Allergen Immunotherapy: Shots for Asthma, Wheezing, and Bee Sting

Allergen immunotherapy, popularly known as “allergy shots,” is often prescribed for treatment of various allergic conditions in children. This article discusses the indications, methodology, efficacy, and risks of this therapeutic modality.

WHAT IS ALLERGEN IMMUNOTHERAPY?

Allergen immunotherapy is defined as “the repeated administration of specific allergens to patients with IgE-mediated conditions for the purpose of providing protection against the allergic symptoms and inflammatory reactions associated with natural exposure to these allergens.”

Allergenic proteins and glycoproteins are extracted from raw materials, such as pollen, fungal cultures, dust mites, animal pelts, or hymenoptera venoms. An allergen extract mixture containing the patient’s specific allergens is administered in gradual increments up to an effective therapeutic dose, which is then continued as the maintenance dose.

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Dr. Lierl has disclosed no relevant financial relationships.

doi: 10.3928/00904481-20110316-06
The patient generally has improvement in allergy symptoms by the time the maintenance dose is reached, but the immunotherapy must be continued for at least 3 to 5 years to decrease the likelihood of a relapse after it is discontinued.

In the US, allergen immunotherapy (IT) is performed by means of subcutaneous injections (“allergy shots”). Sublingual immunotherapy (SLIT), in which the allergen is placed under the tongue, is not yet approved by the Food and Drug Administration but will be discussed briefly below.

IMMUNOLOGIC CHANGES

The immunologic response to IT is complex, involving changes in cellular and humoral immune responses to the allergens. A population of regulatory T cells, which promote immune tolerance, develops in response to IT. The cytokine response to the allergens gradually shifts from a pro-allergic (TH-2) pattern to the nonallergic (TH-1) pattern. The allergen-specific IgE levels increase in the early phase of IT, then decrease as allergen-specific IgG and IgA levels rise. The release of mediators from mast cells and basophils in response to allergen exposures is decreased during and after IT.

Although it is not yet clear which of these immunologic changes is the most important predictor of successful desensitization, the result of all these immunologic effects is a reduction in the clinical response to allergen exposures. Studies have demonstrated decreases in the immediate and delayed allergic responses in the nose, eyes, bronchial mucosa, and skin with administration of IT. Development of new aeroallergen sensitizations is also decreased in patients receiving IT.

WHEN TO REFER

Allergen immunotherapy has been shown to be effective for treatment of allergic rhinitis, allergic conjunctivitis, allergic asthma, and stinging insect hypersensitivity in patients whose allergy testing reveals sensitivity to relevant allergens (see Table 1, page 194).

Patients with allergic rhinitis, conjunctivitis, or asthma who have symptom flares during the pollen and mold spore seasons, or who have year-round symptoms related to indoor aeroallergen exposures, might be candidates for IT under the following circumstances:

- The patient’s symptoms are not well controlled by allergen avoidance measures and a good medication regimen and are significantly affecting the quality of life;
- The patient (often a young child or developmentally impaired patient) is uncooperative with medication administration; or
- The patient has adverse effects associated with allergy medications and/or does not like taking medications long term and would rather take the allergy shots with the goal of reducing medication requirements.

Patients who have a history of a systemic allergic reaction to a Hymenoptera insect sting (bee, wasp, hornet, yellow jacket, or fire ant) and demonstrable spe-
specific IgE antibody to the relevant insect venom are candidates for venom immunotherapy. Even before referring these patients to an allergist, they should be instructed in sting avoidance and provided with an epinephrine injector in case of another systemic reaction.\textsuperscript{13}

In children aged up to 16 years, a systemic reaction limited to the skin (hives, angioedema) with no respiratory or cardiovascular symptoms does not predict a more severe systemic reaction to subsequent stings. Therefore, venom immunotherapy is not usually recommended for such patients.\textsuperscript{14} Any systemic reaction to a hymenoptera sting in a patient older than 16 years, even if limited to the skin, is considered an indication for venom immunotherapy because adult patients are at risk for more severe reactions with future stings.

Some patients with atopic dermatitis (eczema) who are sensitized to Aeroallergens might also benefit from IT.\textsuperscript{15,16} Typically, atopic dermatitis is worse during the cold winter months when the air is dry, leading to dry, itchy skin. Patients who have dermatitis flares during the warmer months of the year often have pollen allergies triggering the atopic dermatitis and can be considered for a course of IT. Patients with dust mite allergy also can benefit from desensitization to this perennial allergen.

There is some evidence that oral allergy syndrome can be treated with IT. Oral allergy syndrome is a condition in which patients experience itching, burning, and sometimes swelling in the mouth and throat when they eat fresh fruits or vegetables. The symptoms are caused by allergens in the plant foods that cross-react with pollen allergens, so in theory, induction of immune tolerance to the pollen allergens through IT could resolve the oral allergy symptoms. One study\textsuperscript{17} found that subcutaneous IT to the cross-reacting pollen did resolve oral allergy syndrome, but another study utilizing sublingual immunotherapy\textsuperscript{18} did not.

There is no lower age limit for consideration of starting allergen IT, as long as the child meets the above criteria. The recent data showing that IT can potentially prevent the development of asthma in children have led to a trend toward starting IT at younger ages.

### Allergic or Non-Allergic Rhinitis

There are several common causes of non-allergic rhinitis in children (see Table 2, page 196). Many young children, especially those in day care, have recurrent viral upper respiratory infections causing almost continuous rhinitis, especially during the fall, winter, and spring. Non-allergic rhinitis can also be caused by chronic exposure to environmental irritants, such as tobacco smoke, air fresheners, scented candles, or incense in the home. Vasomotor rhinitis causes nasal congestion and increased mucus production, which is exacerbated by lying down, exposure to environmental irritants, and cold air.

Chronic sinusitis can also cause chronic rhinorrhea, nasal congestion, post-nasal drainage, and coughing. It is not always easy to distinguish allergic from non-allergic rhinitis, and children often have elements of both. However, the hallmarks of allergic rhinitis are itching of the nose and eyes; fits of sneezing; clear, thin nasal and ocular drainage; exacerbation of symptoms with exposure to allergens (such as playing outdoors during the pollen seasons, visiting a home with cats, etc.); and improvement with antihistamines.

Examination of a nasal scraping reveals numerous eosinophils in children with allergic rhinitis. Children with a history of eczema, asthma, or food allergy are more likely to develop allergic...
rhinitis than are children with no atopic background. A positive family history of allergy also increases the likelihood that a child will develop allergic rhinitis.

**PATIENTS WHO SHOULD NOT BE REFERRED**

Allergen immunotherapy is not effective for treatment of chronic urticaria or angioedema, which are usually not caused by allergy.

There have been numerous attempts to treat food allergies with subcutaneous allergen IT. These studies have generally shown some efficacy, but the high rate of systemic reactions to the injections makes the risk-benefit ratio unacceptable (see Table 3, page 197). Efforts are under way to develop genetically modified food allergens with lower allergenicity, which might be safer for use in IT. There are also ongoing studies of sublingual or oral desensitization for food allergies, but these approaches are still investigational at this time.19

Drug allergies can be temporarily controlled by a process called “drug desensitization,” which entails gradually administering a full dose of the drug over the course of several hours. This process is fundamentally different from allergen IT: Rather than inducing long-term immunologic tolerance to the antigen, drug “desensitization” actually causes a gradual, controlled mast-cell, and basophil degranulation.

The anaphylactic mediators are released too slowly to cause a full-blown anaphylactic reaction, although minor symptoms of itching and hives are common during this procedure. Since re-synthesis of these mediators is a slow process, the mast cell and basophil granules remain depleted as long as regular drug dosing is continued. The patient will “re-sensitize” within a few days of discontinuing the drug, so the drug desensitization procedure will need to be repeated with each future course of the drug.

Certain coexisting medical conditions increase the risk for allergen IT. Children with poorly controlled asthma should not receive IT until their asthma is under good control. Children with severe cardiac disease or chronic lung disease also have increased risk of cardiovascular or respiratory decompensation in the event of an allergic reaction during immunotherapy. Patients who are taking beta-blocker medications might respond poorly to epinephrine given for treatment of anaphylaxis. The risk-benefit ratio for IT should be considered carefully in such patients. The use of angiotensin-converting enzyme (ACE) inhibitors has been found to increase the severity of systemic reactions during venom IT,20 although other studies have not found increased frequency or severity of systemic reactions in patients taking ACE inhibitors during aeroallergen or venom IT.21

**TYPICAL IMMUNOTHERAPY REGIMEN**

An allergen evaluation begins with a thorough history to determine:

- Are the patient’s symptoms suggestive of allergy?
- What type of allergen sensitization is suggested by the symptom pattern?
- What treatments have been tried already, and how did the patient respond to them?

The patient is evaluated by physical examination for findings consistent with allergic disease, and for complications or coexisting conditions.

Allergy testing for specific aeroallergen or hymenoptera venom sensitivity can be done by skin testing or by serum testing for allergen-specific IgE. It is important that testing be done only for allergens that are clinically relevant to the patient, such as pollens of plants that are prevalent in the region; indoor and outdoor fungal spores; dust mite and cockroach species found in the region; and animals or birds that are present in the patient’s home or in homes of the patient’s friends or relatives.

An exception is cat allergen, which is carried on pet-owners’ clothing into many environments, such as schools and public buildings, so that almost every child has cat-allergen exposure. Positive test results are considered clinically significant if they correlate with the patient’s environmental exposures and symptom pattern.

If the patient has clinically relevant allergen sensitization and meets criteria for IT as listed above, the procedure for IT is explained to the patient and family. It is important that the patient and family understand the need for adherence to the regular schedule of injections, as missed doses prevent the buildup to an effective dose. The family must also agree to receive all the injections in a medical facility with a physician present (either the prescribing allergists’ office or the primary care office), and remain at the medical facility for 30 minutes after each injection, in case of an allergic reaction to the injection. A consent form listing the risks, benefits, and procedures of IT should be signed by the patient and parent before IT is started.

Once the decision has been made to start IT, the patient’s allergen extract is prepared. All of the patient’s relevant allergens are included in the extract mix. For aeroallergen IT, the extract is formulated to provide approximately 5 to 20 mcg (or, for nonstandardized extracts, 3,000 to 5,000 protein nitrogen units) per dose of each major allergen in the full strength (maintenance) extract. This dose has been found to be effective for aeroallergen IT. For venom IT, the maintenance dose is 100 mcg per dose of each venom allergen. Some patients with multiple aeroallergen sensitivities, or multiple hymenoptera venom sensitivities, require two or more separate extracts (each given in a separate injection) to deliver a sufficient dose of each allergen.

To prevent allergic reactions to the injections, the full strength extracts are diluted, usually 1,000- to 10,000-fold for aeroallergen IT and 100-fold for venom IT. Some patients who have had severe allergic reactions might require even greater dilutions for their starting doses. The diluted extracts are used for the initial dose, and the patient receives gradually increasing doses one to three times per week until the maintenance dose is reached.
The usual regimen for allergen IT requires 28 doses to reach the maintenance dose, and for venom IT 15 doses are required. Some allergists prefer variations of these build-up regimens. There are also “rush” and “cluster” buildup regimens, in which the dose is increased more rapidly. In “rush” IT, several IT injections are given per day with the maintenance dose reached within one to three days. “Cluster” IT involves giving two to three injections per visit on nonconsecutive days, with the maintenance dose reached within 4 to 8 weeks. These accelerated buildup schedules have the advantage of achieving the maintenance dose more rapidly, but there is an increased risk of systemic allergic reactions to the injections.

The “usual” maintenance dose is a general goal of IT but is not the best dose for each individual patient. Some patients cannot tolerate advancing up to the usual maintenance dose without systemic reactions and might achieve therapeutic benefit at a lower dose. Other patients require a higher maintenance dose to attain optimal results.

The patient should be re-evaluated periodically by the allergist after reaching the maintenance dose, to determine whether dosage adjustments are needed to achieve the desired clinical effect. Once the patient’s maintenance dose has been determined, this dose is continued and the time between doses is gradually increased until the maintenance dose is being given once every 4 weeks.

Allergy shots are given using a syringe with a 26-gauge, 27-gauge, three-eighths-inch, or one-half-inch needle. The injections are given into the posterior arm at the junction of the deltoid and triceps muscles. The area should first be wiped with alcohol. The skin should be pinched up, and the needle inserted at a 90° angle to the skin, so that the injection is given subcutaneously. This will allow slow absorption, lessening the risk of a systemic reaction, and will also prevent intradermal administration, which causes large local reactions.

Before injecting the extract, the plunger should first be pulled back to aspirate, making sure that there is no blood return. Although there are no large blood vessels in this part of the arm, occasionally the needle might be inserted into a venule. Accidental administration of the allergen extract intravenously could result in a systemic allergic reaction. After the injection is given, pressure should be applied over the injection site for about 1 minute, to keep the extract from leaking out.

The length of treatment with IT varies for individual patients. In general, it is considered advisable to continue aeroallergen IT for at least 5 years, as the risk of symptom recurrence is greater with shorter periods of IT.1 If the patient was slow to improve, had severe allergic disease before starting IT, or had developed new allergies requiring revision of the IT during the first few years, an extension of IT might be advisable. Unfortunately, there is no test that predicts which patients will have a relapse of their allergy symptoms after stopping IT.

For patients receiving insect venom IT, it is recommended that at least 3 to 5 years of IT should be completed. Patients with a history of severe anaphylaxis, or anaphylactic reactions occurring during their venom IT treatment should consider continuing their venom IT indefinitely.22 Up to 15% of patients have a systemic reaction to a sting within 10 years of stopping venom IT, although usually the reaction is milder than their reactions before IT.23 Patients who have an elevated baseline serum tryptase level have been found to have more severe reactions to insect stings, more frequent systemic reactions to venom immunotherapy, and a higher risk of fatal systemic reactions after stopping venom immunotherapy.24 Thus, these patients should continue their venom IT injections indefinitely, with special precautions taken in the allergist’s

| TABLE 2. |
| --- | --- | --- | --- | --- | --- |
| **Type of Rhinitis** | **Itching** | **Nasal Secretions** | **Sneezing** | **Nasal Smear** | **Response to Antihistamine** | **Response to Antibiotics** |
| Allergic rhinitis | ++++ | Clear, watery | Frequent fits | Many eosinophils | ++++ | - |
| Recurrent viral URI | - | Clear to green, mucoid | Sporadic | Variable lymphocytes/neutrophils | - | ++++ |
| Chronic rhinosinusitis | - | Green or yellow, thick | Sporadic | Many neutrophils | - | ++++ |
| Irritant rhinitis (tobacco smoke, air fresheners, etc.) | ++ | Clear, thin | Frequent | Few, mixed inflammatory cells | ++ | - |
| Vasomotor rhinitis | + | Clear, mucoid | Rare | Noncellular | ++ | - |

Note: All of these forms of rhinitis are characterized by nasal congestion that improves with decongestants.

+ = present; - = absent

Source: Lierl MB.
office to monitor for systemic reactions to the injections. There is no test that can accurately predict which patients are at risk of a relapse of their venom allergy, although patients with a negative test for venom-specific IgE at the end of their IT course had no subsequent systemic reactions in one follow-up study.25

**BENEFITS**

Ideally, allergen IT induces immunologic tolerance to allergens so that the patient has no further allergy symptoms and can control their symptoms with less medication than required previously. Most studies of IT efficacy have utilized single-allergen IT. Studies have demonstrated efficacy of aeroallergen IT for pollens,26,27 dust mite,28 animal allergens,29,30 and fungal spores.31,32 Fungal spore extracts are somewhat problematic, as fungal cultures grown in laboratory conditions sometimes have different allergen contents than those growing on natural substrates. Also, there are thousands of fungal species for which no extracts are available. Nevertheless, extracts are available for some of the most important allergenic fungi, and these can be included in allergen IT.

Total health care costs are decreased in patients receiving immunotherapy.33,34 Patients are often able to discontinue their allergy medications once they have reached the maintenance dose of IT, and the therapeutic effect of IT persists indefinitely after the IT is completed in most cases. Thus, there is a long-term financial benefit to a course of IT, although the short-term expenses must be considered in relation to the patient’s insurance coverage and financial means.

Aeroallergen IT has been shown to reduce the risk of developing asthma when

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**TABLE 3.**

**Conditions for Which Allergen Immunotherapy is Unproven or Not Indicated**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Indication for IT</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral allergy syndrome</td>
<td>Unproven</td>
<td>Studies have shown conflicting results.</td>
</tr>
<tr>
<td>Chronic idiopathic urticaria/angioedema</td>
<td>Not indicated</td>
<td>This condition is not caused by allergen sensitivity.</td>
</tr>
<tr>
<td>Food allergies</td>
<td>Unproven, investigational</td>
<td>High rate of systemic reactions to IT with food allergens; risk-benefit ratio is unacceptable with methodologies studied to date. Oral, enteric, or sublingual IT may prove safer for food allergen desensitization.</td>
</tr>
</tbody>
</table>

Source: Lierl MB.

**TABLE 4.**

**Requirements for Safe Administration of IT in the Office Setting**

<table>
<thead>
<tr>
<th>Staff</th>
<th>Physician</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Familiar with treatment of anaphylaxis</td>
</tr>
<tr>
<td></td>
<td>• Present in office throughout the visit</td>
</tr>
</tbody>
</table>

**Nurse or medical assistant**

|                                | • Familiar with IT dosing protocol |
|                                | • Double checks patient ID and correct vial/dose of IT injection |
|                                | • Performs asthma assessment prior to IT injection, for patients with asthma |
|                                | • Gives IT injections subcutaneously; aspirates prior to injecting |
|                                | • Documents dose given and any reactions to dose |

**Patient**

|                                | • Signed informed consent |
|                                | • Stays in office for 30 minutes after injection (60 minutes for venom injections) |

**Medications (immediately available)**

|                                | Epinephrine 1:1000 solution for IM administration |
|                                | Diphenhydramine 12.5 mg/5 mL solution |
|                                | Albuterol nebulizer solution |
|                                | Prednisolone suspension or tablets |

**Other Medical Equipment**

|                                | Oxygen |
|                                | IV fluids, IV set-up |
|                                | A ‘clean’ refrigerator to store the extracts (not containing food or specimens), set to 4 to 8°C |

Source: Lierl MB.
given to children with allergic rhinitis.\textsuperscript{35,36} This benefit persists for at least several years, as demonstrated in the PAT study: Children with allergic rhinitis and either no asthma or mild intermittent asthma symptoms were treated with IT or medication management for 3 years. Seven years after completing the 3-year trial, 25\% of the children who were treated with IT had developed asthma, compared with 45\% of the control group.\textsuperscript{35}

Hymenoptera venom IT has also been shown to be effective, with greatly reduced risk of a systemic allergic reaction to subsequent stings once the patient reaches the maintenance dose.\textsuperscript{37} The 100-mcg maintenance dose of venom is approximately equivalent to the amount of venom injected by two stings. The stinging fire-ant extract is a whole body extract that has not been studied in controlled trials, but uncontrolled trials have shown efficacy.\textsuperscript{38}

**RISKS**

The chief risk of IT is a systemic allergic reaction to the injection, characterized by urticaria, angioedema, rhinoconjunctivitis, or asthma symptoms, or in rare instances respiratory failure or circulatory collapse. Systemic allergic reactions to IT are relatively uncommon, occurring in about 1\% of patients receiving conventional IT, and in about 0.01\% of injections. Fatal or near fatal reactions occur in about 5.4 cases per million injections. Allergic reactions can occur after any dose of IT, even when the patient has previously tolerated the same dose without problems.

For this reason, it is recommended that all allergy shots be given in a medical facility that is equipped to manage an anaphylactic reaction (see Table 4, page 197). A physician familiar with the treatment of anaphylaxis must be present, and the patient should remain at the medical facility for at least 30 minutes after every injection. Most severe systemic allergic reactions occur within the first 30 minutes; delayed reactions also occur but are usually not life-threatening. The patient and parent should be asked at each IT visit whether there was a delayed systemic reaction after their previous dose. Patients who have a history of delayed systemic reactions should carry an epinephrine injector.

If a patient has a systemic reaction to an allergy shot, further doses should not be given until the allergist has reassessed the patient, reviewed the risk-benefit ratio of continuing the IT, and adjusted the dose.

Patients with asthma should be examined before each dose of IT to ensure that their asthma is adequately controlled. A brief history of recent symptoms, auscultation of the lungs, and peak flow rate measurement should be standard assessments before IT is administered to children with asthma. If the patient’s asthma is symptomatic, IT should be deferred until the asthma is under good control.

On the other hand, local reactions of erythema, swelling, itching, and/or soreness around the IT injection sites are very common and usually do not require dose adjustments. Patients with local injection site reactions are not at increased risk of a subsequent systemic reaction,\textsuperscript{39} unless the local reactions are very large. Local reactions can be treated with antihistamines and/or an ice pack for symptom relief.

**SUBLINGUAL ALLERGEN IMMUNOTHERAPY**

Children do not like shots, so the question of SLIT is often of interest to them. SLIT involves placing a dose of allergen under the tongue, holding it there for a period of time, and then swallowing it. Usually the dosing is done daily, at home. This method is under investigation in the United States and is not yet approved by the FDA, although it has been used in other countries for a few years. The efficacy and safety of SLIT have been investigated in several studies, with conflicting results.\textsuperscript{40} Most of the controlled trials have studied SLIT for grass pollen or house dust mite. A recent meta-analysis of controlled trials of SLIT with grass pollen allergen found a modest clinical response, with lower efficacy in children than in adults.\textsuperscript{40}

The optimal dosing for SLIT has not been determined, but appears to be about 30 times higher than the effective dose for each allergen with subcutaneous IT. The comparative clinical effectiveness of SLIT versus IT is also unclear, with varying results among the few small comparison trials. Allergic reactions to SLIT include oral itching and sometimes swelling, which occurs in up to 75\% of patients at the beginning of a course of treatment but decreases in frequency after treatment is continued.\textsuperscript{40}

In a meta-analysis of 50 studies of SLIT, about 0.8\% of patients had moderate systemic reaction requiring dose adjustment or withdrawal from the study.\textsuperscript{40} Systemic anaphylactic reactions are very rare but have been reported in 0.3\% of patients. No fatal anaphylactic reactions have been reported. Thus SLIT needs further study but might one day be an option for IT.

**ALTERNATIVE APPROACHES**

The Rinkel method is an older approach to IT, which has been shown to be ineffective in controlled trials.\textsuperscript{41} In this method, very low doses of allergen are administered and the dose is never advanced to an effective maintenance dose. The Rinkel method is still in use by some non-allergist practitioners. Provocation-neutralization therapy is another unproven method. Chiropractic, acupuncture, and other forms of complementary medicine have not been shown to be of benefit in reducing allergen sensitization.

**SUMMARY**

Allergen immunotherapy is an effective treatment option for children with allergic rhinoconjunctivitis, allergic asthma, hymenoptera venom hypersensitivity, and for selected cases of atopic dermatitis. In many cases, the benefits to the patient include relief of bothersome or even life-threatening allergy symptoms and freedom from the need for daily medications. The costs and risk-benefit ratio for the patient...
should be considered in making the decision whether to embark on a course of IT.

REFERENCES


