

Insect Allergy Update

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Learning Objectives

1. Describe the newest approaches to diagnostic evaluation for insect sting allergy
2. Identify risk factors for severe reactions, and indications for venom immunotherapy.
3. Choose the optimal regimen and duration of VIT.
4. Recognize the significance of serum tryptase and mastocytosis in insect sting allergy.



Hymenoptera



Bees

Apis

Honeybee



Bombus

Bumblebee

Vespids

Vespula

Yellow jacket species



Dolichovespula

Yellow hornet, White-faced hornet

Vespa

European, Oriental hornets



Polistes

Paper wasp species

Ants

Solenopsis

Imported fire ants

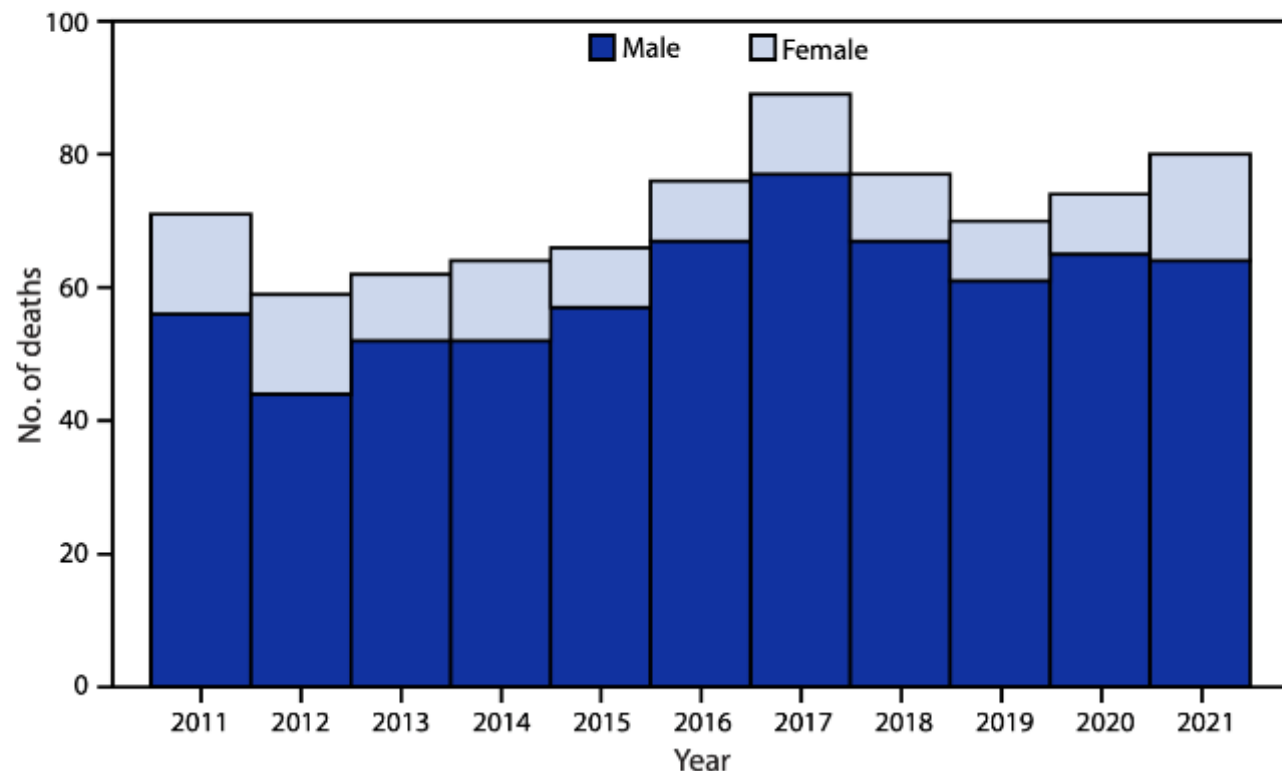


Hornets: The next invasion?

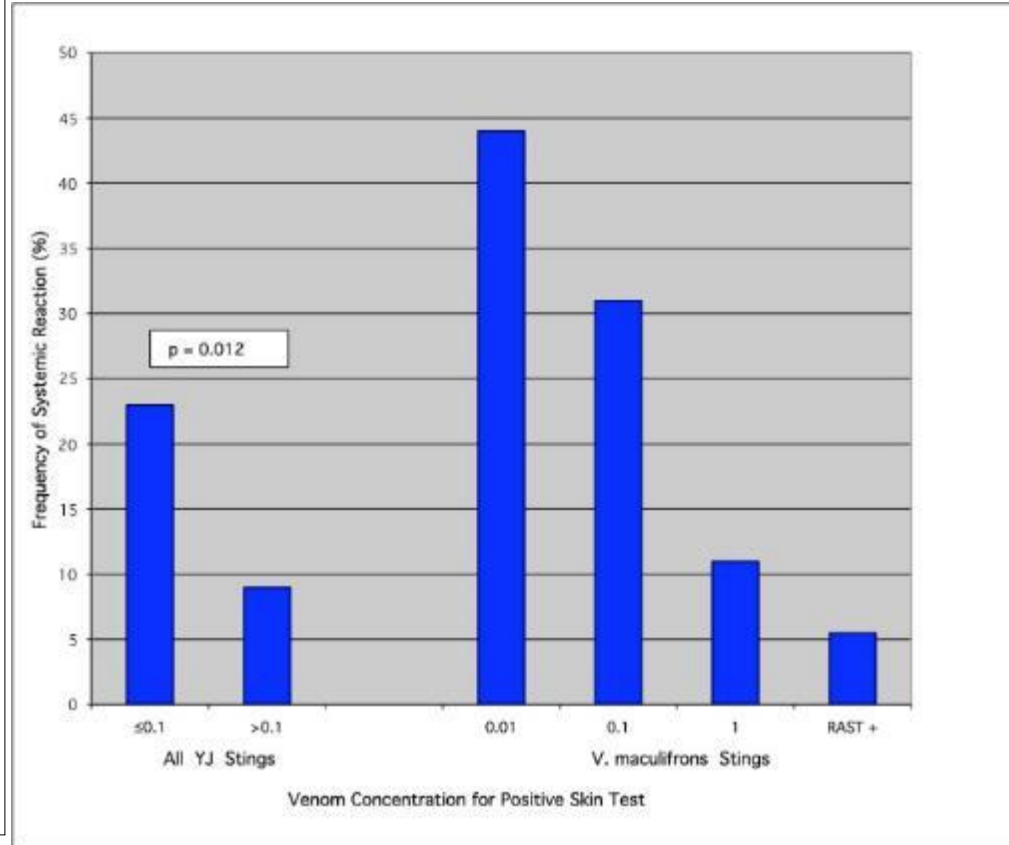
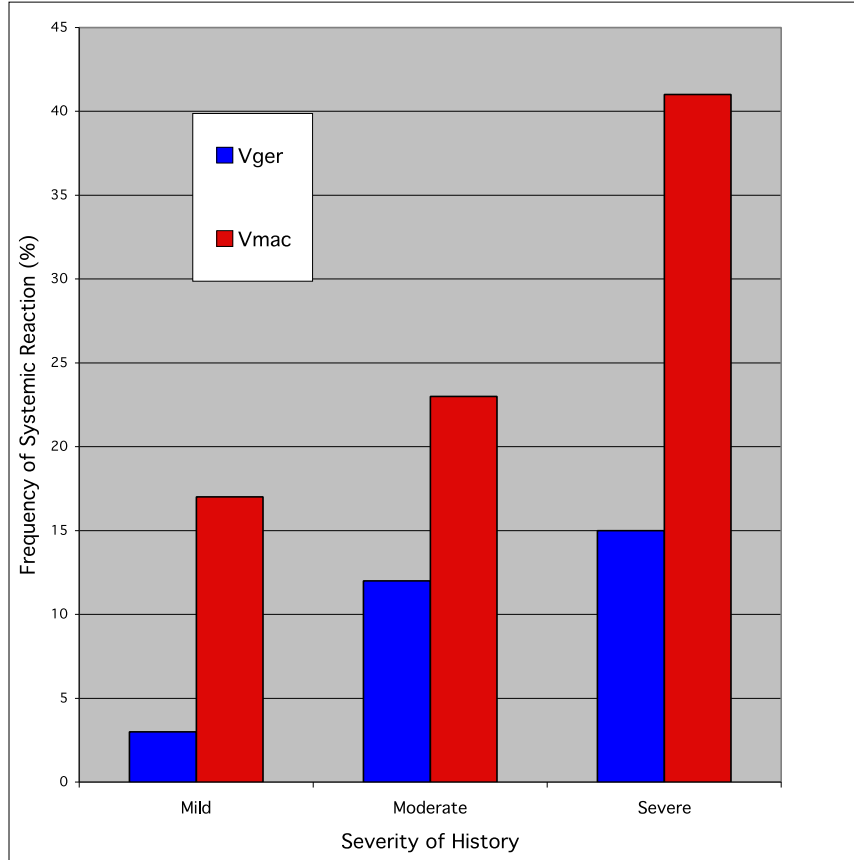


Number of Deaths from Hornet, Wasp, and Bee Stings* Among Males and Females — National Vital Statistics System, United States, 2011–2021

MMWR | July 7, 2023 | Vol. 72 | No. 27 | p.756.



Risk of systemic reaction depends on previous reaction severity, insect species, and venom-IgE/skin test (Golden et al - JACI 2006)



Diagnostic Tests for Insect Sting Allergy

CAVEATS

- Skin or serum tests for insect venom IgE are positive in more than 20% of adults (up to 40% if recently stung) – the great majority have ***asymptomatic sensitization***.
- People who reacted to stings and have positive tests don't react to the next sting more than 50% of the time.
- Allergy tests for insect venoms do not reliably predict how severe a sting reaction will be.
- Testing is confirmatory, but not diagnostic by itself.



Insect Allergy Diagnostic Tests

Winged Hymenoptera [venoms: HB, YJ (spp), YH, WFH, Polistes wasp (spp)]

Prick test (100 mcg/ml) – optional (limited sensitivity)

- I.D. skin test**
- begin at 0.001 mcg/ml; go up to 1.0 mcg/mL
 - or, use 1.0 mcg/mL only?
 - method of application and interpretation

- Serum Venom-IgE**
- slightly less sensitive
 - interference of CCD's; role of CRD
 - clinical significance of 0.1 – 0.35 kU/L?

Imported Fire Ant [Whole body extracts (*S. invicta*/richteri)]

Prick test – 1:1,000,000 w/v

I.D. skin test – 1:100,000 – 1:1:000 w/v

Serum WBE-specific IgE



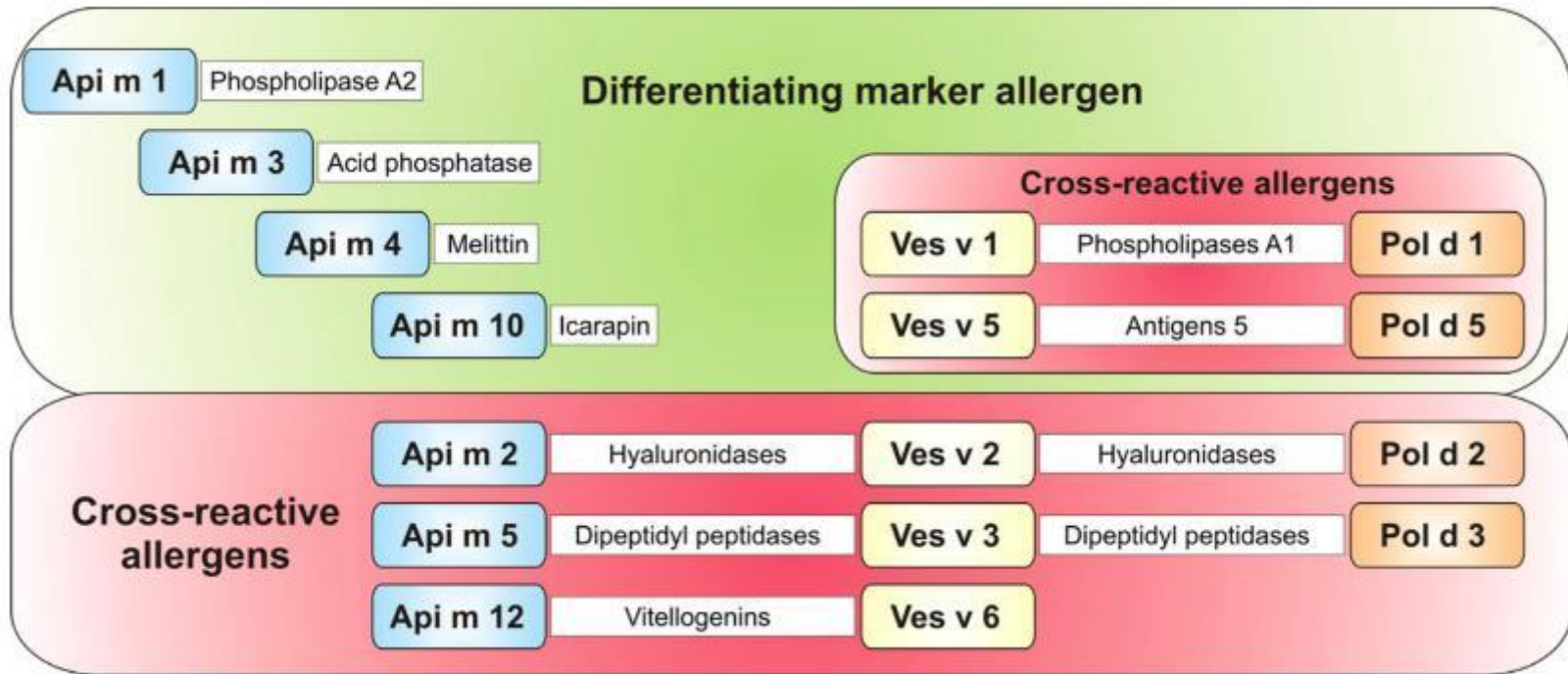
Which is better?

Venom skin test or specific serum IgE test?

- Neither is perfect.
- They both have good sensitivity and limited specificity.
- They both can have refractory periods post-anaphylaxis
- They both quantitatively correlate with the **frequency**, but **not** reliably with the **severity** of sting reactions.
- They are often complementary.



Recombinant Allergens for Specific Diagnosis and Venom Immunotherapy



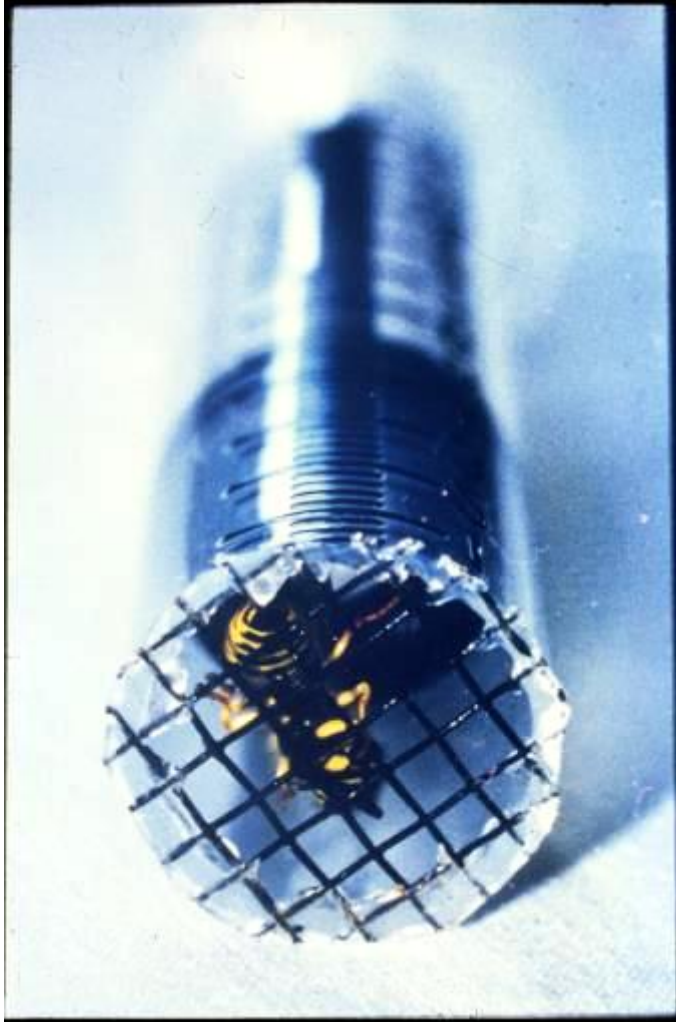
Blank S., Bilo MB, Ollert M. Clin Exp Allergy. 2018;48:354-364.



Component Resolved Diagnosis and Treatment

	Patient 1	Patient 2
Serum IgE positive	HB and YJ	HB and YJ
Components positive	Ves v 1 Api m 1 Api m 2 Api m 10	Ves v 1 Ves v 5 Ves v 2?
Venom Immunotherapy	HB and YJ	YJ only





Predicting the Frequency and Severity of Sting Anaphylaxis



Repeat Systemic Reaction In Sting Allergic Patients

STUDY	(YEAR)	N	SYSTEMIC (%)	
GOLDEN	(1981)	115	75	(65%)
HUNT	(1978)	23	19	(61%)
SETTIPANE	(1979)	119	72	(61%)
LANTNER	(1989)	18	11	(61%)
REISMAN	(1992)	220	124	(56%)
GALATAS	(1994)	27	13	(48%)
PARKER	(1982)	16	7	(44%)
DVORIN	(1984)	19	8	(42%)
BLAAUW	(1985)	86	29	(39%)
FRANKEN	(1994)	228	90	(39%)
vanderLINDEN	(1994)	324	96	(30%)
TOTAL		1195	544	(46%)



Systemic reaction to repeat stings

(Reisman JACI 90:335-9;1992.)

- ≤ 16 y.o. 45/112 (40%)
- > 16 y.o. 79/108 (73%)
- No decline in reaction rate over 10 years
- Variable reaction to repeated stings



Risk Of Systemic Reaction to Re-Challenge After Negative Initial Sting Challenge

Study	Year	N	Systemic (%)
Franken	1994	61	13 (21%)
Golden	1992	28	5 (18%)
Golden	2006	86	17 (20%)



Risk Factors for Severe Allergic Reactions to Insect Stings

(Practice Parameter Update. Golden et al. 2017)

Clinical Markers

Very severe previous reaction

No urticaria/angioedema

Age (>45), Gender (male)

Cardiovascular disease

Multiple or sequential stings

Medications (BB/ACEI)

Laboratory Markers

Venom skin test (inconsistent)

Venom-specific IgE (inconsistent)

Basal serum tryptase

Basophil activation test[‡]

PAF – acetylhydrolase*

Angiotensin converting enzyme (ACE)[#]

[‡] Not FDA-approved, not widely available.

* PAF-AH = lipoprotein-associated phospholipase A2 (Lp-PLA2)

[#] two reports



	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)	

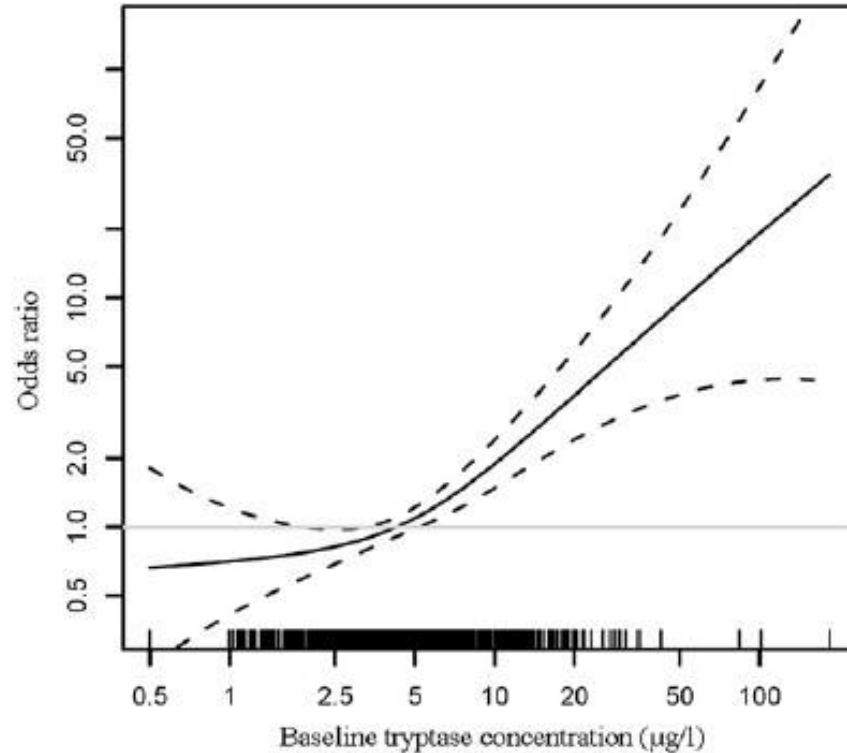
Serum Tryptase Levels and Hymenoptera Sting Allergy

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.



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 (high risk for severe relapse)
- Any patient who is a candidate for VIT

Golden et al. Stinging insect hypersensitivity: A practice parameter update 2016.
Ann Allergy Asthma Immunol 2017; 118:28-54.



Mast Cell Disorders and Insect Sting Allergy

Clonal Mast Cell Disorders – in >10% of patients with sting anaphylaxis.

– 40% of CMD patients get anaphylaxis - insect stings are the #1 cause.

Recommend: In patients with moderate-severe sting anaphylaxis, especially when hypotension and no hives:

- Check baseline serum tryptase (usually elevated; can be normal)
- Check blood c-kit mutation (high-sensitivity PCR digital drop assay)
- Consider bone marrow biopsy to confirm clonal mast cell disorder

Hereditary alpha-tryptasemia (H α T) – extra copies of α -tryptase gene

– baseline tryptase > 8 ng/ml

Frequency: – 6% of adults but **10%-20% in severe sting anaphylaxis**, systemic mastocytosis, or idiopathic anaphylaxis

Symptoms: – may be none (50% - 70%)
– may be similar to MCAS
– severe anaphylaxis

Gianetti MP et al. J Allergy Clin Immunol 2022;150:1225-7.
Lyons JJ et al. J Allergy Clin Immunol 2021;147:622-32.
Luskin, White, Lyons. JACI Prac 2021;9:2235-2242.
Robey RC et al. JACI Prac 2020;8:3549-3556



Relationship Between Anaphylaxis and Use of Beta-Blockers and Angiotensin-Converting Enzyme Inhibitors: A Systematic Review and Meta-Analysis of Observational Studies

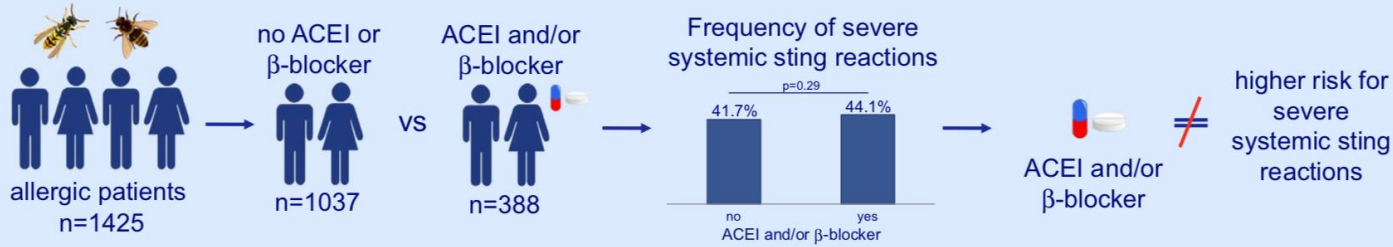


Miguel A. Tejedor-Alonso, MD, PhD^{a,b}, Enrique Farias-Aquino, MD^a, Elia Pérez-Fernández, PhD^a, Eulalia Grifol-Clar, BA^a, Mar Moro-Moro, MD, PhD^a, and Ana Rosado-Ingelmo, MD^a *Madrid, Spain*

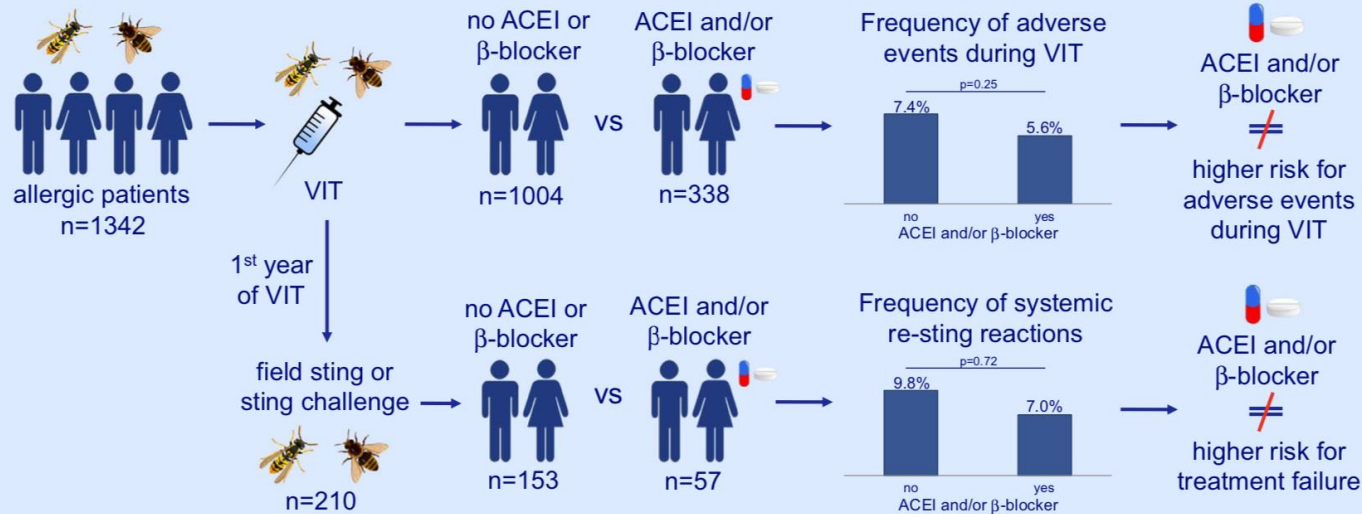
- Both BB and ACEI were associated with increased severity, but not increased incidence of anaphylaxis.
- Not possible to adjust for cardiovascular disease.
- Odds ratio for severe anaphylaxis 3 times higher for C-V disease than for BB.
- Odds ratio for severe anaphylaxis 5 times higher for C-V disease than for ACEI.



Systemic sting reaction



Venom immunotherapy



BB/ACEI: Insect Sting Allergy and VIT

	Recommendation	Strength of Recommendation	Certainty of Evidence
CBS 31	We suggest patients with a history of insect sting anaphylaxis who are not on VIT should continue BB or ACEI when the medical necessity of the daily medication outweighs the chance of increased severity of anaphylaxis to a sting.	Conditional	Low
CBS 32	We suggest VIT should be recommended to patients with a history of insect sting anaphylaxis who are treated with BB or ACEI, with shared decision-making regarding the potential benefits and harms of concurrent VIT treatment and medication, compared to withholding either the treatment or the medication.	Conditional	Low
CBS 33	We suggest in most cases, treatment with BB or ACEI should not be changed or discontinued in patients receiving maintenance VIT.	Conditional	Moderate



Indications for Venom Immunotherapy



Do Systemic Reactions to Insect Stings Become Progressively More Severe?

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%)
Total	(259)	35	9	4	48 (19%)

Venom Immunotherapy: Who Needs It?



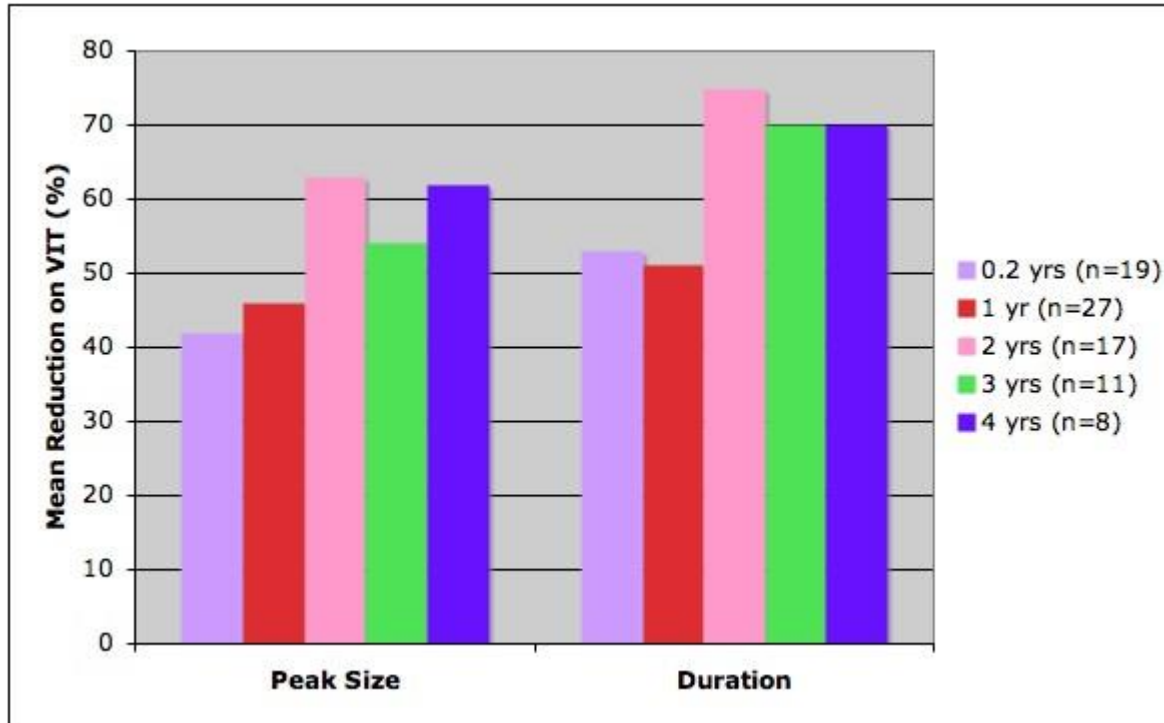
Previous Sting Reaction	<u>Chance of Future Systemic Sting Reaction:</u>		Venom Immunotherapy
	Any	Severe	
Life-threatening	50 - 75%	30%	Yes
Moderate Systemic	30 - 50%	10%	Yes
Cutaneous Systemic	5 - 15%	< 5%	Not required*
Large Local	5 - 10%	< 5%	Not required*



* Not necessary, but optional for those with frequent exposure or impaired quality of life (with shared decision-making).

Mean Reduction of Large Local Reactions During Maintenance Venom Immunotherapy

(Golden et al. JACI 2009;123:1386)



Initial VIT: Dose and Schedule

Summary Statement 20: Begin VIT with initial dose of up to 1 mcg and increase to maintenance dose of at least 100 mcg of each venom. Children might be effectively treated with a 50 mcg maintenance dose.

Summary Statement 21: Choose a buildup dose schedule for optimal safety and convenience. Maintenance dose and protection can be achieved with equal safety using conventional (achieving 100-mcg maintenance dose in 4 months) or modified rush (8 weeks) regimens. The risk of systemic reaction is similar using rush regimens (2-3 days) but may be slightly greater using ultra-rush regimens (4-8 hours).

Golden et al. Stinging insect hypersensitivity: A practice parameter update 2016.
Ann Allergy Asthma Immunol 2017; 118:28-54.



Systemic Reactions During VIT

Potential Actions:

- Check baseline serum tryptase
- Premedication, reduce next dose

If repeated reactions:

- Rush VIT (* preferred approach)
- Omalizumab (* off-label; many reports)



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, mcg/mL	Volume, mL	Dose, mcg	Daily accumulative dose, mcg
1	1	0.05	0.05	58.55
	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	
2	100	0.2	20	100
	100	0.3	30	
	100	0.5	50	
3	100	1.0	100	100

* There were 15-minute intervals between venom injections.



Duration of VIT

- 5 years or 3 years? – 5 years is better
- What do I test or evaluate?
 - History (severe)? – Yes
 - Serum tryptase? – Yes
 - Skin test? – No
 - Specific serum IgE or IgG? – No



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

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

Golden et al. Stinging insect hypersensitivity: A practice parameter update 2016.
Ann Allergy Asthma Immunol 2017; 118:28-54.



Systemic reactions to stings in the 7 to 10 years after stopping VIT – estimated frequency in low-risk and high-risk patients (post-hoc analysis)

Patients	N	Systemic Reaction	Reaction rate (cumulative)
Low-risk	67	2	3%
High-risk	33	15	45%
Total	100	17	17%

High risk (SR to VIT/sting, tryptase-8, near-fatal-7, exposure-5, HB-3)



Acknowledgements: allergyparameters.org

Stinging insect hypersensitivity: A practice parameter update 2016.

Jeff Demain, Ted Freeman, David Graft, Mike Tankersley, Jim Tracy

Anaphylaxis: A 2023 practice parameter update.

**Julie Wang, Susan Wasserman, Cem Akin, Ronna Campbell, Anne Ellis ,
Matt Greenhawt, David Lang, Dennis Ledford, Jay Lieberman, John
Oppenheimer, Marcus Shaker, Dana Wallace**

Stinging insect hypersensitivity: A practice parameter update 2026.

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And the **[Joint Task Force on Practice Parameters of AAAAI/ACAAI](#)**

