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Review Article

# Hymenoptera Venom Anaphylaxis

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**Abstract**

Systemic reactions to insect sting can be life-threatening. Life-threatening systemic reactions to insect sting are estimated to occur in 0.4% to 0.8 % of children and in 3 % of adults. Hymenoptera stings that includes Apoidea (bees), Vespoidea (wasps, hornets, and yellow jackets), and Formicidae (ants) cause more deaths than other insects all over the world. Hymenoptera venom include mixtures of numerous relevant allergens .The diagnosis of venom allergy is based on both of clinical history and positive skin test response, and/or specific immunoglobulin E antibodies. Allergic reactions may develop after stinging by hymenoptera venom. It is ranging from local up to severe systemic reactions and even fatal anaphylaxis. The treatment of large local reactions is oral antihistamines and corticosteroid therapy. Patients with any signs or symptoms of anaphylaxis should immediately receive epinephrine intramuscularly, emergency medical attention and treatment. After acute treatment of a sting reaction, patients should be given a prescription for an epinephrine autoinjector. Patients with experiences of systemic reactions after hymenoptera venom sting with positive specific IgE should receive venom immunotherapy. Venom immunotherapy is the only causal treatment to prevent further systemic sting reactions. The protective rate of venom immunotherapy is reported 98% in patients with had venom anaphylaxis history.

## INTRODUCTION

Hymenoptera stings cause more deaths than other insects all over the world [1]. The Hymenoptera team includes Apoidea (bees), Vespoidea (wasps, hornets, and yellow jackets), and Formicidae (ants) [2]. The venom of these insects is mixture of low molecular weight substances like biogenic amines, lipids and carbohydrates, cationic peptides and high molecular weight substances like enzymes (phospholipases, hyaluronidases), peptides (mellitin, apamin, mastoparans, bombolitins) called allergens. Generally, low molecular weight substances are responsible for local reactions, while systemic reactions are linked to allergenic proteins [3]. Various types of reactions may develop after stinging by Hymenoptera insects [4]. These are non-allergic and allergic reactions.

### Non-allergic reactions

1. Local Reaction: Small area of swelling, redness and pain that lasts less than 24 hours.

2. Systemic Toxic reaction: In multiple stings, the toxin can cause fatal disease. The most frequently serious conditions triggered in this way are rhabdomyolysis, hemolysis, hepatic and renal dysfunctions.

3. Unusual Reactions: Cardiac ischaemia, encephalomyelitis, serum sickness, thrombocytopenic purpura, vasculitis [5].

### Allergic reactions

1. Large Local Reaction: More than 10 cm and persisting longer than 24 hours [6].

2. Systemic reaction: Can be divided into two groups. These reactions include multiple organ system involvement (Anaphylactic reaction) and skin-limited reactions (Generalized cutaneous reaction) [7,8].

## EPIDEMIOLOGY

Among adults the prevalence of systemic reaction after bee sting was reported between 0.5% and 3.3% in the United States and between 0.3 % and 7.5% in Europe [9,10].

In children, the study reported by Novembre et al., showed that the prevalence of systemic reaction with bee sting was 0.34 % and was lower when compared with the reported prevalence (0.8-5.0%) for the general population [11]. The prevalence of systemic reaction with bee sting in adults has been evaluated in a number of studies reported in Turkey. In a study by Kalyoncu et al., the incidence of serious systemic reaction was found 2.2% [12]. Gelincik et al., claimed in their study that the prevalence of hymenoptera sting reactions in their geographical region was comparable with other European studies [13].

## PATHOPHYSIOLOGY

Systemic anaphylactic reactions with bee sting are mostly

immunoglobulin E (IgE) mediated [9]. At least one previous sting is necessary to sensitize a person to venom. When sensitivity occurs, stings can lead to mast cell and basophil degranulation, resulting in the release of histamine and other inflammatory mediators responsible for the symptoms and symptoms of anaphylactic and some major local reactions [14].

## TYPES OF REACTIONS

Allergic reactions to hymenoptera stings are divided into two groups such us local reactions and systemic reactions.

### Large local reactions

Large local reactions to hymenoptera venoms are characterized with edema, erythema and itching, with a diameter more than 10 cm and resolving 3 to 10 days [6].

In a study by golden et al the risk of systemic reaction in patients experiencing large local reaction is reported as 7 % [15].

In a recent study Pucci S et al., suggested that patients with repeated large local reactions to stings had no risk of systemic reaction but a single large local reaction does not exclude such risk [16].

Systemic reactions include multiple organ system involvement (Anaphylactic reaction) and skin-limited reactions (Generalized cutaneous reaction).

Anaphylactic reaction effects more than one organ system. Some of the most serious reactions occur in the absence of any skin findings. Skin reactions (urticaria and angioedema) are seen frequently but respiratory or circulatory symptoms may also be prominent. Some of the serious reactions may occur in the absence of skin reactions [12].

Skin-limited reactions (Generalized cutaneous reactions) include widespread urticaria, flushing and pruritus which are not contiguous with the sting site [6].

Systemic reactions are classified according to their severity. Mueller and Ring-Meisser classifications are most frequently used (Tables 1,2) [17].

In children and adults anaphylaxis clinic can be distinguished when they occur due to bee stings while they do not differ when they are caused by various reasons. Children generally have only cutaneous symptoms. Anaphylaxis, facial or generalized angioedema are rare in children [18].

## RISK FACTORS

### Systemic reaction history

Systemic Reaction can become progressively more severe with each sting in some cases. If the time between stings is short interval; subsequent stings increases the risk of systemic reaction. With increasing interval between stings the risk of reaction generally decreases [14].

### Large local reaction

The study by Pucci and colleagues have confirmed that recurrent large local reactions resulting from bee stings carry the risk of a systemic reaction, but only one large local reaction [16].

### Age

In children, systemic reactions are usually confined to cutaneous findings with urticaria and angioedema, whereas airway obstruction or hypotension is more common in adults [18].

In addition, severe systemic reactions more develop in elderly patients and mortality rates are higher than children and young adults [19].

### Passing time after the last reaction

After stings the risk of the reaction is initially over 50%. It declines by about 35 % after three to five years and 25% after 10 years or more. However, in some cases the risk of anaphylaxis remains the same throughout the intervening period [20].

### Family history

The occurrence of systemic reactions to insect infestations does not correlate with family history except in a few cases. It has been suggested that the result of bee sting in patients with mastocytosis may result in particularly serious and even fatal systemic reactions [21].

In venom-allergic patients, even without mastocytosis, elevation in basal serum tryptase levels was associated with severe anaphylactic reactions [22].

**Table 1:** Classification of systemic reactions according to Mueller after bee sting.

| | |
|---|---|
| Grade 1 | Generalize Urticaria, itching, anxiety |
| Grade 2 | Any of the above + at least two and over Symptoms: Angioedema, chest compression, nausea, vomiting, diarrhea, abdominal pain, dizziness |
| Grade 3 | Any of the above + at least two and over Symptoms: shortness of breath, wheezing, stridor, dysarthria, phobia, confusion |
| Grade 4 | Any of the above + at least two and over Symptoms: hypotension, collapse, unconsciousness, incontinence, cyanosis |

**Table 2:** Classification of Ring-Meismer for systemic reactions resulting after bee sting.

| | |
|---|---|
| Grade 1 | Generalized skin symptoms (redness, generalized urticaria, angioedema) |
| Grade 2 | Moderate pulmonary, cardiovascular and / or gastrointestinal symptoms |
| Grade 3 | Anaphylactic shock, Unconsciousness |
| Grade 4 | Cardiac arrest, apnea |

## DIAGNOSIS

The diagnosis of Hymenoptera allergy is based on anamnesis and supported by testing for the presence of venom-specific IgE antibodies.

### Anamnesis

When the history is taken, the following questions need to be answered

1. When did the sting event happened?

2. The characteristics of previous bee stings.

3. Bee gender: An important distinguishing feature to determine the bee pattern is the color of the bee and the presence of needles in the inserted spot. Honey bees often leave their needles, but wild bees do not leave their needles.

4. Developing reactions large local reaction or systemic reaction?

5. How many stings were exposed? The toxic reactions may develop in multiple stings [17].

Patients with had a history of systemic reactions should be evaluated with testing for the presence of venom-specific IgE antibodies [23].

### Skin testing

It is advisable to wait at least four to six weeks before the skin test as possible, if the reaction history is near. In most cases skin testing is the first method to show venom-specific IgE because it is more sensitive. 70-90% of patients who describe venom allergy have positive skin test. If clinical history is proven by positive skin test *in vitro* testing is not necessary [24].

### *In vitro* testing

*In vitro* testing is less sensitive and more expensive than skin testing. It is necessary in some cases as follows:

1. If patient with positive clinical history has negative skin testing

2. Patients not eligable for skin test (dermographism, urticaria, active skin disease)

3. Patients who cannot discontinue interfering medications (antidepressant drug)

IgE immunoassays: Immunocap is identified as a reliable commercial assay [25].

Skin test and *in vitro* test combination can detect approximately 95% of patients who have a systemic reaction [26].

### Component-resolved diagnostic

Double sensitization to hymenoptera venom often occurs in skin prick test. Carbohydrate determinant of venoms can be cross-reactive. Component-resolved diagnostic provide improved discrimination between primary sensitization and cross-reactivity in hymenoptera venom allergy [27].

If the both skin testing and *in vitro* testing are negative the investigational testing may be considering Basophil activation tests.

The diagnosis of Hymenoptera venom allergy is based on history, skin tests and demonstration of hymenoptera venom-specific IgE-antibodies [28]. Basophil activation is associated with the expression of CD63 and may be valuable for diagnosing immediate type allergic reactions. In a study Erdmann SM, et al., were compared skin tests and specific IgE measurements with CD63-based basophil activation test for wasp venom allergy and they were suggested CD63-based basophil activation test is a useful tool for diagnostic tests such as specific IgE [29]. Furthermore, Basophil sensitivity can be used to monitor allergen specific immunotherapy and anti-IgE treatment response [33,31]. Rodríguez Trabado A, et al., suggested that BAT is an optimal non-invasive test for close monitoring of VIT [32].

### Tryptase

Serum tryptase should be measured for the detection of an underlying mast cell disorder. Some specialists recommend measuring basal tryptase levels in all patients requiring venom immunotherapy. In addition, in some studies, patients with hypotensive syncope after bee sting have been found to have a monoclonal mast cell activation syndrome when the tryptase is normal and the skin is not detected [22,33]. If both the skin tests and the *in vitro* test are negative, if the serum tryptase is normal and there is still a systemic reaction history, the patient should be retested for venom-specific IgE after 3-6 months [14].

## TREATMENT

Local reactions to hymenoptera stings are treated with oral antihistamines and topical corticosteroids. A short course of oral corticosteroids may be needed for large local reactions.

### Immediate treatment

Patients with airway obstruction or hypotension should be treated with adrenaline intramuscularly. Adrenaline is the first drug for treatment of anaphylaxis. However fluid replacement is required with adrenaline. High flow oxygen and beta-agonist therapy should be given for bronchospasm treatment [34].

### Long term treatment

**Adrenaline auto-injector:** Patients with a systemic reaction to bee sting should be prescribed the adrenaline auto- injector and the patient and family should be trained in their use [35].

**Venom immunotherapy:** In adults, venom immunotherapy (VIT) is performed if the systemic reaction is positive and venom-specific IgE antibodies are defined (skin test or immunoassay). In the study reported by Golden DB et al., the protection of VIT from systemic reactions was found to be 75-98% [9]. This protection is higher in vespid allergy than honey bee allergy. VIT should generally be continued for at least 3-5 years after starts [26,36]. There are no specific tests to determine which patients will relapse after VIT, but some patients have a higher risk than others. Factors such as the patient's life style, occupation, coexisting diseases, medications, and severity of stinging reactions should be taken into consideration during the VIT period [37]. Patients with a severe history of anaphylaxis (severe airway obstruction,

shock or loss of consciousness) may still be at risk for a systemic reaction even after 5 years of treatment [30,31,38].

**Venom immunotherapy + Omalizumab:** Anaphylaxis may occur rarely during specific venom immunotherapy (VIT). This ratio is significantly higher for honey bee VIT than vespid VIT [39]. Omalizumab is a recombinant humanized immunoglobulin G1 monoclonal antibody that has provided a treatment option for allergic asthma and chronic idiopathic urticaria diseases [40]. Pretreatment with omalizumab has been implicated in the prevention of anaphylaxis during the VIT administration, as shown in various published reports. This efficacy is associated with a marked lowering of free IgE levels and downregulation of IgE receptors on mast cells, basophils and eosinophils [41-43].

## REFERENCES

1. Prado M, Quirós D, Lomonte B. Mortality due to Hymenoptera stings in Costa Rica, 1985-2006. Rev Panam Salud Publica. 2009; 25: 389-393.
2. Fitzgerald KT, Flood AA. Hymenoptera stings. Clin Tech Small Anim Pract. 2006; 21: 194-204.
3. Perez-Riverol A, Justo-Jacomini DL, Zollner Rde L, Brochetto-Braga MR. Facing Hymenoptera Venom Allergy: From Natural to Recombinant Allergens. Toxins (Basel). 2015; 7: 2551-2570.
4. Ciszowski K, Mietka-Ciszowska A, Hymenoptera stings. Przegl Lek. 2007; 64: 282-289.
5. Przybilla B, Ruëff F. Insect stings: clinical features and management. Dtsch Arztebl Int. 2012; 109: 238-248.
6. Golden DB. Large local reactions to insect stings. J Allergy Clin Immunol Pract. 2015; 3: 331-334.
7. Stoevesandt J, Hain J, Kerstan A, Trautmann A. Over- and underestimated parameters in severe Hymenoptera venom-induced anaphylaxis: cardiovascular medication and absence of urticaria/angioedema. J Allergy Clin Immunol. 2012; 130: 698-704.
8. Golden DB, Demain J, Freeman T, Graft D, Tankersley M, Tracy J, et al. Stinging insect hypersensitivity: A practice parameter update 2016. Ann Allergy Asthma Immunol. 2017; 118: 28-54.
9. Golden DB. Insect sting allergy and venom immunotherapy: a model and a mystery. J Allergy Clin Immunol. 2005; 115: 439-447.
10. Bilo BM, Rueff F, Mosbech H, Bonifazi F, Oude-Elberink JN. Diagnosis of hymenoptera venom allergy. Allergy. 2005; 60: 1339-1349.
11. Novembre E, Cianferoni A, Bernardi R, Veltroni M, Ingargiola A, Lombardi E, et al. Epidemiology of insect venom sensitivity in children and its correlation to clinical and atopic features. Clin Exp Allergy. 1998; 28: 834-838.
12. Kalyoncu AF, Demir AU, Ozcan U, Ozkuyumcu C, Sahin AA, Bariş YI. Bee and wasp venom allergy in Turkey. Ann Allergy Asthma Immunol. 1997; 78: 408-412.
13. Gelincik A, İşsever H, Unal D, Işık E, Demirturk M, Gül H, et al. The prevalence of Hymenoptera venom allergy in adults: the results of a very crowded city in Euroasia. Allergol Int. 2015; 64: 35-40.
14. Golden DB. Insect sting anaphylaxis. Immunol Allergy Clin North Am. 2007; 27: 261-272.
15. Golden DB, Kagey-Sobotka A, Norman PS, Hamilton RG, Lichtenstein LM. Outcomes of allergy to insect stings in children with and without venom immunotherapy. N Engl J Med. 2004; 351: 668-674.
16. Pucci S, D'Alo S, DePasquale T, Illuminati I, Makri E, Incorvaia C. Risk of anaphylaxis in patients with large local reactions to Hymenoptera stings: a retrospective and prospective study. Clin Mol Allergy. 2015; 13: 21-23.
17. Freeman TM. Clinical practice. Hypersensitivity to hymenoptera stings. N Engl J Med. 2004; 351:1978-1984.
18. Yavuz ST, Sahiner UM, Buyuktiryaki B, Soyer OU, Sackesen C, Sekerel BE, et al. Clinical features of children with venom allergy and risk factors for severe systemic reactions. Int Arch Allergy Immunol. 2013; 160: 313-321.
19. Ruëff F, Przybilla B, Biló MB, Müller 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.
20. Reisman RE. Natural history of insect sting allergy: relationship of severity of symptoms of initial sting anaphylaxis to resting reactions. J Allergy Clin Immunol. 1992; 903: 335-339.
21. Bonadonna P, Zanotti R, Müller U. Mastocytosis and insect venom allergy. Curr Opin Allergy Clin Immunol. 2010; 10: 347-353.
22. Haeberli G, Brönnimann M, Hunziker T, Müller U. Elevated basal serum tryptase and hymenoptera venom allergy: relation to severity of sting reactions and to safety and efficacy of venom immunotherapy. Clin Exp Allergy. 2003; 33: 1216-1220.
23. Graif Y, Confino-Cohen R, Goldberg A. Reproducibility of skin testing and serum venom specific IgE in Hymenoptera venom allergy. Ann Allergy Asthma Immunol. 2006; 96: 24-29.
24. Krishna MT, Ewan PW, Diwakar L, Durham SR, Frew AJ, Leech SC, et al. Diagnosis and management of hymenoptera venom allergy: British Society for Allergy and Clinical Immunology (BSACI) guidelines. Clin Exp Allergy. 2011; 41: 1201-1220.
25. Heinzerling L, Mari A, Bergmann KC, Bresciani M, Burbach G, Darsow U, et al. The skin prick test - European standards. Clin Transl Allergy. 2013; 3: 3.
26. Bonifazi F, Jutel M, Bilo BM, Birnbaum J, Muller U, EAACI. Prevention and treatment of Hymenoptera venom allergy: guidelines for clinical practice. Allergy. 2005; 60: 1459-1470.
27. Jakob T, Müller U, Helbling A, Spillner E. Component resolved diagnostics for hymenoptera venom allergy. Curr Opin Allergy Clin Immunol. 2017; 17: 363-372.
28. Eberlein-König B, Schmidt-Leidescher C, Rakoski J, Behrendt H, Ring J. *In vitro* basophil activation using CD63 expression in patients with bee and wasp venom allergy. J Investig Allergol Clin Immunol. 2006; 16: 5-10.
29. Erdmann SM, Sachs B, Kwiecien R, Moll-Slodowy S, Sauer I, Merk HF. The basophil activation test in wasp venom allergy: sensitivity, specificity and monitoring specific immunotherapy. Allergy. 2004; 59: 1102-1109.
30. Golden DB, Kagey-Sobotka A, Lichtenstein LM. Survey of patients after discontinuing venom immunotherapy. J Allergy Clin Immunol. 2000; 105: 385-390.
31. Reisman RE. Duration of venom immunotherapy: relationship to the severity of symptoms of initial insect sting anaphylaxis. J Allergy Clin Immunol. 1993; 1992: 831-836.
32. Rodríguez Trabado A, Cámara Hijón C, Ramos Cantariño A, Romero-Chala S, García-Trujillo JA, Fernández Pereira LM. Short-, Intermediate-, and Long-Term Changes in Basophil Reactivity Induced by Venom Immunotherapy. Allergy Asthma Immunol Res. 2016; 8: 412-420.

33. Castells MC, Hornick JL, Akin C. Anaphylaxis after hymenoptera sting: is it venom allergy, a clonal disorder, or both? J Allergy Clin Immunol Pract. 2015; 3: 350-355.

34. Golden DB, Moffitt J, Nicklas RA, Freeman T, Graft DF, Reisman RE, et al. Stinging insect hypersensitivity: A practice parameter update. 2011. J Allergy Clin Immunol. 2011; 127: 852-854.

35. Oude-Elberink JN, De Monchy JG, Vander Heide S, Guyatt GH, Dubois AE. Venom immunotherapy improves health-related quality of life in yellow jacket allergic patients. J Allergy Clin Immunol. 2002; 110: 174-182.

36. Graft DF, Golden DB, Reisman R, Valentine M, Yunginger J. The discontinuation of Hymenoptera venom immunotherapy. Report from the Committee on Insects. J Allergy Clin Immunol. 1998; 101: 573-575.

37. Lerch E, Muller U. Long-term protection after stopping venom immunotherapy. J Allergy Clin Immunol 1998; 101: 606-612.

38. Golden DB, Kwiterovich KA, Kagey-Sobotka A, Lichtenstein LM. Discontinuing venom immunotherapy: extended observations. J Allergy Clin Immunol. 1998; 101: 298-305.

39. Boni E, Incorvaia C, Mauro M. Dose-dependence of protection from systemic reactions to venom immunotherapy by omalizumab. Clin Mol Allergy. 2016; 14: 14.

40. Baker DL, Nakamura GR, Lowman HB, Fischer SK. Evaluation of IgE Antibodies to Omalizumab and Their Potential Correlation to Anaphylaxis. AAPS J. 2016; 18: 115-123.

41. Palgan K, Bartuzi Z and Gotz-Zbikowska M. Treatment with a combination of omalizumab and specific immunotherapy for severe anaphylaxis after a wasp sting. Int J Immunopathol Pharmacol. 2014; 27: 109-112.

42. Galera C, Soohun N, Zankar N, Caimmi S, Gallen C, Demoly P. Severe anaphylaxis to bee venom immunotherapy: Efficacy of pretreatment and concurrent treatment with omalizumab. J Investig Allergol Clin Immunol. 2009; 19: 225-229.

43. Ruëff F, Przybilla B, Biló MB, Müller 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.

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