Which Factors Might Enhance Safety of Immunotherapy in Your Clinic?

David I. Bernstein MD FAAAI
Professor of Medicine and Environmental Health
Division of Immunology and Allergy
University of Cincinnati
Disclosures

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Objectives

1. Recognize factors in an allergy clinic associated with a higher rate of adverse events with subcutaneous AIT

2. Recommend actions that might augment safety of subcutaneous AIT
AAAIA/ACAAI surveys: 39 yr experience of fatal anaphylaxis to allergen injections in North America

83 confirmed fatal reactions
1990-2001: 1 in 2.5 million injection visits or 3.4 events per year*

Lockey et al. JACI 1987
Reid et al. JACI 1993
Bernstein et al. JACI 2004 *
Bernstein et al. Annals 2010


Number of deaths with SCIT injections
1 confirmed fatal reaction in the US 2008-2011.
Safety: Factors implicated in fatal SCIT reactions 
(n=34)

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<thead>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>Uncontrolled asthma</td>
<td>62%</td>
</tr>
<tr>
<td>2.</td>
<td>Prior systemic reactions</td>
<td>53%</td>
</tr>
<tr>
<td>3.</td>
<td>Pollen season</td>
<td>47%</td>
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<td>4.</td>
<td>Epi delay, not given</td>
<td>43%*</td>
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<tr>
<td>5.</td>
<td>Dosing/Admin Errors</td>
<td>35%</td>
</tr>
<tr>
<td>6.</td>
<td>None reported</td>
<td>17%*</td>
</tr>
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<td>7.</td>
<td>Inadequate wait</td>
<td>12%</td>
</tr>
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<td>8.</td>
<td>Home administration</td>
<td>9%</td>
</tr>
<tr>
<td>9.</td>
<td>$\beta$ blockers/ACE Inhibitors?</td>
<td>2%/2%</td>
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Reid M et al. JACI 1993; n=17  
* Bernstein et al. JACI 2004; n=17
### Lessons Learned in Assessing Risk of SCIT

<table>
<thead>
<tr>
<th>Study findings</th>
<th>Proposed recommendations</th>
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<tr>
<td>One fatal reaction to skin prick testing with multiple food allergens</td>
<td>Avoid skin testing in patients with uncontrolled asthma. Minimize the number of test antigens in severe asthmatics.</td>
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<td>Asthma symptoms not optimally controlled in 60% of fatal reactors and pretreatment FEV&lt;sub&gt;1&lt;/sub&gt; &lt; 70% in 50% of asthmatic patients</td>
<td>Consider risk versus benefit before initiating immunotherapy. Withhold immunotherapy if asthma is not well controlled. Assess asthma and PEFR before injections. Dispense self-injectable epinephrine in high-risk patients. Extend the waiting period beyond 30 minutes in high-risk patients.</td>
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<td>Fatal reactions at home or in unsupervised clinics</td>
<td>Administer immunotherapy in fully equipped clinic by trained personnel and never at home. Administer epinephrine 1:1000 IM 0.3-0.5 mg; repeat 2× if needed. If no response to IM dosing, give 1:10,000 epinephrine IV infusion.</td>
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<tr>
<td>Inadequate epinephrine dosing</td>
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<tr>
<td>Difficulty in establishing an airway</td>
<td>Clinical staff must be prepared to establish and maintain airway when necessary.</td>
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Fatal Reaction (2009)

- 43 year old male, morbidly obese
- Hx of severe asthma, controlled but not on ICS
- Positive prick tests 67% of allergens
- Hypertension, AODM, lisinopril 40 mg qd x 2 wks
- 1:10 buildup vial
- Immediate pruritus, urticarial, angioedema, GI symptoms, upper/lower airway obstruction, hypotension and shock
- Immediate Treatment ➔ 0.3 mg Epi x 5 (IM), IV fluids, tracheostomy by EMS.

Epstein et al. JACI in practice (in press)
AAAIAI/ACAAI surveillance study
(initiated in 2008)

Project AIMS:

1. Estimate annual incidence of fatal reactions from SCIT and skin testing in North America

2. Define relative incidence of systemic allergic reactions of varying severity

3. Identify clinical practice patterns that may impact risk of fatal and non-fatal reactions

Bernstein, Ann Allergy 2010
Participation – 4 year study

Population: AAAAI and ACAAI member practices prescribing SCIT

- **June 2008 - June 2009**
  - 1,922 prescribers of SCIT
  - 49%

- **August 2009 – July 2010**
  - 1,453 prescribers
  - 37%

- **August 2010 – August 2011**
  - 1,072 prescribers
  - 27%

- **September 2011-September 2012**
  - 1,073 prescribers
  - 27%

WAO Severity Grading of SRs (Years 4 & 5)

• Grade I → Symptom(s)/ signs of 1 organ system present: generalized urticaria with/without angioedema (NOT laryngeal, tongue, or uvular) or nausea or upper respiratory symptoms (e.g., itching of the palate and throat, sneezing) or conjunctival symptoms.

• Grade 2 → Asthma RESPONDING to an inhaled bronchodilator and/or GI symptoms including abdominal cramps, vomiting, or diarrhea, or uterine cramps.

• Grade 3 → Severe asthma NOT RESPONDING to a bronchodilator or laryngeal, uvular, or tongue edema, with or without stridor

• Grade 4 → Respiratory failure or hypotension with or without loss of consciousness

Modified from Cox JACI 2010
Systemic reactions — 0.1% of injection visits and 14% of injections begin 30 min after injections*. 4% of all SRs are severe (↓BP, airway compromise)*
AAAIA/ACAAI Year 3 Survey

Do you perform pre-injection screening of asthmatics?

Practices with Grade 3 SRs were no more likely to screen for asthma symptoms than those with only Grade 1 or no SRs
Does adjusting doses during peak pollen seasons impact SR rates? (Year 4, n=235)

Epstein et al. JACI in practice (in press)

Practices never reducing doses during peak pollen seasons in build-up or maintenance vials were significantly more likely to report Grade 3 or 4 SRs.
There were significantly more SRs during Grass and Tree Season combined, p<0.001
AAAI/ACAAI Year 4 Survey
Number of practices using various build-up strategies

- 268 practices = 93% of patients
- 73 practices = 4.6% of patients
- 32 practices = 2.1% of patients
- 6 practices = 0.5% of patients

As in Year 3, Cluster and Rush Build-up were associated with an increased risk of Systemic Reactions (p<0.001)

Epstein et al. JACI in practice (in press)
What clinical practices decrease the risk of SRs associated with cluster and rush? (Year 4; n=74 practices)

- Pre-medication did not lower the risk of SRs (p=0.2)

- Practices with an earlier change to conventional SCIT had fewer SRs (16.8 per practice vs 35.3 per practice), but this was not significant (p=0.2)
  
  - There was a trend suggesting that an earlier change to conventional SCIT was associated with fewer Grade 3 SRs (p=0.07)

_Epstein et al. JACI in practice (in press)_
IT Practice Parameter 3\textsuperscript{rd} update – ACE Inhibitors?

• Summary Statement 40: ACE inhibitors have been associated with greater risk for more severe reaction from venom IT and field stings. ACE inhibitor discontinuation should be considered for patients receiving venom immunotherapy. No enhanced risk in patients on aeroallergen IT. 

\textit{JACI Immunotherapy Practice Parameter 2011 3\textsuperscript{rd} update}

– Case reports of anaphylaxis with VIT in 2 pts. on ACE INH, tolerated injections after discontinuing drug.

– Risk for severe anaphylaxis to VIT in pts treated with ACE INH was confirmed in a prospective study.
Clinical Practice Recommendations

1. Action plan for managing late onset systemic reactions (self-injectable EPI in high risk pts)
2. Reduce doses during patients’ peak pollen season
3. Exclusion of at high risk patients: prior anaphylaxis; severe poorly controlled asthma; cardiac disease.
4. Universal pre-injection screening for asthma control (symptoms ± lung function).
5. 30 minute post-injection observation period
6. Facility prepared to immediately treat anaphylaxis with epinephrine especially during accelerated build-up
7. Double check patients ID (e.g. birth date)
8. Avoidance of ACE inhibitors for venom AIT
   • What high dose ACEi in patients receiving aeroallergen SCIT?
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References