Hymenoptera Venom Allergy

David F. Graft, M.D.
Stinging Insect Hypersensitivity: A Practice Parameter Update 2010 *

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* Publication pending
FIG 1. Algorithm: management of stinging insect reactions.

1. Patient Presents with History of Insect Sting Reaction

2. History and Physical Examination

3. Was there a systemic reaction?
   - Yes
   - Prescribe epinephrine for self-administration. Refer to an Allergist/Immunologist. Recommend insect avoidance.
   - No

4. Was there a large local reaction?
   - Yes
   - 4A: Provide symptomatic treatment if needed. Consider need for guidance regarding further stings.
   - No
   - 4B: Provide symptomatic treatment if needed.

5. Is the patient a child whose reaction was limited to the cutaneous system?
   - Yes
   - 6A: Do special circumstances exist?
     - No
     - 6B: Skin test/immunotherapy unnecessary
     - Yes
     - 6C: Consider skin test and possible immunotherapy
   - No

6. Perform skin tests

7. Skin test positive?
   - Yes
   - 8A: Is further evaluation needed?
     - No
     - 8B: Further test and consideration of immunotherapy usually unnecessary.
     - Yes
     - 8C: Perform Ivites and/or repeat skin tests
   - No

8. Recommend and give immunotherapy

9. Immunotherapy failure?
   - Yes
   - 10A: Reassess, consider dosage adjustment
   - No

10. Consider stopping immunotherapy after 3-5 years

11. Immunotherapy not indicated
FIG 1. Algorithm: management of stinging insect reactions.
Algorithm: Managing Sting Reactions

Review of important historical points

- Type of insect
- Type of reaction
  - Expected
  - Large local
  - Systemic
Biology of Hymenoptera

Figure 4. Taxonomy of Hymenoptera. Examples of common species are given below:

Order: Hymenoptera

Family:
- Apidae
- Vespidae
- Formicidae

Genus:
- Apis
- Bombus
- Vespa
- (Para) vespula
- Dolichovespula
- Polistes
- Solenopsis

Species:
- A. mellifera (honey bee)
- B. terrestris (bumble bee)
- V. crabro (Eur.hornet)
- V. vulgaris (yellow jacket)
- D. media (yellow hornet)
- Polistes sp. (paper wasps)
- S. invicta (imported fire ant)
FIG 1. Algorithm: management of stinging insect reactions.
Algorithm: Managing Sting Reactions

General population risk
= ~5%

Systemic spectrum
- Cutaneous only
- Bronchospasm
- Upper airway obstruction
- Hypotension and shock
- GI
Patient Presents with History of Insect Sting Reaction

1. History and Physical Examination

3. Was there a systemic reaction?
   - Yes
     - Prescribe epinephrine for self-administration. Refer to an Allergist/Immunologist. Recommend insect avoidance.
   - No

5. Is the patient a child whose reaction was limited to the cutaneous system?
   - Yes
     - 6A Do special circumstances exist?
       - No
         - 7 Perform skin tests
       - Yes
         - 8 Skin test positive?
           - Yes
             - 9 Recommend and give immunotherapy
           - No
             - 8D Immunotherapy not indicated

   - No

8. Is further evaluation needed?
   - No
     - 8B Further test and consideration of immunotherapy usually unnecessary
   - Yes
     - 8C Perform ivig and/or repeat skin tests

10. Immunotherapy failure?
    - Yes
      - 10A Reassess, consider dosage adjustment
    - No
      - 11 Consider stopping immunotherapy after 3-5 years

4. Was there a large local reaction?
   - Yes
     - 4A Provide symptomatic treatment if needed. Consider need for guidance regarding future stings.
   - No
     - 4B Provide symptomatic treatment if needed.

FIG 1. Algorithm: management of stinging insect reactions.
Algorithm: Managing Sting Reactions

Large local therapy
- Cold compresses
- Antihistamines
- Analgesics
- Possibly steroids

Future stings
- Up to 10% chance of future systemic
- Epi Rx - optional
- Immunotherapy may reduce reaction

Flowchart:
- Question: Was there a large local reaction?
  - No
    - 4A: Provide symptomatic treatment if needed. Consider need for guidance regarding future stings.
  - Yes
    - 4B: Provide symptomatic treatment if needed.
Patient Presents with History of Insect Sting Reaction

2 History and Physical Examination

3 Was there a systemic reaction?
   No
   4 Was there a large local reaction?
      Yes
      4A Provide symptomatic treatment if needed. Consider need for guidance regarding future stings.
      No
      4B Provide symptomatic treatment if needed.
   Yes
   5 Prescribe epinephrine for self-administration. Refer to an Allergy/Immunologist. Recommend insect avoidance.

6 Is the patient a child whose reaction was limited to the cutaneous system?
   No
   7 Perform skin tests
   Yes
   8 Skin test positive?
      No
      9 Recommend and give immunotherapy
      Yes
      10 Immuotherapy failure?
         Yes
         10A Reassess, consider dosage adjustment
         No
         11 Consider stopping immunotherapy after 3-5 years
      No
   8A Is further evaluation needed?
      No
      8B Further test and consideration of immunotherapy usually unnecessary.
      Yes
      8C Perform ivitro and/or repeat skin tests

6A Do special circumstances exist?
   No
   6B Skin test/immunotherapy unnecessary
   Yes
   6C Consider skin test and possible immunotherapy

FIG 1. Algorithm: management of stinging insect reactions.
Algorithm: Managing Sting Reactions

Initial plan

- Rx: Epi for self-administration
- Recommend medical alert bracelet
- Avoid insects

Future prophylaxis – Refer to an Allergist

2005: 617 pts; 15 EDs
Sys rxn: 12% epi in ED; discharge;
27% epi, 20% ref to allergist
FIG 1. Algorithm: management of stinging insect reactions.

1. Patient Presents with History of Insect Sting Reaction

2. History and Physical Examination

3. Was there a systemic reaction?
   Yes
   No
   6. Is the patient a child whose reaction was limited to the cutaneous system?
      Yes
      7. Perform skin tests
      No

4. Was there a large local reaction?
   Yes
   4A. Provide symptomatic treatment if needed. Consider need for guidance regarding future stings.
   No
   4B. Provide symptomatic treatment if needed.

5. Do special circumstances exist?
   Yes
   6A. Consider skin test and possible immunotherapy
   No
   6B. Skin test/immunotherapy unnecessary

8. Is further evaluation needed?
   Yes
   8A. Further test and consideration of immunotherapy usually unnecessary.
   8B. Perform ivitro and/or repeat skin tests
   No
   8D. Immunotherapy not indicated

9. Recommend and give immunotherapy

10. Immunotherapy failure?
    Yes
    10A. Reassess, consider dosage adjustment
    No
    11. Consider stopping immunotherapy after 3-5 years

Negative
Algorithm: Managing Sting Reactions

Cutaneous in Children
(< 16 yo)
- Risk of future systemic ~ 10%

Cutaneous in Adults - Lack evidence to withhold IT

Limited data for children and fire ants
Patient Presents with History of Insect Sting Reaction

2 History and Physical Examination

3 Was there a systemic reaction?

   5 Prescribe epinephrine for self-administration. Refer to an Allergist/Immunologist. Recommend insect avoidance.

   6 Is the patient a child whose reaction was limited to the cutaneous system?

   No

   Yes

4 Was there a large local reaction?

   4A Provide symptomatic treatment if needed. Consider need for guidance regarding future stings.

   4B Provide symptomatic treatment if needed.

6A Do special circumstances exist?

   No

   Yes

6B Skin test/immunotherapy unnecessary

6C Consider skin test and possible immunotherapy

7 Perform skin tests

8 Skin test positive?

   No

   Yes

8A Is further evaluation needed?

   No

   Yes

8B Further test and consideration of immunotherapy usually unnecessary.

8C Perform ivrino and/or repeat skin tests

8D Immunotherapy not indicated

9 Recommend and give immunotherapy

10 Immunotherapy failure?

   Yes

   10A Reassess, consider dosage adjustment

   No

   Consider stopping immunotherapy after 3-5 years

   11 Immunotherapy not indicated

FIG 1. Algorithm: management of stinging insect reactions.
Algorithm: Managing Sting Reactions

Special considerations

- Increased risk
- Parents request IT

Need to carry Epi

- determine after discussion

---

6A
Do special circumstances exist?

---

No

6B
Skin test/immunotherapy unnecessary

Yes

6C
Consider skin test and possible immunotherapy
FIG 1. Algorithm: management of stinging insect reactions.
Algorithm: Managing Sting Reactions

Prick at 1.0 - 100µg/ml

Intracutaneous
- Initial 0.001 to 0.001 µg/ml
- Then 10-fold increments
- Maximum 1.0 µg/ml

Usually all venoms tested
- Due to poor identification
- Except for fire ants

No correlation between level of reactivity and severity of clinical reaction
Why Start Venom Immunotherapy ????
Insect Sting Deaths in USA from 1982-1991

Mean Insect Deaths in USA Per Year

- < 10
- 10-20
- 20-29
- 30-39
- 40-49
- 50-59
- 60-69
- > 70
Controlled Trial of Venom Immunotherapy

59 Insect-Allergic Patients

19 Venom
20 Placebo
20 WBE
## Controlled Trial of Venom Immunotherapy

<table>
<thead>
<tr>
<th></th>
<th>Venom</th>
<th>WBE</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number stung</strong></td>
<td>18</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td><strong>Number reacted</strong></td>
<td>1</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Patient</td>
<td>epi (mg)</td>
<td>norepi</td>
<td>plasm (ml)</td>
</tr>
<tr>
<td>---------</td>
<td>---------</td>
<td>--------</td>
<td>------------</td>
</tr>
<tr>
<td>1</td>
<td>0.5</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>3.5</td>
<td>Yes</td>
<td>875</td>
</tr>
<tr>
<td>3</td>
<td>7.5</td>
<td>Yes</td>
<td>1750</td>
</tr>
</tbody>
</table>
Natural History of Insect Sting Allergy

Risk of Systemic Reaction (%)

YEARS

ST+ Hx+

Untreated

VIT x 5 yrs

VIT x 1-2 yrs
Freeman TM, et al.
IFA Immunotherapy: Effectiveness of WBE.

76 patients with anaphylaxis post-IFA stings

- 11 refused immunotherapy
  - 4 re-skin tested - all positive
  - 6 field stings - all reacted
- 65 accepted WBE IT
  - 31 re-skin tested - all decreased
  - 47 field stings - 1 reaction
  - 30 challenged - no reactions

Why does WBE work?
It works because there is enough venom

- 100 ng/sting, 1 µg/event
- 1.5 to 2.4 µg delivered at maintenance
FIG 1. Algorithm: management of stinging insect reactions.
Algorithm: Managing Sting Reactions

Skin test negative patients with a hx c/w anaphylaxis

- Should have specific IgE determined *in vitro*
- Repeat determinations may be necessary
- Consider baseline tryptase

Flowchart:
- **8A** Is further evaluation needed?
  - No
  - 8B Further test and consideration of immunotherapy usually unnecessary.
  - Yes
    - 8C Perform invtro and/or repeat skin tests
      - Positive
      - Immunotherapy not indicated
    - Negative
Tryptase...what’s new?

- Baseline serum tryptase an important predictor
  - freq of systemic rxns during VIT  Rueff, JACI, 2010
    BonadonnaP, JACI, 2009
  - chance of VIT failure
  - risk of relapse if VIT is stopped  OudeElberinkJNG, JACI, 1997
Predictors of Systemic Reactions During Buildup Phase of VIT

- Observational prospective study
- 57 (8.4%) of 680 pts req emerg intervention (def: any type of measure/medication felt necessary to control systemic side effect assoc with VIT)
- Freq of interventions increased by:
  - Higher basal tryptase; 68 (10%) had >11.4; 18 (2.6%) >20; odds ratio 1.556 (p=0.004)

Ruëff F et al. JACI; 2010 126:105-111
## Risk to need an emergency intervention during buildup phase of immunotherapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>$P$ value</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy with HB venom</td>
<td>&lt;.001</td>
<td>3.60</td>
<td>2.36 5.50</td>
</tr>
<tr>
<td>Venom specific IgE</td>
<td>.013</td>
<td>6.243</td>
<td>1.435 27.159</td>
</tr>
<tr>
<td>Index sting grade III/IV</td>
<td>.149</td>
<td>1.421</td>
<td>0.874 2.310</td>
</tr>
<tr>
<td>Female sex</td>
<td>.157</td>
<td>1.349</td>
<td>0.883 2.061</td>
</tr>
<tr>
<td>Any BP med during VIT</td>
<td>.032</td>
<td>2.144</td>
<td>1.051 4.374</td>
</tr>
<tr>
<td>Age at therapy (per year)</td>
<td>.034</td>
<td>0.984</td>
<td>0.970 0.999</td>
</tr>
<tr>
<td>Conventional dose increase during VIT</td>
<td>.044</td>
<td>0.397</td>
<td>0.158 0.995</td>
</tr>
<tr>
<td>Ultrarush dose increase during VIT</td>
<td>.008</td>
<td>1.787</td>
<td>1.153 2.770</td>
</tr>
<tr>
<td>Interval from most recent sting reaction and VIT</td>
<td>.039</td>
<td>1.199</td>
<td>1.006 1.429</td>
</tr>
<tr>
<td>BTC at first office visit</td>
<td>.004</td>
<td>1.556</td>
<td>1.149 2.108</td>
</tr>
</tbody>
</table>
Honeybee Sensitivity More Problematic

• Untreated: higher recurrence rate
• More SR during VIT
• VIT less effective
• More sting rxns after VIT stopped
FIG 1. Algorithm: management of stinging insect reactions.
Algorithm: Managing Sting Reactions

VIT reduces risk to as low as 2% on subsequent stings

Protocol
- 0.1 to 1.0 µg initial
- 100 µg maintenance
- Q 4 wk interval first year
- Q 6-8 wks subsequent years
Algorithm: Managing Sting Reactions

Fire ants use WBE
- Less well defined
- Maintenance = 0.5 ml of 1:100 wt/vol

Rapid protocols have been used safely and effectively
Algorithm: Managing Sting Reactions

Special Considerations

β- adrenergic blockers
- Increased risk of severe reactions
- Prefer to d/c β-blockers
- Can receive VIT if must have β-blockers

Angiotensin-converting enzyme inhibitors
- One study (Rueff et al JACI 2009) showed increased risk of severe reactions
FIG 1. Algorithm: management of stinging insect reactions.
Algorithm: Managing Sting Reactions

If has systemic reaction on maintenance VIT

- If same insect consider increased dose to 200 µg/ml
- If unknown or different check for specific IgE
Algorithm: Managing Sting Reactions

Stopping IT

Consider after 3-5 yrs
- Esp if IgE negative
- Future risk ~ 10 %

Special considerations
- Life style, occupation
- Coexistent diseases
- Medications
- Severity of reactions

No definitive recommendation for fire ants
Discontinuation of VIT: Hopkins

- 74 pts: ≥ 5 yrs of VIT
- Every 1-2 yrs, VST, venom-specific IgE, sting challenge
- Usual group of VIT pts: 75% ↓BP
- Neg VST when VIT stopped = 26%

Golden DBK, JACI 1996; 97:579
Change in VST and IgE level during and after VIT
## Discontinuation of VIT: Hopkins

<table>
<thead>
<tr>
<th>Year</th>
<th>GROUP 1</th>
<th>GROUP 2</th>
<th>GROUP 3</th>
<th>ALL PTS</th>
<th>ALL STGS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Pt</td>
<td># Stg</td>
<td># Pt</td>
<td># Stg</td>
<td># Pt</td>
</tr>
<tr>
<td></td>
<td>Rxn</td>
<td>Rxn/#Pt</td>
<td>Rxn/</td>
<td>Rxn/</td>
<td>Rxn/#Pt</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td># Pt</td>
<td># Stg</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0/29</td>
<td>0/29</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>1/28</td>
<td>1/28</td>
<td>2/25</td>
<td>2/25</td>
<td>1/20</td>
</tr>
<tr>
<td>3</td>
<td>1/26</td>
<td>1/26</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>4</td>
<td>0/24</td>
<td>0/48</td>
<td>3/24</td>
<td>3/48</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>0/26</td>
<td>0/26</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>2/29</td>
<td>2/157</td>
<td>4*/25</td>
<td>5/73</td>
<td>1/20</td>
</tr>
</tbody>
</table>

*One of pts in Group 2 reacted in both yr2 and yr 4.

Golden, JACI 1996; 97:579
## Sting Reactions After Stopping VIT

<table>
<thead>
<tr>
<th>Study Group/Yrs</th>
<th>Patients (N)</th>
<th>Patients (Stung)</th>
<th>Stings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (Yrs 1-5)</td>
<td>74</td>
<td>7/74 (9.5%)</td>
<td>8/270 (3%)</td>
</tr>
<tr>
<td>Group 1 (Yrs 6-7)</td>
<td>74</td>
<td>1/11</td>
<td>2/14</td>
</tr>
<tr>
<td>Group 2</td>
<td>51</td>
<td>4/15</td>
<td>4/25</td>
</tr>
<tr>
<td>TOTAL (to date)</td>
<td>125</td>
<td>12/89 (13.5%)</td>
<td>14/309 (4.5%)</td>
</tr>
</tbody>
</table>
### Sting Rxns After Stopping VIT

<table>
<thead>
<tr>
<th></th>
<th>Patients (N)</th>
<th>No Reaction</th>
<th>Systemic Reaction</th>
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</thead>
<tbody>
<tr>
<td>No reaction during VIT</td>
<td>76</td>
<td>70</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Systemic reaction during VIT</td>
<td>13</td>
<td>7</td>
<td>6 (46%)</td>
</tr>
</tbody>
</table>
## Severity of Systemic Reactions Before VIT and After VIT Stopped

<table>
<thead>
<tr>
<th>Sting Reaction</th>
<th>Before VIT</th>
<th>After VIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Gen. Urt/angio only</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory*</td>
<td>41</td>
<td>3</td>
</tr>
<tr>
<td>Hypotension#</td>
<td>35</td>
<td>1</td>
</tr>
</tbody>
</table>

* Dyspnea, throat tightness, asthma, cough
# Dizziness, unconscious, BP < 90/60
Considerations in Decision to Start/Stop VIT

1. VIT very effective
2. Maintenance VIT can be extended to 8-12 wk
3. Patients with most severe reactions at most risk
4. Coexistent health problems
5. Occupation and leisure exposures
Perhaps VIT Shouldn’t Be Stopped If:

• Severe pre-VIT reaction
• VIT duration < 5 years
• Honeybee sensitivity
• Rxns to injections or stings on VIT
• Venom sensitivity doesn’t decline
However, the majority of even these most-at-risk patients tolerate discontinuation of VIT after 5 years of treatment.
BEES

Worker

Queen

Drone

Consultant

McRae Ford