Current Approaches to Diagnosis And Management of Insect Sting Allergy

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Venom Immunotherapy: Who Needs It?

- Positive venom skin test or serum test, AND
- History of systemic reaction to sting
  - Life-threatening
  - Moderate throat/airway symptoms or dizziness
  - Cutaneous systemic?
  - Large local?

Assessment of Risk in Patients with Insect Sting Allergy

- History (severity and pattern of reaction)
- Venom-specific IgE by skin or serum tests
- Natural History / Progression
- Baseline serum tryptase
- Quality of life
- Age / Medical condition

Risk of Systemic Reaction Depends on Severity of Previous Reactions and Insect Species

(Golden et al - JACI 2006)

Risk of Sting Reaction Related to Venom Skin Test

(Golden et al - JACI 2006)
Negative Venom Skin Tests with History of Sting Anaphylaxis

- Refractory (anergic) period
- Variability of venom skin tests
- Mast Cell Disorder
- No longer allergic / Never was allergic?

Negative skin test and serum IgE
- 5% chance of systemic reaction

Elevated Tryptase (Mastocytosis) and Insect Sting Anaphylaxis

- Elevated baseline serum tryptase in:
  - 5 - 10% of patients with sting anaphylaxis
  - up to 25% of patients with hypotensive shock
- Elevated tryptase associated with:
  - more severe reactions to insect stings
  - more frequent systemic reactions during VIT
  - more frequent VIT treatment failure
  - more frequent relapse after stopping VIT

VIT in Patients with Mastocytosis

DeOliveira et al. JACI 2008;121:519

<table>
<thead>
<tr>
<th>Male / Female</th>
<th>Male / 18</th>
<th>Female / 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vespid allergic / HB allergic</td>
<td>75% / 17</td>
<td>25% / 4</td>
</tr>
<tr>
<td>Systemic reactions during VIT</td>
<td>6 (28%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>up-dosing</td>
<td>3 (14%)</td>
<td></td>
</tr>
<tr>
<td>maintenance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic reaction to sting (n=12)</td>
<td>3 (25%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Venom IgE pre/post VIT</td>
<td>4.1 / 1.2</td>
<td></td>
</tr>
</tbody>
</table>

Natural History of Insect Allergy: Risk Based on Severity of Previous Reactions

Chance of Future Systemic Sting Reaction:

- Any
- Severe

<table>
<thead>
<tr>
<th>Previous Sting Reaction</th>
<th>Life-threatening</th>
<th>Moderate Systemic</th>
<th>Cutaneous Systemic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50 - 75%</td>
<td>30 - 50%</td>
<td>1 - 10%</td>
</tr>
<tr>
<td></td>
<td>50 - 50%</td>
<td>30 - 10%</td>
<td>1 - 10%</td>
</tr>
<tr>
<td></td>
<td>5 - 10%</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td></td>
<td>5 - 10%</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

Mean Reduction of Large Local Reactions During Maintenance Venom Immunotherapy

Golden et al. JACI 2009;123:1386

Controlled Trial of Venom Immunotherapy

Hunt et al, NEJM 1978

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Stung</th>
<th>Systemic (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venom (n=15)</td>
<td>18</td>
<td>1 (5%)*</td>
</tr>
<tr>
<td>W B E (n=20)</td>
<td>11</td>
<td>7 (64%)</td>
</tr>
<tr>
<td>Placebo (n=20)</td>
<td>12</td>
<td>7 (58%)</td>
</tr>
</tbody>
</table>

* after crossover, total 1/55 = 2% on VIT (p<0.01)
Mechanisms of Venom Immunotherapy


Pre-medication During Venom Immunotherapy

Terfenadine     Placebo

Brockow et al (JACI 1997)
Systemic during VIT     1/82 (1%)     6/39 (15%)
Large Local during VIT   20/80 (24%)    17/39 (45%)

Muller et al (JACI 2001)
Systemic during VIT     5/24 (21%)     13/23 (56%)
Systemic to challenge sting  0/20     6/21 (29%)

Montelukast reduces Large Local Reactions to VIT
(Wold S et al. Int. Arch Allergy Immunol 2007;144:137)

Safety of Initiating VIT at 1 mcg dose.
Roumana et al. JACI 2009.

Table 5. Systemic reactions caused by rush and ultra-rush VIT

<table>
<thead>
<tr>
<th>Venom concentration</th>
<th>Dose (in µg)</th>
<th>Injections (in.)</th>
<th>Observed reactions (%)</th>
<th>Expected reactions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 µg/mL</td>
<td>1 µg</td>
<td>780</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5-10 µg/mL</td>
<td>1.40</td>
<td>25</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>100 µg/mL</td>
<td>3.00</td>
<td>84</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2.30</td>
<td>219</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Problems During VIT

- Large local reactions
- Systemic reactions
- Treatment failure
- Medications
- Pregnancy

Venom Immunotherapy with a 50 µg Maintenance Dose in Children

Houliston 2011
85 children on HB-VIT
34 stung during VIT – 7 SR (21%)
44 stung after VIT – 6 SR (14%)

Konstantinou 2011
53 children (29 HB, 26 YJ)
2 SR to HB-VIT (dose increased to 100 µg)
10 stung (2 HB) during VIT (3.2 ±1.4 yrs)
7 (3 HB) stung again 2 wks-2 yrs later
11 stung (5 HB) 3.5±2.9 yrs post-VIT
Systemic Reactions During VIT

- Premedication
- Single venom
- Cluster VIT
- Rush VIT
- Omalizumab
- Increase dose

Rush VIT in Patients Having Systemic Reactions to VIT (Goldberg et al., Ann Allergy 2003;91:405)

<table>
<thead>
<tr>
<th>Day</th>
<th>Venom concentration, g/mL</th>
<th>Volume, mL</th>
<th>Dose, g</th>
<th>Daily accumulative dose, g</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.05</td>
<td>1</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>0.5</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

* There were 15-minute intervals between venom injections.

Omalizumab treatment in patients with severe anaphylactic reactions to VIT

- Galera 09 (couldn’t stop Xolair!)
- Gomis 2008 (failure of Xolair)
- Kontou-Fili 2008 (high dose Xolair in masto)
- daSilva 2013 (rush HB in monoclonal MCAS)
- 5 other cases of successful rush VIT on Xolair, all stable off Xolair after 6-12 months.

Predictors of severe systemic reactions in patients with insect allergy.

Factors correlating with the severity of anaphylaxis (Stoevesandt et al., JACI 2012)
Maintenance VIT

- Maintenance interval
  - 4 wks, 6 wks, 8 wks (x 12-18 mo each)
  - 12 weeks (Goldberg 2001; Cavallucci 2010)
- Monitoring
  - Skin test
  - Specific serum IgE or IgG
  - Medications (β-blockers; ACE inhibitors)

Duration of VIT – When to Stop

- 5 years or 3 years?
- Time or testing?
- What do I test or evaluate?
  - Skin test?
  - Specific serum IgE or IgG?
  - Serum tryptase?
  - History?

Venom-IgE and Skin Test During and After Venom Immunotherapy

Extended Observations After Discontinuing Venom Immunotherapy

Golden et al. JACI 1998;101:298

Severity of Sting Reactions Before VIT and After Discontinuing VIT (n=89)

- Minimal
  - Before VIT: 0
  - After VIT: 6
- Gen. Urticaria angioedema (only)
  - Before VIT: 13
  - After VIT: 2
- Respiratory
  - Before VIT: 41
  - After VIT: 3
- Hypotension
  - Before VIT: 35
  - After VIT: 1

Mean Duration of VIT = 6.5 years (5-9 years)
Mean Interval After VIT = 3.5 years (2-7 years)

Discontinuing Venom Immunotherapy: Caveats

- Extreme / Near-fatal reaction
- Systemic reaction during VIT (injection or sting)
- Mast cell disorder/elevated tryptase
- Honeybee allergy
- Age / Medical condition
- Quality of Life