Stinging Insect Hypersensitivity

Golden et al. Stinging insect hypersensitivity Practice Parameter JACI 2011;127:852-8

1) Emergency departments
   - Need for better recognition
   - Need for appropriate use of epinephrine

2) Bumblebees are important cause of sting reaction in some settings, such as greenhouse pollination
   - Bumblebee venom is distinct from honeybee venom
   - There is cross-reactivity between honeybees in some patients
   - Where available, use bumblebee specific venom

3) More guidance on when not to test
   - Negative predictive value is very high
   - Positive predictive value is lower (25% false positive)
   - Venom testing and treatment might not be required
4) Growing evidence
   - Fire ant sting evaluation & management
   - Demographic information on scope and distribution
5) Measurement of Baseline Serum Tryptase
   - Severity of sting reactions
   - Frequency of systemic reactions with VIT
   - Chance of VIT failure
   - Risk of relapse if VIT stopped
6) More discussion & Guidance
   - Self-injectable epinephrine
7) New evidence on relative risk of
   - ACE Inhibitors
8) Important predictors of outcomes of sting reaction
   - Severity of previous reaction - Age
   - Mast Cell Tryptase level - Male gender
   - Cardiovascular drug use
9) Updates on VIT
   - Use of Antihistamines on the day of shot
   - Regimens for VIT progression
   - Appropriate maintenance dose of VIT
   - When to discontinue VIT

The Usual Suspects
Hymenoptera Taxonomy

Solenopsis (Imported Fire Ant) - Formicidae (Ants)

Apis mellifera (Honey Bee) - Apidae (Bees)

Vespera (Old World Wasp) - Vespidae

Vespula (Yellow Jacket)

Dolichovespula (Hornet)

Polistes (Wasp) - Vespinae

Wasp (Polistes spp.)

- Long and slender, many different colors
- Paper comb nests on eaves or rafters
- Stinger retractable
  - may sting > once
- Less aggressive unless nest threatened
- Small colonies
  - 10-25 workers

Hornet (Dolichovespula spp.)

- European hornet \( \rightarrow \) Vespa crabro
- Bald-faced hornet \( \rightarrow \) Dolichovespula maculata
- Large, differing colors
- Large paper-like nests in trees, on buildings
- Painful stings from kinins
- Active at night, seek light
- Colonies
  - 200-1,000
Yellow Jacket
(*Vespula* spp.)
- Two genera
  - *Vespula vulgaris* (common yellow jackets)
  - *Dolichovespula arenaria* (aerial yellow jacket)
- Yellow and black
- Nests
  - Subterranean nests
    - 500 – 5000 in a colony
  - Small aerial nests
    - 100 – 700 in a colony
- Aggressive scavengers and foragers
  - Agitated by vibration
  - Causes most stings in USA

Hymenoptera Taxonomy

**Solenopsis** (Imported Fire Ant)  
**Formicidae** (Ants)  
**Apis mellifera** (Honey Bee)  
**Bombus spp.** (Bumble Bee)  
**Apidae** (Bees)  
**Vespula** (Old World Wasp)  
**Dolichovespula** (Hornet)  
**Vespinae**  
**Polistes** (Wasp)  
**Polistinae**  
**Vespidae**  
**Hymenoptera**  
**Apidae** (Bees)

Occupational Allergy to Bumblebees
- Greenhouse pollination
- Two distinct groups
  - Honeybee cross-reactive
  - Bumblebee specific
- Four species of bumblebee
- Recommendation
  - Specific Bumblebee species venom be used for testing and VIT (if available)
- Bumblebee venom is not available in the US and some European Countries
Honeybee 
(*Apis mellifera*)
- Stout, hairy body
- Around lawns and pollinating plants
- Attracted by bright colors
- Barbed stinger
  - Remains in skin
  - Eviscerates the bee
- Bumblebee cross reacts
  - In some, but not all patients
- Africanized “killer” bee cross reacts
- Large domesticated colonies
  - >65,000 workers

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Killer Bee 
(*Apis mellifera scutellata*)
- Africanized “killer” bee cross reacts with honeybee
- Introduced into Brazil in 1956 and began expanding northward in 1957
- Present in southern US
- More aggressive
  - Swarm at slight provocation (vibration)
  - Pursuit over 1 mile
  - Deliver 8 times number stings of honeybee
- High temperatures and low rainfall (Brazil)
  - greater activity of bees
  - larger number of wandering swarms

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Killer Bee (*Apis mellifera scutellata*).

Distribution of Africanized Bees in the US in 2009.

US Department of Agriculture.

Killer Bee (*Apis mellifera scutellata*)
Venom Components

- Studied the venom of
  - 103 EU Bees and 92 Africanized bees
- Africanized bees contained significantly less venom but more phospholipase than did EU bees.
- Biogenic amines
  - Histamine - Acetylcholine
  - Dopamine - Norepinephrine
- Polypeptide Toxins
  - Melittin - Kinins
- Enzymes
  - Phospholipase - Hyaluronidase

Hymenoptera Taxonomy

Solenopsis species

- S. invicta - red imported fire ant
  - Dominant species in USA
  - Significant cross reactivity with others (venom and WBE)
- S. richteri - black imported fire ant
  - Northern Mississippi & Alabama
  - Hybridized with S. invicta
- S. xyloni - California
- S. geminata - Florida and Pacific islands
Imported Fire Ant

Reactions to IFA

- Local - pustule, erythema, and/or pruritis
- Systemic
    - 20,755 treated annually for IFA sting
    - 13,139 (63%) local reactions
    - 413 (2%) anaphylaxis
    - Retrospective physician survey
    - 32 deaths

IFA Sting Attack Rate

- Retrospective Survey Data
  - 58% 1 year sting attack rate (DeShazo, et al 1984)
  - 29% 3 month sting attack rate (Glemmer, et al 1975)
    - 55% sting attack rate among children < 10
- Prospective Study (Tracy, Demain, et al JACI, 1995)
  - N = 137
  - 3 week period in San Antonio
  - 50% sting attack rate
  - 7% sensitivity rate (based on RAST & Skin Test)
RAST Inhibition: "C. vittatus" and IFA

Distribution of Imported Fire Ants in the US in 2009

Distribution of Imported Fire Ants throughout the Globe
North to Alaska: Changing distribution of Hymenoptera

Increasing Hymenoptera in Alaska

- The number of hymenoptera in Fairbanks estimated to have increased 10 fold **
- Jack Whitman, a biologist with the Department of Fish & Game *
  - Used 3 homemade traps
  - (soda bottles & whitefish)
  - Trapped 3,461 YJ on his property in a week
- Destroyed 9 aerial nests in three weeks
- Estimated over 12,000 YJ
- This pattern was similar throughout the state
- Insects adapt well to warmer temperature ***

* Mowry T, Fairbanks Daily Miner, Aug 13, 2006
**Conversation with Derek Sikes, PhD, UAF Entomology

Hymenoptera Related Deaths in Alaska

- 2 deaths from hymenoptera stings in Fairbanks during the summer of 2006

Does temperature change correlate with changing patterns of insects?


Retrospective analysis of the Alaska Medicaid Database (132,000 subjects)

Epidemiologic Regions of Alaska

http://climate.gi.alaska.edu/ClimTrends/Change/TempChange.html

<table>
<thead>
<tr>
<th>Region</th>
<th>Largest Community</th>
<th>Annual temperature increase*</th>
<th>Winter temperature increase*</th>
<th>1999-2001 insect sting incidence</th>
<th>2004-2006 insect sting incidence</th>
<th>Percent change in insect sting incidence ($\chi^2$ for trend, p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern</td>
<td>Barrow</td>
<td>3.8</td>
<td>6.1</td>
<td>16</td>
<td>119</td>
<td>600% (13, p&lt;0.001)</td>
</tr>
<tr>
<td>Southwest</td>
<td>Bethel</td>
<td>3.7</td>
<td>6.9</td>
<td>62</td>
<td>133</td>
<td>514% (6, p&lt;0.005)</td>
</tr>
<tr>
<td>Interior</td>
<td>Fairbanks</td>
<td>3.6</td>
<td>8.1</td>
<td>133</td>
<td>509</td>
<td>53% (26, p&lt;0.001)</td>
</tr>
<tr>
<td>Southcentral</td>
<td>Anchorage</td>
<td>3.4</td>
<td>7.2</td>
<td>276</td>
<td>405</td>
<td>47% (22, p&lt;0.001)</td>
</tr>
<tr>
<td>Southeast</td>
<td>Juneau</td>
<td>3.6</td>
<td>6.8</td>
<td>221</td>
<td>279</td>
<td>27% (22, p&lt;0.001)</td>
</tr>
<tr>
<td>Gulf</td>
<td>Kotlik</td>
<td>3.5</td>
<td>1.5</td>
<td>417</td>
<td>487</td>
<td>19% (6, p&lt;0.05)</td>
</tr>
<tr>
<td>Statewide</td>
<td></td>
<td>3.8</td>
<td>6.3</td>
<td>254</td>
<td>364</td>
<td>43% (54, p&lt;0.001)</td>
</tr>
</tbody>
</table>
Diagnosis of Hymenoptera Hypersensitivity

- History
  - Age & Gender
  - Type of reaction
  - Type of insect
  - Co-morbidity, including medications
  - Impact on lifestyle and risk of future exposure
- Assessment of venom specific IgE (systemic rxns)
  - Prick and intradermal skin testing - preferred method
  - RAST / Immuno-Cap Assay - complementary method
- Measurement of Baseline Mast Cell Tryptase

Diagnosis of Hymenoptera Hypersensitivity

- Local reactions = 80% - 85%
- Large local reactions = 10% - 15%
- Systemic reactions = 0.5% - 5%
  - Incidence of deaths worldwide is largely unknown
  - 40 - 50 deaths/year in US
    - likely underestimated
  - 5% of fatalities under age 20
  - 80% of fatalities over age 40

Insect Sting Anaphylaxis


- Anaphylaxis following insect stings
  - Adults 3%
  - Children 1%
- Cutaneous systemic reactions
  - More common in children
- Hypotensive shock
  - More common in adults
- Respiratory events
  - Equal among age groups
- Recurrence rates of reactions (untreated)
  - 30% - 60%, dependent on severity of prior reaction
Predictors of Severe Sting Anaphylaxis

- N= 962 with bee or vespid venom allergy
  - Untreated
- Data collected
  - Tryptase concentration
  - Age
  - Gender
    - 54% male
  - Culprit insect
  - Cardiovascular medication
    - 5.4\% Beta-blocker
    - 4.4\% ACE Inhibitor
  - Number of minor reactions prior to index field sting

- 21.4\% severe reaction following field sting
- Higher Baseline Serum Tryptase
- Vespid venom
- Older age
- Male
- ACE Inhibitor use
- One or more previous less severe event

- Grade I Generalized skin symptoms (e.g., flush, generalized urticaria, angioedema) 15.2\%
- Grade II Mild-to-moderate pulmonary, cardiovascular, and/or gastrointestinal symptoms 63.4\%
- Grade III Anaphylactic shock, LOC 21.0\%
- Grade IV Cardiac arrest, apnea 0.4\%

Baseline Mast Cell Tryptase

- Mean baseline tryptase 5.84 mcg/L +/- 8.36
- >5 mcg/L increased O.R. of severe event
- 11.4 mcg/L normal level
  - OR >2
  - 8.4\% of patients had elevated tryptase level

Correlation Tryptase with severe event (III/IV)

OR of severe event with increasing Tryptase

5 mcg/L 11.4 mcg/L
Higher Tryptase Level

- Higher baseline serum tryptase concentrations predicts more severe reaction
  - Increased OR if level >5 mcg/L
  - Normal tryptase of 11.4 mcg/L may be inadequate (OR >2)
  - Consider Mast Cell Tryptase level when offering Immunotherapy

Baseline serum tryptase an important predictor of:

- severity of sting rxns
  - Rueff F, JACI, 2009

- freq of systemic rxns during VIT
  - Rueff F, JACI, 2010
  - Bonadonna P, JACI, 2009

- chance of VIT failure

- risk of relapse if VIT is stopped
  - OudeElberink JNG, JACI, 1997

Predictors of Severe Sting Anaphylaxis

- 21.4% severe reaction following field sting
- Higher Baseline Serum Tryptase
- Vespid venom
- Older age
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Interesting: most studies have reported Honeybee causes higher rates of severe systemic reaction
Predictors of Severe Sting Anaphylaxis

• 21.4% severe reaction following field sting
• Higher Baseline Serum Tryptase
• Vespid venom
• Older age  Increase OR of 1.029 per year of age
  (Age >38 at higher risk: p <0.001)
• Male
• ACE Inhibitor use
• One or more previous less severe event

Grade I Generalized skin symptoms 15.2%
  (eg, flush, generalized urticaria, angioedema)
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Insect Sting Deaths in USA
from 1982-1991

Mean Insect Deaths in US per year

AGE

Predictors of Severe Sting Anaphylaxis

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• Higher Baseline Serum Tryptase
• Vespid venom
• Older age
• Male
• ACE Inhibitor use
• One or more previous less severe event

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Grade IV Cardiac arrest, apnea 0.4%
Angiotensin Converting Enzyme Inhibitor

- Use of ACE-Inh was associated with increased risk for more severe anaphylaxis (OR 2.27; p=0.019)

- ACE Inhibitor use
  - only if no reasonable alternative
  - Individual risk-benefit basis


Risk of severe anaphylaxis (grade III/IV)


<table>
<thead>
<tr>
<th>Variable</th>
<th>P-value</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index sting VESPID</td>
<td>.008</td>
<td>1.730</td>
<td>1.147, 2.607</td>
</tr>
<tr>
<td>Preceding, less severe rxn</td>
<td>&lt;.001</td>
<td>4.687</td>
<td>2.913, 7.542</td>
</tr>
<tr>
<td>Female gender (less risk)</td>
<td>&lt;.001</td>
<td>0.553</td>
<td>0.387, 0.791</td>
</tr>
<tr>
<td>ACE inhibitor at index sting</td>
<td>.019</td>
<td>2.299</td>
<td>1.129, 4.558</td>
</tr>
<tr>
<td>Age at index sting (per year)</td>
<td>&lt;.001</td>
<td>1.029</td>
<td>1.018, 1.041</td>
</tr>
<tr>
<td>(&gt;38 y/o at higher risk p &lt;0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Venom Testing

**Anaphylaxis Practice Parameter. J Allergy Clin Immunol 2010;126:477-80**

- Venom skin test (I)
  - Most accurate for diagnosis

- In vitro test (II)
  - An important complementary test

- Neither test reliably predicts severity of reaction (II)
  - Serum specific IgE in 51 cases of fatal sting anaphylaxis did not predict severity (10% < 0.35, 24% < 0.65)

- Diagnosis cannot be made by testing alone (III)
  - Asymptomatic sensitization in 25%
  - History is essential
Venom Immunotherapy

- Should be recommended (I)
  - Patients with systemic sensitivity to venom
    - Except children with cutaneous only
  - Immunotherapy highly effective (90-98%)

- Most patients can discontinue VIT after 5 years
  - Low residual risk of severe sting reaction (<10%)
  - Consider
    - Severity of initial event
    - Tryptase level
    - Age
    - Co-morbid conditions

Stinging Insect Hypersensitivity
Golden et al Stinging insect hypersensitivity Practice Parameter JACI 2011;127:852-4

- Patients with a h/o systemic reaction
  1) Education to avoid stinging insects
  2) Carry self-injectable epinephrine
  3) Should be referred to an Allergist/Immunologist
  4) Undergo thorough history and physical exam
  5) Undergo appropriate venom testing
  6) Initiate Venom Immunotherapy (if indicated)
  7) Consider carrying medical identification

- Identification of the responsible insect may be helpful
- Consider a Mast Cell Tryptase level

Thank you