Venom Hypersensitivity

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Disclosures

• Consultancy agreement:
  – Novartis
  – Deciphera
  – Blueprint Medicines

• Patent:
  – LAD2 cell line
Stinging insect hypersensitivity: A practice parameter update 2016

David B.K. Golden, MD; Jeffrey Demain, MD; Theodore Freeman, MD; David Graft, MD; Michael Tankersley, MD; James Tracy, DO; Joann Blessing-Moore, MD; David Bernstein, MD; Chitra Dinakar, MD; Matthew Greenhawt, MD; David Khan, MD; David Lang, MD; Richard Nicklas, MD; John Oppenheimer, MD; Jay Portnoy, MD; Christopher Randolph, MD; Diane Schuller, MD; Dana Wallace, MD

Ann Allergy Asthma Immunol 118 (2017) 28e54

Acknowledgment: Dr. Rajan Ravikumar
Epidemiology

• US population – 56-94% reported at least 1 sting.
  – Prevalence of large local reactions – 2.4-26.4%
  – Prevalence of systemic reactions
    • 0.15-0.8% of children
    • 0.5-3.3% of adults
Epidemiology

- 3rd most common cause of anaphylaxis in US EDs
  - 10% of all patients presenting with anaphylaxis
  - 20% of all fatal anaphylaxis in US
  - ≈ 40 deaths per year in the US
- may be under-reported cases
Annual incidence of fatal anaphylaxis in an unselected population

- Fatal venom anaphylaxis
- Fatal drug anaphylaxis
- Fatal food anaphylaxis

Epidemiology

- **Patient Risk factors for systemic reactions:**
  - Age >45
  - Males
  - Concurrent cardiovascular disease
  - B-blocker and ACE-inhibitor use
  - Atopic background

- **Other Risk Factors:**
  - History of Systemic Rxn
  - Multiple Stings at once
  - Recent sting
  - Serum tryptase level above 5 ng/ml
**Hymenoptera Taxonomy**

**TABLE II.** Most common stinging insects causing allergy

<table>
<thead>
<tr>
<th>Family and subfamily</th>
<th>Scientific name</th>
<th>Common name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apidae</td>
<td><em>Apis mellifera</em></td>
<td>Honeybee</td>
</tr>
<tr>
<td></td>
<td><em>Bombus spp.</em></td>
<td>Bumblebee</td>
</tr>
<tr>
<td></td>
<td><em>Megabombus spp.</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Halictus spp.</em></td>
<td>Sweat bee</td>
</tr>
<tr>
<td></td>
<td><em>Dialictus spp.</em></td>
<td></td>
</tr>
<tr>
<td>Vespidae</td>
<td><em>Vespula spp.</em></td>
<td>Yellow jacket</td>
</tr>
<tr>
<td>Vespinae</td>
<td><em>Dolichovespula arenaria</em></td>
<td>Yellow hornet (aerial yellow jacket)</td>
</tr>
<tr>
<td></td>
<td><em>Dolichovespula maculata</em></td>
<td>White-faced hornet (aerial yellow jacket)</td>
</tr>
<tr>
<td>Polistinae</td>
<td><em>Polistes spp.</em></td>
<td>Paper wasp</td>
</tr>
<tr>
<td>Formicidae</td>
<td><em>Solenopsis invicta</em></td>
<td>Fire ant</td>
</tr>
<tr>
<td></td>
<td><em>Myrmecia spp.</em></td>
<td>Jack jumper ant (Australia)</td>
</tr>
<tr>
<td></td>
<td><em>Pogonomyrmex spp.</em></td>
<td>Harvester ant (Southwest United States)</td>
</tr>
<tr>
<td></td>
<td><em>Pachycondyla spp.</em></td>
<td>Chinese needle ant (Australia)</td>
</tr>
<tr>
<td></td>
<td><em>Rhytidoponera metallica</em></td>
<td>Green-head ant (Australia)</td>
</tr>
</tbody>
</table>

Hymenoptera Taxonomy

- Honeybee (Apid mellifera)
  - Herbivorous
  - Hairy bodies
  - Non-aggressive
  - Evisceration upon stinging
  - Usually accidental sting
  - Nests
    - Above ground
    - Trees
### Honey Bee Allergens

**Table IV.** Physicochemical and biochemical characteristics of injected arthropod-derived allergens

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Frequency of reactivity (%)</th>
<th>Mol. size (kDa)</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Envenomating insects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Apidae</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Honeybee <em>(Apis mellifera, Apis cerana, Apis dorsata)</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 (eg, Api m 1)</td>
<td>&gt;90</td>
<td>16</td>
<td>Phospholipase A₂</td>
</tr>
<tr>
<td>Group 2 (eg, Api m 2)</td>
<td>95</td>
<td>39</td>
<td>Hyaluronidase</td>
</tr>
<tr>
<td>Group 3 (eg, Api m 3)</td>
<td>&gt;50</td>
<td>43</td>
<td>Acid phosphatase</td>
</tr>
<tr>
<td>Group 4 (eg, Api m 4)</td>
<td>&lt;50</td>
<td>3</td>
<td>Melittin</td>
</tr>
<tr>
<td>Group 5 (eg, Api m 5)</td>
<td>60</td>
<td>100</td>
<td>Dipeptidyl peptidase IV</td>
</tr>
<tr>
<td>Group 6 (eg, Api m 6)</td>
<td>&gt;42</td>
<td>8</td>
<td>Function unknown</td>
</tr>
<tr>
<td>Group 7 (eg, Api m 7)</td>
<td>?</td>
<td>39</td>
<td>CUB serine protease</td>
</tr>
<tr>
<td>Group 8 (eg, Api m 8)</td>
<td>46</td>
<td>70</td>
<td>Carboxylesterase</td>
</tr>
<tr>
<td>Group 9 (eg, Api m 9)</td>
<td>?</td>
<td>60</td>
<td>Serine carboxypeptidase</td>
</tr>
<tr>
<td>Group 10 (eg, Api m 10)</td>
<td>?</td>
<td>50-55</td>
<td>Icarapin variant 2</td>
</tr>
<tr>
<td>Group 11 (eg, Api m 11)</td>
<td>?</td>
<td>50</td>
<td>Major jelly protein</td>
</tr>
</tbody>
</table>

Africanized honey bee
Venom identical to European honey bee
More aggressive
Hymenoptera Taxonomy

- Vespids – Yellow jacket
  - Carnivorous
  - Scavengers
  - Highly aggressive
  - Stings more frequently in autumn
- Nests
  - In-ground
  - In cracks in buildings
Hymenoptera Taxonomy

- Vespids – Yellow hornet (aka aerial yellow jacket)
  - Nests – trees and shrubs
  - Aggressive (esp. with vibration)
  - Similar behavior and anatomy to yellow jackets
Hymenoptera Taxonomy

- **White-faced hornet**
  - Black and white color
  - Three white stripes at the end
  - Omnivorous
  - Aggressive
    - Squirt venom from stinger into the eyes of nest intruders
      - Triggers temporary blindness
Hymenoptera Taxonomy

• Paper Wasps
  – Nests – open combs
  – Located on eaves of a house
  – Not as aggressive
  – Feed on other insects
  – Dangling legs
Hymenoptera Taxonomy

• Fire Ants
  – Bite to get hold
  – Sting from abdomen
  – Will sting repeatedly nearby
  – Colony
    • Nested in soil
    • 1-2 ft in diameter and elevated 6-12 in or higher
Imported Fire Ant Quarantine

Restrictions are imposed on the movement of regulated articles from the quarantined areas into or through the non-quarantined areas. Consult your State or Federal plant protection inspector or county agent for assistance regarding exact areas under regulation articles. See 7 CFR 301.81 for quarantine details and regulations.

As of 1 June 2016
Fire Ant

- Sterile pustules
  - Develop 24 hours after sting
  - Clustered
Venom Skin Testing

• False Positives:
  – 20-30% of the general population have detectable specific IgE to venom
  – Sting occurred <3 years ago - 35%
  – Sting occurred >3 years ago – 20%
  – 5-15% of these pts will have systemic reactions on stings

• Positive Result defined as:
  – Prick testing
    • ≥3mm wheal with surrounding erythema greater than the negative control
  – Intradermal testing (at 1ug/ml or less)
    • 0.02-0.03ml volume
    • “3-5mm wheal with surrounding erythema greater than the negative control”
• Skin testing recommended 3-6 weeks after systemic event
• “Use skin tests as the preferred test for initial demonstration of venom-specific IgE.”
• “Consider basal serum tryptase in patients with anaphylaxis, esp. with severe or hypotensive reactions and negative test results.”
• “In vitro venom testing should be performed in patients with negative skin test responses who are VIT candidates”

Golden et al. Stinging Insect Hypersensitivity Update Annals Jan 2017
Diagnostic Testing

• ≤ 20% with positive venom skin test responses have negative in vitro test result in patients with a history of venom hypersensitivity.
• 10% of patients with negative skin test responses have positive in vitro results.
• Value of specific IgE level or skin test size does not correlate with severity of reaction.
• Small subset of patients with a convincing history are negative to both (≈1%)
  – Must be repeated 3-6 months later
  – May involve underlying systemic mastocytosis ??
Venom Skin Testing

- Yocum et al; JACI 1996; 97: 1424-5

<table>
<thead>
<tr>
<th>Standard venom testing method</th>
<th>Modified venom testing method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Prick tests with venom at 0.01 μg/ml, diluent control, prick control: 20 min to place, read, and record</td>
<td>1. Prick tests with venom at 1 μg/ml, diluent control, prick control: 20 min to place, read, and record</td>
</tr>
<tr>
<td>2. Intradermal tests with venom at 0.001 μg/ml, histamine at 0.05 mg/ml, diluent control: 20 min to place, read, and record</td>
<td>2. Intradermal tests with venom at 0.2 μg/ml and 1 μg/ml, histamine at 0.05 mg/ml, diluent control: 20 min to place, read, and record</td>
</tr>
<tr>
<td>3. Intradermal test with venom at 0.01 μg/ml: allow 20 min to place, read, and record</td>
<td></td>
</tr>
<tr>
<td>4. Intradermal test with venom at 0.1 μg/ml: 20 min to place, read, and record</td>
<td></td>
</tr>
<tr>
<td>5. Intradermal test with venom at 1.0 μg/ml: 20 min to place, read, and record</td>
<td></td>
</tr>
<tr>
<td>Total time = 1 hr and 40 min</td>
<td>Total time = 40 min</td>
</tr>
</tbody>
</table>
Venom Skin Testing

- Yocum et al. JACI 1996; 97: 1424-5
  - 331 positive (74%); 115 negative (26%)
  - No large local reactions noted
  - 4/331 and 4/115 patients experienced dizziness, itching, shortness of breath, or nausea during test
  - 1 patient experienced hypotension in negative skin test group – likely vasovagal response
Fire Ant Skin Testing

Whole-body extract is the only extract available

• Initial skin prick testing
• Serial Concentration ID testing is still recommended
  – Starting dose of $1 \times 10^{-6} = 1:1,000,000$
  – Increase 10 fold with each ID testing dose
  – Maximum concentration of $1 \times 10^{-3} = 1:1,000$
Other Diagnostic Tools

• **Basophil Activation Tests**
  – Limited utility currently due to lack of standardization of response (ie. CD203c vs. CD 63 expression)
  – **Potential Uses**
    • May identify double negative patients (neg. ST and neg serum IgE) with clinical history of venom allergy
    • May predict outcomes with venom IT
      – Frequency of systemic reactions
      – Successful protection during treatment
      – Relapse after stopping IT

Other Diagnostic Tools

Serum Tryptase

Table 5
When to Measure Basal Serum Tryptase

Recommended:
- Severe reaction to a sting
- Hypotensive reaction
- Lack of urticaria in systemic reaction to a sting
- Systemic reaction to a sting with negative venom IgE test results

Consider:
- Systemic reaction during VIT (to injection or sting)
- Before discontinuing VIT
- Any patient who is a candidate for VIT

Abbreviation: VIT, venom immunotherapy.

Golden et al. Stinging Insect Updated Parameters Annals 118(2017)
**Table 3**

**Measures for Avoiding Insect Stings**

<table>
<thead>
<tr>
<th>Effective measures</th>
<th>Ineffective measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid preparing, grilling, or eating outdoors</td>
<td>Avoiding fragrances</td>
</tr>
<tr>
<td>Avoid flowering plants</td>
<td>Avoiding brightly colored or floral clothing</td>
</tr>
<tr>
<td>Avoid drinking from straws, cans, or bottles outdoors</td>
<td>Using insect repellants</td>
</tr>
<tr>
<td>Remove fallen fruit or pet feces</td>
<td>Running; flailing the arms</td>
</tr>
<tr>
<td>Cover trashcans</td>
<td></td>
</tr>
<tr>
<td>Watch for nests in bushes or in the ground when mowing</td>
<td></td>
</tr>
<tr>
<td>Avoid going barefoot outdoors</td>
<td></td>
</tr>
</tbody>
</table>

Golden et al. Stinging Insect Updated Parameters Annals 118(2017)
“What if I get a LLR?”

- **Characteristics**
  - Peaks in size 24-48 hours
  - ≥10cm diameter swelling
  - Resolve over 3-10 days

- **Treatment**
  - Remove Stinger
  - Scrape or flick stinger away
  - DO NOT GRASP VENOM SAC
Large Local Reactions

Treatment (continued)

– Cold Compresses
– NSAID’s
– Oral antihistamines (ie. Cetirizine 10mg qd)
– Oral prednisone for 2-5 days (no controlled trials)
– EpiPen - not absolutely indicated
– 5-10% of patients will progress to systemic symptoms on subsequent sting
Large Local Reactions

- Venom IT may reduce LLR’s:
  - high-risk of frequent stings
  - Extremely large local rxn’s
  - Personal history of CV disease
  - Alleviate patient’s anxiety
- Risk of progression to systemic symptoms = 5-10%

**Risk of Systemic Reactions**

- **Cutaneous Systemic Reactions < 16**
  - 86 Children < age 16 not treated with venom IT – 9.2% developed systemic reactions, none were more severe than the initial reaction
  - 36 Children < age 16 treated with venom IT – 1.2% developed systemic reactions
- Authors concluded IT is not necessary

(Valentine et al. NEJM 1990; 323: 1601-3)
Systemic Reactions

- Cutaneous Systemic Reactions age > 16
  - Risk of systemic reaction after 1-9 years – 20%
  - Risk of systemic reaction after 10-20 years – 10%
  - Only 3% had a chance of a more severe reaction
  - Risk is greater in honeybee than vespid stings
  - IT is not indicated

  *recently changed in Stinging Insect Hypersensitivity Practice Parameter (Annals Jan 2017)
Systemic Reactions

• Anaphylaxis
  – 70-90% of adults develop cardiopulmonary symptoms
  – 30% of children develop cardiopulmonary symptoms
  – Lack of cutaneous manifestations is associated with more severe reactions.
  – Onset of symptoms within 5 minutes associated with more severe symptoms
Systemic Reactions

• Venom Anaphylaxis
  – Child (age < 16) – untreated with IT
    • Risk of systemic reaction 1-9 years = 40%
    • Risk of systemic reaction 10-20 years = 30%
  – Adult (Age > 16) – untreated with IT
    • Risk of systemic reaction 1-9 years = 60%
    • Risk of systemic reaction 10-20 years = 40%
  – Venom IT would be indicated for both age groups
Venom IT

• Indications
  – Anaphylaxis History with venom-specific IgE Ab’s
  – Especially consider in high-risk patients
    • Cardiopulmonary symptoms
    • Mastocytosis
    • Older patients with CAD

• Not Indications
  – Large Local Reactions (except in rare occasions)
  – Cutaneous Systemic Reactions
    • Risk of subsequent cutaneous systemic – 10%;
      Risk of more severe cutaneous systemic – 3%
    • Risk of anaphylaxis – 1%
## Traditional Protocols

### Schedule 1

<table>
<thead>
<tr>
<th>Week</th>
<th>Concentration, μg/mL</th>
<th>Volume, mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>0.05</td>
</tr>
<tr>
<td>2</td>
<td>1.0</td>
<td>0.1</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>0.2</td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>0.4</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>0.05</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>0.1</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>0.2</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>0.4</td>
</tr>
<tr>
<td>9</td>
<td>100</td>
<td>0.05</td>
</tr>
<tr>
<td>10</td>
<td>100</td>
<td>0.1</td>
</tr>
<tr>
<td>11</td>
<td>100</td>
<td>0.2</td>
</tr>
<tr>
<td>12</td>
<td>100</td>
<td>0.4</td>
</tr>
<tr>
<td>13</td>
<td>100</td>
<td>0.6</td>
</tr>
<tr>
<td>14</td>
<td>100</td>
<td>0.8</td>
</tr>
<tr>
<td>15</td>
<td>100</td>
<td>1.0</td>
</tr>
<tr>
<td>16</td>
<td>100</td>
<td>1.0</td>
</tr>
<tr>
<td>17</td>
<td>100</td>
<td>1.0</td>
</tr>
<tr>
<td>18</td>
<td>100</td>
<td>1.0</td>
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<td>19</td>
<td>100</td>
<td>1.0</td>
</tr>
<tr>
<td>Monthly</td>
<td>100</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Stinging Insect Hypersensitivity: Practice Parameters Annals 2016
## Cluster Protocols

### Table 2. Built-up protocol in venom immunotherapy: cluster protocol

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Volume (ml)</th>
<th>Dose (µg)</th>
<th>Cumulative dose (µg)</th>
<th>Day</th>
<th>Hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01 µg/ml</td>
<td>0.1</td>
<td>0.01</td>
<td>0.01</td>
<td>1</td>
<td>0</td>
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<tr>
<td>0.1 µg/ml</td>
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<td>0.1</td>
<td>0.1</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>1 µg/ml</td>
<td>0.1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1 µg/ml</td>
<td>0.1</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>0.30</td>
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<tr>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 µg/ml</td>
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<td>0.1</td>
<td>10</td>
<td>1</td>
<td></td>
</tr>
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<td>0.1</td>
<td>15</td>
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<tr>
<td></td>
<td>0.5</td>
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<td>30</td>
<td>0.30</td>
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<tr>
<td></td>
<td>1</td>
<td></td>
<td></td>
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<td>0.30</td>
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<tr>
<td>100 µg/ml</td>
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<td>22</td>
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<td>0.30</td>
</tr>
<tr>
<td>0.2</td>
<td></td>
<td>0.4</td>
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<tr>
<td>0.3</td>
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<td>0.9</td>
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<td>0.30</td>
</tr>
<tr>
<td>0.5</td>
<td></td>
<td>1.1</td>
<td></td>
<td></td>
<td>0.30</td>
</tr>
<tr>
<td>0.5</td>
<td></td>
<td>1.3</td>
<td></td>
<td></td>
<td>0.30</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>2.2</td>
<td></td>
<td></td>
<td>0.30</td>
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</tbody>
</table>

## Rush Protocols

### Table 3. Built-up protocol in venom immunotherapy: rush protocol

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Volume (ml)</th>
<th>Dose (µg)</th>
<th>Cumulative dose (µg)</th>
<th>Day</th>
<th>Hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01 µg/ml</td>
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<td>0.01</td>
<td>0.01</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>0.1 µg/ml</td>
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<td>0.1</td>
<td>0.11</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>1 µg/ml</td>
<td>1</td>
<td>1</td>
<td>1.11</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>10 µg/ml</td>
<td>0.2</td>
<td>2</td>
<td>3.11</td>
<td>6</td>
<td></td>
</tr>
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<td></td>
<td>0.3</td>
<td>3</td>
<td>5.11</td>
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<td>0</td>
</tr>
<tr>
<td></td>
<td>0.35</td>
<td>3.5</td>
<td>9.61</td>
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</tr>
<tr>
<td></td>
<td>0.35</td>
<td>3.5</td>
<td>13.11</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>100 µg/ml</td>
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<td>10</td>
<td>23.11</td>
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### Ultra Rush Protocols

#### Table 4. Built-up protocol in venom immunotherapy: ultrarush protocol [12].

<table>
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<tr>
<th>Concentration</th>
<th>Volume (ml)</th>
<th>Dose (µg)</th>
<th>Cumulative dose (µg)</th>
<th>Minute</th>
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<tr>
<td>0.1 µg/ml</td>
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<td>0.01</td>
<td>0.011</td>
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Safety of Venom IT

- ACE-Inhibitors – 2017 Parameter Update
  “…, in patients receiving IT, there is limited and conflicting evidence that these medications increase the risk of anaphylaxis”.
- Systemic Reaction (SR) risk - not significantly increased
- Conflicting data on the effect of SR severity
- “…limited evidence that the risk…is minimized by withholding the medication for 24 hours before VIT”
Safety of Venom IT

- Large Local Reactions (LLR’s) – 40-50% of patients
  - do not predict systemic reactions if < 4 in. in diameter.
- Premedication:
  - “H1-blockers reduce LLR’s and mild systemic reactions but not anaphylaxis” *(JACI. 1997; 100: 458-63)*
  - Montelukast MAY improve LLR’s *(Int Arch Allergy Immunol. 2007; 144: 137-42).*
  - H1-anti-histamines were found to improve efficacy in one retrospective study but this has not been reproduced in prospective trials.
Safety of Venom IT

• **Risk of Systemic Reactions**
  – Traditional Protocol –<5% during dose-increase phase and 0.5% during maintenance phase
  – Rush Protocols – 5-10% of patients
  – Ultrarush Protocol – 0-28% (median was 11%) of patients
Efficacy of Venom IT

- Begins upon achieving maintenance dosing regardless of protocol used
- >95% of patients allergic to yellow jacket and wasp will not react if re-stung during venom IT
- 80-90% of patients allergic to honeybee will not react if re-stung during venom IT
- If a patient experiences a treatment failure on maintenance dose, increase the antigen dose to 200ug
Long Term Efficacy

- One Year of Treatment – 22% reaction rate over the next 3-4 years (retrospective)
- More than 3 years of Treatment – 83-100% protected against recurrent systemic reactions 1-3 years after stopping – most of which were mild
- 5% rate of systemic reactions with >50 months
Duration of Venom IT

- 3-5 years of therapy
- Add an additional 2 weeks to the interval for every year of maintenance
  - Q4 weeks – year 1
  - Q6 weeks – year 2
  - Q8 weeks – year 3
  - Q10 weeks – year 4
- 12 weeks intervals found to be effective but not 6 months
Table 6
Factors for Elevated Risk of Relapse After Discontinuing VIT

Proven:
- Very severe reaction to previous stings
- Elevated basal serum tryptase level
- Systemic reaction during VIT (to injection or sting)
- Less than 5 years of maintenance VIT
- Honeybee anaphylaxis
- Frequent exposure

Possible:
- No decrease in venom IgE or skin tests
- Underlying cardiovascular or respiratory disease
- Use of ACEIs or β-blockers

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; VIT, venom immunotherapy.

Golden et al. Stinging Insect Updated Parameters Annals 118(2017)
Serum baseline tryptase increases the risk of anaphylactic reactions in hymenoptera venom allergy

Serum baseline tryptase increases the risk of anaphylactic reactions in venom immunotherapy

Clonal mast cell disorders in patients with systemic reactions to Hymenoptera stings and increased tryptase Bonadonna et al, JACI 2009

- 379 patients with systemic reactions to hymenoptera
- 11.6% had elevated baseline tryptase >11.4 ng/ml
  - 62% mastocytosis
  - 27% MMAS
- Venom immunotherapy recommended for life if skin test or RAST positive
- Check baseline tryptase in systemic hymenoptera reaction
Clonal mast cell disorders in patients with systemic reactions to Hymenoptera stings and tryptase < 11.4 ng/ml
Bonadonna et al, JACI 2015

- 22 patients with hypotensive anaphylaxis
- No urticaria pigmentosa
- 15 had systemic mastocytosis
- 1 had MMAS
- The majority had tryptase 5-11.4 ng/ml
Venom Allergy in ISM

Diagnostic Workup

- Refer patients for bone marrow if:
  - Baseline tryptase > 11.5ng/ml
  - Baseline tryptase values between 5-11.4ng/ml with hypotensive syncope without cutaneous symptoms

- Consider sIgE first in this population and then skin testing if sIgE is negative.

- Repeat at least 6 weeks after the 1st test if initial testing is negative
Is preemptive venom testing necessary in patients with mastocytosis?


- 75 year old female with a 10 year history of MPCM and systemic mastocytosis, asymptomatic
- Tryptase 30 ng/ml, KIT D816V +
- No history of atopy.
- Stung in 20 years ago with no reactions
- Skin testing to honeybee and yellowjacket was negative
Is preemptive venom testing necessary in patients with mastocytosis?


– Recently stung, lost consciousness within a few minutes with hypotension, had wheezing and ST elevations
– Skin test now positive for yellowjacket, IgE 0.83 kU/L, negative for honeybee
– Venom immunotherapy, tolerated well
Venom immunotherapy in mastocytosis: Safety and efficacy
Bonadonna et al. JACI In Practice 2013;1:474-8

- 84 patients from Italy and Spain
  - 81 had grade 4 reactions
- 10 adverse reactions during buildup
  - 3 with conventional
  - 7 with rush
  - None required epinephrine
- 50 patients stung again (95 episodes)
  - 83% fully protected
  - 7 reactions – dose increased to 200 ug, all tolerated well
Anaphylaxis after stopping VIT in mastocytosis

Bonadonna et al. JACI In Practice 2017 In press

- 19 patients with mastocytosis
- 4-17 years of VIT
- Initial stings 18 with grade 4 (syncope)
- 13 stings during immunotherapy: LR or LLR
- Restung after VIT: 18 had hypotensive syncope without urticaria/angioedema

- Conclusion: Indefinite VIT
Case report

- 51 year old male with hypotensive anaphylaxis after hymenoptera sting
- Baseline tryptase 25 ng/ml
- Bone marrow biopsy positive for indolent systemic mastocytosis
- Skin test positive for yellowjacket and hornets
- Had 2 attempts on VIT but had systemic reactions during buildup
Case report

- Placed on Omalizumab 300 mg once monthly
- After 2nd injection, admitted to ICU for ultra rush desensitization
- Tolerated well and is currently on maintenance
Tryptase levels in children with venom allergy

Yavuz et al, Allergy 68:376, 2013
Audience Response Question 1

- Avoidance of which of the following is not effective to reduce the risk of hymenoptera stings?
  - A. Grilling or drinking outdoors
  - B. Fragrances
  - C. Flowering plants
  - D. Waking barefoot outdoors

Answer: B
Audience Response Question 2

• Which of the following patients are candidates for lifelong immunotherapy?
  – A. History of a life threatening reaction
  – B. Elevated baseline tryptase
  – C. Ongoing frequent exposure
  – D. All of the above

Answer: D
Audience Response Question 3

• Serum baseline tryptase should be checked in patients presenting with:
  – A. Large local reactions
  – B. Generalized hives
  – C. Hypotension
  – D. Angioedema

Answer: C