needed in rare cases, but may be difficult due to laryngeal or oropharyngeal edema. Inhaled beta-agonists are used to counteract bronchospasm and should be administered to patients having wheezing. For large-volume intravenous fluid resuscitation, isotonic crystalloid solutions (ie, normal saline, Ringer lactate) are preferred. With mild cutaneous reactions, an antihistamine alone may be sufficient. In patients with systemic manifestations of anaphylaxis, epinephrine is to be administered. Patients taking beta-blockers may be resistant to the effects of epinephrine. Glucagon may be effective in this situation. Administration of corticosteroids is used in anaphylaxis primarily to decrease the incidence and severity of delayed or biphasic reactions. Corticosteroids may not influence the acute course of the disease, therefore, they have a lower priority than epinephrine and antihistamines.

Essential equipment/drugs (emergency kit) for the treatment and monitoring of systemic anaphylactic reactions[35] should be available, while skin testing and injection(s) for IT, as follows:

- 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.

*Precautions for systemic side effects*

Before deciding the dose of allergen, a careful evaluation of the patient suitability to receive the scheduled dose is required to avoid systemic side-effects. The precautions recommended[35,109] are, (1) immunotherapy should not be started during peak allergen season, and (2) injections should not be administered when the patient has clinical symptoms or the symptoms should be controlled by adequate medication[52]. As a safety precaution, a reduction in allergen dose during allergen season is commonly recommended.

- IT injections (SCIT) in patients with airway infection or other significant diseases within the last 3 days can be postponed.
- Injections (SCIT) in patients with deterioration of allergy symptoms or increased need for anti-allergic drugs due to recent allergen exposure within the last 3 days should be postponed.
- Injections (SCIT) should be postponed in patients with decreased lung function <80% of personal best value. In asthmatic patients measuring lung function before each injection is mandatory (peak flow measurement is sufficient).
- The scheduled dose of antigen can be reduced, if the interval between injections has been exceeded. The magnitude of reduction depends on the degree exceeded and should be defined in the Clinical Guidelines.
- The scheduled allergen dose should be reduced, 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).
- Allergen injections (vaccine) should be administered separately from other vaccination for infectious diseases by at least a gap of 1 week.
- Traditionally, the late local reaction at the injection site is used to adjust the allergen dosage for the next allergen administration. However 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[109].

Pre-injection 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. Here the $\beta$-blockers are the most important example[110]. Heavy drinking of beer may similarly increase risk due to inhibition of the histamine-converting enzyme diamine oxidase[111].

Antihistamine pretreatment during the initial phase of IT has shown to reduce the frequency and severity of systemic side effects[112] (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[113] (category of evidence Ib). However, further studies are required on this aspect. A potential problem is that the use of antihistamine pre-treatment may mask a mild reaction, which would otherwise help in dose modification.

Compliance with the injection regimen may be affected by age and may be problematic particularly during the adolescent years. Children should accompany a parent, guardian or other responsible person with them at each visit. It is recommended to start immunotherapy at an early age in allergic children to modify the natural course of allergic disease. Airway remodelling may start early in life, especially in children with severe asthma[114], and ongoing airway inflammation and remodelling in adolescents and young adults may increase the risk of asthma later in life[115]. As documented earlier, there is evidence that early specific injection immunotherapy reduces the risk of asthma in children with allergic rhinoconjunctivitis[68] and diminishes the risk of new sensitizations in monosensitized children[64,65].

*Position statement*

- The treatment of allergic diseases is based on allergen avoidance, pharmacotherapy, allergen immunotherapy and patient education. Immunotherapy should be used in properly selected cases with history, precipitation of attack after allergen exposure, positive skin test and wherever possible specific IgE estimation. Immunotherapy is used in combination with pharmacotherapy to make the patient symptom free.
- Allergen immunotherapy should be practiced only by Allergy trained physician/ENT Surgeon and in

a place where facilities for managing anaphylaxis are available.

- Allergen immunotherapy is the administration of gradually increasing dose of a vaccine (w/v or protein µg/ml) in allergic patients reaching to optimal maintenance dose. The maintenance dose should be effective in ameliorating the symptoms associated with subsequent exposure to the causative allergen.
- The response of immunotherapy is antigen specific administered to the patient. Unrelated/irrelevant antigens based on skin text (sensitization) alone should not be included in allergen vaccine.
- The treating physicians should be aware of local and regional allergens prevailing in patient's environment.
- Skin testing is to be done by intradermal or prick method to detect sensitization. Prick method is preferred being more specific and safe, whereas intradermal test is more sensitive.
- Standardized allergen extracts of known potency and defined shelf life should be used both for allergy diagnosis and immunotherapy. However, efforts are required to upgrade the standardization of antigen defined with Allergy Unit, etc.
- The Manufacturers should maintain a high quality of antigens, especially the potency, purity, and specificity.
- Allergen extracts/vaccine (diagnostic/therapeutic antigen) should be stored at 4-8°C and transported using cool device to maintain the allergenic potency.
- Clinico-immunologic controlled studies, Meta-analysis and Cochrane reviews have demonstrated that allergen immunotherapy is an effective treatment for patients with allergic rhinitis/ conjunctivitis, allergic asthma and allergic reaction against insect sting/venom.
- The optimal duration of immunotherapy is still debated. According to reports, IT can be prescribed for 3-5 years in patients with a good therapeutic response. But the decision to discontinue immunotherapy after 5 years should be based on individual patient basis.
- Studies suggest that venom immunotherapy can be discontinued after 3-5 years in most of the patients. However, decision to discontinue venom IT should be taken on the response of patient to treatment.
- Skin testing as well as immunotherapy can give severe systemic reaction (anaphylaxis) at times. Therefore, skin testing and /or immunotherapy should be administered under the supervision of a trained physician who can recognize early symptoms and signs of anaphylaxis and administer requisite treatment in emergency unit.
- Immunotherapy is a slow process and the clinical response starts generally after 6 months. This should be explained to the patient.
- The cost effectiveness of immunotherapy can be assessed based on clinical response with reduction in medicine requirements and also persistence of benefit for 5-6 years after discontinuation of immunotherapy.

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