

ORIGINAL ARTICLE

Anaphylaxis caused by Hymenoptera stings: from epidemiology to treatment

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Abstract

Hymenoptera venom allergy occasionally causes fatal reactions. The prevalence of systemic reactions (SRs) is 0.3–8.9%, with anaphylaxis in 0.3–42.8% of cases. Factors contributing to reaction severity include older age, insect type, a previous less severe SR, preexisting diseases, concomitant treatments, mast cell diseases and elevated baseline tryptase serum concentration. Venom immunotherapy (VIT) is highly effective, as shown by sting challenge and spontaneous field stings. Indications for VIT are based on history of an SR, positive diagnostic tests, natural history and established risk factors for a severe outcome. Current strategies for reducing adverse reactions include anti-IgE monoclonal antibody pretreatment, and purified aqueous and purified aluminium hydroxide adsorbed preparations. New strategies for VIT, mostly using recombinant allergen, are in development. Further improvements will increase the safety and efficacy of VIT.

Hymenoptera stings can cause systemic and occasionally fatal anaphylaxis. Epidemiological population-based studies over the last decade show a prevalence of systemic reaction from hymenoptera stings ranging from 0.3% to 8.9%, with the lowest occurrence in children (1). Data on anaphylaxis from insect stings can also be extrapolated from hospital admissions and emergency department visits for anaphylaxis for any cause. Insect stings prevalence as a percent of all-cause anaphylaxis ranges from 1.5% to 34.1%. Many factors may account for this wide variability such as lack of a universal consensus for the definition of anaphylaxis, and different classifications, risk exposures, population profiles and insect behaviours. The incidence of insect sting fatalities from anaphylaxis ranges from 0.03 to 0.48 fatalities per one million inhabitants per year. Cases of fatal insect sting anaphylaxis account for around 20% of fatal anaphylaxis from any cause.

Risk factors for outcome and diagnosis of systemic reaction to insect sting

Factors determining the severity of reaction to hymenoptera sting include history of previous severe systemic reaction, insect type, older age, pre-existing cardiovascular and respiratory disease, and use of some medications. Mastocytosis and

monoclonal mast cell activation syndrome are a risk factor for severe systemic reactions in allergic patients. Mastocytosis may provoke fatal anaphylaxis in spite of venom immunotherapy (VIT), but so far this has been observed only after discontinuing treatment.

A recent multicentre study (2) examined about 1000 hymenoptera venom allergic patients without mastocytosis and found a significant nonlinear continuous correlation between baseline serum tryptase levels and severe systemic reactions in untreated patients during in-field sting. Other important risk factors for severe systemic reaction were a previous, less severe systemic sting reaction and use of angiotensin-converting enzyme (ACE) inhibitors. Therefore, preventive measures for VIT should include discontinuation of ACE inhibitors, and consideration of baseline tryptase levels in deciding who should have VIT.

Currently, diagnosis of hymenoptera venom allergy is based on clinical history, skin test and allergen-specific IgE (3). Current practice parameters were published by the American and European Academies of Allergy and Clinical Immunology. Although new *in vitro* methods like basophil activation tests seem to improve hymenoptera venom allergy diagnosis, many pitfalls remain. These include a few known cases of IgE-negative anaphylaxis and multiple sensitisations with a single history. Recombinant venom allergen will

probably improve diagnosis and clarify cross-reactivity between venom allergens from different species and families. A combination of at least two or three nonglycosylated bee and wasp recombinant venom allergens may allow physicians to diagnose the majority of patients with double reactivity (4, 5).

Goals in venom immunotherapy

Venom immunotherapy is the only specific treatment that can prevent morbidity and mortality, maintain a low risk of systemic reaction during and after treatment, and improve quality of life by removing fear of recurrence (6, 7). Venom immunotherapy has been studied in prospective controlled and uncontrolled studies and by meta-analysis (8). These analyses showed the protection rate is better with vespids than honeybee extract and is better in children than in adults. Venom immunotherapy is effective in most patients immediately after a conventional maintenance dose of 100 µg, even after 3–5 days administration in a rush protocol. Factors that influence the risk of incomplete protection after VIT include honeybee venom allergy; venom dose; which sometimes needs to be increased to up to 200 µg; elevated baseline serum tryptase concentration; mastocytosis; or repeated side effects during VIT. Currently, no conclusive data are available on age or concomitant drug use.

Venom immunotherapy indication is based on clinical history of systemic reaction, positive skin test and knowledge of the history and risk factors for a severe reaction (Table 1) (6). Recommendations differ by country. Venom immunotherapy is recommended for patients with severe anaphylactic reactions, but less agreement exists on whether VIT should be given to children with mild systemic reactions, because prognosis in these cases is generally good. European guidelines state that in children and adults with mild systemic reactions, many other factors may account for the decision to start immunotherapy. Individual risk factors include concomitant disease or medication, and anxiety, which can impair patient quality of life.

How long to continue VIT for long-term protection after discontinuation has been debated for many years. Venom immunotherapy was first suggested to continue for life, until guidelines on discontinuation emerged, such as conversion to a negative skin test and *in vitro* blood test, usually after 3–

5 years of VIT. Long-term studies showed that most patients remain protected for years after discontinuation of 3–5 years of VIT (9). Relapse risk after discontinuation is more frequent in patients with honeybee allergy, severe pretreatment reactions or severe reactions during treatment or resting and mast cell diseases (6). European guidelines suggest considering a longer treatment or life-long treatment for some patients.

Venom immunotherapy can cause local or systemic reactions. Multicentre studies showed that the percentage of patients experiencing reactions during VIT ranged from 2% to 20%. Epinephrine was used in 0.6–5% of patients. Side effects were more common with honeybee than with vespid treatment (6). Safety can be improved by defining risk factors for systemic reactions to VIT, as currently, we do not have a reliable test to predict the occurrence of side effects during VIT. Factors that affect the risk of systemic anaphylactic reactions to VIT include honeybee *vs* vespid venom, and buildup *vs* maintenance phase. The concomitant use of β -blockers does not seem to increase efficacy or the overall risk of systemic reactions; however, more severe reactions are a possibility in patients using β -blockers. Side effects are probably more frequent in patients with mast cell diseases, especially those with concomitant vespid allergy (10). An elevated baseline serum tryptase level is an important risk factor for side effects during the buildup phase (2, 11). Another predictor is an ultrarush protocol *vs* rush and convention buildup-phase protocols (11).

Premedication has been suggested to increase VIT safety. So far, six of seven honeybee venom allergic patients who developed severe systemic reactions during treatment were later able to tolerate treatment after administration of the anti-IgE monoclonal antibody Omalizumab. Two cases with systemic mastocytosis tolerated VIT treatment. However, in one patient with normal baseline tryptase levels, Omalizumab could not reduce side effects (12). Unknown factors include optimal time and doses for administration, and long-term effects. Therefore, Omalizumab should probably be limited to patients with repeated severe side effects with injections and only if antihistamines have failed.

In some European countries, purified and nonpurified aqueous extracts are available as well as purified aluminium hydroxide-absorbed extracts (13). There is a good theoretical

Table 1 Indication for venom immunotherapy

Type reaction	Diagnostic tests (ST and/or IgE)	Decision regarding venom immunotherapy
Adults/children		
Respiratory and cardiovascular symptoms	Positive	Yes
	Negative	No
Urticaria if risk factor or quality of life impairment present	Positive	Yes
	Negative	No
Large local	Positive or negative	No
Unusual	Positive or negative	No

Bonifazi *et al.* (6). ST, skin test.

basis for believing that purified extracts, whose efficacy is comparable to that of nonpurified aqueous preparations, have the potential to reduce the incidence of VIT's side effects. In comparative studies, purified extract appeared to be safer than nonpurified preparations in preventing local reactions, and in two studies, systemic reactions. Among the purified extracts, absorbed seemed to be safer than aqueous extracts, especially for preventing severe local reactions. However, further prospective studies are needed to evaluate the ability of purified extracts to reduce the frequency of severe systemic reactions compared with the corresponding nonpurified preparation under the same protocol (13).

Future VIT will probably use chemically modified and recombinant venom allergens, for both efficacy and safety. Patient-tailored cocktails can be prepared once all the

relevant allergens of a venom are available in recombinant form. Currently, the only study performed in humans is a pilot study on five bee-allergic patients using a mixture of three dominant T-cell peptides of phospholipase. This preparation was safe and gave complete protection against challenge in three patients but gave incomplete protection in two. Therefore, preparations with only one major allergen may be insufficient for a majority of patients. Thus, we have room for improvement in developing new forms and routes of VIT (14).

Conflict of interest

Beatrice Bilò has received lecture fees from ALK-Abelló, AstraZeneca and Schering-Plough.

References

1. Bilò MB, Bonifazi F. The natural history and epidemiology of insect venom allergy: clinical implications. *Clin Exp Allergy* 2009;**39**:1467–1476.
2. Rueff F, Przybilla B, Bilò MB, Muller U, Scheipl F, Aberer W et al. Predictors of severe systemic anaphylactic reactions in patients with Hymenoptera venom allergy: importance of baseline serum tryptase—a study of the European Academy of Allergology and Clinical Immunology Interest Group on Insect Venom. Hypersensitivity. *J Allergy Clin Immunol* 2009;**124**:1047–1054.
3. Bilò BM, Rueff F, Mosbech H, Bonifazi F, Oude-Elberink JN. Diagnosis of Hymenoptera venom allergy. *Allergy* 2005;**60**:1339–1349.
4. Muller UR, Johansen N, Petersen AB, Fromberg-Nielsen J, Haeberli G. Hymenoptera venom allergy: analysis of double positivity to honey bee and *Vespula* venom by estimation of IgE antibodies to species-specific major allergens Api m1 and Ves v5. *Allergy* 2009;**64**:543–548.
5. Mittermann I, Zidarn M, Silar M, Markovic-Housley Z, Aberer W, Korosec P et al. Recombinant allergen-based IgE testing to distinguish bee and wasp allergy. *J Allergy Clin Immunol* 2010;**125**:1300–1307.
6. Bonifazi F, Jutel M, Bilò BM, Birnbaum J, Muller U. Prevention and treatment of hymenoptera venom allergy: guidelines for clinical practice. *Allergy* 2005;**60**:1459–1470.
7. Oude Elberink JN, Dubois AE. Quality of life in insect venom allergic patients. *Curr Opin Allergy Clin Immunol* 2003;**3**:287–293.
8. Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of hymenoptera venom hypersensitivity: a meta-analysis. *Clin Ther* 2000;**22**:351–358.
9. Golden DB. Discontinuing venom immunotherapy. *Curr Opin Allergy Clin Immunol* 2001;**1**:353–356.
10. Niedoszytko M, de Monchy J, van Doormaal JJ, Jassem E, Oude Elberink JN. Mastocytosis and insect venom allergy: diagnosis, safety and efficacy of venom immunotherapy. *Allergy* 2009;**64**:1237–1245.
11. Rueff F, Przybilla B, Bilò MB, Muller U, Scheipl F, Aberer W et al. Predictors of side effects during the buildup phase of venom immunotherapy for Hymenoptera venom allergy: the importance of baseline serum tryptase. *J Allergy Clin Immunol* 2010;**126**:105–111.
12. Soriano Gomis V, Gonzalez Delgado P, Niveiro Hernandez E. Failure of omalizumab treatment after recurrent systemic reactions to bee-venom immunotherapy. *J Investig Allergol Clin Immunol* 2008;**18**:225–226.
13. Bilò MB, Antonicelli L, Bonifazi F. Purified vs. nonpurified venom immunotherapy. *Curr Opin Allergy Clin Immunol* 2010;**10**:330–336.
14. Muller UR. Recent developments and future strategies for immunotherapy of insect venom allergy. *Curr Opin Allergy Clin Immunol* 2003;**3**:299–303.