Venom Immunotherapy
WAC Cancun 2011
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Disclaimer

* Invited contributor for UptoDate®
* No other conflicts of interest

* Brevity is the Soul of Whit....
  * Hamlet, Act 1, Scene II
Adults stung with systemic reactions
- Risk of systemic reaction to subsequent sting 30-60%
- Severe life-threatening reaction at highest risk
- Other factors – hymenoptera species, immune status, mast cell disease, etc. may play role
- Children stung with systemic reactions
- Risk of systemic reaction to subsequent sting ~ 30%
- Severe life-threatening reaction at highest risk
- Children < 17 yrs, limited to skin sx have 10% risk
- Most of these subsequent reactions minor

Children stung with systemic reactions
- Risk of systemic reaction to subsequent sting ~ 30%
- Severe life-threatening reaction at highest risk

Natural History

Effectiveness of VIT
- In adult with VIT risk is reduced from 30-60% to ~ 5%
- Individual who do react have less severe reactions
- Honeybee vs vespid
  - HB have a higher rate of subsequent reactions
  - VIT somewhat less effective for HB vs. vespid ~ 75 vs. 91%
  - Improved quality of life for VIT vs. avoidance

Indication of VIT
- Reliable history of a systemic reaction to a hymenoptera sting
- Evidence of venom-specific IgE by skin test or in vitro methods

TO BE A VIT CANDIDATE BOTH CRITERIA ARE REQUIRED
North American vs. European Differences in VIT Indications

- Severe Systemic reaction – NA and EU VIT Indicated
- Moderate severe
  - NA – VIT indicated
  - EU – VIT strong consideration
- Less Severe Reaction
  - NA – Usually indicated
  - EU – Usually not indicated w/o other risk factors such as occupation or increased exposure risk, increased tryptase or quality of life considerations
- Children
  - EU – Because usually less severe reactions, generally VIT not indicated
  - NA – VIT indicated based on age and symptom. Le Skin vs. other

Indication – Local vs. Systemic Reactions

Systemic Reactions - Reactions distant from the sting site
- Generalized urticaria
- Angioedema
- Bronchospasm
- Laryngeal edema
- Hypotension
- Loss of Consciousness

Indication – Local vs. Systemic Reactions

Local Reaction – Reaction contiguous to the sting site
- Local Reactions
  - Large Local Reactions
    - > 2 inches or 5 cm
    - > 24 hours duration
  - Small Local Reactions
    - < 2 inches or 5 cm
    - < 24 hours duration
Indication for VIT - Adults

* Reliable history of a systemic reaction to a hymenoptera sting
* Evidence of venom-specific IgE by skin test or in vitro methods
* TO BE A VIT CANDIDATE BOTH CRITERIA ARE REQUIRED

Indications for VIT– Children

* Children
  * EU – Because usually less severe reactions, generally VIT not indicated. Individual considerations
  * NA – VIT indicated based on age and symptom.
  * Generally NOT indicated for systemic non-life-threatening symptoms – urticaria, angioedema, erythema or pruritis
  * Indicated for systemic life-threatening symptoms - laryngeal edema, bronchospasm, hypotension or shock

VIT – Particularly Advantageous*

* Occupational or Recreational Considerations
  * Landscapers, Roofers, Bee Keepers
  * Outdoor Enthusiasts
    * Campers and hunters
    * Remote life style
  * “High Anxiety” Individuals or Families

  * Still require fulfillment of other parameters: i.e. positive venom-specific IgE and history of a systemic reaction
Predictors of Systemic Reactions in Patients with Insect Allergy

ACE and Beta-blockers

* ACE Inhibitor - Controversial
  * Theoretical increased risk to anaphylaxis
    * Inhibition of angiotensin II during hypotension
    * Increased bradykinin a potent vasodilator
  * Overall incidence risk of anaphylaxis during VIT with ACE does not appear to be correlated.
  * NA 2011 Insect Practice Parameter – if possible find an alternative to an ACE inhibitor

ACE and Beta-blockers

* Beta-blockers
  * Inhibit effects of epinephrine in anaphylaxis
  * Beta-blockers may increase the risk of anaphylaxis
  * Beta-blockers may make treating anaphylaxis more difficult
  * Co-morbid condition need to be considered
  * Consider, if possible, alternatives or withholding during build-up dosing
  * However, after considering risk vs. benefit, the benefit may still out weigh the potential risks
Immunotherapy – Fire Ants
*S. invicta and S. richteri*

- Indication same as other hymenoptera
- History of systemic reaction and Skin test or in vitro evidence of specific IgE
- Whole-body Extract versus purified venom
- Dosing schedules based on wt/volume
- Safe and Effective Therapy

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Dose and Schedules
Imported Fire Ant

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<th>Dose</th>
<th>Volumes</th>
<th>Time (weeks)</th>
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Adapted from 2011 Insect Practice Parameter. JACI;127:852-4

Injections are generally given weekly or, in some cases, 2 times per week. After the maintenance dose of 0.5 mL of 1:100 wt/vol. is administered safely several times, the dosage interval can be advanced to every 2 weeks and eventually can be extended to 4 weeks. Schedule 1 is provided by Drs. Anne Yates, Sitesh Roy, and John Moffitt of the University of Mississippi Medical Center. Schedule 2 is provided by Dr. Ted Freeman.

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Dose and Schedules
North American

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Dose and Schedules
United Kingdom

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Adapted from 2011 British Guidelines.

1. Adapted from 2011 Insect Practice Parameter. JACI;127:852-4
2. Adapted from 2011 British Guidelines.
Duration of Therapy

- Duration of VIT remains unclear
- Majority sufficiently protected after 3-5 years
- Some authors have suggested repeat testing, however loss of reactivity not a guarantee of no risk
- Consider life-long treatment if:
  - Severe (grade III or IV), near fatal reactions
  - Honeybee allergy
  - Individuals requiring higher than usual treatment doses
  - Elevated serum tryptase or mast cell disease
  - Severe anxiety

Duration of Therapy - Natural History of Insect Sting Allergy

Large Local Reactions and VIT

- LLR often caused by IgE mediated late-phase response
- Generally not considered life-threatening with 5-10% risk of future systemic reaction
- Venom-specific testing generally not indicated
- Occasionally these reactions are debilitating or progressively worsening
- VIT may be beneficial and venom testing is indicated1,2,3
Large Local Reactions and VIT


- Methods: 41 patients with LLR and + ST (3.4 > 16 cm) 29 consented
- 19 treated with VIT, 10 untreated controls
- Sting challenge at 7 to 11 wks, the untreated started VIT
- Results: after 7 to 11 wks LLR decreased 42% and 53% respectfully After 2 to 4 yrs decreased to 60% and 70%
- Conclusion: VIT significantly decreased size and duration of LLR and improved over a 2 to 4 year period

Large Local Reactions and VIT

VIT – Serum Tryptase and Mast Cell Disease

**VIT and omalizumab**

- Our understanding of the role of clonal mast cell disorders and the management role serum tryptase has expanded in recent years.
- Omalizumab has been a useful adjunct in occult or indolent mast cell disease and difficult to treat insect anaphylaxis.
- Use is investigational, with only selective case reports to date.

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**VIT and omalizumab**


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**Predictors of side effects during the buildup phase of venom immunotherapy for Hymenoptera venom allergy: The importance of baseline serum tryptase**


Linear function and 95% confidence band (dashed lines) for the effect of BTC on the risk to need an emergency intervention during the buildup phase of venom immunotherapy (final multivariate generalized additive model). Odds ratios are referred to those of the median of tryptase concentration. The odds ratio of the latter has been set at 1.
**Gene expression analysis in predicting the effectiveness of insect venom immunotherapy**

- **Methods:** 46 patient – Whole genome gene expression analysis performed on RNA samples. Three groups:
  - Patients who achieved and maintained LT protection w/ VIT
  - Patients where protection relapsed after VIT
  - Patients still on maintenance VIT
- **Conclusion:** Gene expression profiling might be useful to assess long-term effectiveness of VIT


**Conclusion**

- Venom immunotherapy should be considered and offered to any patient with a history of a systemic allergic reaction to a Hymenoptera sting and evidence by of venom-specific IgE.
- VIT can provide a protective level of up to 98% against future sting events.
- Individuals with elevated serum tryptase are at increased risk for reactions to VIT, but still benefit.
- Usual duration is 3-5 years, but may be lifelong.