

Natural History

- * 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

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 – 7% 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. i.e 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

TABLE II. Distribution of the severity grade of systemic anaphylactic reactions (grade III or IIIIV) after the index sting with respect to baseline parameters

Parameter	Grade I or II reaction (n = 736)	Grade III or IIIIV reaction (n = 298)	P value
β-Blocker medication at the time of the index sting			.024
Yes	34 (6.4%)	18 (4.0%)	
No	322 (79.3%)	188 (20.7%)	
ACE inhibitor medication at the time of the index sting			.002
Yes	24 (5.1%)	18 (4.2%)	
No	232 (29.8%)	188 (24.4%)	
Any antihypertensive medication at the time of the index sting			<.001
Yes	61 (8.5%)	38 (8.5%)	
No	695 (80.4%)	170 (19.6%)	
Sex			<.001
Male	385 (23.6%)	138 (26.4%)	
Female	371 (84.4%)	68 (15.5%)	
One or more preceding, less severe systemic sting reactions before index sting			<.001
Yes	46 (6.4%)	43 (11.6%)	
No	710 (81.9%)	157 (18.1%)	
Insect responsible for index sting and associated allergic reaction			.016
Bee	241 (33.4%)	46 (16.6%)	
Vespid	115 (16.6%)	158 (22.3%)	
Age (y) at index sting according to median			<.001
<38	424 (88.2%)	68 (13.8%)	
≥38	332 (76.0%)	138 (29.4%)	

Ruff et al. EAACI Insect Group on Insect Allergy. JACI 2009; 124:1047

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-blocker 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

Dose and Schedules Imported Fire Ant

Schedule 1		Schedule 2			
Time	Concentration (µg/ml)	Time	Volume		
1	1:100,000	0.05 ml	1	1:100,000	0.05 ml
2	1:100,000	0.10 ml	2	1:100,000	0.15 ml
3	1:100,000	0.20 ml	3	1:100,000	0.25 ml
4	1:100,000	0.30 ml	4	1:100,000	0.30 ml
5	1:100,000	0.40 ml	5	1:100,000	0.35 ml
6	1:100,000	0.50 ml	6	1:100,000	0.40 ml
7	1:100,000	0.60 ml	7	1:100,000	0.45 ml
8	1:100,000	0.70 ml	8	1:100,000	0.50 ml
9	1:100,000	0.80 ml	9	1:100,000	0.55 ml
10	1:100,000	0.90 ml	10	1:100,000	0.60 ml
11	1:100,000	1.00 ml	11	1:100,000	0.65 ml
12	1:100,000	1.10 ml	12	1:100,000	0.70 ml
13	1:100,000	1.20 ml	13	1:100,000	0.75 ml
14	1:100,000	1.30 ml	14	1:100,000	0.80 ml
15	1:100,000	1.40 ml	15	1:100,000	0.85 ml
16	1:100,000	1.50 ml	16	1:100,000	0.90 ml
17	1:100,000	1.60 ml	17	1:100,000	0.95 ml
18	1:100,000	1.70 ml	18	1:100,000	1.00 ml
19	1:100,000	1.80 ml	19	1:100,000	1.05 ml
20	1:100,000	1.90 ml	20	1:100,000	1.10 ml
21	1:100,000	2.00 ml	21	1:100,000	1.15 ml
22	1:100,000	2.10 ml	22	1:100,000	1.20 ml
23	1:100,000	2.20 ml	23	1:100,000	1.25 ml
24	1:100,000	2.30 ml	24	1:100,000	1.30 ml
25	1:100,000	2.40 ml	25	1:100,000	1.35 ml
26	1:100,000	2.50 ml			
27	1:100,000	2.60 ml			
28	1:100,000	2.70 ml			



Injections are generally given weekly or, in some cases, 2 times per week. After the maintenance dose of 6.5 ml of 1:100,000, 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, Sidesh Roy, and John Moffitt of the University of Mississippi Medical Center. Schedule 2 is provided by Dr Ted Freeman.

Adapted from 2011 Insect Practice Parameter. JACI127:852-4

Dose and Schedules

North American*			United Kingdom [†]		
Week	Concentration (µg/ml)	Volume	Week	Concentration (µg/ml)	Volume
1	1:10	0.05 ml	15	0.1	0.1 ml
2	1:10	0.1 ml	20	0.1	0.1 ml
3	1:10	0.2 ml	25	0.1	0.1 ml
4	1:10	0.4 ml	30	0.1	0.1 ml
5	1:10	0.6 ml	35	0.1	0.1 ml
6	1:10	0.8 ml	40	0.1	0.1 ml
7	1:10	1.0 ml	45	0.1	0.1 ml
8	1:10	1.2 ml	50	0.1	0.1 ml
9	1:10	1.4 ml	55	0.1	0.1 ml
10	1:10	1.6 ml	60	0.1	0.1 ml
11	1:10	1.8 ml	65	0.1	0.1 ml
12	1:10	2.0 ml	70	0.1	0.1 ml
13	1:10	2.2 ml	75	0.1	0.1 ml
14	1:10	2.4 ml	80	0.1	0.1 ml
15	1:10	2.6 ml	85	0.1	0.1 ml
16	1:10	2.8 ml	90	0.1	0.1 ml
17	1:10	3.0 ml	95	0.1	0.1 ml
18	1:10	3.2 ml	100	0.1	0.1 ml
19	1:10	3.4 ml			
20	1:10	3.6 ml			
21	1:10	3.8 ml			
22	1:10	4.0 ml			
23	1:10	4.2 ml			
24	1:10	4.4 ml			
25	1:10	4.6 ml			
26	1:10	4.8 ml			
27	1:10	5.0 ml			
28	1:10	5.2 ml			
29	1:10	5.4 ml			
30	1:10	5.6 ml			
31	1:10	5.8 ml			
32	1:10	6.0 ml			
33	1:10	6.2 ml			
34	1:10	6.4 ml			
35	1:10	6.6 ml			
36	1:10	6.8 ml			
37	1:10	7.0 ml			
38	1:10	7.2 ml			
39	1:10	7.4 ml			
40	1:10	7.6 ml			
41	1:10	7.8 ml			
42	1:10	8.0 ml			
43	1:10	8.2 ml			
44	1:10	8.4 ml			
45	1:10	8.6 ml			
46	1:10	8.8 ml			
47	1:10	9.0 ml			
48	1:10	9.2 ml			
49	1:10	9.4 ml			
50	1:10	9.6 ml			
51	1:10	9.8 ml			
52	1:10	10.0 ml			

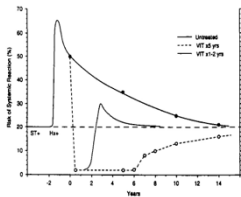
^{*}May be lower depending on patient's reactivity.
[†]As per manufacturer's recommendations. All UK manufacturers use the same concentration. For a more detailed description refer to the manufacturer's product information.

1. Adapted from 2011 Insect Practice Parameter. JACI127:852-4
 2. Adapted from 2011 British Guidelines. CI Exp All 44:1210-1220

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



Golden D, et al. Survey of patients after discontinuing venom immunotherapy JACI 2000;105:385-90.

FIG 2. Natural history of insect sting allergy showing the risk of systemic reaction to a sting in untreated patients (solid line) and in patients who received venom immunotherapy (dashed lines) for a duration of either 1 to 2 years or for a mean of 6 years.

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 indicated^{1,2,3}

1. Graft DF, et al. A prospective study of the natural history of large local reactions after Hymenoptera stings in children. J Pediatr 1986; 106: 664 - 668.
 2. Abaruelo PA, et al. Natural history of large local reactions from stinging insects. J Allergy Clin Immunol 1984; 74 (part 3): 494 - 498.
 3. Golden DBK, et al. Venom immunotherapy reduces large local reactions to insect stings. J Allergy Clin Immunol 2009; 123: 1371 - 1375.

Large Local Reactions and VIT

Golden DBK, et al. VIT reduces LLR to insect stings. JACI 2009; 123: 1371 – 1375

- * Methods: 41 patients with LLR and + ST (34 >16 cm) 29 consented
 - * 19 treated with VIT, 10 untreated controls
 - * Sting challenge at 7 to 11wks, the untreated started VIT
- * Results: after 7 to 11 wks LLR decreased 42% and 53% respectively 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

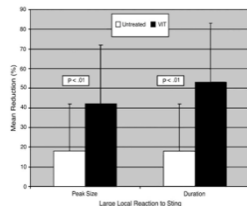


FIG 8. Mean reduction \pm SD (%) in the peak size and duration of large local reactions to stings after 7 weeks (range, 4-11) of either single VIT (19 subjects) or no treatment (10 subjects). There was a significantly greater improvement in the treated subjects.

Golden DBK, et al. Venom Immunotherapy reduces large local reactions to insect stings. *J Allergy Clin Immunol* 2009; 123: 1371 – 1375.

VIT – Serum Trypsinase and Mast Cell Disease

- * Ruëff F, Przybilla B, Bilo MB, et al. Predictors of severe systemic, anaphylactic reactions in patients with Hymenoptera venom allergy: importance of baseline serum trypsinase-study of the European Academy of Allergology and Clinical Immunology Interest Group on Insect Venom Hypersensitivity. *JACI* 2009; 124:1047-1054.
- * Ruëff F, Przybilla B, Bilo MB, Muller U, et al. Predictors of side effects during build-up phase of venom immunotherapy for Hymenoptera venom allergy: the importance of baseline serum trypsinase. *J Allergy Clin Immunol* 2010; 126:105 – 111.
- * Bonadonna P, Perbellini O, Passalacqua G, et al. Clonal mast cell disorders in patients with systemic reactions to Hymenoptera stings and increased serum trypsinase levels. *J Allergy Clin Immunol* 2009; 123:680-686.
- * Niedoszytko M, de Monchy J, van Doormaal JJ, et al. Mastocytosis and insect venom allergy: diagnosis, safety and efficacy of venom immunotherapy. *Allergy* 2009; 64:1237 – 1245.

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

VIT and omalizumab

- * Kontou-Filli K, Fillis CI, Voulgari C, Panayiotidis PG. Omalizumab monotherapy for bee sting and unprovoked 'anaphylaxis' in a patient with systemic mastocytosis and undetectable specific IgE. *Ann All Asthma Immunol* 2010; 104:537 – 539.
- * Douglass JA, Carroll K, Voskamp A, et al. Omalizumab is effective in treating systemic mastocytosis in a nonatopic patient. *Allergy* 2009; 65:926 – 927
- * Kontou-Filli K. High omalizumab dose controls recurrent reactions to venom immunotherapy in indolent mastocytosis. *Allergy* 2008; 63:376–378.

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

Rueff F, et al. *JACI* 2010;126:105-111

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 vespid 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

Niedoszytko M, Bruinenberg, M, de Monchy J, et al. JACI 2010; 125:1092-7

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 increase risk for reactions to VIT, but still benefit.
- * Usual duration is 3-5 years, but may be life-long.

Conclusion

