Speaking the Same Language: Grading System for Subcutaneous Immunotherapy Systemic Reaction

World Allergy Organization Symposium Immunotherapy & Biologics 2012

Chicago

Linda Cox, MD, FAAAAAI
Linda Cox, MD Disclosure

Allergist: solo private practice
Associate Clinical Professor of Medicine Nova Southeastern University
Affiliate Associate Professor of Clinical Biomedical Science
Florida Atlantic University College of Medicine
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 reactions
• 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

• **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.

AAAAl/ACAAI AIT Surveillance Study

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

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

AAAII/AACAAI 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

Bernstein et al, Ann Allergy Asthma Immunol 2010;104:530-5.2.
Are these results comparable?

AAAAL/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 4: cardiovascular** (cyanosis, hypotension, collapse, arrhythmias, or angina pectoris)
The many ‘languages’ of AIT SR Grading Systems

TABLE V. Grading system for generalized hypersensitivity reactions

<table>
<thead>
<tr>
<th>Grade</th>
<th>Defined by</th>
</tr>
</thead>
<tbody>
<tr>
<td>1—Mild (skin and subcutaneous tissues only)*</td>
<td>Generalized erythema, urticaria, periorbital edema, or angioedema</td>
</tr>
<tr>
<td>2—Moderate (features suggesting respiratory, cardiovascular, or gastrointestinal involvement)</td>
<td>Dyspnea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness, or abdominal pain</td>
</tr>
<tr>
<td>3—Severe (hypoxia, hypotension, or neurologic compromise)</td>
<td>Cyanosis or SpO₂ ≤ 92% at any stage, hypotension (SBP &lt; 90 mm Hg in adults), confusion, collapse, LOC, or incontinence</td>
</tr>
</tbody>
</table>

System for Subcutaneous Immunotherapy Systemic Reactions

<table>
<thead>
<tr>
<th>Reaction within 30 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>vs</td>
</tr>
<tr>
<td>ons</td>
</tr>
</tbody>
</table>

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

*Mild reactions can be further subclassified into those with and without angioedema (see text).
Clinical Criteria for Diagnosing Anaphylaxis

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

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus of 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
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.

Cox et al, J Allergy Clin Immunol 2010;125:569-74
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 ± loss of consciousness
- The Grade is determined by the physician’s clinical judgment after the event is over.

Endorsed by AAAAI, ACAAI, the Latin American Society of Allergy and Immunology, the Asia Pacific Association of Allergy, Asthma and Clinical Immunology,
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

<table>
<thead>
<tr>
<th>Final report: Mary A. Choo Grade 1a; Urticaria:15 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comments</td>
</tr>
<tr>
<td>Patient takes antihistamine daily but forgot to take this morning</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>PATIENT ID NUMBER</th>
<th>DATE</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>First symptom(s)</th>
<th>PATIENT ID NUMBER</th>
<th>TIME OF ONSET AFTER INJECTION (MIN)</th>
<th>YES</th>
<th>NO</th>
<th>TOTAL EPI DOSE (MG)</th>
<th>IM</th>
<th>SU-B-Q</th>
<th>TREATMENT GIVEN</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>JF3001</td>
<td>01/6/09</td>
<td></td>
<td></td>
<td>Urticaria</td>
<td></td>
<td>JF3001 90 x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≤5 MINS</td>
<td></td>
<td></td>
<td></td>
<td>patient did not report the reaction until the following day.</td>
</tr>
<tr>
<td>MW678</td>
<td>02/1/09</td>
<td></td>
<td>Nasal</td>
<td></td>
<td></td>
<td>MW678 20x 0.3 x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≤10 MINS</td>
<td></td>
<td></td>
<td></td>
<td>symptoms resolved within 10 minutes of epinephrine</td>
</tr>
<tr>
<td>SF76543</td>
<td>4/15/2009</td>
<td></td>
<td>Urticaria</td>
<td></td>
<td></td>
<td>SF76543 15x 0.3 x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;5-10 MINS</td>
<td></td>
<td></td>
<td></td>
<td>cough, and wheezing 5 minutes later, given neb albuterol</td>
</tr>
<tr>
<td>AP36490</td>
<td>6/2/009</td>
<td></td>
<td>Asthma</td>
<td></td>
<td></td>
<td>AP36490 25x 0.3 x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;10-20 MINS</td>
<td></td>
<td></td>
<td></td>
<td>also given albuterol via neb</td>
</tr>
</tbody>
</table>

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 ≥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 ≤ or > palm of hand:
- 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

Survey of 249 SCIT patients-those who experienced LR
- 81.9% deemed LR not to be bothersome.
- 96.0% stated they would not stop SCIT because of these LR

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 updosing 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

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

Kleine-Tebbe Allergy 2006; 61: 181-184
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

**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

---

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

<table>
<thead>
<tr>
<th>Symptom/sign (see Table I)</th>
<th>Grade 1: Mild</th>
<th>Grade 2: Moderate</th>
<th>Grade 3: Severe</th>
<th>Unknown severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fruritus/swelling of mouth, tongue, or lip; throat irritation, nausea, abdominal pain, vomiting, diarrhea, heartburn, or uvular edema</td>
<td>• Not troublesome AND • No symptomatic treatment required AND • No discontinuation of SLIT because of local side effects</td>
<td>• Troublesome OR • ReQUIRES symptomatic treatment AND • No discontinuation of SLIT because of local side effects</td>
<td>• Grade 2 AND • SLIT discontinued because of local side effects</td>
<td>Treatment is discontinued, but there is no subjective, objective, or both description of severity from the patient/physician.</td>
</tr>
</tbody>
</table>

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

*See Table 1 for the MedDRA code that applies to exactly report and describe the AE.*

---

• Reactions involving the lower digestive tract, such as diarrhea or abdominal discomfort, could be part of a “system reaction, 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

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

*Canonica et al, Sublingual Immunotherapy: WAO Position Paper Update.2013 in progress*
**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

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

| Table IV: Grading system for SLIT local AEs
<table>
<thead>
<tr>
<th>Symptom(s)</th>
<th>Grade 1: Mild</th>
<th>Grade 2: Moderate</th>
<th>Grade 3: Severe</th>
<th>Unknown severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local AE(s)</td>
<td>No symptoms OR SLIT discontinued</td>
<td>Treatment required OR SLIT discontinued</td>
<td>Treatment required OR SLIT discontinued</td>
<td>Treatment is documented, but there is no subjective, objective, or both description of severity from the patient, physician.</td>
</tr>
</tbody>
</table>

WAO Grading System for Systemic Reactions and SLIT Local Reactions

..please use!!!!