About 20% of the population suffers from IgE-mediated allergy to various allergens in the environment. Subcutaneous immunotherapy (SCIT) is an allergen-specific treatment for allergy to both inhaled and insect-sting allergens. SCIT, commonly known as “allergy shots,” is one of the most effective forms of treatment available for symptoms caused by exposure to specific allergens and can actually change the natural history of the disease process. While airborne allergens can cause severe respiratory symptoms (allergic rhinitis/sinusitis, conjunctivitis, and asthma), insect-sting venom can provoke anaphylaxis in venom-allergic individuals.

When allergen avoidance is ineffective and medications are inadequate, then immunotherapy may present a viable treatment option for allergic individuals. Treatment with SCIT can induce specific immunologic tolerance in most allergy sufferers, resulting in diminished symptoms, reduced need for medication and long-lasting benefits. Further, SCIT reduces complications directly related to upper-respiratory allergy—such as allergic sinusitis, eustachian tube dysfunction and otitis media—and may prevent the future development of asthma in patients with allergic rhinitis.¹

The use of SCIT in the U.S. began in 1911 by Noonan and Friedman, and now more than 30 million injections are administered annually. SCIT is administered by subcutaneous injection of gradually increasing doses of an allergen. Increasing doses of the allergy serum are given weekly over a period of months until a target dose or maintenance dose is achieved.

The maintenance dose is the optimum dose which induces immunologic tolerance to the injected allergen(s). A maintenance dose is then administered every 3-4 weeks for a period of 3-5 years, or even longer in unique situations. Many studies of SCIT have shown a significant reduction of symptoms within 1-2 years. The treatment is often associated with long-term benefits far beyond the treatment period. In some cases, immunologic tolerance can last a lifetime.

Allergen-specific Immunotherapy

How it works

The mechanism underlying allergen-specific immunotherapy relates to changes in T- and B-cell responses to an allergen, as well as alteration of allergen-specific antibody production. SCIT also affects cells involved in the inflammatory process (i.e. eosinophils, basophils and mast cells).

Immunotherapy changes the immunoregulation of responses to allergens by first modulating T regulator cells that orchestrate the allergic response. In turn, T regu
latory cells act by stimulating or suppressing peripheral T-cells that stimulate or suppress specific anti-allergen antibody production, and cellular secretions (cytokines) that affect the response to allergen exposure. Research reveals that SCIT results in a loss of reactivity to the specific allergen when the same allergen is applied to nasal and conjunctival mucosa of the SCIT-treated patients. Allergy skin testing reactivity also decreased as a result of this treatment. Finally, many controlled clinical trials support the efficacy of subcutaneous immunotherapy for both allergic rhinitis and asthma.¹ ²

### Which diseases benefit from SCIT?

1. **Allergic rhinitis and conjunctivitis**
   
   Immunotherapy helps control the symptoms of respiratory allergy due to pollen (including ragweed, see Figure 2), dust mites, animal dander and airborne mold spores. Complications of allergic rhinitis, such as eustachian tube dysfunction, recurrent otitis media, and sinusitis may also improve as a result of SCIT.
   
   Many studies support the effectiveness of SCIT in allergic rhinitis, including a meta-analysis which consisted of 16 prospective, blinded, and placebo-controlled studies of immunotherapy for allergic rhinitis published in English between 1966 and 1996.¹ The studies included grass extract, ragweed, dust mite, cedar pollen, and the mold *Alternaria*. In 15 of the 16 studies, the outcome favored the active treatment.

2. **Allergic or extrinsic bronchial asthma**
   
   A meta-analysis was performed based on 75 randomized, controlled trials including 3,188 subjects with asthma. Participants who underwent immunotherapy for allergies to house dust mites, pollen, animal dander, mold (*Cladosporium*), latex, and other allergens experienced a significant improvement in asthma symptoms.²

3. **Insect venom hypersensitivity**
   
   Purified insect venoms have been used in immunotherapy since 1980 and have proven more than 95% effective in preventing insect-sting anaphylaxis (See Figure 1).

4. **Other possible disease entities that SCIT may benefit:**
   
   - Chronic rhino sinusitis
   - Allergic fungal sinusitis

### The allergens

Allergens used to treat respiratory allergy include pollen (tree, grass, weed), pet dander (e.g. cat pelt), dust mites, airborne molds, and occupational aeroallergens. Allergens used to treat insect hypersensitivity include honey bee, yellow jacket, hornets, wasps, and fire ant. Honey bee, yellow jacket, hornet and wasp venoms are biologically standardized and collected by electroshock or dissecting out the venom sac. SCIT with these insect allergens has yielded extraordinary protection from insect-sting anaphylaxis, offering recipients up to 95% protection.

### Allergy testing

**Allergy skin testing**

Careful selection of appropriate allergens used in testing, combined with excellent skin testing technique and a thorough clinical history leads to the formulation of an optimum allergy serum. Allergy skin testing offers the most sensitive method for identification of IgE-mediated allergy.

A distinct advantage of allergy skin testing over lab studies (e.g. RAST or Immunocap™) in detecting allergy is that the same allergen(s) used to skin test are also used to prepare the allergy serum used in treatment. The same is not true for treatment based on lab studies, in which the allergy serum often comes from a different source than the one used in testing. Using the same allergen source for testing and preparation of the allergy serum insures that all relevant allergens are present. This level of attention to detail may lead to a better clinical outcome.

**RAST assay or Immunocap™** are accurate laboratory tests that can identify circulating allergen-specific IgE (allergy antibody). These lab tests have the advantage of convenience, do not require physician’s time and expertise, are not affected by antihistamines, and pose no risk of systemic reaction. However, they appear to be less sensitive than skin testing in diagnosing allergy.
Observed immunologic efficacy of subcutaneous immunotherapy reactivity also decreased as a SCIT of reactivity to the specific allergen IL4 (TH2 associated) decreases. Cytokine changes: TNF decreases, in T-suppressor cells. Decrease in seasonal rise of tests. Decrease in allergen-specific IgE (IgG1 and IgG4), also known as affect the response to body production, or suppress specific pressor cells. Specific cells act by results in a loss that stimulate peripheral...

Allergens used to treat respiratory allergy include Alternaria, dust mites, pollen, animal dander, and other allergens used to treat insect hypersensitivity. Purified insect venoms have been used in allergic rhinitis, such as eustachian tube effects. Insect venom hypersensitivity includes allergic fungal sinusitis. Complications of allergic rhinitis, such as eustachian tube effects. Insect venom hypersensitivity includes allergic fungal sinusitis. Complications of allergic rhinitis, such as eustachian tube effects. Insect venom hypersensitivity includes allergic fungal sinusitis. Complications of allergic rhinitis, such as eustachian tube effects. Insect venom hypersensitivity includes allergic fungal sinusitis. Complications of allergic rhinitis, such as eustachian tube effects. Insect venom hypersensitivity includes allergic fungal sinusitis. Complications of allergic rhinitis, such as eustachian tube effects. Insect venom hypersensitivity includes allergic fungal sinusitis. 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mended since it appears to elicit the best results. Initially, diluted allergy serum beginning with a subcutaneous injection of 0.05 cc is gradually increased by .05 cc weekly until a dose of .35 to 0.5 cc is reached. This process is repeated with more concentrated allergen serum until a maintenance dose is achieved.

■ **Dosage adjustments**
Since individual patients vary in their tolerance to allergens, dosage schedules are modified in order to prevent reactions. The standard SCIT dose may be adjusted according to the patient’s history of response to previous injections, seasonal allergies (for Delaware Valley pollen counts, visit asthmacentre.com, updated daily) or diagnosis of pregnancy.

The goal is to raise the dose as quickly as possible without inducing reactions. Local reactions causing a quarter-sized wheal that resolves quickly will usually not require a change in dose. Large local reactions (wheels larger than a golf ball) lasting more than one day are considered precursors to a systemic reaction and in this case, the next dose is lowered by 30-50%. Patients developing hives, respiratory allergy symptoms, or evidence of anaphylaxis require a 90% reduction in their next dose.

**Alternative routes of immunotherapy**

Although SCIT is the most common form of immunotherapy in the U.S., some other methods of allergen-specific therapy have been investigated and proven effective in controlled studies.

- **Nasal immunotherapy:** Allergens are sprayed onto the nasal mucosa. This technique is not currently available or FDA-approved, though it appears to be effective. Clinical trials have revealed frequent local side effects.

- **Oral immunotherapy:** Allergens are orally ingested. This technique has proven effective in some studies, though it is not currently available or FDA-approved. Oral immunotherapy offers some promise as a future treatment for food allergy.

- **Sublingual immunotherapy (SLIT)** has proven effective in European studies, using much higher concentrations of allergens than that used in injection therapy (SCIT) here in the U.S. Although there appears to be no consensus on the most effective dose, allergen concentrations may be as high as 50-300 times the amount of allergen currently used in SCIT allergy serums.

**Understanding SUB-LINGUAL IMMUNOTHERAPY**

In a 6-year study comparing SCIT to sub-lingual immunotherapy (SLIT), Taha-miler, et al (2008) enrolled 193 patients with allergic rhinitis due to dust mite allergy. Half the participants received SCIT, while the other half received SLIT for 3 years, followed by 3 more years of follow-up. Prick tests showed a greater reduction in sensitivity with SCIT. No systemic reactions occurred in either group. However, side effects with SLIT included oral pruritus (48%), rhinitis (31%), and gastro-intestinal symptoms (12%). SLIT studies generally revealed a 30% reduction in symptoms. It would appear that SLIT is most effective for patients suffering from mild to moderate symptoms. In addition, investigators felt that SCIT was more effective than SLIT for treatment in perennial allergic rhinitis due to dust mites. It should also be noted that anaphylaxis with SLIT has been reported as well.6

SLIT appears to work best as a mono-therapy, when a single allergen, such as grass pollen, is the cause of symptoms. SLIT does not appear to work well when used to treat patients with multiple allergies.

While there is a distinct possibility that SLIT will be approved in the future for high-dose mono-therapy in the U.S., its availability may be limited to just a few allergens. Further, SLIT may be significantly less effective than SCIT, especially when multiple allergens need to be administered as part of the treatment program.

Physicians currently offering SLIT therapy in the U.S. are prescribing an allergy serum not approved by the FDA for SLIT. Therefore, SLIT is not recommended for treatment at this time by the American Academy of Allergy and Im-

**Special considerations**

**Pregnancy:** Pregnancy is not a contraindication to immunotherapy. However, it is wise to reduce the immunotherapy dose and not raise it again until delivery.

**Use of beta-blockers:** In the event of an adverse reaction to an allergy injection, a beta-blocker would interfere with effective emergency treatment by suppressing the response to treatment (epinephrine) and possibly worsening any underlying asthma.

**Patient’s history of previous severe reactions to SCIT:** Patients who have repeated or serious previous reactions may not be good candidates for SCIT for non-life-threatening allergic disease.

**Severe or unstable asthma:** When asthma is unstable, it is prudent to withhold immunotherapy.

**Duration of treatment**

The length of therapy can vary according to the patient’s response. Most patients who show improvement by the second year of treatment will be likely to maintain improvement in the future. Once maintenance is reached, therapy is usually continued over a period of 3-5 years. Patients that show no improvement during the first year of maintenance are unlikely to benefit from treatment.

**Cost vs. Benefit**

Once a patient has reached the maintenance dose, the cost of a
year’s treatment, including the allergy serum and monthly injections is often less than $1000 per year. However, the cost rises for patients requiring multiple vials of allergens. In contrast, the cost of medications (including prescription antihistamines, physician visits nasal sprays and eye drops and other medication) can often exceed $2500 each year and may be less effective than SCIT in controlling severe allergy symptoms.

Causes of immunotherapy failure

- Lack of good correlation between allergy testing results and clinical history
- Inadequate dosing. Use of low dose treatment, mixing too many antigens in the same vial causing dilution of dose, mixing incompatible antigens in the same vial (i.e. dust and pollen or mold and pollen)
- Missing clinically relevant allergens in allergy serum
- Poor compliance with scheduled dosing
- As with any other medication failure, immunotherapy just may not work for certain patients.

The future of immunotherapy

SCIT is currently the most effective form of immunotherapy available and has been the subject of many studies which support its efficacy. However, the cost of production of these allergens is high and there is a risk of systemic reactions.

As a result of these limitations, scientists have tried to modify the allergens used in SCIT to lower their allergenicity and increase their immunogenicity. In this way, lower doses of less-reactive allergens could induce tolerance with a much lower incidence of side effects and perhaps greater convenience.

Experimental chemical treatments of allergens have produced new preparations—including polymerized allergens, formaldehyde-treated allergens and allergen conjugates. These have proven successful in some clinical trials. However, they are not yet approved for treatment in the U.S.

Another approach has been to absorb allergens by using an aluminum-precipitated extract or product in order to slow the release of injected allergy serum and reduce allergic reactions. However, the variety of allergens is limited with this form of allergen extract.

Finally, a new immunologic treatment with anti-IgE (Xolair) which is a non-specific allergy treatment, can benefit allergy sufferers by globally removing much of the circulating IgE. Unfortunately, its approved use is currently limited to moderate to severe extrinsic asthma patients and its associated cost can top $30,000 per year per patient.

References


