

## Practice Parameter on Insect Sting Allergy 2016 Update

David B.K. Golden, M.D.  
Johns Hopkins University, Baltimore

### What's New in 2016 Update of Practice Parameter on Insect Allergy

- Indications for VIT in adults with cutaneous SR?
- Baseline serum tryptase and mastocytosis
  - When to measure, clinical significance
- Venom skin test technique and interpretation
- Risk of ACE inhibitors or beta-blockers?
- When to prescribe epi (high risk vs. low risk)
- Venom immunotherapy:
  - Starting dose (for skin tests and VIT)
  - Rush regimens
  - Management of adverse events
  - Maintenance interval
  - When to discontinue or not discontinue (high vs. low risk)

## Severity of Reaction to Sting Challenge vs Severity of Previous Sting Reaction

Golden et al 2007;119:S149 (Abstr)

Previous Reaction (Hx)	(n)	Sting Challenge Reaction			
		Mild	Mod	Severe	Total
Mild	(81)	10	2		12 (15%)
Moderate	(137)	18	5		23 (17%)
Severe	(41)	7	2	4	13 (32%)
<b>Total</b>	<b>(259)</b>	<b>35</b>	<b>9</b>	<b>4</b>	<b>48 (19%)</b>

## Anaphylaxis in Patients with Cutaneous SR

	Systemic Reaction	More Severe
<b>Adults (sting challenge):</b>		
vanderLinden 1994		0 / 47 (0)
Golden 2007 (abstr) 1/30]		2 / 81 (2.5%) [2006
<b>TOTAL</b>		<b>2 / 128 (1.6%)</b>
<b>Children (field stings):</b>		
Valentine 1990 (4 years)	16 / 86 (18.6% pts) (9.2% stings)	0 / 86 (0)
Shuberth 1987 (abstr) years)		2 / 180 (1.1%) (9 [2 / 490 (0.4%) stings]
Golden 2004	12 / 80 (13%)	6 / 80 (6.7%)

## When to order 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

### Consider:

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

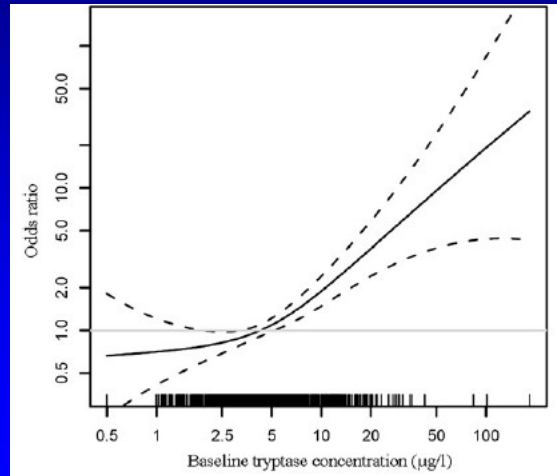
	Patients with normal sBT levels, no. (%)	Patients with increased sBT levels (>11.4 ng/mL), no. (%)	P value
Total	335 (88.4)	44 (11.6)	—
Sex			
Male	233 (69.5)	33 (75.0)	.290*
Female	102 (30.5)	11 (25.0)	—
Ratio	2.28	3.00	
Age (y)			
Mean (SD)	42.3 (16.3)	48.1 (15.6)	.038* §
Median (range)	42.5 (6-78)	48.1 (17-77)	
Pediatric (<18 y)	29 (8.7)	1 (2.3)	.230*
Adult	306 (91.3)	43 (97.7)	
Allergy tests for HVA			
Negative	0 (0.0)	4 (9.1)	.0001*
Positive to:	335 (100)	40 (90.9)	
Apis mellifera	68 (20.3)	7 (15.9)	
Vespula species	199 (59.4)	23 (52.3)	.743*
Polistes dominulus	67 (20.0)	10 (22.7)	
Vespa crabro	1 (0.3)	0 (0.0)	
Grade of allergic reaction			
I	33 (9.8)	2 (4.5)	.0001*
II	93 (27.7)	7 (15.9)	
III	116 (34.6)	4 (9.1)	
IV	93 (27.7)	31 (70.5)	

## Serum Tryptase Levels and Hymenoptera Sting Allergy

Bonnadonna et al. JACI 2009;123:680.

## Baseline serum tryptase predicts severe systemic reactions to stings.

Rueff et al. EAACI Interest Group on Insect Allergy, JACI 2009;124:1047.



## Mastocytosis and insect venom allergy.

Niedoszytko et al. Allergy 2009;64:1237.

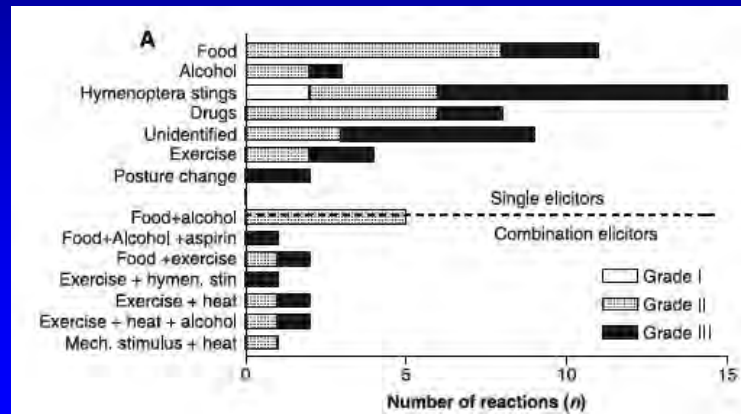
### Mastocytosis in patients with insect venom allergy

Table 1. Epidemiology of mastocytosis in insect venom allergic (IVA) patients

Author (ref.)	Number of patients evaluated	<i>n</i> (%) of patients suffering from mastocytosis
Rueff F (11)	1102	2.6%
Dubois A (10)	2375	0.9%
Bonadonna P (17)	552	2.9%
Bonadonna P (18)	379	5.5%
<b>Total</b>	<b>4408</b>	<b>1.97%</b>

## Anaphylaxis in patients with mastocytosis. (N=120)

Brockow et al. Allergy 2008;63:226.



## Elevated Tryptase (Mastocytosis) and Insect Sting Anaphylaxis

- Elevated baseline serum tryptase in:
  - 5 -10% of patients with sting anaphylaxis
  - up to 25% of patients with hypotensive shock
- Elevated tryptase associated with:
  - more severe reactions to insect stings
  - more frequent systemic reactions during VIT
  - more frequent VIT treatment failure
  - more frequent relapse after stopping VIT

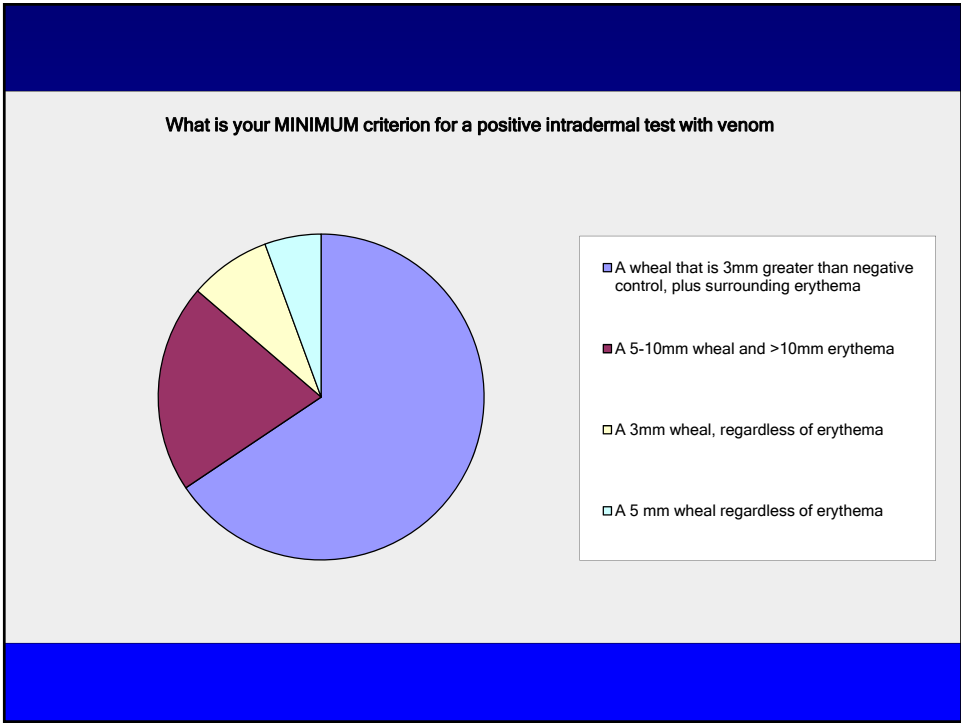
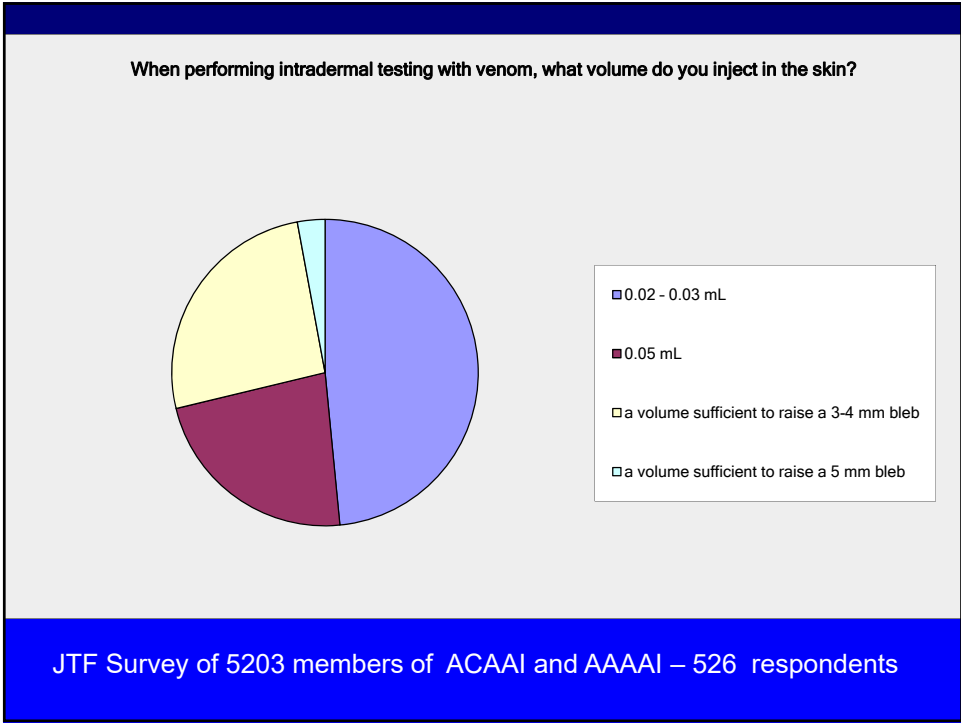
## VIT in Patients with Mastocytosis

deOlana et al. JACI 2008;121:519

Male / Female	17 / 4
Vespid allergic / HB allergic	75% / 25%
Systemic reactions during VIT	6 (28%)
up-dosing	3 (14%)
maintenance	3 (14%)
Systemic reaction to sting (n=12)	3 (25%)
Venom IgE pre/post VIT	4.1 / 1.2

## Diagnostic Testing for Insect Sting Allergy

### Technique and Interpretation of Venom Skin Tests

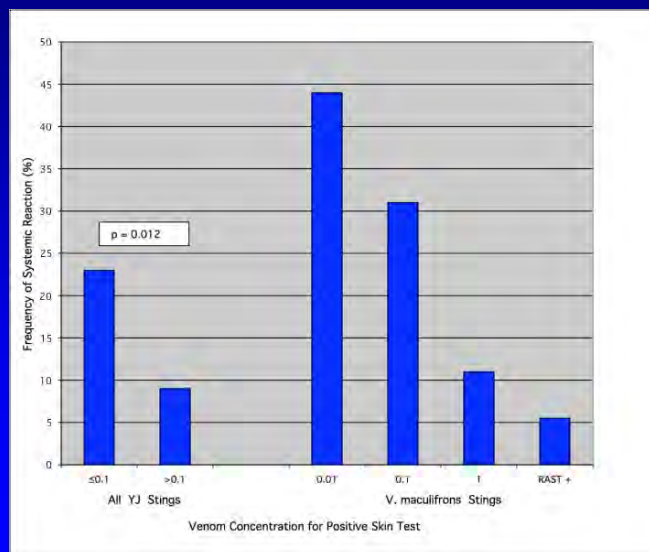


## Diagnostic Tests for Venom – IgE

- Venom-IgE (skin test or serum) is positive in 15%-25% of asymptomatic (history-neg) adults.
- History-pos / IgE-pos patients have no reaction to sting in 30% - 70% of cases.
- Presence of venom-IgE is not necessarily predictive of clinical reactivity or severity.

## Risk of Sting Reaction Related to Venom Skin Test

(Golden et al - JACI 2006)





### Initial Venom Skin Tests at 1.0 mcg/mL

	Method	N	AE
Strohmeier 2013	Simultaneous	478	3
Quirt 2016	Single conc.	300	1

### Negative Venom Skin Tests with History of Sting Anaphylaxis

- Refractory (anergic) period
- Variability of venom skin tests
- Mast Cell Disorder
- No longer allergic / Never was allergic ?

Negative skin test and serum IgE

– 5% chance of systemic reaction

## Spontaneous Changes in Venom Skin Tests (n=30)

[Kelly, Golden et al. JACI 2007;119:S79. (abstr)]

Sting Date Skin Test (mcg/mL)	Screening Visit Skin Tests		
	0.01	0.1	1.0
0.01	1	2	0
0.1	2	7	2
1.0	0	2	11
Negative	0	0	3

## Basophil Activation / Sensitivity Tests in Insect Sting Allergy

Peternelj 2008 – Basophil CD63 expression higher in patients not responding to VIT

Korosec 2009 – CD63 expression more sensitive than ID skin tests in patients with negative serum IgE and negative venom prick tests.

Kucera 2010 – BAT a helpful tool in predicting clinical sensitivity to HB after VIT (specificity 80%, sensitivity 83%)

Zitnik 2011 – Basophil CD63 sensitivity seems to be a promising tool for monitoring protective immune response to HB VIT in children.

## Recombinant Allergens for Diagnosis of Venom Allergy

Muller 2009 – IgE to both rApi m 1 and rVes v 5 indicates true double sensitization to both venoms.

Mitterman 2010 – rApi m 1, rApi m 2 and rVes v 5 allow identification of patients with HB and YJ allergy, and should facilitate accurate prescription of VIT.

Sturm 2011 – The approach of using rApi m 1 and rVes v 5 is insufficient because the genuine sensitization to other major allergens might be missed.

Korosec 2011 – Current CAP-FEIA rApi m 1 has low diagnostic sensitivity to detect HB allergy.

## Diagnostic Tests for Insect Sting Allergy

(Golden. Ann Allergy Asthma Immunol 2013;11:84-89)

Reason for test	Hx	ST	sIgE	BAT	Recomb allergen	RAST inhib	Tryptase baseline
<b>Diagnosis</b>							
No rxn	X						
LLR	X						
Mild SR	X	X	X				
Ana	X	X	X	X	X	X	X
<b>Predict ana (sting / VIT)</b>							
	X			X			X
<b>Cross-reactivity (HB / YJ)</b>							
					X	X	
<b>Stop VIT</b>							
	X			X			X

## ACE Inhibitor and Beta-Blocker Medications in Patients with Insect Sting Anaphylaxis or Venom Immunotherapy

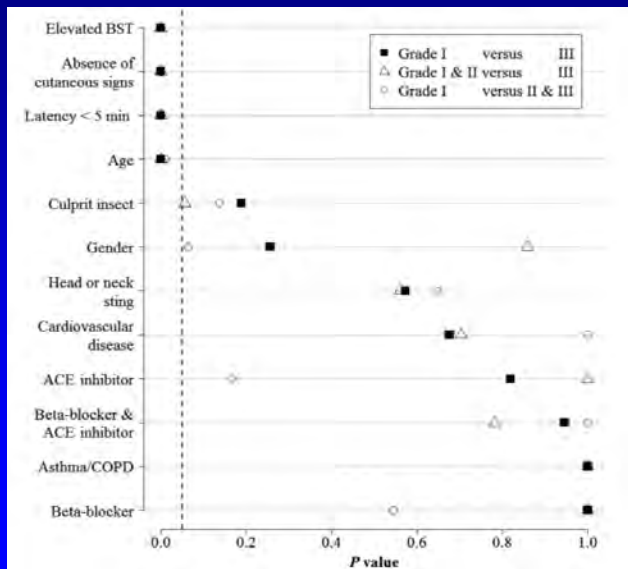
### Predictors of severe systemic reactions in patients with insect allergy.

Rueff et al. EAACI Interest Group on Insect Allergy, JACI 2009;124:1047.

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

Parameter		Grade I or II reaction (n = 756)	Grade III or IV reaction (n = 206)	P value
b-Blocker medication at the time of the index sting	Yes	34 (65.4%)	18 (34.6%)	.024
	No	722 (79.3%)	188 (20.7%)	
ACE inhibitor medication at the time of the index sting	Yes	24 (57.1%)	18 (42.9%)	.002
	No	732 (79.6%)	188 (20.4%)	
Any antihypertensive medication at the time of the index sting	Yes	61 (63.5%)	36 (36.5%)	<.001
	No	695 (80.4%)	170 (19.6%)	
Sex	Male	385 (73.6%)	138 (26.4%)	<.001
	Female	371 (84.5%)	68 (15.5%)	
One or more preceding, less severe systemic sting reactions before index sting	Yes	46 (48.4%)	49 (51.6%)	<.001
	No	710 (81.9%)	157 (18.1%)	
Insect responsible for index sting and associated allergic reaction	Bee	241 (83.4%)	48 (16.6%)	.016
	Vespid	515 (76.5%)	158 (23.5%)	
Age (y) at index sting according to median	<38	424 (86.2%)	68 (13.8%)	<.001
	≥ 38	332 (70.6%)	138 (29.4%)	

## Factors correlating with the severity of anaphylaxis (Stoevesandt et al. JACI 2012)



## VIT Failure (Rueff F, et al. Clin Exp Allergy 2014;44:736-46)

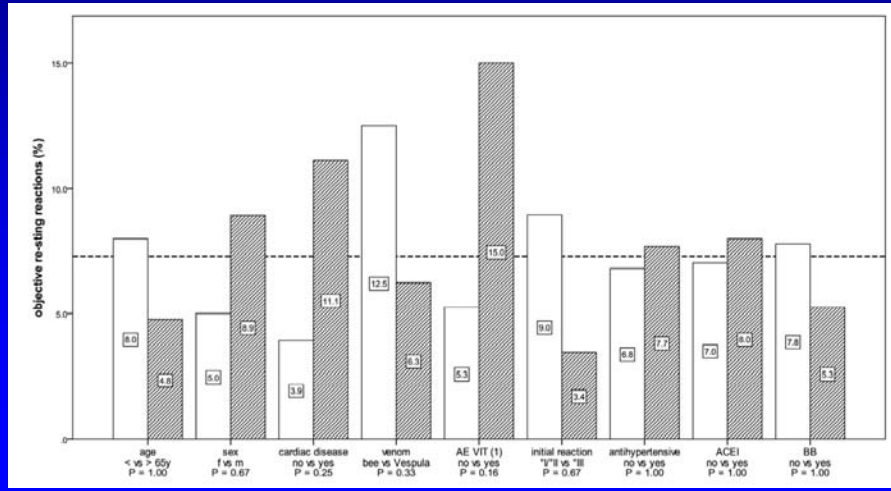
Variable	P-value	Odds ratio	95% Confidence interval	
ACE inhibitor medication at sting challenge	< 0.001	5.24	1.83	13.00
Therapy with honeybee venom	< 0.001	5.09	3.17	8.15
Systemic allergic reaction during VIT	< 0.001	3.07	1.79	5.14
BTC > 20.0 µg/L and/or adult-onset MIS (high likelihood to suffer from SM)	0.003	2.74	1.37	5.22
Time interval between the end of build-up and sting challenge (per month) <sup>1</sup>	0.017	0.68	0.50	0.93
Double VIT for a simultaneous bee and vespid venom allergy	0.027	0.51	0.27	0.90
High venom dose (200 µg) during maintenance therapy	0.075	0.58	0.31	1.04

<sup>1</sup>After logarithmic transformation.

## Venom Immunotherapy While on ACEI or BB.

(Stoevesandt et al. Ann Allergy Asthma Immunol 2015;114:411)

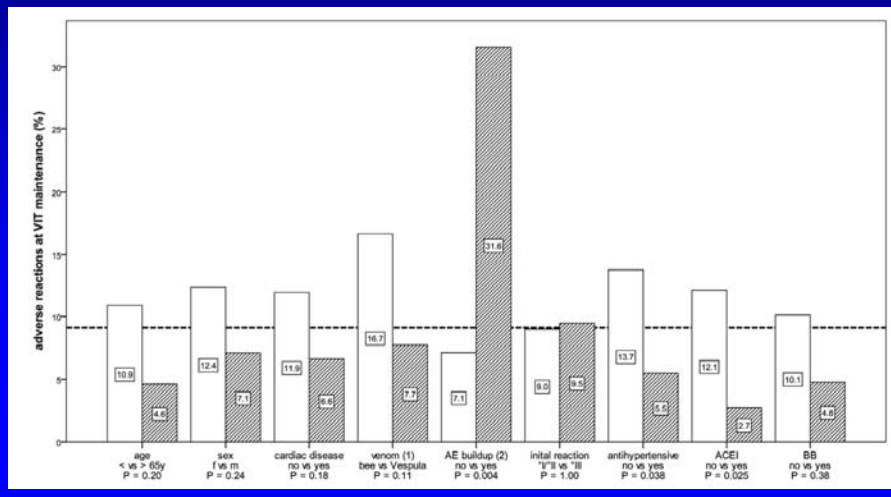
### Objective systemic reactions during maintenance VIT



## Venom Immunotherapy While on ACEI or BB.

(Stoevesandt et al. Ann Allergy Asthma Immunol 2015;114:411)

### Objective and subjective reactions during maintenance VIT



## When to Prescribe Epinephrine Autoinjector ?

### Epinephrine Auto-injectors for Insect Allergic Patients

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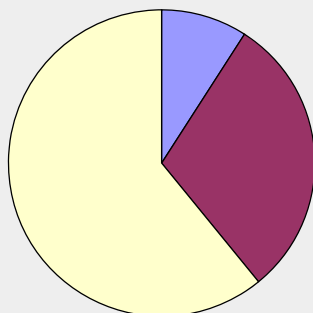
#### Low risk

- large local reactors?
- children with cutaneous systemic reactions?
- on VIT?
- discontinued VIT?
- affected relative?

#### High Risk

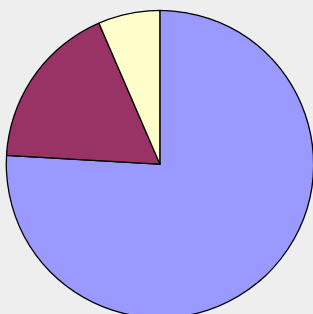
- Systemic reaction during VIT
- Severe history
- Elevated baseline tryptase

Do you recommend a patient carry an Epinephrine Auto-injector if they only had large local reaction following a sting?



- Yes, usually
- Yes, on a case-by-case basis (eg, occupational, rural or wilderness activities)
- No, hardly ever

Once your patient is on maintenance venom immunotherapy, do you recommend they continue to carry an Epinephrine auto-injector?



- Yes, usually
- Yes, on a case-by-case basis (eg, occupational, rural or wilderness activities)
- No, hardly ever



## Venom Immunotherapy

### Survey of Members of ACAAI / AAAAI by Joint Task Force on Practice Parameters

Do you recommend venom testing and venom immunotherapy if a patient only had a large local reaction following a sting?

	Usually	Only if frequent and severe	Hardly ever
Adults	3%	27%	70%
Children	1%	15%	84%

## Risk factors for severe reactions to stings.

### Clinical Markers

Very severe previous reaction  
 Insect species  
 No urticaria/angioedema  
 Age (>45), Gender (male)  
 Multiple or sequential stings  
 Medications (ACE inhibitors)

### Laboratory Markers

Venom skin test  
 Venom-specific IgE  
 Basal serum tryptase  
 Basophil activation test  
 (PAF)-acetylhydrolase  
 Angiotensin converting enzyme

## Natural History of Insect Allergy: Risk Based on Severity of Previous Reactions

Previous Sting Reaction	Chance of Future Systemic Sting Reaction:	
	Any	Severe
Life-threatening	50 - 75%	30%
Moderate Systemic	30 - 50%	10%
Cutaneous Systemic		
– child	1 - 10%	<3%
– adult	10 - 20%	<5%
Large Local	5 - 10%	2%

## Safety of Initiating VIT at 1 mcg dose.

Roumana et al. JACI 2009.

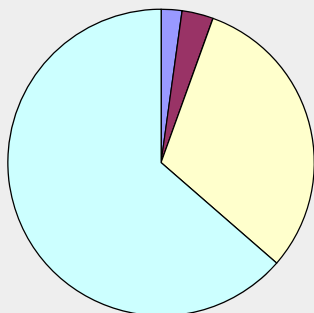
**TABLE II. Systemic reactions caused by rush and ultrarush VIT**

Venom concentration	Dose (in µg)	Injections (no.)	Observed reactions (no.)	Injections causing reaction (%)
10 µg/mL	1 µg	730	0	0
	3-6 µg	1,460	25	1.7
100 µg/mL	10-50 µg	3,650	84	2.3
	>50 µg	2,190	110	5
Total		8,030	219	2.7

Dose	Reactors to bee venom			Reactors to vespid venom		
	Mild	Moderate	Severe	Mild	Moderate	Severe
3-6 µg	8	3	–	5	–	–
>6-50 µg	39	11	3	6	0	–
>50 µg	41	23	8	7	1	–
Patients*	71	31	9	18	1	0
Total†	83/428 (19.3%)			18/302 (5.9%)		
Mean RR	13.8%					

Which schedule do you MOST COMMONLY use when advancing venom immunotherapy?



- Ultra-rush (1 day to achieve maintenance)
- Rush (2 or 3 days to achieve maintenance)
- Semirush-Cluster (7-10 weeks to achieve maintenance)
- Traditional (16-24 weeks to achieve maintenance with injections once or twice a week)

## Rush VIT in Patients Having Systemic Reactions to VIT (Goldberg et al, Ann Allergy 2003;91:405)

Table 2. Rush Venom Immunotherapy Protocol\*

Day	Venom concentration, $\mu$ g/mL	Volume, mL	Dose, $\mu$ g	Daily accumulative dose, $\mu$ g
1	1	0.05	0.05	
	1	0.1	0.1	
	1	0.2	0.2	
	1	0.4	0.4	
	1	0.8	0.8	
	10	0.2	2	
	10	0.5	5	
	10	1.0	10	
	100	0.2	20	
	100	0.2	20	58.55
2	100	0.2	20	
	100	0.3	30	
	100	0.5	50	100
3	100	1.0	100	100

\* There were 15-minute intervals between venom injections.

## Venom Immunotherapy

### 50 $\mu$ g Maintenance Dose in Children

#### Houliston 2011

85 children on HB-VIT  
 34 stung during VIT – 7 SR (21%)  
 44 stung after VIT – 6 SR (14%)

#### Konstantinou 2011

53 children (29 HB, 26 YJ)  
 2 SR to HB-VIT (dose increased to 100  $\mu$ g)  
 10 stung (2 HB) during VIT ( $3.2 \pm 1.4$  yrs)  
 7 (3 HB) stung again 2 wks-2 yrs later  
 11 stung (5 HB)  $2.5 \pm 2.0$  yrs post VIT

## Duration of VIT

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- 5 years or 3 years?
- Time or testing?
- What do I test or evaluate?
  - Skin test?
  - Specific serum IgE or IgG?
  - Serum tryptase?
  - History?

## Candidates for Indefinite or Extended (> 5 years) Treatment with VIT

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### Candidates for Indefinite Treatment:

- Very severe reaction to previous stings
- Elevated basal serum tryptase
- Systemic reaction during VIT (to injection or sting)
- Honeybee anaphylaxis
- Frequent exposure

### Candidates for Extended (>5 years) Treatment:

- No decrease in venom IgE or skin tests
- Underlying cardiovascular or respiratory disease
- Use of ACE inhibitors or beta-blockers
- Impaired quality of life

### Survey of Members of ACAAI / AAAAI by Joint Task Force on Practice Parameters

How long do you MOST COMMONLY recommend continuing Venom Immunotherapy?

	3 years	5 years	Lifelong	Based on tests	Other
Adults	3%	58%	9%	11%	17%
Children	6%	66%	4%	12%	11%

### 13 Differences between venom package insert and the 2016 Practice Parameter I

	Package insert	2016 Practice Parameter
Indications for testing	History of SR	SR; Some LLR; Mastocytosis
ST technique/interpretation	0.05 cc /5-10 mm	0.2-0.5 cc / 3-5 mm wheal
Tryptase / mastocytosis	No mention	When to measure, Clin. significance
Cutaneous SR	VIT	VIT not required (optional)
Large local reactors	No VIT	VIT optional
Rush regimens	No mention	Safe and effective
Pre-medication	No mention	Reduces LLR (and mild SR)

### 13 Differences between venom package insert and the 2016 Practice Parameter II

	Package insert	2016 Practice Parameter
Starting dose	0.001 – 0.01 mcg	1.0 mcg
Cardiac meds	Standard warnings	Guidance on when to change
Children	Same as adults	Dose, Duration
Adverse reactions to VIT	No mention	Pre-med, cluster, rush, omalizumab
Maintenance Interval	4 weeks	Up to 12 weeks
Duration	indefinite	5 years Indefinite (if high risk factors)