

HYPERSENSITIVITY TO STINGING INSECTS

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ABSTRACT

Stings from bees, bumblebees, wasps and ants usually cause a transient local reaction which may last for several days and which generally resolves without treatment. Occasionally, life-threatening anaphylaxis may occur. Such severe reactions may be refractory to single doses of adrenaline. Each year in the USA about 40 individuals die from anaphylaxis caused by stinging insects. In South Africa, bee-sting hypersensitivity is the most common form of stinging insect allergy. Venom immunotherapy is available and effective for bee venom hypersensitivity but many individuals with stinging-insect allergy are not referred to an allergist for evaluation and are thus never offered this potentially life-saving therapy.

INTRODUCTION AND EPIDEMIOLOGY

Potentially life-threatening reactions to insect stings occur in 0.6% of children and 3% of adults.¹⁻⁴ These reactions may require multiple doses of adrenaline. Sensitivity to bee venom is a leading cause of fatal anaphylaxis⁵ and bee stings cause about 40 deaths annually in the USA.⁶ However, the true incidence of fatal reactions may be underestimated as sudden deaths occurring outdoors may mistakenly be attributed to myocardial infarction or stroke.

Half the individuals who die as a result of anaphylaxis induced by stinging insects are not known to be allergic to bee venom prior to the reaction¹ and it is very likely that venom allergy is both under-recognised and underdiagnosed.

RISK FACTORS FOR STINGS/SEVERE REACTIONS

Certain risk factors are associated with a higher chance of sustaining an insect sting. These include occupations and hobbies such as gardening, beekeeping,⁷ farming, greenhouse workers and other outdoor activities. Climate, temperature and insect behaviour also moderate this risk.

Individuals with cardiovascular disease are at particular risk for severe and fatal anaphylaxis,^{8,9} as are those who have multiple simultaneous stings or a very short interval between episodes of stinging.¹⁰ Patients treated with non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitor medication or beta-blockers¹¹ have an increased risk of a severe sting reaction.

Systemic reactions in children are generally mild¹² but, in contrast, 70% of adults who have systemic reactions exhibit cardiovascular or respiratory symptoms.¹³ The elderly are at particular risk for severe reactions.¹³ Individuals with mastocytosis and those with an elevated baseline level of serum tryptase are also at high risk.^{11,14}

Adult males, especially bee keepers, are at highest risk for severe venom allergy.⁷

The risk of a severe systemic reaction to a honeybee sting is greater than to those of other stinging insects.

TAXONOMY OF STINGING INSECTS

The majority of insects causing stinging reactions belong to the order Hymenoptera. Three families in this order are medically significant:

- Apidae – honeybee (Fig. 1), bumblebee (Fig. 2)
- Vespidae – yellow jacket, yellow hornet, white-faced hornet, paper wasp
- Formicidae – fire ant, harvester ant, bulldog ant, jack jumper ant.



Fig. 1. Honeybee, reproduced with permission.

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Fig. 2. Bumblebee, reproduced with permission.

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The European honeybee, *Apis mellifera*, has 28 sub species, including two that originated in Africa, *Apis mellifera scutellata* and *Apis mellifera capensis*. Most insect-sting hypersensitivity reactions in South Africa are due to honeybee stings while wasp stings are infrequent. African honeybees are known to be more aggressive than European honeybees. They guard their hives more closely, are more defensive, swarm more and will pursue perceived threats over longer distances from the hive.

The honeybee is the only insect to leave a stinger behind, thus a sting from a bee is more easily identifiable than that from a wasp or ant.

COMPOSITION OF VENOM

The major allergens identified in bee venom are glycoproteins of 10-50 kDa. These include phospholipase A (Api m 1), hyaluronidase (Api m 2), acid phosphatase (Api m 3), mellitin (Api m 4) and Api m 6 and 10. Phospholipase A and hyaluronidase are the most commonly implicated major proteins (Table I).

CLINICAL FEATURES

Venom hypersensitivity reactions are usually immediate but, rarely, may be delayed. Reactions are classified as local, large local, systemic, systemic toxic and unusual reactions.

Local reactions

Local reactions are confined to the tissues contiguous with the sting site. Symptoms include a stinging, burning or painful sensation as well as erythema and swelling at the site of envenomation. There is typically an area of erythema at the site that develops within minutes and fades within a few hours.

Large local reactions

These reactions enlarge over 24-48 hours and resolve over 5-10 days.^{16,17} They may be as large as 10 cm in diameter and may blister and cause lymphangitis and lymphadenopathy. If they occur in areas such as the eyelids or lips, they may cause great discomfort. Non-specific symptoms such as malaise, fever and headache may accompany this type of reaction.

Systemic reactions

Systemic reactions range from mild to life-threatening. Mild systemic reactions are limited to the skin and may include flushing, urticaria and angio-oedema. More severe reactions may include bronchospasm, laryngeal oedema and hypotension (anaphylaxis). Most episodes of venom anaphylaxis escalate rapidly and resolve with treatment. A small percentage may follow a biphasic course with the recurrence of symptoms hours later.¹⁸

The most severe cardiovascular symptoms tend to occur in adults more frequently than in children.¹⁹

Occasionally, vasovagal reactions to insect stings occur and these must be differentiated from true allergic reactions.

Allergic reactions were categorised into four grades by Mueller²⁰ in 1966 (Table II).

A more recent classification by Mosbech and Muller²¹ included large local reactions as an additional grade (Table III).

Systemic toxic reactions

These reactions occur as a result of multiple (usually more than 50) stings, and are dose-dependent. Symptoms develop over hours or days and may include acute renal failure, liver dysfunction, rhabdomyolysis,

Table I. Composition of Hymenoptera venom

Venom	Allergen	Common name	MW (kDa)
Honeybee (<i>Apis mellifera</i>)	Api m 1	Phospholipase A2	16
	Api m 2	Hyaluronidase	43
	Api m 3	Acid phosphatase	49
	Api m 4	Mellitin	2.9
	Api m 6		7.9
	Api m 10		
		Protease	39
Bumble bee (<i>Bombus</i>)	Bom p 1	Phospholipase A2	
	Bom p 4	Protease	
Common wasps, German wasp, eastern yellowjacket (<i>Vespa vulgaris</i> , <i>germanica</i> and <i>maculifrons</i>)	Ves v 1	Phospholipase A1	35
	Ves v 2	Hyaluronidase	45
	Ves v 5	Antigen 5	25
Bald-faced hornet, aerial yellowjacket, median wasp (<i>Dolichovespula maculate</i> , <i>arenaria</i> , and <i>media</i>)	Dol m 1	Phospholipase A1	35
	Dol m 2	Hyaluronidase	45
	Dol m 5	Antigen 5	25
Paper wasps (<i>Polistes annularis</i> , <i>dominulus</i> , <i>gallicus</i> and <i>fuscatus</i>)	Pol a 1	Phospholipase A1	
	Pol a 2	Hyaluronidase	
	Pol a 5	Antigen 5	25
European hornet (<i>Vespa carbro</i>)	Vesp c 1	Phospholipase A1	
	Vesp c 5	Antigen 5	
Red imported fire ant (<i>Solenopsis invicta</i>)	Sol i 1	Phospholipase A1	37
	Sol i 2		13.2
	Sol i 3	Antigen 5	24
	Sol i 4		13.4

From Bilo *et al.*¹⁵

Table II. Classification of systemic reactions to insect stings (Mueller²⁰)

Grade	
1	Itch, urticaria, malaise, anxiety
2	Any of the above plus two or more of the following: angio-oedema, tight chest, nausea, vomiting, diarrhoea, abdominal pain, dizziness
3	Any of the above plus two or more of the following: dyspnoea, wheeze, stridor, hoarseness, weakness, feeling of impending doom
4	Any of the above plus two or more of the following: hypotension, collapse, loss of consciousness, cyanosis

Table III. Classification of systemic reactions to insect stings (Mosbech and Muller²¹)

Grade	
0	Large local reaction
1	Itch, urticaria, malaise, oedema, anxiety
2	Chest tightness, palpitations, dizziness, nausea, abdominal pain
3	Somnolence, respiratory difficulties, vomiting, diarrhoea, incontinence
4	Confusion, (drop) fall in blood pressure, feeling of impending doom, cyanosis, unconsciousness, death

disseminated intravascular coagulopathy, haemolysis and myocardial dysfunction. The phospholipase and hyaluronidase components of venom are thought to be responsible for this type of reaction.

Unusual reactions

Unusual reactions include serum sickness, peripheral neuropathy, Guillain-Barré-like polyradiculomyelitis, encephalomyelitis, systemic vasculitis and interstitial nephritis. The mechanisms are unclear but may be toxic or non-IgE-mediated.

Secondary bacterial infection: most stings do not become infected secondarily. Infection should be suspected when the erythema, swelling and pain increase 3-5 days after the sting, by which time the typical large local reaction is beginning to clear. The presence of fever suggests infection, and in this case a course of oral antibiotic should be considered.

DIAGNOSIS

History

A thorough history should be taken in order to determine whether the patient's reaction was local or systemic, immediate or delayed.

Questions to be asked include:

- When did the sting occur?
- Environment and activities prior to the sting?
- How many stings were sustained?
- What was the time delay between the sting and the development of symptoms?
- Where on the body did the sting occur?
- Which insect caused the sting?
- Was there a 'stinger' or not?
- What symptoms occurred? Ask specifically about the different symptoms of anaphylaxis

- Any concurrent medication, specifically beta-blockers and ACE-inhibitors?
- What treatment was given (including first aid and subsequent treatment)?
- Were there any delayed symptoms?
- What previous reactions to insect stings have occurred?

Special investigations

Diagnostic tests should be done on all patients with a history of a systemic reaction to detect sensitisation. They are not recommended for those with large local reactions unless the reactions are becoming progressively larger or there is a high risk of sustaining multiple or recurrent stings.

There is no correlation between the level of venom-specific IgE or skin test reactivity and the severity of the reaction to a sting. If blood and skin tests are negative but the history is suggestive, the tests should be repeated several weeks later.

Blood tests

Serum tryptase taken at the time of reaction may confirm anaphylaxis. A baseline tryptase should also be taken in order to ascertain future risk of severe reactions, as well as to screen for mastocytosis and other disorders of mast cell function. It is also recommended to measure the baseline serum tryptase levels prior to administering venom immunotherapy (VIT). A baseline tryptase level of >10 µg/l may indicate a high risk of a severe allergic reaction during VIT.¹¹

Specific IgE should be performed 4-6 weeks after the sting has occurred in order to avoid false-negative results. This test is approximately 85% sensitive for bee venom.²² Test with complete natural venom extracts for highly efficient and sensitive detection of bee and wasp venom sensitisation. Complete extracts such as those provided by Thermo Fisher Scientific (previously Phadia) include i1 (honey bee), i3 (common wasp) and i77 (paper wasp).

Skin testing/venom challenge

Skin tests and direct challenges are not routinely performed in South Africa, but are included for the sake of completeness.

Skin tests may be done for any patient who might be a candidate for VIT and should be accompanied by the appropriate positive and negative controls. Skin-prick tests are done at concentrations of 1.0-100 µg/ml. If they are negative, intradermal tests should be done at incremental concentrations of 0.001-1 µg/ml and a volume of 0.02 ml. Concentrations of greater than 1 µg/ml are likely to cause irritant reactions.²³

The sensitivity of intradermal testing is about 90% for a concentration of 1 µg/ml.²³

Extracts of honeybee, bumblebee, yellow jacket (common wasp), white-faced hornet, European hornet, yellow hornet and paper wasp venom are commercially available for skin testing and VIT. Recombinant component tests are also now available and are discussed further below.

Direct sting challenges

Sting challenges with live insects are associated with considerable risk and are used mainly for research purposes. They are not currently performed in South Africa. The practical aspects of performing these challenges are described elsewhere.²⁴ Sting challenges are useful for the initial diagnosis of clinical reactivity, as well as for patients who are undergoing maintenance VIT in order to determine whether or not they are protected.

Other tests

Additional *in vitro* tests include basophil histamine release, cellular antigen stimulation and basophil activation tests.

CROSS-REACTIVITY AND DOUBLE SENSITISATION

Cross-reactivity occurs when IgE antibodies recognise similar epitopes within the different venoms. This is due to sequence homology among the venoms, for example hyaluronidase in bee and wasp venom, but can also be due to cross-reactive carbohydrate determinants (CCDs). This can result in multiple positive skin and IgE antibody test results of uncertain significance. IgE antibodies to CCDs rarely have clinical relevance.

A further complication is the fact that an individual may be truly sensitive to more than one type of venom (true double sensitisation). This may become a clinical problem if VIT is being considered.²⁵

IgE inhibition assays can help to distinguish genuine double sensitisation from cross-reactivity.²⁶

More recent methods to assess patients with possible cross-reactivity or double sensitisation involve component-resolved diagnostics. CCD-free recombinant components can help to differentiate whether or not double positive venom extract tests are due to true co-sensitisation to bee and wasp allergens or CCD-dependent cross-reactivity between venoms. Api m 1 (phospholipase A2) of honeybee venom and Ves v 5 (antigen 5) of *Vespula* venom do not cross-react with carbohydrate determinants and are thus useful for the accurate diagnosis of venom allergy.^{27,28}

Recombinant components available (Fig. 3) include Api m 1 (honeybee), Ves v 1 (common wasp, phospholipase A1), Ves v 5 (common wasp) and Pol d 5 (paper wasp, antigen 5). Recombinant components are CCD-free and will therefore not be influenced by IgE directed at CCDs. The cross-reactivity marker for CCDs is also used in specific cases. There is cross-reactivity between antigen 5 from different wasps, hornets and paper wasps. Cross-reactivity is very limited between bee and wasp protein parts.

MANAGEMENT

Acute management

If a venom sac indicating a bee sting is present, it should be carefully removed without bursting the sac.

Most insect stings cause mild local reactions and require no specific treatment apart from analgesia and a cold compress. An oral antihistamine may be helpful if the sting is itchy.

Large local reactions are treated with cold compresses, elevation of the affected limb, antihistamines, non-steroidal anti-inflammatories and a short course of an oral corticosteroid, although proof of efficacy via controlled studies is lacking.

Mild systemic reactions in children (cutaneous symptoms alone) may be treated with antihistamines and close observation.

Severe systemic reactions should be treated with intramuscular adrenaline with the usual anaphylaxis protocols, supportive therapy and transport to an emergency department. The most important principle in the management of a systemic reaction is prompt recognition and rapid initiation of treatment.

Long-term management

Patients and their caregivers should be informed that venom allergy is potentially fatal. An adrenaline autoinjector should be prescribed together with

written instructions on how and when to use it. Clear instructions must be given to carry the autoinjector at all times and consideration given to the need to carry two doses of adrenaline in case of a refractory reaction. A MedicAlert bracelet should be worn. Instructions on how to prevent being stung include avoidance of:

- Wearing perfumes
- Black and brightly coloured clothing
- Eating or drinking anything sweet outdoors
- Walking barefoot outside
- Outdoor rubbish bins.

Patients who are candidates for VIT should be referred to an allergist for evaluation.

Indications for referral to an allergist

These include individuals

- With systemic reactions to insect venom
- Who are potential candidates for VIT
- Who are taking a medication that may complicate a potential reaction to a sting
- Who have a concomitant medical condition that may complicate a potential reaction to a sting
- Who require further education or detailed information regarding insect venom allergy.

Immunotherapy

VIT reduces the risk of systemic reactions in up to 98% of patients.¹⁷ Apart from preventing life-threatening reactions, it also alleviates the anxiety associated with having a severe insect venom allergy.

Indications

Adults with a systemic reaction and a positive skin or *in vitro* test to venom are candidates for VIT. Those who have had large local reactions are not at high risk of systemic reactions and do not usually undergo VIT. However, VIT reduces the size and duration of large local reactions and may be considered in individuals at high risk for frequent and multiple stings.^{17,29}

VIT is not usually necessary for children who experience isolated cutaneous symptoms without other systemic manifestations. They have a very low risk of having a subsequent severe systemic reaction.¹⁷ VIT may be considered for various specific circumstances should the child be considered at high risk for frequent or multiple stings.

Which venoms to include in the immunotherapy regimen

There is controversy as to whether or not all venoms eliciting a positive response on testing should be included. If the culprit insect is identified and its cross-reactivity known, then some experts believe only that venom should be used for VIT. Others believe that all insects for which positive test results were obtained should be included in the VIT.¹⁷

Administration of VIT

In general VIT is administered once a week beginning with doses around 0.1-1.0 µg and increased incrementally according to tolerance to a maintenance dose of 100 µg (Table IV). Rush and ultra-rush schedules are also available. Maintenance is usually achieved within 2-4 months depending on the protocol used and the patient's tolerance.

Once maintenance levels have been achieved, the interval between doses is increased to monthly during the first year. After that intervals may be lengthened to 6-8 weeks and even as long as 12 weeks.^{17,30}

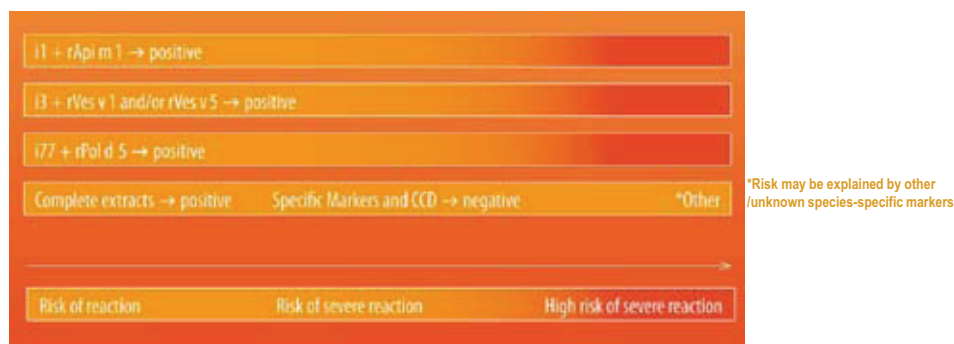
Both complete extracts and recombinant components for a precise risk assessment



To differentiate between bee and wasp allergy we strongly suggest to:

1. Test with complete natural venom extracts for highly efficient and sensitive detection of bee & wasp venom sensitization.
2. In cases of double-positivity to the complete venom extracts test with rApi m 1, rVes v 1, rVes v 5/rPol d 5 to discriminate between bee & wasp venom sensitization.

Both complete extracts and recombinant components for a precise patient assessment



CCD-free recombinant components can help differentiate if double positive venom extract tests are due to:

- True co-sensitization to bee and wasp allergens
- CCD dependent cross-reactivity between venoms

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- i1 (Honey bee)
- i3 (Common wasp)
- i77 (Paper wasp)

ImmunoCAP® Venom components:

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- Specific marker for honey bee venom sensitization
- Common wasp rVes v 1 - Phospholipase A1
- Specific marker for sensitization to venom of vespids, particularly common wasps and hornets. There is a cross-reactivity between Phospholipase A1 from different wasps and hornets rVes v 5 - Antigen 5
- Specific marker for sensitization to venom of vespids, particularly common wasp and hornets. There is a cross-reactivity between antigen 5 from different wasps, hornets and paper wasps
- Paper wasp rPol d 5 - Antigen 5
- Specific marker for sensitization to venom of vespids, particularly paper wasp. There is a cross-reactivity between antigen 5 from different wasps, hornets and paper wasps

Fig.3. Patient and risk assessment venom algorithm (reproduced with permission from Phadia/Thermo Fisher).

Table IV. Example of a dosing schedule for venom immunotherapy

Week number	Dose number per day 30-minute	Concentration (µg/ml) to be used Intervals)	Volume (ml) to be given
1	1	0.01	0.1
	2	0.1	0.1
	3	1.0	0.1
2	1	1.0	0.1
	2	1.0	0.5
	3	10	0.1
3	1	10	0.1
	2	10	0.5
	3	10	1.0
4	1	100	0.1
	2	100	0.2
5	1	100	0.2
	2	100	0.3
6	1	100	0.3
	2	100	0.3
7	1	100	0.4
	2	100	0.4
8	1	100	0.5
	2	100	0.5
9	1	100	1.0
Monthly		100	1.0

Based on the package insert for ALK-Abelló venom extracts.

Safety precautions are the same as for any other form of immunotherapy. Informed, written consent must be obtained and emergency equipment and drugs must be readily available should a reaction occur. Patients should wait 30 minutes after each injection in case of systemic reactions.

Side-effects during VIT

Systemic reactions during VIT may occur in up to 12% of cases³¹ although most are mild and develop during the dose-escalation phase. Those receiving VIT for honeybee and with other medical illnesses are at highest risk.¹¹ Rush protocols do not appear to increase the risk of having a systemic reaction.^{32,33}

Premedication with antihistamines may reduce the incidence of systemic reactions.³⁴ The dose following a systemic reaction is generally decreased.

A more common side-effect is the development of a local reaction that occurs in 25% of children and 50% of adults. These are uncomfortable but do not increase the risk of a future systemic reaction.

Indications for stopping VIT

Once initiated, VIT should be continued for 3-5 years.³⁰ Criteria for stopping VIT are evolving but may include a decrease in venom-specific IgE and diminishing skin test responses.³⁵

Some authors recommend continuing VIT for longer, perhaps indefinitely, in those with certain risk factors. These include a history of severe anaphylaxis, underlying mastocytosis, raised basal tryptase levels, concurrent medical conditions and those with frequent exposures. These patients have been shown to be at continued risk of systemic reactions even after 5 years of VIT.³⁶

Treatment failure occurs when a patient has recurrent systemic reactions to insect stings despite VIT. This may be seen in patients with underlying mastocytosis. In these patients the maintenance dose should be

increased to 200 µg per dose and this is usually effective in inducing tolerance.³⁷

Monitoring of VIT

Although VIT is very effective, complete immunological protection will not be obtained in 5-15% of patients receiving VIT. Therefore it would be beneficial to be able to monitor the success of the therapy. Currently there are exciting possibilities for monitoring VIT efficiency. These include the use of basophil activation tests (BAT). This involves the measurement of an activation marker called CD63 on the cell surface of basophils to identify bee-venom-tolerant patients.

A recent study by Eržen *et al.* looked at the possibility of predicting the induction of tolerance by measuring basophil responsiveness to determine the level of tolerance obtained as a result of immunotherapy.³⁸ They have demonstrated a fourfold decrease in basophil responses in all tolerant subjects after completing their VIT course indicating that VIT is a very successful treatment method and that a decrease in basophil responsiveness can be associated with induction of tolerance.

Quality of life

The impact of a severe insect sting allergy on an individual's quality of life cannot be underestimated. The patient as well as family members may develop severe anxiety around the possibility of sustaining a sting¹⁸ and care should be taken to assess and manage this.

Declaration of conflict of interest

The author declares no conflict of interest.

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[S4] AVAMYS Nasal Spray (Suspension). REGISTRATION NUMBER: 41/21.5.1/0968. Each 50 µl spray contains 27,5 µg of fluticasone furoate. Preservative: Benzalkonium chloride 0,015% m/m. PHARMACOLOGICAL CLASSIFICATION: A.21.5.1 Corticosteroids and analogues. APPLICANT: GlaxoSmithKline South Africa (Pty) Ltd, 57 Sloane Street, Bryanston 2021.



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GlaxoSmithKline South Africa (Pty) Ltd, (co. reg. no.: 1948/030135/07), 57 Sloane Street, Bryanston 2021. Tel: +27 11 745 6000. Fax +27 11 745 7000. Marketed by Aspen Pharmacare, Building 12, Healthcare Park, Woodlands Drive, Woodmead, 2191. For full prescribing information refer to the package insert approved by the medicines regulatory authority. AVA/0911/12 A13634 09/11 141022