Allergy skin testing
&
Subcutaneous Immunotherapy

Dana V. Wallace, MD
Assistant Clinical Professor
Nova Southeastern University
Davie, Florida
drdanawallace@gmail.com

Disclosure Statement

Dana V. Wallace, MD

I participate in the following Speaker's Bureau and/ or Advisory Boards:

- **Myland Labs**
- **TEVA**
- **Sunovian**
- **Sanofi**

Lecture objectives

Following this presentation, you will be able to:

- Discuss when and how to skin test for allergies
- Discuss and define indications for specific allergen immunotherapy (SIT)
- Describe the safety and benefits of SIT
- Explain the mechanisms of action of SIT
- Discuss the current status of alternative methods of immunotherapy

Definition

- Allergen immunotherapy is the administration of gradually increasing quantities of an allergen vaccine to an allergic subject, reaching a dose which is effective in ameliorating the symptoms associated with subsequent exposure to the causative allergen.

WHO Position Paper 1998

Effects of Immunotherapy

- Symptom improvement and/or reduction of the need for symptomatic drugs in allergic rhinitis and asthma
- Long-lasting effect once discontinued
- The only treatment that can modify the immune response to allergens and alter the course of allergic diseases
- Prevention of the onset of new skin sensitizations.
- Prevention of the onset of asthma

Allergen Immunotherapy for Asthma

- 76 trials with 3,188 patients
- Significant improvement in asthma symptom scores
- Significant reduction of allergen specific bronchial hyperreactivity
- Some reduction also in non-specific bronchial hyperreactivity

Abramson, Weiner and Puy, Cochrane Database Systematic Review 2003

Long-Lasting Efficacy of Subcutaneous IT: Controlled Studies

Author	Allergen	Duration
Hedlin, 1995	Cat/dog	3 yrs
Ariano, 1999	Parietaria	4 yrs
Durham, 2000	Grass	5 yrs
Eng, 2002	Grass	3 yrs

IT: Prevention of New Sensitizations

New sensitizations after 3 years:
55% SIT group vs 100% control group.

Des Roches et al, JACI 1997

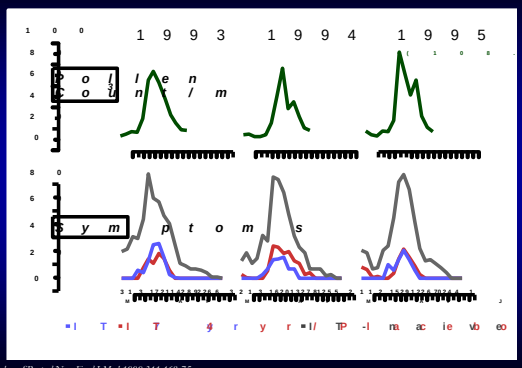
New sensitizations after 3 years:
25% SIT group vs 67% control group.

Pajno et al, Clin Exp Allergy 2001

New sensitizations after 4 years
23% SIT group vs 68% control

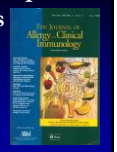
Purello D'Ambrosio et al, Clin Exp Allergy 2001

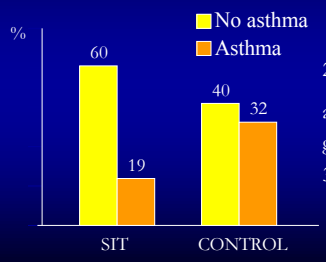
Grass pollen immunotherapy: long-term efficacy



Durham SR et al New Engl J Med 1999;341:468-75

Specific immunotherapy prevents the development of asthma in children with allergic rhinitis (the PAT study)





205 children with rhinitis
age: 6-14 yrs
grass or birch allergy
3 yrs immunotherapy

Moller C et al, JACI 2002

The essential components of allergy diagnosis

Clinical History and Physical Examination
Symptoms versus Exposure

Diagnostic Confirmatory Test
Skin Test (Puncture, Intradermal)
Allergen-specific IgE antibody serology

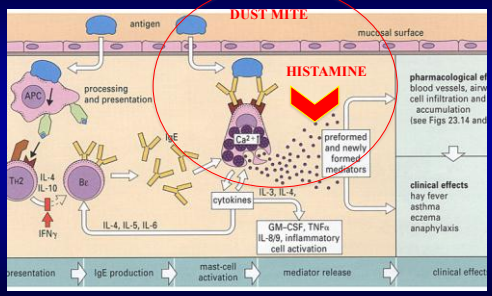
Provocation Test
Oral, Nasal, Bronchial Challenge

Key concepts in allergy diagnosis

- Allergic history
  - Symptom complex
  - Relationship to allergen exposure
- Physical examination, looking for the specific signs of allergy
- Confirmatory allergy test
  - Skin tests – prick/puncture and intradermal
  - Specific IgE antibody serology, an accepted alternative

1. *Oppenheimer Ann Allergy 2006;S1:6-12.*
2. *Bousquet Clin Allergy 17:529-36, 1987*
3. *Cockroft Am Rev Respir Dis 135:264-7., 1987*

Pathophysiology of an allergic reaction



Skin Prick Testing

- Skin prick testing (SPT) remains the primary confirmatory test
  - Safe
  - Fast
  - Inexpensive
  - Sensitive
  - Minimally invasive
  - Correlates well with nasal and bronchial challenge

1. Oppenheimer Ann Allergy 2006;S1:6-12,
2. Bousquet Clin Allergy 17:529-36, 1987
3. Cockroft Am Rev Respir Dis 135:264-7., 1987

What is an allergen?

- An antigen causing an allergic disease is called an "allergen"
- Most allergens are glycoproteins with a molecular weight of 5 to 100 kD, **most around 20 kD.**
- Many pollen allergens are surface enzymes
- Some food allergens are remarkably stable and are stable even after cooking
- A genetically predisposed (atopic) person can become IgE-sensitized after several years of inhaling <1 µg of grass pollen allergen per season

Spectrum of allergen sources

Stinging Insects

Allergen extracts

- An allergen extract is prepared by incubating the allergenic material in a physiological buffer (e.g., phosphate buffered saline) followed by lipid extraction
- The allergen content was commonly expressed in crude terms such as protein nitrogen units (PNU) or **weight : volume**
- It may now be expressed as micrograms of specific allergen per ml

Allergen extracts

- Several commercial extracts used in skin testing are **"standardized"** regarding allergen protein concentration, composition and lack of irritating contaminants.
- Standardized allergens used in the USA
  - Grass
  - Ragweed
  - Dust Mites
  - Cat

Allergen Standardization

- Many different units are used:
  - Protein nitrogen units (PNU- world wide)
  - Allergy unit (AU- U.S. FDA)
  - Bioequivalent allergy unit (BAU)
  - Biologic units (BU- Europe)
  - International unit (IU- WHO)
  - Index of reactivity (IR- Europe)
  - Specific treatment unit (STU)
  - Activity Units by RAST (AUR- Europe)

Selection of aeroallergens

- An understanding of **pollen aerobiology** and knowledge of **allergenic cross-reactivity** between regional pollinating plant families is necessary in selecting appropriate aeroallergens
  - Example: Extensive allergenic cross-reactivity exists between **northern pasture grasses**, permitting the use of a single northern grass pollen for testing in most regions outside of southern regions of North America and Europe.

Major Allergens in India

- Mesquite
- Castorbean
- Indian Elm
- Sagebrush
- Cedar
- Dust Mite
- Pigweed
- Parthenium
- Johnson grass
- Bermuda grass
- Mallotus Phillipensis

General rules for successful SPT

- It is imperative that the technician performing the skin tests as well as the clinician ordering/interpreting these tests understands the characteristics of the specific tests they are administering.
- This includes:
  - type of skin testing
  - device used
  - placement of tests (location and adjacent testing)
  - the particular extracts (source, concentration) being used
  - the potential confounder of medications that may suppress skin test response.

Suppression of skin tests by medication

- Most antihistamines and anti-depressants suppress skin tests for 3-7 days
- No significant effect of short-acting beta agonists, H2 antagonists, monteleukast, low-dose corticosteroids
- High dose/prolonged corticosteroids may be a problem
- Consider doing histamine & control PRIOR to SPT on all patients

Cook J Allergy Clin Immunol 1973;51:71-7
Rao KS J Allergy Clin Immunol 1988;82:752-7
Miller J J Allergy Clin Immunol 1989;84:895-99
Slott RIJ Allergy Clin Immunol 1974;554:229-34

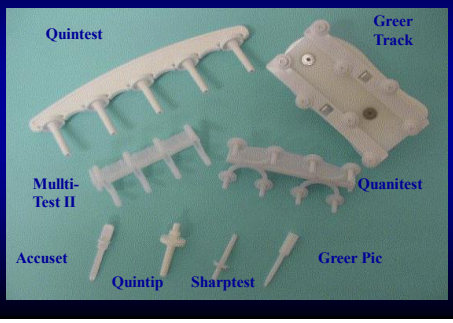
Skin prick testing

- SPT is easy to perform and rarely causes generalized reactions.
- Patients may have positive SPT but no clinical disease. A positive SPT indicates the presence of IgE antibodies against that allergen but does not indicate clinical sensitivity. A correlation between the history and SPT is essential.
- Approximately 3 x 10^{-6} ml of allergen extract is delivered with each prick
- Prick/puncture tests may be performed in infants as young as 1 month

SPT testing solutions with dropper caps

http://www.mayoclinic.com/health/allergy-tests/MM00385

Common SPT devices Prick & Puncture



Skin Prick Testing Devices

Not all SPT devices are the same

Devices for which a 3 mm wheal would be significant as a positive test (.99 quantile at the neg control site listed)		Devices that require > 3 mm wheal for a positive test (.99 quantile at the neg control site listed)	
Quintest (HS) puncture	0 mm	DuoTip (LincolnO twist	3.5 mm
Smallpox needle *HS) prick	0 mm	Bifurcated needle (ALO) Prick	4.0
DuoTop (Lincoln) ptick	1.5	MultiTest (Lincoln) puncture	4.0
Lancet (HS)	2.0	Bifurcated needle (ALO) puncture	4.5
Lancet (ALK)	3.0	Quick Test (Pantrax)	4.0
DermaPICK II	0	Greer Track (Greer)	3,5

A

SPT based on body region tested

Comparison of Prick Skin Test Reactions on the Back and Arm

	Forearm	Back	p-
	(reaction diameters)		
Wheal histamine (n=50)	4.08 mm	3.99 mm	NS
Flare histamine (n=50)	21.67 mm	23.52 mm	0.003
Wheal allergen (n=50)	8.53 mm	11.61 mm	0.001
Flare allergen	31.81 mm	36.78 mm	0.001

HS Nelson, et al. JACI 1996;97:596

Characteristics of different regions

Prick Skin Test Reactions by Region of the Back

Location	Histamine	Allergen
Top (n=96)	7.24mm	7.82mm
Mid (n=96)	8.19mm	10.41mm
Bottom (n=96)	8.94mm	11.11mm ★

Gradient for both significant p<0.0001

HS Nelson, et al. JACI 1996;97:596

SPT drops placed on skin that has been marked with lines/numbers

http://www.mayoclinic.com/health/allergy-tests/MM00385

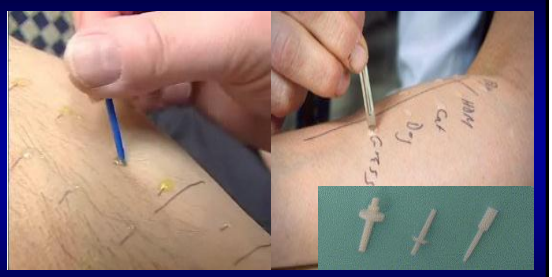
Allergen drops placed on skin that has been marked with lines/numbers

http://www.mayoclinic.com/health/allergy-tests/MM00385

Positive and negative controls

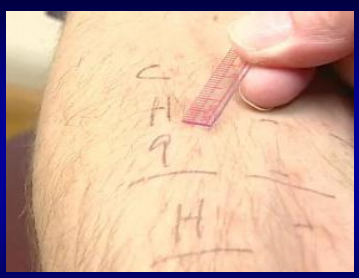
- Prick Positive control:
  - 1.0 mg/mL histamine base (2.75 mg/mL histamine phosphate aqueous)
  - 1.8 mg/mL histamine base (5 mg/mL histamine phosphate, glycerinated)
  - Need minimum of 2-7 mm flare
- Prick Negative control:
  - 50% glycerinated HSA-saline
- ID Positive control:
  - 0.10 mg/mL histamine base (0.275 mg/mL histamine phosphate aqueous)
- ID negative control:
  - HSA-saline

SPT using Lancet



http://www.mayoclinic.com/health/allergy-tests/MM00385

SPT reading using ruler



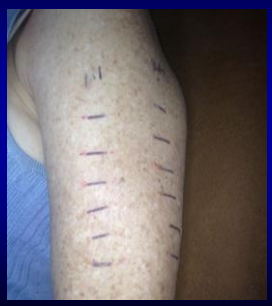
Read prick histamine and control at 15 minutes; read allergens at 15-20 minutes

http://www.mayoclinic.com/health/allergy-tests/MM00385

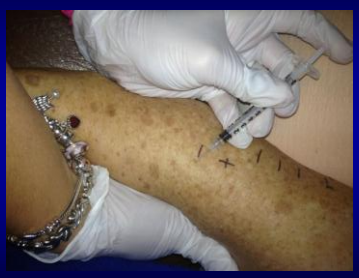
SPT on arm

SPT on back

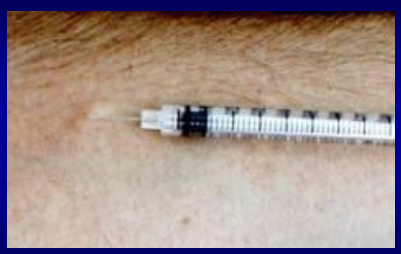
Intradermal Skin Testing (Upper Arm)



Intradermal Skin Testing (Upper arm)

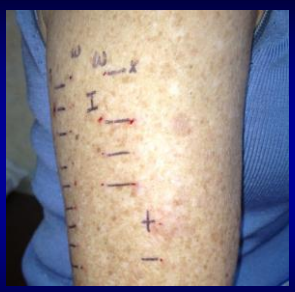


Intradermal skin testing



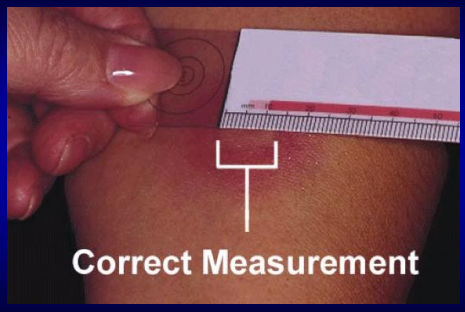
Deliver 0.02 to 0.05 mL of a diluted (100-1000 fold) prick extract concentration.
This is usually a 1:100 to 1:1000 w/v or 10-100 BAU or AU
Use 26-30 gauge needle.

Intradermal Test Reading

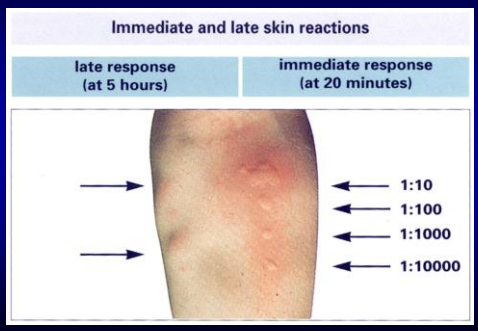


Read ID testing to histamine and control at 10 minutes and to allergens at 15 minutes.

Correct skin test measurement



ID End Point Titration



Skin testing elements to record

- Patient demographics
- Technician
- Date and time of day
- Last use of antihistamine (day/time)
- Testing device used
- Location of tests
- Testing concentration (W:V, PNU, AU, BAU)
- Extract manufacturer for each allergen
- Time read after placement (e.g. 15 minutes)

Recording skin test responses

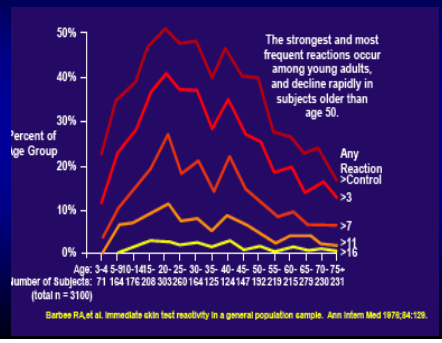
- Useful to report both wheal and flare measurements in **mm** (not a 1+ to 4+ grading)
  - Recommended method is to measure the reaction in mm across the longest diameter and the orthogonal diameter
    - Wheal (e.g. 12 mm x 8 mm)
    - Erythema (e.g. 22 mm X 20)

Inter-individual variation in SPT

Test result	Nurse 1	Nurse 2	Nurse 3	Nurse 4	CV
Negative control	0.1 mm	0.4 mm	0.2 mm	0.2 mm	55.9%
Histamine	11.7 mm	9.7 mm	12.9 mm	14.5 mm	16.6%
Grass	2.1 mm	2.5 mm	4.7 mm	5.2 mm	42.8%
Mugwort	7.7 mm	4.8 mm	7.4 mm	9.1 mm	24.7%
Dog	1.5 mm	1.1 mm	3.0 mm	2.5 mm	43.3%
House dust mite	1.7 mm	2.2 mm	1.6 mm	2.8 mm	26.5%

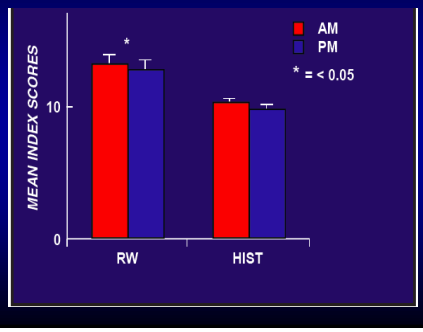
CV= coefficient of variation, target < 25%

Skin test reactivity based on age

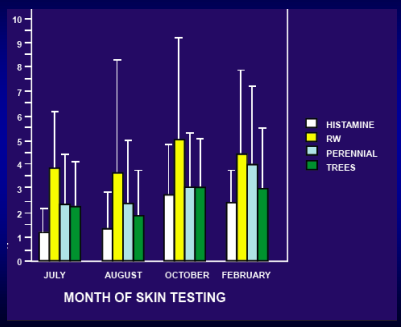


Circadian Skin Reactivity

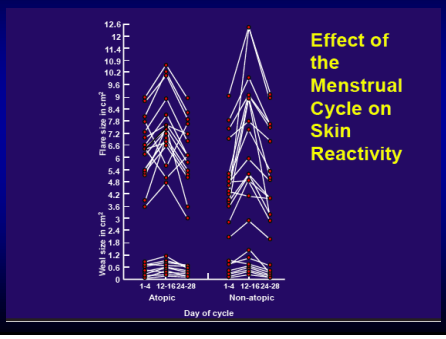
Statistically but not clinically significant



Seasonal variations in SPT



Menstrual Cycle and SPT



SPT vs. ID Testing

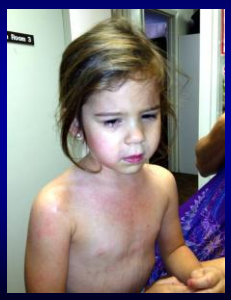
Advantages of SPT	Advantages of ICT
Safer	More sensitive:
More rapid	(300 to >1000 fold)
Less discomfort to patient	More reproducible
Technically less demanding	More positives
More specific	
More allergens in one session	
Allergen more stable (50% glycerin)	
Positive and negative tests more easily distinguished	
Steeper dose response curve	
Positive tests correlate better with clinical disease	

Skin test safety

- Review of surveys of fatal reactions to skin testing between 1959-2001
- 9 deaths associated with skin testing
- 1 death associated with SPT
  - History of unstable asthma with FEV-1 36% 1 week prior
  - Tested to 90 foods
- 8 deaths associated with intradermal testing

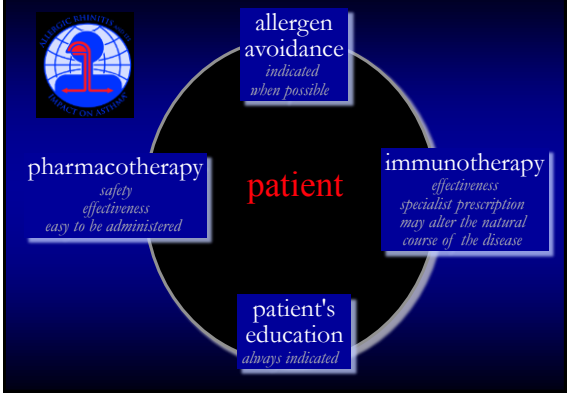
Lockey JACI 1987;79:660-77
Reid JACI 1993;92:6-15
Bernstein JACI 2004;113:1129-36

Be Prepared to Treat Anaphylaxis



Be Prepared to Treat Anaphylaxis

Modified from



Mechanisms

It has been demonstrated that specific immunotherapy (SIT) decreases allergen-induced inflammation in allergic rhinitis and allergic asthma.

ARIA 2001

The Experimental Evidence

SIT decreases the migration of eosinophils

Nagayata H, 1996

SIT decreases eosinophil numbers and airways BHR

Van Oosterhat AJ, 1988

SIT decreases the number of mast cells

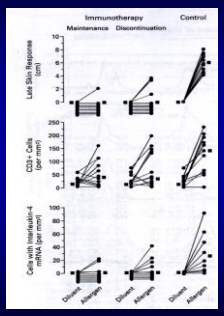
Durham, S R, 1997

SIT decreases the number and activity of eosinophils

Rak 1988, Durham 1996

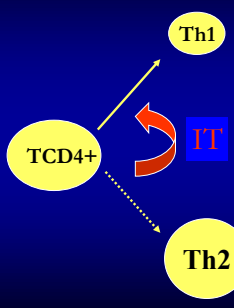
Mechanisms

- Reduction in late skin reactions
- Decrease in CD3+ cells
- Decrease in IL-4 cells
- Mechanisms are probably:
  - Heterogeneous
  - Allergen dependent
  - Allergic dz site dependent
  - Vary with route, dose, and duration of SIT



Durham S R, N Engl J Med 1996

Mechanisms

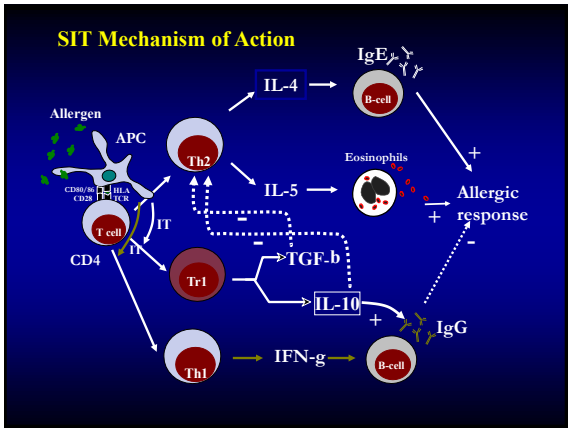


IL-2
INF-g

IMMUNE DEVIATION?

Both TH1 and TH2 play a role

IL-4
IL-5
IL-9



Factors to be Considered Before Prescribing Immunotherapy

- Presence of an IgE-mediated disease (allergic rhinitis, allergic asthma hymenoptera hypersensitivity)
- Symptoms are caused by specific allergen(s).
- Non-allergic triggers identified
- Severity and duration of symptoms
- Response to allergen avoidance and pharmacotherapy

Factors to be Considered Before Prescribing Immunotherapy

- Contraindications

Modified from WHO, 1998

Contraindications for Allergen Immunotherapy

- Failure to be able to communicate effectively with the physician, based on mental or physical disabilities
- Poor compliance
- Severe or unstable asthma

Relative Contraindications for Allergen Immunotherapy Must determine risk vs. benefit

- Medical conditions that might significantly reduce survival from anaphylaxis or the treatment thereof, e.g. severe cardiovascular disease
- Continued use of beta adrenergic blocking agents

Factors to be Considered Before Prescribing Immunotherapy

- Contraindications
- Cost/ benefit ratio
- Availability of standardized extracts
- Documented efficacy of allergen used for SIT
- Patient's previous experience with SCIT

Modified from WHO, 1998

Subcutaneous Specific Immunotherapy

Based on Survey Data

- ***Near-Fatal Systemic reactions occur:***
  - up to **5.4** (unconfirmed) per million injections[4]
- ***Fatal Systemic reactions occur:***
  - **1 in 2.5** million[5,6,7]

1. Rogala, Markiewicz-endkowska et al.2007. 2. Greenberg MA, et al. J Allergy Clin Immunol 1986;77:865-870
3. Cox, L. Allergen Immunotherapy 2011. 4. Amin, Liss et al. JACI 2006; 117 (1) 169-72.
5. Lockey RF, Nicoara-Kasti CL, et al. Ann Allergy Asthma Immunl 2001;87:47-55
6. Lockey, Benedict et al. 1987 7. Reid, Lockey et al. 1993. 8. Bernstein, Wanner et al. 2004 9. Webber, C. M. et al. "Assessing the safety of subcutaneous immunotherapy dose adjustments." Annals of Allergy 105(5): 369-75.

Fatalities from SCIT *(excluding skin testing)*

Author	Yrs	Total #
Bernstein (2010)	2008-2009 2001-2007	0** 6
Bernstein (2004)	1990-2001	41
Turkeltaub (1994)	UK	35
Reid (1993)	1985-1989	17
Lockey (1987)	1973-1984 1959-1973	18 6
United Kingdom (1986)	1957-1986	26
Case reports (Lamson, Waldbon, Vaughn, Vance, Janes, Rands, Pollard)	1929-1980	7
TOTAL		**156**

Systemic reactions are not rare!

Review of 38 studies[1]

- Per allergy injection: 0.95 to **3.2%**
- Per patient on SCIT: 0.8% to **46.7%** with mean of **12.2%**

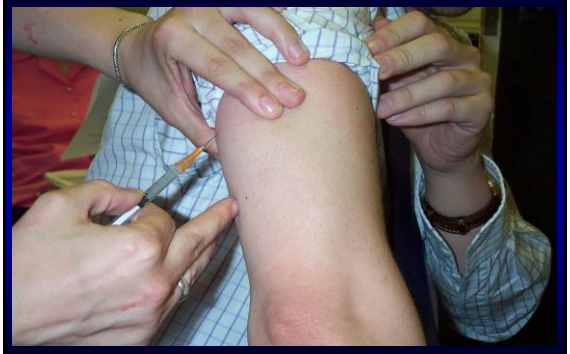
1. Stewart GE 2nd, Lockey RF: Systemic reactions from allergen immunotherapy. JACI 1992, 90:567-78

Risk Factors Based on Fatal and Non-Fatal Reactions

- Uncontrolled asthma
- Severe asthma
- Use of beta-blockers
- Rush immunotherapy
- Build-up phase
- Use of new vials
- Technical errors
- Delayed administration of epinephrine

PROVIDE ADEQUATE TRAINING FOR AI NURSE

Administration of Immunotherapy



Injection Technique

- Use upper outer surface of arm
- Ensure sterile technique
- Use 1 ml syringe
- Inject at 45º by deep subcutaneous route
- Record any local/systemic reaction

ALLERGY INJECTION OBSERVATION TIME

- **2007 & 2011** Joint Task Force on Practice Parameters on Immunotherapy=**30 minutes**[1]
- **2010** Joint Task Force Practice Parameters on Anaphylaxis=**30 minutes**
- 1990-2001 AAAAI survey found 77% fatal reactions and 96% Non-fatal reactions were ≤ 30 minutes= recommendation of **30 minutes**[2]

1. Cox, L., J. Li, et al. "Allergen immunotherapy: A PP 2nd update." JACI**120(3): S25-S85**
2. Bernstein, D, Wanner M, et al. J allergy Clin Immunol 2004; *113:1129-1136.*

Beyond SCIT
Now & in the Future

Non-Injection or Local Routes (common)

- Oral immunotherapy (OIT): allergen immediately swallowed, as drops, tablets or capsules.
- Sublingual immunotherapy (SLIT): allergen kept under the tongue for 1-2 minutes, then swallowed (the sublingual- spit mode is no longer in use).

Non-Injection or Local Routes (uncommon)

- Local nasal (LNIT): allergen sprayed into the nostrils as aqueous solution or dry powder.
- Local bronchial (LBIT): allergen inhaled with a deep inspiration.
- Intralymphatic injections with polymerized vaccines

Why do we need SLIT?

- **Only 2.5% of US AR patients are on SIT**
  - **Inconvenient and time consuming**
  - **Requires in-office treatment**
  - **Takes too long to start to work**
  - **Has undesirable side effects**
    - **Anaphylaxis**
    - **Large local reactions**
  - **Fear of injections, especially children**
  - **Pharmacological oral medications are preferred**

SLIT-Swallow: Efficacy

A meta-analysis of 22 DBPC trials has shown that SLIT is effective in rhinitis caused by pollens and mites.

There are fewer studies showing additional efficacy on asthma symptoms.

SLIT-Swallow: Efficacy

The long-lasting effect has been demonstrated in children with mite-induced asthma.

Di Rienzo et al Clin Exp Allergy 2003

The preventive effect on new skin sensitizations has been demonstrated.

Marogna et al Allergy 2004

SLIT: Safety

- In post-marketing studies, the overall rate of side effects (all grades) ranges between 3% and 8% of patients.
- The most frequently reported side effects are local (gastrointestinal); oral itching/swelling, nausea, stomach-ache.
- The side effects are usually mild and treatment discontinuation is rarely required.

SLIT: Safety

- Gastrointestinal side effects are dose-dependent.
- No life-threatening side effect or fatality has ever been reported since the introduction of SLIT in 1986.
- The occurrence of systemic effects in controlled trials does not differ from the placebo treated patients.

Local Routes: Sublingual-Swallow Immunotherapy

May be indicated in pollen and mite induced rhinitis and asthma in adults and children, using maintenance dosages 5 - 100 times higher then injection IT.

Efficacy of sublingual immunotherapy in allergic rhinitis in pediatric patients 4 to 18 years

Meta-analysis of RCT

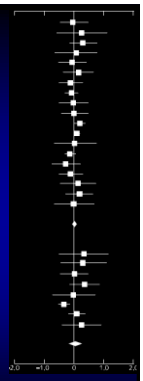
Penagos M., Compalati E., Tarantini F.,Baena Cagnani R., Huerta Lopez J., Passalacqua G., & Canonica G.W.

Annals of Allergy Asthma and Immunology 2006

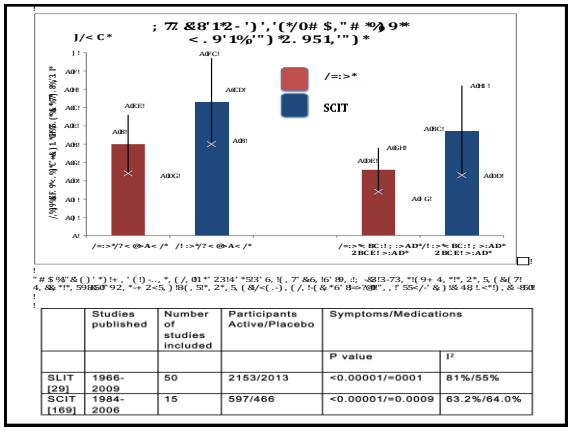
Conclusion:

SLIT reduces both symptom and medication scores in pediatric patients with

allergic rhinitis.



Penagos et al. Annals of Allergy Asthma and Immunology 2006



	Studies published	Number of studies included	Participants Active/Placebo	Symptoms/Medications	
				P value	I²
SLIT [29]	1966-2009	50	2153/2013	<0.00001/=0001	81%/55%
SCIT [169]	1984-2006	15	597/466	<0.00001/=0.0009	63.2%/64.0%

SLIT in Children

- Subsequently, several large clinical trials demonstrated that grass pollen SLIT was as efficacious in the pediatric allergic rhinitis population as in the adult populations[1,2]
- Pediatric AR Meta-analysis of 10 studies (1990-2004), 484 pts (245 SLIT, 239 placebo) showed:

1. Halken,S., et al., Five-grass pollen 300IR SLIT tablets: efficacy and safety in children and adolescents. Pediatr Allergy Immunol, 2010. 21(6): p. 970-6.
2. Wahn, U., et al., Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. J Allergy Clin Immunol, 2009. 123(1): p. 160-166 e3.

SLIT in Children

- **Significant symptom reduction** (SMD, 0.56, 95% CI, 1.01-0.10; P = .02)
- **Significant reduction in medication use** (SMD, 0.76; 95% CI, 1.46-0.06; P = .03)
- SLIT for **> 18 months was more effective**
- SLIT for **pollen allergy** was more effective than that for **dust mite**

1. Halken,S., et al., Five-grass pollen 300IR SLIT tablets: efficacy and safety in children and adolescents. Pediatr Allergy Immunol, 2010. 21(6): p. 970-6.
2. Wahn, U., et al., Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. J Allergy Clin Immunol, 2009. 123(1): p. 160-166 e3.

The Oral (SLIT) Route for SIT

- Oral mucosa has natural tolerogenic characteristics:
  - High bacterial colonization without inflammation
  - Rapid wound healing without scar formation
  - High permeability
- Langerhans cells (dendritic cells)
  - Present in large numbers in oral mucosa
  - Have high affinity IgE receptor on surface

SLIT: Mechanism of action

- Exact mechanism less well studied than SCIT
- Appears to have common mechanisms
  - ↓ Mast cell & basophil degranulation (within hours following the 1st Tx)
    - Decreased response to allergen challenge
  - T Reg cells producing inhibitory cytokines
    - IL-10, IL-12, TGF-β (↑ in nasal mucosa)
  - Increase in sublingual FOXP3-expressing cells (also ↑ in nasal mucosa)

SLIT: Mechanism of action

- Increase in s-IgG4 **(IL-10 stimulate B cells to produce)** and s-IgA antibodies **(TGF-B stimulate B cells to produce)**
- IgE-blocking antibodies
- Reduction of # and binding of s-IgE antibodies
- Blunting of seasonal increases in s-IgE
- IFN-□ production following Th1 cell stimulation

Allergen Immunotherapy Can Modify the Natural History of Allergy

- **Allergen immunotherapy is the only treatment that can modify the natural history of allergic disease.**
- **SCIT and SLIT- swallow can prevent the onset of new sensitizations.**

SLIT: Unanswered questions

- What is the ideal dose?
  - 0.17 to 500 x SCIT dose for monthly maintenance has been used
- When does it start to work?
  - 4-8 wks for most patients
  - However, up to 38% may not show improvement at 12 months

SLIT: Unanswered questions

- Is there a dose response?
  - Earlier studies did not always show this, but more recent studies suggest a dose response in relationship to:
    - Symptom reduction
    - Immunological changes
      - Increase in specific IgG4
      - Reduction in specific-IgE
      - Increase in IgE blocking antibody

SLIT: Unanswered questions

- Do the benefits continue after treatment is stopped?
  - Persistent improvement 3 yr after stopping has been shown
- Does SLIT have disease-modifying effect?
  - Indeed, this seems to be the case
- Does monotherapy work in polysensitized pts?
  - It seems equal efficacy in mono or polysensitized pt for the item used in treatment

SLIT: Unanswered questions

- What is the proper dosing interval?
  - Studies have varied, usually daily to 3 times/week
  - Daily may improve compliance
  - Noncompliance is relatively high but better than taking oral or intranasal medications

SLIT: Unanswered questions

- Does multiallergen SLIT work in polysensitized pts
  - Most US AR pts are allergic to ≥ 3 allergens
  - Very limited research on multiallergen SLIT
  - One study showed more improvement when multiallergens used[1]
  - One study showed that grass monotherapy was ineffective when administered as part of a multiple allergen mix[2]
  - **THE VERDICT IS STILL TO BE DETERMINED**

Marogna M, S.I., Massolo A, Zanon P, Berra D,Chiodini E, Canonica W, Passalacqua G, Effects of sublingual immunotherapy for multiple or single allergens in polysensitized patients. Annals of Allergy, Asthma and Immunology 2007. 98(3): p. 274 – 280
Amar, S.M., et al., Response to sublingual immunotherapy with grass pollen extract: monotherapy versus combination in a multiallergen extract. J Allergy Clin Immunol, 2009. 124(1): p. 150-156 e1-5.

Allergen Immunotherapy Can Modify the Natural History of Allergy

- **SCIT and SLIT-swallow administered for several years (3 to 5 years) - efficacy is maintained for up to 3 or more years after discontinuation.**
- **SCIT could prevent the onset of asthma in children with allergic rhinitis.**

Allergen Specific Immunotherapy vs. Pharmacologic Treatment

- **Specific immunotherapy does not take the position of being an ultimate treatment principle. It should be part of the global treatment, and should be used in the early phase of disease.**

Modified from ARIA JACI 2001

Conclusion

- **Allergen Specific Immunotherapy is an effective and safe treatment of allergic rhinitis, allergic asthma and hymenoptera venom allergy**