



**Speaking the Same Language: Grading System for  
Subcutaneous Immunotherapy Systemic Reaction**  
World Allergy Organization Symposium  
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Chicago

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# Linda Cox, MD Disclosure

Allergist: solo private practice

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Medical advisory board/consultant: Stallergenes,

**Safety Data Monitoring Committee:** Circassia

**Adjudication Committee:** Novartis

Organizational interests:

- FDA Allergenic Products Advisory Committee: consultant
- AAAAI: President
- ABAI Board of Directors -member

# Learning Objectives:

Attendees will be able to discuss:

- Sublingual and subcutaneous immunotherapy adverse reactions: types and incidence per published studies ,post marketing surveillance & surveys
- Risk factors for immunotherapy adverse reaction
- The WAO Grading systems for SCIT/SLIT systemic reactions and SLIT local reactions
- Provide a common language through the New WAO initiatives on the AIT Adverse Reactions SCIT or SLIT to be used across the world to indicate those effects.

# Allergen Immunotherapy: The Pros

AIT is only disease modifying treatment for allergic respiratory disease

- Can provide sustained clinical benefits after discontinuation
- Prevent new allergy sensitivities
- Prevent asthma
- Is cost-effective –studies have demonstrated 30 to 80%cost-savings compared to pharmacotherapy alone



# AIT: The Con

- **SCIT SR rate** varies greatly depending on several factors: allergen dose, extract type, induction schedule, premeditation, extract type, etc.
- **SR rate:** review of SCIT studies that reported SR rate from 1995 -2010:
  - Per injection frequency was ~0.2%
  - Per patient rate of 2% to 7% in US studies with conventional schedules
- Purported advantage of accelerated schedules
  - Reduced number of visits to target dose BUT
  - Possible with increased risk of SR
    - Cluster risk may be the same or increased

# Allergy Immunotherapy Cochrane Database Systematic Reviews

Asthma 2010 , Allergic Rhinitis 2007



- ***Asthma:*** “ *If 9 patients were treated with SCIT, expect 1 to develop a SR of any severity*”
- **Allergic rhinitis:** “Adrenaline was given in 0.13% (19 of 14085 injections) of those on active treatment and in 0.01% (1 of 8278 injections) of the placebo group for treatment of adverse events.”

Abramson et al., Allergen immunotherapy for asthma Cochrane Database Syst Rev. 2010;8:CD001186.

Calderon et al, Allergen injection immunotherapy for seasonal allergic rhinitis. Cochrane Database Syst Rev. 2007(1):CD001936.

# AAAAI/ACAAI AIT Surveillance Study

- **Population:** Annual electronic survey of AAAAI and ACAAI member practices
- About 8 million injection visits a year
- In the 3 years from 2008-2011, no fatalities reported

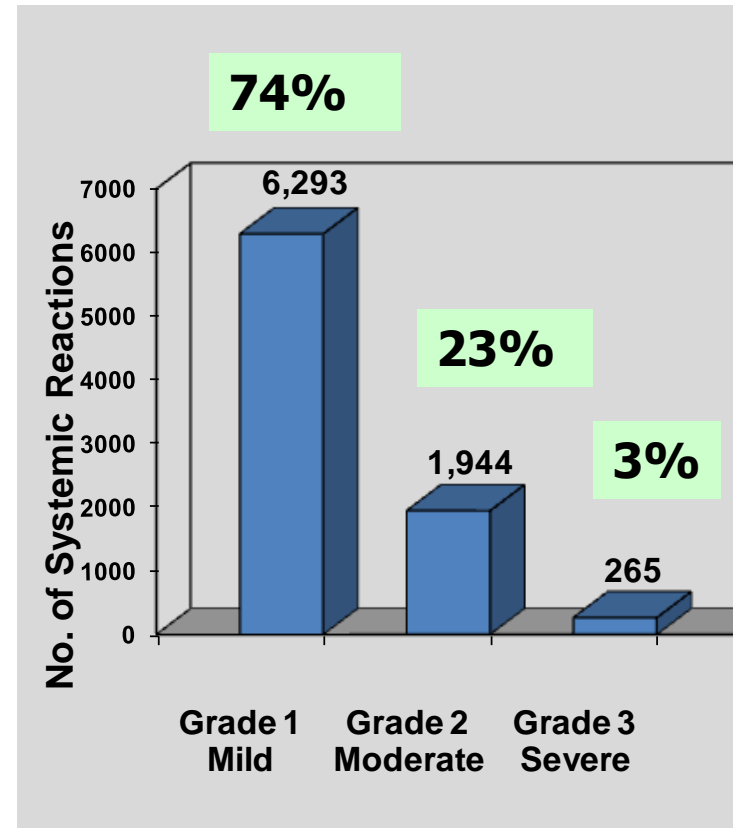
Year/Number of prescribers/ Number of injection visits	% Participation
<b>2008 - 2009:</b> 806 practices → 1,922 prescribers of SCIT; 8.1 million injection visits	37%
<b>2009 –2010:</b> 630 practices → 1,453 prescribers; 5.6 million injection visits	28%
<b>2010 – 2011:</b> 517 respondents →1,135 prescribers; 5.1 million injection visits	27%

# AAAAI/ACAAI Surveillance Study of SCIT Safety: 10.2 SRs per 10,000 injection visits (0.1% for all 3 years)

About 8 million injections visits per year

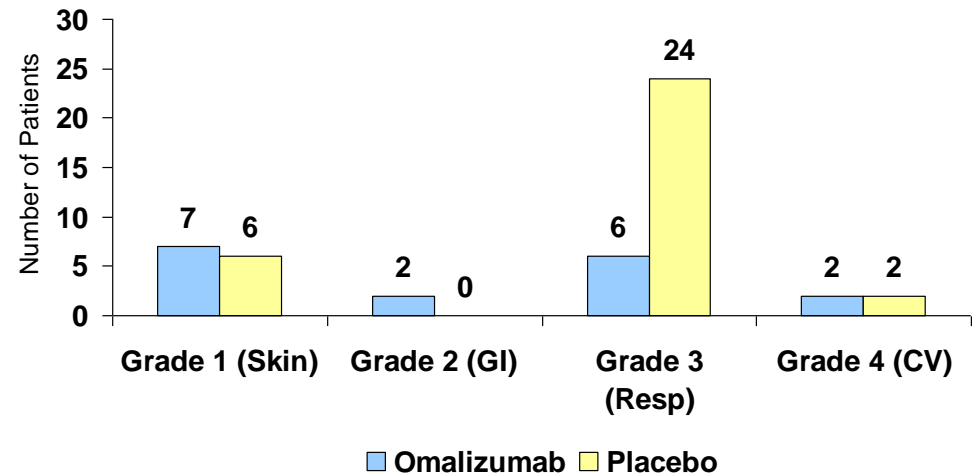
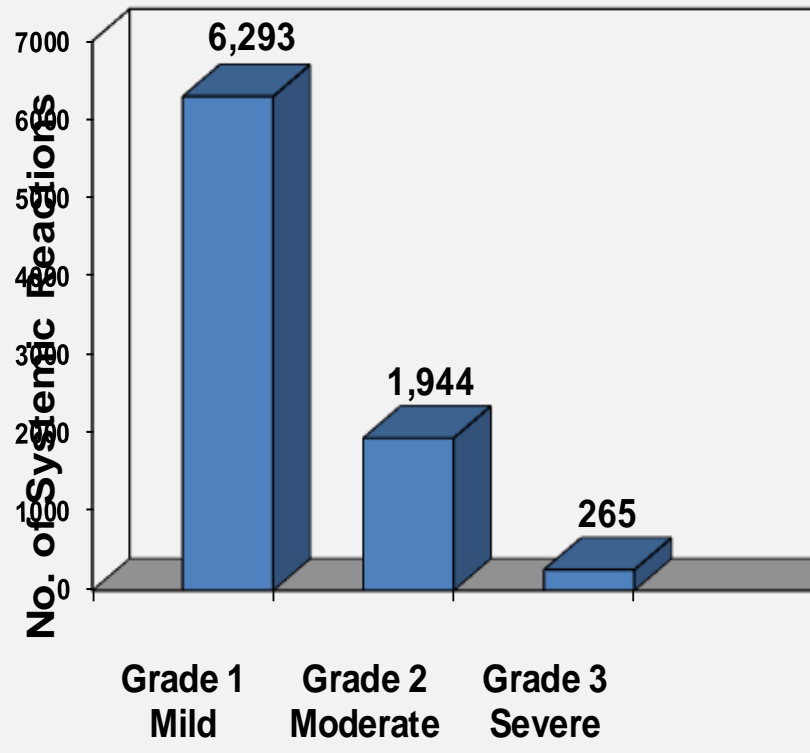
Per injection SR rate &  
number (%) practices reporting

- **Grade 1 mild SR:**
  - 1 per 1,287 (.07% injection visits)
  - 613 (76%) practices
- **Grade 2 moderate SR:**
  - 1 per 4,166 (.02% injection visits)
  - 436 (54%) practices
- **Grade 3 severe SR:**
  - 1 per 30,566 (.003%)
  - 144 (18%) practices





# Are these results comparable?



## AAAAI/ACAAI 3 Year Annual National Immunotherapy Safety Surveillance Study

- **Grade 1** → **Mild systemic reactions:** generalized urticaria and/or upper respiratory symptoms (e.g., itching of the palate and throat, sneezing)
- **Grade 2** → **Moderate systemic reactions:** asthma (e.g., PEFR falls 20-40%) with or without generalized urticaria, upper respiratory symptoms or abdominal symptoms (nausea, cramping)
- **Grade 3** → **Severe life threatening anaphylaxis:** severe airway compromise due to severe bronchospasm (e.g., PEFR falls more than 40%), or upper airway obstruction with stridor and/or hypotension (with or without loss of consciousness)

- **Grade 1:** skin (generalized urticaria, itching, or erythema)
- **Grade 2:** gastrointestinal (stomach pain, nausea, or vomiting)
- **Grade 3:** respiratory (clinically significant nasal symptoms and/or dyspnea, wheezing, persistent cough, chest tightness, stridor, or hoarseness) or angioedema of the lips or tongue
- **Grade 4:** cardiovascular (cyanosis, hypotension, collapse, arrhythmias, or angina pectoris)

# The many 'languages' of AIT SR Grading Systems

## Portnoy Method for Numeric Grading of Reactions to A

- Grade 1: skin (generalized urticaria, itching, or
- Grade 2: gastrointestinal (stomach pain, nausea,
- Grade 3: respiratory (clinically significant nasal congestion, wheezing, persistent cough, chest pain, or
- Grade 4: cardiovascular (cyanosis, hypotension, or angina pectoris)



## System for Subcutaneous Immunotherapy Systemic Reactions<sup>20</sup>

### Reactions within 30 minutes

1	Reactions probably not IgE-mediated. i.e., discomfort, headache, arthralgia, etc.
2	Mild rhinitis or asthma responding adequately to antihistamines or beta <sub>2</sub> -agonist spray.
3	Urticaria, angioedema, or severe asthma, responding

**TABLE V.** Grading system for generalized hypersensitivity reactions

Grade	Defined by
1—Mild (skin and subcutaneous tissues only)*	Generalized erythema, urticaria, periorbital edema, or angioedema
2—Moderate (features suggesting respiratory, cardiovascular, or gastrointestinal involvement)	Dyspnea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness, or abdominal pain
3—Severe (hypoxia, hypotension, or neurologic compromise)	Cyanosis or SpO <sub>2</sub> ≤ 92% at any stage, hypotension (SBP < 90 mm Hg in adults), confusion, collapse, LOC, or incontinence

SBP, Systolic blood pressure; LOC, loss of consciousness.

\*Mild reactions can be further subclassified into those with and without angioedema (see text).

reaction of itching, flushing, facial obstruction, etc. requiring treatment.

### Systemic Safety Surveillance

urticaria and/or upper airway obstruction (e.g., PEFR falls 20-40%) and/or respiratory symptoms or

severe airway obstruction (PEFR falls more than 50% or hypotension (with or

	of increased congestion, mouth
4+ Systemic reaction	Pulmonary breath decrease
5+ Systemic reaction	Anaphylaxis, frequent laryngospasm
6+ Cardiopulmonary arrest.	

(angioedema), immun

# Clinical Criteria for Diagnosing Anaphylaxis

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Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

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1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)  
*AND AT LEAST ONE OF THE FOLLOWING*
    - a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    - b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
  2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    - a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
    - b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    - c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
    - d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
  3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
    - a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP\*
    - b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline
- 

Second symposium on the definition and management of anaphylaxis: Summary report – Second National Institute of Allergy and Infectious Disease /Food Allergy and Anaphylaxis Network symposium JACI 2006;117:391

## Rule of Two & Three

**Anaphylaxis is highly likely when any one of the following three criteria are fulfilled:**

1. Acute onset of an illness (minutes to hours) with involvement of the skin and/or mucosal tissue and respiratory compromise and/or reduced blood pressure.
2. Symptoms involving **two or more organ systems**( skin /mucosal, respiratory, cardiovascular, GI) that occur rapidly after exposure to a likely allergen for that patient.
3. Reduced BP following exposure to a known allergen for that patient.

# Development of Universal AIT Safety Reporting Language



- An international Joint Task Force composed of members of the academic, clinical, and research allergy community was formed to develop a universal grading system for immunotherapy SRs.
- Existing grading programs formed the template for the grading system. In addition to information derived from the task force members' clinical experience, data from SR symptoms recorded in the literature and symptoms documented in fatal and near-fatal reactions were utilized

A photograph of a man and a woman in profile, facing each other and shouting with their mouths wide open. The man is on the left, wearing a light-colored shirt and a dark tie. The woman is on the right, wearing a patterned top. The background is plain white.

## Anaphylaxis vs. Systemic Reaction

- Unlike the multidisciplinary group's criteria for defining anaphylaxis, a symptom/sign representing a single organ system would be considered an SR in this grading system, as included in the epinephrine statement by the WAO

# WAO Subcutaneous Immunotherapy Systemic Reaction Grading Systems

- **5 Grades:** based on organ system involved and severity.
- Organ systems are defined as:
  - Cutaneous, conjunctival, upper respiratory,
  - Lower respiratory, gastrointestinal, cardiovascular and other.
- **Grade 1:** single organ system such as cutaneous, conjunctival, upper respiratory, **but not** asthma, gastrointestinal or cardiovascular
- **Grade 2 & 3.** Symptoms from >1 organ system or asthma, gastrointestinal, cardiovascular
- **Grade 4:** Respiratory failure, hypotension  $\pm$  loss of consciousness
- **The Grade is determined by the physician's clinical judgment after the event is over.**

# Speaking the same language: The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System

**TABLE I.** World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System (see text)

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
<p><i>Symptom(s)/sign(s) of 1 organ system present*</i></p> <p><b>Cutaneous</b> Generalized pruritus, urticaria, flushing, or sensation of heat or warmth† or Angioedema (not laryngeal, tongue or uvular) or <b>Upper respiratory</b> Rhinitis - (eg, sneezing, rhinorrhea, nasal pruritus and/or nasal congestion) or Throat-clearing (itchy throat) or Cough perceived to originate in the upper airway, not the lung, larynx, or trachea or <b>Conjunctival</b> Erythema, pruritus or tearing <b>Other</b> Nausea, metallic taste, or headache</p>	<p><i>Symptom(s)/sign(s) of more than 1 organ system present</i></p> <p>or</p> <p><b>Lower respiratory</b> Asthma: cough, wheezing, shortness of breath (eg, less than 40% PEF or FEV<sub>1</sub> drop, responding to an inhaled bronchodilator) or <b>Gastrointestinal</b> Abdominal cramps, vomiting, or diarrhea or <b>Other</b> Uterine cramps</p>	<p><b>Lower respiratory</b> Asthma (eg, 40% PEF or FEV<sub>1</sub> drop NOT responding to an inhaled bronchodilator) or <b>Upper respiratory</b> Laryngeal, uvula, or tongue edema with or without stridor</p>	<p><b>Lower or upper respiratory</b> Respiratory failure with or without loss of consciousness or <b>Cardiovascular</b> Hypotension with or without loss of consciousness</p>	<p>Death</p>

The final reaction grade will not be determined until the event is over, regardless of the medication administered. The final report should include the first symptom(s)/sign(s) and the time of onset after the SCIT injection and A letter that denotes if and when epinephrine is or is not administered



The final reaction grade will not be determined until the event is over, regardless of the medication administered.

- The final report should include the first symptom(s)/sign(s) and the time of onset after the SCIT injection and
  - **A letter that denotes if and when epinephrine is or is not administered in relationship to symptom(s)/sign(s) of the SR:**
    - a.  $\leq 5$  minutes
    - b.  $>5$  minutes to  $\leq 10$  minutes
    - c.  $>10$  to  $\leq 20$  minutes
    - d.  $>20$  minutes
    - z. epinephrine not administered

Final report: Mary A. Choo Grade 1a; Urticaria:15 minutes

Comments

Patient. takes antihistamine daily but forgot to take this morning

**PATIENT TRACKING LOG FOR SYSTEMIC REACTIONS TO ALLERGEN INJECTIONS**

**PATIENT TRACKING LOG FOR SYSTEMIC REACTIONS TO ALLERGEN INJECTIONS**

WAO Subcutaneous Immunotherapy Systemic Reaction Grading System							EPI GIVEN							TREATMENT GIVEN					Comments
PATIENT ID NUMBER	DATE	Grade1	Grade 2	Grade 3	Grade 4	First symptom(s)	PATIENT ID NUMBER	TIME OF ONSET AFTER INJECTION (MIN)	YES	NO	TOTAL EPI DOSE (MG)	IM	SUB-Q	≤ 5 MIN	>5- ≤10 MIN	>10 - ≤20 MIN	>20 MIN		
JF3001	01//6/09	x				Urticaria	JF3001	90	x									patient did not report the reaction until the following day.	
MW678	0/2/19/09	x				Nasal	MW678	20	x		0.3		x					symptoms resolved within 10 minutes of epinephrine	
SF76543	4/15/2009		x			Urticaria	SF76543	15	x		0.3							cough, and wheezing 5 minutes later, given neb albuterol	
AP36490	6/2/2009		x			Asthma	AP36490	25	x		0.3							also given albuterol via neb	

Cox L et al . Speaking the same language: The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. J Allergy Clin Immunol. 2010;125(3):569-74, 74 e1-74 e7.

# Individuals with a greater frequency of LLR may be a greater risk for SR



- **Methods:** Retrospective review of a database: comparing LLR rate in pts who had SRs with pts who did not have SRs
  - LLR= redness & swelling  $\geq 25$  mm
- **Results:** 258 pts had 283 SRs in 108,621 injections
  - **LLR rate 4 times higher** in pts with SRs than pts with no SRs
  - **SR group:** LLR rate: 35.2% of visits and 19.5% of injections
  - **No SR group:** LLR rate: 8.9% of visits and 5.3% of injections (P < .001 each).
- **Conclusions:** Patients with increased frequency of LLR may have increased risk for future SR .

## Uniform AIT Systemic Reaction Reporting

*speaking the same language will help the specialty*

- Consistent use of this 5-stage grading system in clinical trials and surveillance studies will allow better comparisons of SRs between different immunotherapy formulations and practice patterns.
- These, in turn, may help determine the best approach to treat SCIT SRs—that is, when to administer epinephrine, e.g. do all Grade 1 need to be treated??

# SCIT Local reactions '*pearls/myths*'



- Small or large LR rate defined as  $\leq$  or  $>$  palm of hand,<sup>1</sup>
  - Not related to glycerin content but
  - Small LR rate higher with increasing allergen content.
- LLR found not to be predictive of local or systemic reactions with subsequent injections<sup>2-4</sup>
- Survey of 249 SCIT patients-those who experienced LR<sup>5</sup>
  - 81.9% deemed LR not to be bothersome.
  - 96.0% stated they would not stop SCIT because of these LR

1. Calabria et al., J Allergy Clin Immunol. 2008;121:222-6. 2. Calabria et al., J Allergy Clin Immunol. 2009;124:739-44. 3. Tankersley et al, J Allergy Clin Immunol. 2000;106(5):840-3. 4. Kelso Ann Allergy Asthma Immunol. 2004;92(2):225-7. 5. Coop et al, Ann Allergy Asthma Immunol. 2008;101(1):96-100

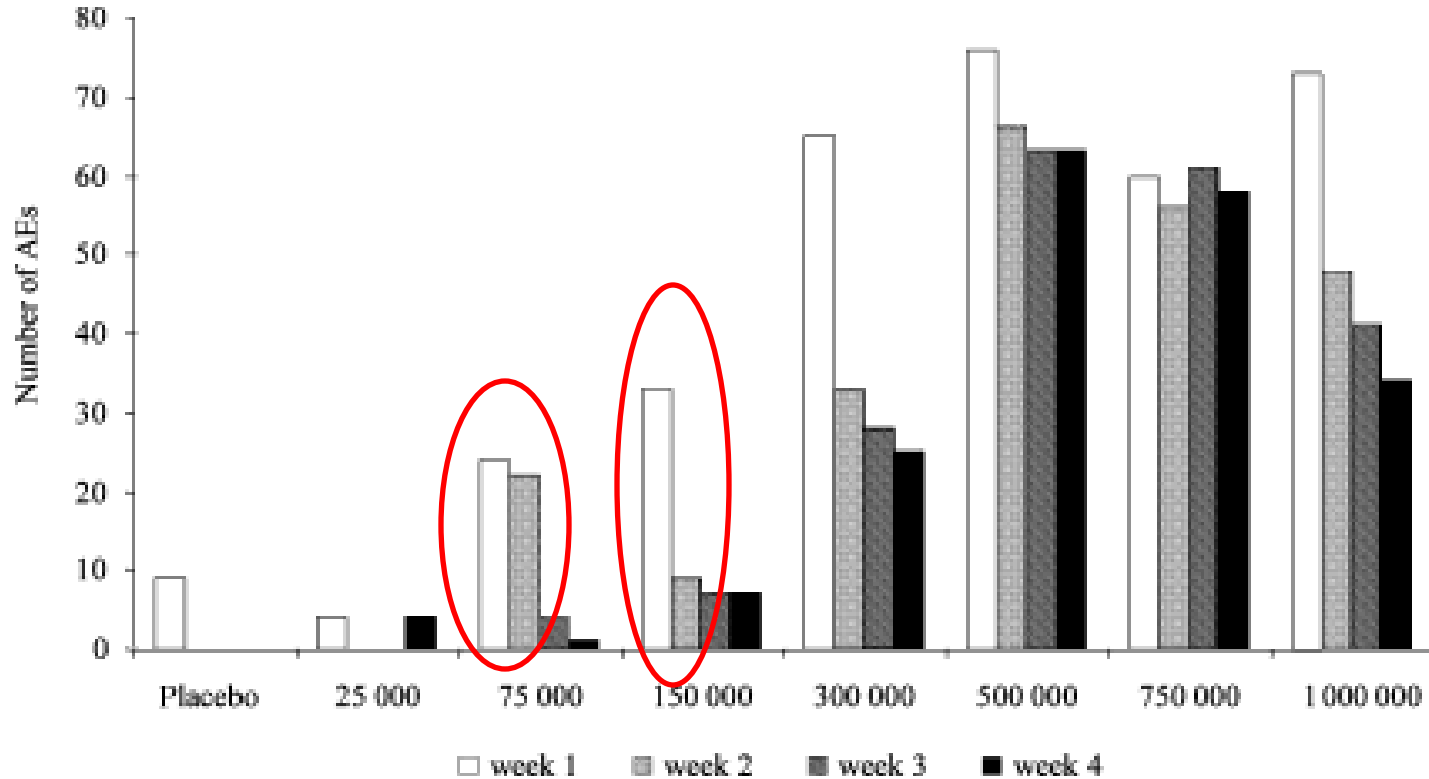
# SLIT Safety in Published Literature



- SLIT appears to be better tolerated than SCIT.
- No reports of SLIT-related fatalities to date in an estimated one billion doses
- Majority of SLIT AEs are local reactions in the mouth and throat are common at the beginning of treatment, but resolve within a few days or weeks without any medication intervention
- Dose-response relationship with AEs in some studies
- No apparent relationship with up dosing schedule and AEs
- Risk factors for the occurrence of SLIT severe adverse events have not yet been established
- Few reported cases of anaphylaxis (at least 11)\*. A few had prior SCIT

SR

# Most Adverse Reactions Occur During Beginning of SLIT Treatment



Dosing Range 5 to 200 mcg Phl p 5:

- Most AEs occurred within the 1<sup>st</sup> few weeks then declined
- Pattern similar to other studies
- Higher doses=more AEs

## Grading System for SLIT Local Reactions

A similar grading system is also necessary for the local side effects of SLIT because they most commonly occur in clinical practice and their severity, persistence, or both can result in discontinuation of SLIT.

There are no objective parameters, such as changes in FEV1 or blood pressure, to quantify the severity of the local AE; therefore a certain degree of subjectivity is unavoidable in grading these reactions.

In general, the severity of local side effects depends on the signs and symptoms and their duration

Local reactions leading to discontinuation included in criteria



# Grading local side effects of sublingual immunotherapy for respiratory allergy: Speaking the same language

**TABLE IV.** Grading system for SLIT local AEs\*

Symptom/sign (see Table I)	Grade 1: Mild	Grade 2: Moderate	Grade 3: Severe	Unknown severity
Pruritus/swelling of mouth, tongue, or lip; throat irritation, nausea, abdominal pain, vomiting, diarrhea, heartburn, or uvular edema	<ul style="list-style-type: none"> <li>• Not troublesome AND</li> <li>• No symptomatic treatment required AND</li> <li>• No discontinuation of SLIT because of local side effects</li> </ul>	<ul style="list-style-type: none"> <li>• Troublesome OR</li> <li>• Requires symptomatic treatment AND</li> <li>• No discontinuation of SLIT because of local side effects</li> </ul>	<ul style="list-style-type: none"> <li>• Grade 2 AND</li> <li>• SLIT discontinued because of local side effects</li> </ul>	Treatment is discontinued, but there is no subjective, objective, or both description of severity from the patient/physician.

Each local AE can be early (<30 minutes) or delayed.

\*See Table I for the MedDRA code that applies to exactly report and describe the AE.

**Mild:** symptoms that persist for greater than 10 days and require no treatment and the patient does not regard them as bothersome

**Moderate :** troublesome symptoms that might or might not require treatment but not result in discontinuation

- Reactions involving the lower digestive
- tract, such as diarrhea or abdominal discomfort, could be part of a “systemreaction, but in general, such reactions are classified
- as local
- Lower gastrointestinal tract reactions are local, unless they occur with other systemic manifestations, in which case they are classified as systemic reactions then WAO SR Grading System applies.

# Cases Reports of SLIT Anaphylaxis

Author, year	Sex (age)	Allergen (producer)	Phase	Onset	Description	Epinephrine
De Groot, 2009	M (13)	Grass (Grazax, ALK-Abellò)	First dose	15 min	Generalized urticaria, swelling of tongue	No
De Groot, 2009	F (27)	Grass (Grazax, ALK-Abellò)	First dose	5 min	Abdominal cramps, asthma, generalized itching, hypotension	Yes (SC)
Blazowski, 2008	F (16)	HDM (Staloral, Stallergenes)	Maintenance overdose (60 drops)	10 min	Hypotension-collapse, flushing, urticaria	Yes (IM)
Eifan, 2008	F (11)	Mixture (dust mite + grass pollen mix (Stallergenes)	Maintenance.	3 min	Abdominal pain, chest pain, fever, nausea	Not specified
Dunski, 2006	F (31)	Alternaria, cat, dog grass, ragweed, (Greer)	2 <sup>nd</sup> day of up dosing	5 min	Angioedema, dizziness, dyspnea, generalized itching	No
Antico, 2006	F (36)	Latex	End of rush buildup	10 min	Asthma, generalized urticaria	Not specified

# AIT Safety Summary

## SCIT:

- Incidence of SRs dependent on multiple factors at a rate ~0.2% of injections and 2-5% of patients
- Delayed & biphasic do occur and are not rare
- Fatalities rare in previous surveys but none from June 2008-July 2011 (8 million **injection visits/yr**)

## SLIT:

- SLIT appears to be better tolerated than SCIT
- Majority of SLIT AE's are oromucosal & occur during the beginning of treatment
- WAO position paper recommendations
  - Should only be prescribed by physicians with appropriate allergy training and expertise.
  - Specific instructions should be provided to patients regarding the management of adverse reactions, unplanned interruptions in treatment and situations when SLIT should be withheld.

# Speaking the Same Language in Terms of AIT Safety Reporting



## Speaking the same language: The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System

### Grading local side effects of sublingual immunotherapy for respiratory allergy: Speaking the same language

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# WAO Grading System for Systemic Reactions and SLIT Local Reactions

..please use!!!!