New Frontiers in Allergen Immunotherapy

Bryan Martin, DO, MMAS, FACP, FACOI, FAAAI, DFACAAI

President, The American College of Allergy, Asthma & Immunology
Emeritus Professor of Medicine and Pediatrics

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER
Disclosures

- Speakers Bureau:
  - MEDA
Objectives

1. Review the state of the art for Immunotherapy in the United States
2. Understand the current concerns regarding the mixing of immunotherapy extracts
3. Explain the differences between standardized and non-standardized extracts
4. Recognize the effective dosing range of each component of the extract
First:
A little History
Immunotherapy: the beginning

- In 1911 Leonard Noon first used the technique of specific immunotherapy.
- First two publications:
- Noon dies of tuberculosis in 1913.
PROPHYLACTIC INOCULATION AGAINST HAY FEVER.

By L. NOON, B.C. Cant. (For the Laboratory of the Department for Therapeutic Inoculation, St. Mary's Hospital.)

Hay fever is a form of recurrent catarrh afflicting certain individuals during the months of May and June, and it is caused by a soluble toxin found in the pollen of grasses. The patients present the idiosyncrasy of being sensitive to this specific antigen. The idiosyncrasy may be detected during any season of the year by placing a drop of the suspected patient's serum on an area of skin that is then observed. If the reaction is positive, the patient is then treated for the same number of seasons as the number of times the test was positive, or for a period of six months. When the patient has been treated for six months, the reaction is retested and, if negative, the patient is allowed to resume outdoor activities.

Toxoid (1878) has recognized the seasonal recurrence of hay fever, and has noted that it is accompanied by a specific idiosyncrasy of the patient. He has observed that the idiosyncrasy is transmitted by the pollen of grasses, which contains a specific antigen that is responsible for the symptoms. The patient is then treated with a series of doses of the pollen extract, and the reaction is observed to determine the appropriate dosage. If the reaction is negative, the patient is allowed to resume outdoor activities.

In order to express the strength of the pollen extract and its effect on the patient, the following scale is used: 1-2, 2-4, 4-8, 8-16, and 16-32. The patient is then treated with the lowest dose that produces a positive reaction. The dosage is then increased until the patient is able to resume outdoor activities without symptoms. If the patient is able to tolerate the 16-32 dosage, he is allowed to resume outdoor activities.

In the case of the patient described, the pollen extract was administered in a dosage of 16-32, and the patient was able to resume outdoor activities without symptoms. The patient was then observed for a period of six months, during which time he was able to resume outdoor activities without symptoms. The patient was then allowed to resume outdoor activities without symptoms.

1 John Backer, Medical and Therapeutical Transactions, vol. 19, p. 186.

Further report after the present hay fever season. This work is now in the hands of my colleagues, Dr. J. Freeman, who is very kind to me, and the reports of the observations during my absence are to be expected in a few days.
1911-2011
100 years of Immunotherapy
If Dr. Noon Walked into your shot room…

- He would be familiar with much of what being done, and many of our concerns.
- The issue of standardization was identified as early as 1916
  - Dr. R.A. Cooke established standardization by the nitrogen unit
X-ray room: 1910

Copies of picture available from Star Stationery Shop, Lower Stuart St, or www.otagoimages.co.nz
Allergen immunotherapy: A practice parameter third update

Chief Editors: Linda Cox, MD, Harold Nelson, MD, and Richard Lockey, MD
Workgroup Contributors: Christopher Calabria, MD, Thomas Chacko, MD, Ira Finegold, MD, Michael Nelson, MD, PhD, and Richard Weber, MD
Task Force Reviewers: David I. Bernstein, MD, Joann Blessing-Moore, MD, David A. Khan, MD, David M. Lang, MD, Richard A. Nicklas, MD, John Oppenheimer, MD, Jay M. Portnoy, MD, Christopher Randolph, MD, Diane E. Schuller, MD, Sheldon L. Spector, MD, Stephen Tilles, MD, and Dana Wallace, MD

Key words: Allergy immunotherapy, subcutaneous immunotherapy, sublingual immunotherapy, allergic rhinitis, asthma, Hymenoptera, atopic dermatitis, anaphylaxis, epinephrine, β-blockers, angiotensin-converting enzyme inhibitor, epicutaneous immunotherapy, intralymphatic immunotherapy

These parameters were developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology. The American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma & Immunology have jointly accepted responsibility for establishing “Allergen immunotherapy: A practice parameter third update.” This is a complete and comprehensive document at the current time. The medical environment is a changing environment, and not all recommendations will be appropriate for all patients. Because this document incorporated the efforts of many participants, no single individual, including those who served on the Joint Task Force, is authorized to provide an official AAAAI or ACAAI interpretation of these practice parameters. Any request for information about or an interpretation of these practice parameters by the AAAAI or the ACAAI should be directed to the Executive Offices of the AAAAI, the ACAAI, and the Joint Council of Allergy, Asthma & Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion. A current list of published practice parameters of the Joint Task Force on Practice Parameters for Allergy and Immunology can be found in Table E1 in this article’s Online Repository at www.jacionline.org.

CONTRIBUTORS
The Joint Task Force has made a concerted effort to acknowledge all contributors to this parameter. If any contributors have been excluded inadvertently, the Task Force will ensure that appropriate recognition of such contributions is made subsequent to publication. The Joint Task Force gratefully acknowledges the AAAAI Board of Directors and the ACAAI Board of Regents for their review and support of this document.

The authors and editors gratefully acknowledge Susan Grupe and Jessica Karle for their administrative assistance.

CHIEF EDITORS
Linda Cox, MD
Department of Medicine, Nova Southeastern University College of Osteopathic Medicine Davie, Florida
Richard Lockey, MD
Division of Allergy and Immunology Department of Internal Medicine

2003: First Allergen Immunotherapy Practice Parameter
2007: Allergen Immunotherapy: Practice Parameter Second Update

Declaration of potential conflict of interest: L. Cox is a consultant for Genentech/Merck, Hollister-Stier, and Stallergenes; is on the Board of Directors for the American Board of Allergy and Immunology; and is on the US Food and Drug Administration’s (FDA’s) Allergenic Product Advisory Committee. H. Nelson has received research support from Stallergenes; is on the Board of Directors for the American Board of Allergy and Immunology; and is on the US Food and Drug Administration’s (FDA’s) Allergenic Product Advisory Committee. R. Weber is on the speakers’ bureau for Astrazeneica and Genentech, has received research support from Novartis and GlaxoSmithKline, and is a consultant for the ACAAI. D. I. Bernstein is a consultant and, on the advisory board for ALK, is on the advisory board for Merck; and has received research support from Merck and Schering-Plough. J. Bledsoe is a speaker for Merck-Schering/AstraZeneca, Novartis, and TEVA; and has received research support from ALK. A. Khan is a speaker for Astrazeneica and Merck; has received research support from the Varberg Foundation and the Billings Foundation; is a Co-chair of the Board of Directors of the ACAAI; and is a past president of the Texas Asthma, Allergy, and Immunology Society. D. M. Lang is a speaker and consultant for GlaxoSmithKline; is a speaker for AstraZeneca, Merck, TEVA, Sanofi-Aventis, and Genentech/Novartis; and has received research support from Genentech/Novartis. R. A. Nicklas is a fellow for the ACAAI. J. Oppenheimer is a consultant and has provided lectures for Astaanzeneca, Merck, and GlaxoSmithKline; and has received research support from Astaarzeneca, Merck, GlaxoSmithKline, and Genentech. J. M. Portnoy is a speaker for Phadia, Merck, and CSL Behring; has received research support from the US Department of Housing and Urban Development; and is a board member of the ACAAI board of regents. S. L. Spector has received research support from Genentech, GlaxoSmithKline, Schering-Plough, Aventis, Novartis, Pharmacia, Boehringer Ingelheim, Amgen, Roche, and Sanofi; has received research support from the US Department of Housing and Urban Development; and is a board member of the ACAAI board of regents. S. Tilless is a speaker for AstraZeneca; has received research support from AstraZeneca; and is a board member of the ACAAI board of regents. D. Wallace is a speaker and advisor for AstraZeneca; is a speaker for Merck and Sanofi-Aventis; and is President-Elect of the ACAAI. The rest of the authors have declared that they have no conflict of interest.

Received for publication September 18, 2010, accepted for publication September 23, 2010.
Available online December 7, 2010.
Reprint requests: Joint Council of Allergy, Asthma & Immunology, 50 N Wickersley St, Suite 53, Evanston, IL 60201. E-mail: lindacoxx@asn.com.
© 2010 American Academy of Allergy, Asthma & Immunology doj:10.1067/j.aai.2010.09.034

2011

THE OHIO STATE UNIVERSITY WEXNER MEDICAL CENTER
Why is this so Important?

- Estimated that 30% of the general population is affected by at least one allergic condition.
- Allergen Immunotherapy is the only therapy that can provide long lasting tolerance.
The Practice of Immunotherapy

- **Subcutaneous**
  - Allergy shots

- **Sublingual**
  - Tablets or drops under the tongue

- **Investigational**
  - Oral
    - Swallowed
  - Epicutaneous
  - Intradermal
  - Intralymphatic (ILIT)
    - 3 injections into an inguinal lymph node
Subcutaneous Immunotherapy (SCIT)

- First randomized controlled study published in 1954*
- Generally weekly or biweekly injections during build up phase followed by monthly maintenance injections for 3-5 years
  - Majority of Immunotherapy in the US
  - Multiple allergens mixed into single injection is the norm rather than monotherapy

**CONCERNS**

- **Safety:** Risk of anaphylaxis: Shots given in physician’s office
- **Standardization** of extracts

Sublingual Immunotherapy (SLIT)

- Attempt to provide immunotherapy with a safer technique
- 1986: first randomized, double-blind placebo-controlled trial with SLIT*
- 1998: First mentioned as a possible alternative to SCIT in a WHO position Paper+
- 2009: World Allergy Organization position paper provides official acceptance of SLIT^ 
- SLIT has numerous variables:
  - Administration by drops, monodose vials, tablets
  - Schedules and doses are not standardized

Sublingual Immunotherapy (SLIT) in the US

- No liquid extracts are approved for SLIT
  - Being used in US “Off Label”
- US FDA approved sublingual tablets in April 2014
  - Oralair
    - 100 and 300 IR tablets
    - Mixture of freeze dried extracts from the pollens of 5 grasses (Kentucky Blue Grass, Orchard, Perennial Rye, Sweet Vernal & Timothy)
  - Grastek
    - 2800 BAU Timothy grass pollen
  - Ragwitek
    - 12 Amb a 1-unit of Short Ragweed
Although SLIT tablets were approved by the FDA in 2014, utilization has been low.

2013: 11% of American practices prescribe off label SLIT* with liquid extracts

If safety is a concern with SCIT and SLIT was conceived as part of the solution to safety concerns why isn’t SLIT more popular among American allergists?

- Older allergists did not learn about SLIT during fellowship
- Current Practice Parameters only address SCIT

Box 1
Shared and differing attributes of SCIT and SLIT

**Shared**

1. Effective treatment of allergic rhinitis and allergic asthma, with some support for use in selected patients with atopic dermatitis.

2. Defined optimal doses for standardized liquid extracts (SCIT) and SLIT tablets.

3. Underlying immunologic response
   a. Early induction of regulatory T cells.
   b. Later immunodeviation from a predominant Th2 to a Th1 response to the administered allergen.
   c. Suppression of Th17 responses.

4. Evidence for disease modification
   a. Reduction of additional sensitization in monosensitized patients.
   b. Reduction in the development of asthma in patients with allergic rhinitis.
   c. Persisting benefit after stopping an effective course of treatment.

**Differing**

1. Frequency and severity of systemic reactions (favors SLIT).

2. Clinical efficacy with Hymenoptera venom (favors SCIT) and for food allergy (favors SLIT).

3. Lack of defined optimal doses for SLIT liquids (favors SCIT).

4. Proven effectiveness of multiple allergen mixes with SCIT but not SLIT (favors SCIT).

5. Clinical efficacy (currently available studies favor SCIT).
Oral Immunotherapy (OIT)

- OIT is NOT new!
  - First described in 1908
  - Dr. Schofield reported the successful oral desensitization to raw egg in a teenage boy with anaphylactic egg allergy*.

- Clinical trials are underway using OIT in food allergy
  - Single food and multi-food studies have shown promise
  - Adverse reactions are common in OIT trials
  - Thought to utilize GALT pathways that underlie physiologic responses to food antigens and oral tolerance

- Not yet a US FDA approved option

Schofield AT. A Case of egg poisoning. Lancet (1908) 1:716
Concerns about standardization date back to 1916

Standardized extracts provide better understanding of the allergenicity of the extract & increase safety

A number of methods have been developed to standardize allergen extracts

Different standardized units measured in different ways
Current US Allergy Units
Why we need to standardize our products

- **Weight per volume** (w/v) = grams per mL (note that 1:10=1/10)
- **Protein nitrogen units** (PNU/mL) = mg protein per mL
- **Micrograms major allergen** (mcg/mL)
- **Allergy units** (AU/mL) = potency of reference vials at the FDA
- **Bioequivalent allergy units** (BAU/mL) = potency that gives 50mm erythema
- **Index of Reactivity** (IR) = 100 IR/ml induces 7 mm wheal in 30 sensitized patients
Protein Nitrogen Unit (PNU)

- Early attempts at standardization were based on total protein contents of the vial
- Uniformative measure
US Standardized products (n = 19+3)

- D. farinae
- D. pteronyssinus
- Cat hair
- Cat pelt
- Short ragweed pollen
- Hymenoptera
  - Honey bee
  - Wasp
  - Yellow jacket
  - Yellow hornet
  - White-faced hornet
  - Mixed vespid
- Grass pollens
  - Bermuda grass
  - Red top
  - June (Kentucky blue)
  - Perennial rye
  - Orchard
  - Timothy
  - Meadow fescue
  - Sweet vernal
- Sublingual
  - Grass (Oralair and Grastek)
  - Ragweed (Ragwitek)
US Unitage for standardized allergens

- **SCIT**
  - Hymenoptera venoms - µg protein
  - Mites - AU
  - Grass pollens - BAU
  - Cat hair and cat pelt – BAU and Fel d 1 U

- **SLIT**
  - Grass (Oralair) – IR
  - Grass (Grastek) - BAU
  - Ragweed (Ragwitek) - Amb a 1-unit of Short Ragweed
Why is standardization so important?
# Major Allergen Content: U.S. Unstandardized Extracts

<table>
<thead>
<tr>
<th>Extract</th>
<th>Conc.</th>
<th>Major Allergen</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>olive</td>
<td>1:10 w/v</td>
<td>Ole e 1</td>
<td>470</td>
</tr>
<tr>
<td>Birch</td>
<td>1:10 w/v</td>
<td>Bet v 1</td>
<td>380</td>
</tr>
<tr>
<td>Eng plant</td>
<td>1:10 w/v</td>
<td>Pla l 1</td>
<td>30</td>
</tr>
<tr>
<td>Brome</td>
<td>1:10 w/v</td>
<td>Group 5</td>
<td>215</td>
</tr>
<tr>
<td>Dog</td>
<td>1:10 w/v</td>
<td>Can f 1</td>
<td>5</td>
</tr>
<tr>
<td>Dog (AP)</td>
<td>1:100 w/v</td>
<td>Can f 1</td>
<td>140</td>
</tr>
<tr>
<td>Alternaria</td>
<td>1:10 w/v</td>
<td>Alt a 1</td>
<td>1 - 5</td>
</tr>
<tr>
<td>Cockroach</td>
<td>1:20 gly</td>
<td>Bla g 2</td>
<td>8-66*</td>
</tr>
</tbody>
</table>

* ALK-Abello 2004  * Jay Slater
Probable effective SCIT dose range for allergen extracts: US units

<table>
<thead>
<tr>
<th>Allergenic extract</th>
<th>Labeled potency or concentration</th>
<th>Probable effective dose range</th>
<th>Range of estimated major allergen content in US-licensed extracts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dust mites: <em>D. farinae</em> and <em>D. pteronyssinus</em></td>
<td>3,000, 5,000, 10,000, and 30,000 AU/mL</td>
<td>500-2,000 AU</td>
<td>10,000 AU/mL - 20-160 μg/mL Der p 1, Der f 1*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2-180 μg/mL Der p 2, Der f 2*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>78-206 μg/mL Der p 1, Der f 1†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>13-147 μg/mL Der p 2, Der f 2†</td>
</tr>
<tr>
<td>Cat hair</td>
<td>5,000 and 10,000 BAU/mL</td>
<td>1,000-4,000 BAU</td>
<td>10,000 BAU/mL - 20-50 μg/mL Fel d 1*†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10,000 BAU/mL - 30-100 μg/mL cat albumin§</td>
</tr>
<tr>
<td>Cat pelt</td>
<td>5,000-10,000 BAU/mL</td>
<td>1,000-4,000 BAU</td>
<td>10,000 BAU/mL - 20-50 μg/mL Fel d 1*†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>400-2,000 μg/mL cat albumin§</td>
</tr>
<tr>
<td>Grass, standardized</td>
<td>100,000 BAU/mL</td>
<td>1,000-4,000 BAU</td>
<td>100,000 BAU/mL - 425-1,100 μg/mL Phil p 5*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>506-2,346 μg/mL group 1‖</td>
</tr>
<tr>
<td>Bermuda</td>
<td>10,000 BAU/mL</td>
<td>300-1,500 BAU</td>
<td>10,000 BAU/mL - 141-422 Cyn d 1 μg/mL*</td>
</tr>
<tr>
<td>Short ragweed</td>
<td>1:10, 1:20 wt/vol, 100,000 AU/mL</td>
<td>6-12 μg of Amb a 1</td>
<td>1:10 wt/vol - 300 μg/mL Amb a 1†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or 1,000-4,000 AU</td>
<td>Concentration of Amb a 1 is on the label of wt/vol extracts</td>
</tr>
<tr>
<td>Nonstandardized AP Dog</td>
<td>1:100 wt/vol</td>
<td>15 μg of Can f 1</td>
<td>80-400 μg/mL Can f 1†</td>
</tr>
<tr>
<td>Nonstandardized extract, dog</td>
<td>1:10 and 1:20 wt/vol</td>
<td>15 μg of Can f 1</td>
<td>10-20 μg/mL dog albumin§</td>
</tr>
<tr>
<td>Nonstandardized extracts: pollen</td>
<td>1:10 to 1:40 wt/vol or 10,000-40,000 PNU/mL</td>
<td>0.5 mL of 1:100 or 1:200 wt/vol</td>
<td>NA</td>
</tr>
<tr>
<td>Nonstandardized extracts: mold/fungi, cockroach</td>
<td>1:10 to 1:40 wt/vol or 10,000-40,000 PNU/mL</td>
<td>Highest tolerated dose</td>
<td>NA</td>
</tr>
<tr>
<td>Hymenoptera venom</td>
<td>100 μg/mL single venom 300 μg/mL in mixed vespid extract</td>
<td>50-200 μg of each venom</td>
<td>100-300 μg/mL of venom protein</td>
</tr>
<tr>
<td>Imported fire ant</td>
<td>1:10 to 1:20 wt/vol whole-body extract</td>
<td>0.5 mL of a 1:100 wt/vol to 0.5 mL of a 1:10 wt/vol extract</td>
<td>NA</td>
</tr>
</tbody>
</table>
Proteases become a problem when certain extracts are introduced into a mixed extract vial.

When extracts contain mixed allergens one must consider how each allergen extract affects others in the mix.

Extracts with high levels of protease include:
- Cockroach
- Molds
## Protease Content of Various Extracts

<table>
<thead>
<tr>
<th></th>
<th>Trypsin Equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pollens</td>
<td>&lt; 1 μg</td>
</tr>
<tr>
<td>Cat &amp; dog dander</td>
<td>&lt; 1 μg</td>
</tr>
<tr>
<td>House dust mites (US)</td>
<td>&lt; 5 μg</td>
</tr>
<tr>
<td>Alternaria alternata</td>
<td>29 μg</td>
</tr>
<tr>
<td>American cockroach</td>
<td>168 μg</td>
</tr>
<tr>
<td>Aspergillus fumigatus</td>
<td>212 μg</td>
</tr>
<tr>
<td>Penicillium notatum</td>
<td>242 μg</td>
</tr>
</tbody>
</table>

Robert Esch PhD, Greer Laboratories
<table>
<thead>
<tr>
<th>Allergenic Extract</th>
<th>Insects</th>
<th>Fungi</th>
<th>Mites</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insects</td>
<td>Ø</td>
<td>Ø</td>
<td>+</td>
<td>Whole-body insect extracts contain very high protease levels; susceptible to endogenous proteases unless stored in 50% glycerin</td>
</tr>
<tr>
<td>Fungi</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Fungal extracts do not appear to be adversely affected by proteases;</td>
</tr>
<tr>
<td>Mites</td>
<td>Ø</td>
<td>Ø</td>
<td>+</td>
<td>Mite allergens resistant to insect and fungal proteases if stored in ≥ 10% glycerin.</td>
</tr>
<tr>
<td>Pollens</td>
<td>×</td>
<td>×</td>
<td>+</td>
<td>Pollen extracts susceptible to insect and fungal proteases; compatible with mite extracts when stored in ≥ 10% glycerin.</td>
</tr>
<tr>
<td>Cat hair/epithelia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Fel d 1 in cat extract is highly resistant to fungal and insect proteases</td>
</tr>
<tr>
<td>Dog hair/epithelia</td>
<td>+</td>
<td>Ø</td>
<td>+</td>
<td>Dog allergens susceptible to most fungal extracts, but more stable when mixed with insect extracts.</td>
</tr>
</tbody>
</table>

Fig 1. Combinations producing low (X), moderate or risky (Ø), and favorable (+) compatibilities when allergenic extracts are mixed with protease-containing insect, fungal, and mite extracts are shown.

Esch JACI 2008;122:659-660
There is always a possibility of a reaction to immunotherapy

Perceived risks

Medical errors are in the American public perception

42% of the public report they have experienced an error in medical care
  - Themselves
  - Family member

Blendon et al, NEJM, 2002;347:1933-40
Immunotherapy Clinic

- Are our immunotherapy clinics a particular risk?

Personalized Health Care
- Individually compounded medication
  - Allergist devises based on his/her testing
- Allergist and team responsible for mixing
- Allergist and team responsible for delivery of medication
- Allergist and team responsible for monitoring
  - Both pre and post injection
Allergy Shot Room Risks: Errors

- 2004 JCAAI survey of 1717 allergists
- Know of an incorrect injection administered within the past 5 years in their office
  - Incorrect dose: 74%
  - Some one else’s injection: 58%

Aronson and Gandhi, JACI, 2004; 113(6):1117-1121
1655 Total Reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>No. Reported</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Reaction Only</td>
<td>1128</td>
<td>68</td>
</tr>
<tr>
<td>Systemic: No hospital care</td>
<td>443</td>
<td>27</td>
</tr>
<tr>
<td>Systemic: ED care</td>
<td>59</td>
<td>4</td>
</tr>
<tr>
<td>Systemic: Hospitalized</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Adapted from: Aronson and Gandhi, JACI, 2004; 113(6):1117-1121
Near-Fatal Reactions to IT

- 273/646 responding allergists reported a NFR
  - Respiratory compromise and/or hypotension
- 68 of these confirmed and evaluated using a 105-item questionnaire.

**Contributing Circumstances**

- Injections at height of season: 46%
- Dosing errors: 25%
- Asthma control issues: 10%
- Previous systemic rxn to IT: 9%
- Concomitant medication: 3%
- Premature departure: 3%

Amin et al, JACI, 2006, 117(1): 169-175
First SCIT fatality reported in 1929*

- **American studies regarding Death/Near Death to ST & IT**

*Lamson RW. JAMA. 1929;93:1776*
Limitations of the Studies

- Each of the 8 studies reviewing the fatal reactions to skin testing and SCIT were retrospective reviews.
  - Response rate on average was approximately 25% of allergists contacted
  - Fatal reactions are likely underreported due to methodology
  - Recall bias is a factor in individual responses
- Questions were not equivalent from survey to survey
- 2008 the US moved to an annual survey methodology focusing primarily on systemic reactions overall.
- Data has been & will continue to be used to increase safety of SCIT.
- US SCIT death reported in 2016
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reported Deaths</td>
<td>&gt;70</td>
<td>30</td>
<td>17</td>
<td>20 + 21 review</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Skin Testing</td>
<td>&gt;70: 61 to Ag no longer used</td>
<td>6: 5 due to ID w/o initial prick</td>
<td>0</td>
<td>1 90 food allergens placed</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Build Up</td>
<td>7</td>
<td>11</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maint</td>
<td>9</td>
<td>10</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In Season</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Extract</td>
<td>4</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>16</td>
<td>13</td>
<td>15</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Error</td>
<td>4</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Best Immunotherapy Clinic

- What systems can I put into place to minimize errors?
- What systems can I put into place to maximize safety?
- What additional training or documentation must office personnel have?
  - Standardized labels and markings
  - Training and testing of mixing personnel
### Suggested nomenclature for labeling dilutions from the maintenance concentrate

<table>
<thead>
<tr>
<th>Dilution</th>
<th>Vol/vol</th>
<th>label No.</th>
<th>Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maint. concentrate</td>
<td>1:1</td>
<td>1</td>
<td>Red</td>
</tr>
<tr>
<td>10-fold</td>
<td>1:10</td>
<td>2</td>
<td>Yellow</td>
</tr>
<tr>
<td>100-fold</td>
<td>1:100</td>
<td>3</td>
<td>Blue</td>
</tr>
<tr>
<td>1000-fold</td>
<td>1:1000</td>
<td>4</td>
<td>Green</td>
</tr>
<tr>
<td>10,000-fold</td>
<td>1:10,000</td>
<td>5</td>
<td>Silver</td>
</tr>
<tr>
<td>Advancement</td>
<td>Description</td>
<td>Comments</td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Route of administration</td>
<td>ILIT</td>
<td>The ILIT allows short courses of administration with lower doses of antigens. EPIT is totally noninvasive and, therefore, particularly suitable for children.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epicutaneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intradermal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formulation</td>
<td>Nanoparticles</td>
<td>At early experimental stage, with positive results in animal models</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Slow release/mucoadhesive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extract + adjuvants</td>
<td>Bacteria-derived adjuvants</td>
<td>Bacterial adjuvants already are commercially available for SCIT. Low number of injections. DNA-adjuvants are under experimental investigation, with a single human trial.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DNA-derived adjuvants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peptides</td>
<td>Long or short peptides</td>
<td>Under investigation, mainly with Fel d 1 allergen</td>
<td></td>
</tr>
<tr>
<td>Molecules</td>
<td>Recombinant/highly purified sensitizing molecules</td>
<td>Some trials available in humans. The single molecules seem not to perform better than the crude extracts.</td>
<td></td>
</tr>
<tr>
<td>New indications</td>
<td>Food allergy</td>
<td>Despite the existence of numerous trials with positive results, none of these indications is currently approved for clinical practice. Latex SLIT products are commercialized and used.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atopic dermatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Latex allergy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nickel allergy?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Summary

- SCIT is safe and effective
  - And has been for over 100 years
  - Current guidelines have helped make SCIT safer
  - There is still much room for improvement
- SLIT is safe and effective
  - Lags in popularity among US allergists
  - Only 3 FDA approved SLIT tablets
  - Ongoing studies may lead to additional approved antigens
- Standardization of allergens and the “mechanics” of providing IT can help continue to improve safety
Thank You

Questions?