INSECT IMMUNOTHERAPY

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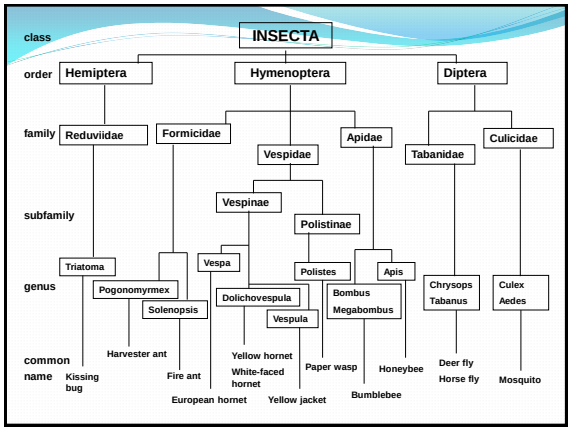


Hymenoptera Venom Allergens

Source	Allergen	Mol Wt (kD)	Function
Honey bee	Api m 1	16	Phospholipase A2
(*Apis mellifera*)	Api m 2	44	Hyaluronidase
	Api m 4	3	Mellitin
	Api m 6	7-8	
Bumble bee	Bom p 1	16	Phospholipase
(*Bombus pennsylvanicus*)	Bom p 4		Protease
Vespids	Group 1	34-35	Phospholipase A1
(*Dolichovespula spp,*	Group 2	44	Hyaluronidase
Vespa spp, Vespula spp,	Pol d 4	32-34	Serine protease
Polistes spp)	Group 5	23	Antigen 5
Fire ant	Sol i 2	13	
(*Solenopsis invicta*)	Sol i 3	24	
	Sol i 4	13	
Australian jumper ant	Myr p 1		
(*Myrmecia pilosula*)	Myr p 2		

Venom immunotherapy for preventing allergic reactions to insect stings. Boyle RJ et al Cochrane Database Syst Rev 2012 Oct 17;10:CD008838.doi:10.1002

- Search Methods: numerous literature & research databases, abstracts. Selection criteria: RCT of venom immunotherapy using standardized venom
- Main Results:
  - 6 RCT & 1 quasi-randomized CT; 392 total subjects
  - Bias risk due to non-blinding of outcome assessors
  - Interventions bee, wasp, ant; 1 SLIT, 6 SCIT
  - 3/113 VIT systemic reaction subsequent sting vs 37/93 untreated = RR 0.10 (C.I. 0.03-0.28); 112 decreased large local reaction RR 0.41 (C.I. 0.24-0.69)
  - 11 observational studies: systemic rxs to VIT 131/921 (14.2%) bee venom; 8/289 (2.8%) wasp venom

Safety of hymenoptera venom immunotherapy: a systematic review. Incorvaia C et al Expert Opin Pharmacother 2011;12:2527-32

- Systematic review aqueous and depot vespid and honeybee venom extracts
- Incidence systemic reactions 25.5% honeybee venom & 5.8% vespid venom ($p<0.0001$)
- No significant differences between aqueous & depot extracts

Report from the Hymenoptera Committee of Spanish Society of Allergology and Clinical Immunology: Immunotherapy with bumblebee venom. Cruz S et al J Investig Allergol Clin Immunol 2012;22:377-8

- Bumblebee stings primarily occupational hazard
- Little cross-reactivity to honeybee venom; poor response to honeybee VIT
- Bumblebee venom available in Spain from ALK-Abelló since 2005
- Recommendations: greenhouse workers experiencing systemic reaction to bumblebee sting need evaluation and treatment with bumblebee venom

Negative venom skin test results in patients with histories of systemic reaction to a sting.

Golden et al: JACI 2003;112:495-8.

- New Recommendations of the Insect Committee
- Negative VST in (+) Hx may be more common than thought & not exclude presence of VS IgE
- VST & VS IgE may be complementary & need to be repeated
- (-) VST or in vitro assay is not guarantee of safety, & pts should be counseled about avoidance & emergent care
- Management of Hx (+) VST (-) pts requires clinical judgment & ongoing research

Insect sting anaphylaxis in patients without detectable serum venom-specific IgE.

Clayton et al: Clin Allergy 1985;15:329-33

- >500 patients with systemic reactions to insect sting, IDST & VS IgE (RAST)
- 25 had (-) VS IgE; 22 evaluated within 1 year, 15 within 6 months
- ID VST: 11 (-), 7 (1+), 2 (2+), 4 (3+), 1 (4+)
- SXS: hives/angioedema 20, shock & hypotension 3, respiratory 6, GI 1

Indications for Venom Immunotherapy

Sting Reaction	(+) ST or sIgE	(-) ST or sIgE
Systemic	Yes	No (judgement required)
Cutaneous NLT		
Adult	Yes	No
Child (≤16 years)	Not required	No
Large local	No	No
Absence of history	No (?)	No

Rush Hymenoptera immunotherapy: A safe and practical protocol for high-risk patients.

Sturm et al: J Allergy Clin Immunol 2002;110:928-33

- 101 Hymenoptera allergic pts with 4-day Rush IT: 1st 0.001, .01, .1, .2, .4; 2nd .8, 1, 2, 4, 6; 3rd 8, 10, 20, 40, 60; 4th 80, 100mcg
- Pretreated with IV H_1 antihistamine
- 52 honey bee venom, 49 yellow jacket venom
- 100 pts reached maintenance dose
- 8 systemic reactions (0.47% all injections) in 7 pts
- HBV SR 12%, YJV 2%

Safety and efficacy of a 12-week maintenance interval in patients treated with Hymenoptera venom immunotherapy.

Kochuyt, Stevens: Clin Exp Allergy 1994;24:35

- Methods
  - 5 day rush IT with 100μg maintenance dose
  - interval between injections progressively increased by 1 week increments until 12 week interval achieved after ~19 months
  - field re-stings monitored

Safety and efficacy of a 12-week maintenance interval in patients treated with Hymenoptera venom immunotherapy.

Kochuyt, Stevens: Clin Exp Allergy 1994;24:35

- Results
  - 12 week interval achieved in 117/128 (91%) YJV & 35/50 (70%) HBV patients
  - 152 Rx'd ~2yrs without VIT reactions
  - 48 YJV restung 77x without systemic reaction
  - 17 HBV restung >213x with 1 large local & 1 mild systemic reaction

Systemic T-cell unresponsiveness during rush bee-venom immunotherapy.

Segura et al: Allergy 1998;53:233-40

- Methods
  - Rush IT in 7 patients with bee venom sensitivity
  - PBMC depleted of phospholipase A_2 binding cells (specific B-cells & basophils)
  - stimulated with PMA & analysed for CD69, $CD45RO^+$, IL-2, IL-4, & IFN-γ production
  - cells studied @ day 0, day 3, & day 5 of IT

Systemic T-cell unresponsiveness during rush bee-venom immunotherapy.

Segura et al: Allergy 1998;53:233-40

- Results
  - reduced levels of CD69, IL-4, & IFN-γ compared to normal donors
  - progressive reduction during IT
  - no change in IL-2
  - cells from atopics showed greater degree of IL-4 & IFN-γ expressing cells among $CD45RO^-$ T-cells than normals

Systemic T-cell unresponsiveness during rush bee-venom immunotherapy.

Segura et al: Allergy 1998;53:233-40

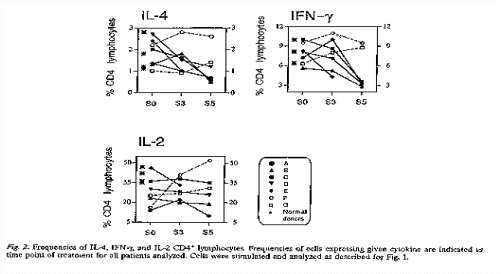
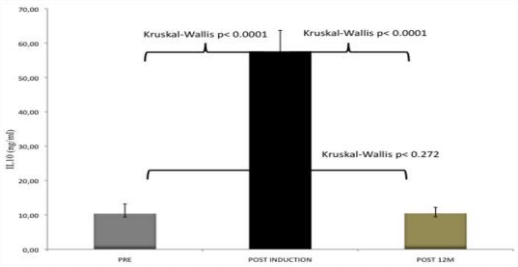


Fig. 2. Frequencies of IL-4, IFN-γ, and IL-2 $CD4^+$ lymphocytes. Frequencies of cells expressing given cytokine are indicated at time point of treatment for all patients analyzed. Cells were stimulated and analyzed as described for Fig. 1.

Effects of different up-dosing regimens for hymenoptera venom immunotherapy on serum CTLA-4 and IL-10. Riccio AM et al PLoS ONE 2012;7:e37980.



Discontinuing venom immunotherapy: Outcome after five years.

Golden et al: JACI 1996;97:579-87

- Methods
  - volunteers stopped VIT after 5 yrs maintenance
  - sting challenges, ST & IgE q1-2yrs after d/c VIT
- Results
  - systemic reactions occurred in 8/270 stings, or 7/74 patients; only 2 clinically significant
  - venom ST negative in 28% after 5 yrs VIT; negative in 56-67% of patients 2-4yrs after stopping VIT with parallel decrease in venom-specific IgE

Discontinuing venom immunotherapy: Outcome after five years.

Golden et al: JACI 1996;97:579-87

- Results (con't)
  - challenge stings did not prevent decline in sensitivity, nor increase risk of reaction even with stings 1 month apart
- Conclusions
  - venom IT can be safely stopped after 5 years of maintenance in virtually all patients (? except for those with unchanged sensitivity?)
  - venom sensitivity decreases with time, & stings do not cause resensitization
  - late onset, non-IgG long-term suppression

Imported fire ant immunotherapy: Effectiveness of whole body extracts. Freeman TM et al JACI 1992;90:210-5

- Retrospective review 65 IFA sensitive patients on IFA-WBE & 11 sensitive patients not treated
- 47 IT patients had 112 field stings, 1 systemic (2.1%)
- 6/11 non-IT patients had field stings, all had systemic reactions
- Sting challenge in 30, local reactions only
- ST negative in 26/31 IT patients, lesser in 5
- ST unchanged in 4 non-IT patients