

A CLINICAL APPROACH TO BEE-STING ALLERGY

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ABSTRACT

Bee-venom hypersensitivity is an important cause of death in highly sensitive individuals. Not all patients who have adverse reactions to bee stings require immunotherapy. The majority of stings produce a localised reaction involving redness, swelling, itching and pain around the sting site. In some cases a large local reaction may persist for days. These patients require symptomatic treatment and no further diagnostic tests are required, as they are not at risk for systemic reactions.

Individuals who experience a systemic reaction (e.g. dizziness, wheezing, generalised urticaria or tightness of the throat) are at risk. They should keep injectable adrenaline on their person and a supply of antihistamines to administer if stung. These individuals are at risk of developing a more serious reaction and should receive bee venom immunotherapy as this will provide more than 85% protection.

Sensitivity can be confirmed using the ImmunoCAP RAST or using a specific skin-prick test. Some patients are CAP RAST positive, but skin-prick test negative.

Bee-venom immunotherapy is given using an up-dosing regimen over 8-12 weeks, incrementally until a maintenance dose of 100 µg hymenoptera venom is achieved and continued 6-8 weekly for 3-5 years.

Immunotherapy may be stopped after 5 years in most patients even though specific IgE tests remain positive. After completing a course of immunotherapy there is only a 5-10% risk of a systemic reaction and a 2% risk of a reaction requiring epinephrine. Insect allergy in children is believed to be more benign than in adults. Venom immunotherapy has provided protection for up to 20 years.

INTRODUCTION

Allergy to bees is an important cause of death in highly sensitive individuals and is the most common hypersensitivity to stinging insects in South Africa. Hypersensitivity may also develop to wasps and hornets, but severe reaction to these insects is relatively uncommon in South Africa.

Allergy to stinging insects typically occurs in individuals who are non-atopic, but atopic individuals may also have exquisite sensitivity. Most non-allergic individuals will experience reactions to bee stings, which may be painful and result in localised swelling. They are not at risk for anaphylactic reactions. Beekeepers typically get stung up to 100 times a day, without any adverse reactions. By careful evaluation of the nature of their reac-

tions, the clinician is able to decide whether immunotherapy is indicated or not. In this review, sensitivity to the African honeybee, *Apis mellifera*, is reviewed, but the principles of management apply to other stinging insects as well.

COMPONENTS OF HONEYBEE VENOM

Bee venom consists of a mixture of protein and non-protein elements. Glycoproteins (enzymes) and polypeptides are the major allergens. Major allergens are those proteins to which more than 50% of the sensitive population make specific IgE.

These include phospholipase A (PLA₂), acid phosphatase, hyaluronidase, allergen C and smaller polypeptides, including melittin. Api M 6 is a recently identified new honeybee-venom allergen, to which about 40% of bee-sensitive subjects react.¹ The most important allergen appears to be phospholipase A.

Allergenic components in the honeybee are different to those of other hymenoptera (Fig. 1) and therefore specific IgE testing for other stinging insects is required if the clinical circumstances suggest that the sting was not from a bee.

Other important causes of anaphylactic reactions to insect bites worldwide include black ants in the Middle East, Jack jumper ants in Australia and Tasmania,² and yellow jacket hornets, wasps and fire ants in the USA, Canada and Europe.

CLINICAL REACTIONS TO BEE STINGS

A normal reaction to a bee sting in a non-sensitised individual is an intense stinging and painful sensation at the site of the injection, with associated erythema and tenderness, which lasts a few hours.

A thorough inquiry into the circumstances surrounding the sting is important and the stinging insect must be positively identified. Bees will generally leave a 'stinger' at the site. Wasps typically inject their venom and leave no stinger, but a puncture mark may be seen. Occasionally a sting may be infected and a lymphangitis may develop with swelling of the draining lymph nodes.

Swelling that occurs rapidly and spreads well beyond the site of the sting suggests an allergy. If distant sites become involved rapidly, this virtually confirms that the patient is hypersensitive.

Occasionally however, some non-allergic individuals develop dizziness from a vasovagal reaction through fear of a possible allergen and this must be distinguished from a true allergic reaction. The pulse may be rapid during an anxiety reaction and slow following a vasovagal reaction.

Allergic reactions have been conveniently categorised into four grades by Mosbech and Muller (Table I).³ In children Grade I and II reactions are not indications for bee-venom immunotherapy but in adults a Grade II reaction may be an indication for immunotherapy, if the reaction is extensive and severe. In general, 'localised' reactions, even if they involve an entire limb, are not indications for immunotherapy.

If patients develop intense generalised itching, sweating, fainting, pounding headache, stomach cramps, vomiting, a feeling of 'impending doom', tightness of

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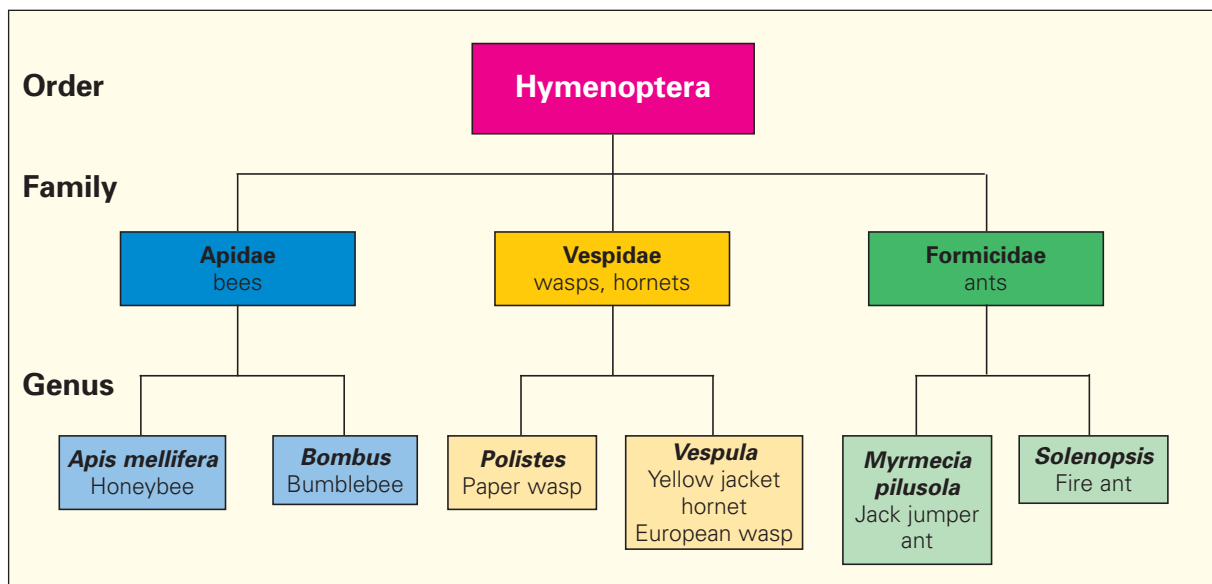


Fig. 1. Classification of hymenoptera.

the chest, choking and swelling of the throat and extreme weakness, they are having a systemic reaction and need emergency and life-saving treatment.

DIAGNOSIS

The most convenient way to confirm an allergy to bee venom is by the ImmunoCAP RAST test. It is best performed 4-6 weeks after the sting. This will confirm specific sensitivity in 80-85% of patients. However, it is negative in 15% of skin-prick-test-positive allergic patients.

On the other hand, the RAST can be positive in 10-30% of patients who have negative venom skin-prick tests (Golden DB, Johns Hopkins University, American College of Allergy, Asthma and Immunology; Immunotherapy Collegium II).

Skin tests can also be conducted using titrated skin-prick tests (0.01-0.001 µg/ml to 1 µg/ml), but are not indicated when patients have large localised reactions. However, skin-prick tests may be negative in 30% of patients who are positive according to history.

Skin-prick tests should only be done by allergy specialists, when RAST tests have not provided useful diagnostic information. In some countries in Europe a direct sting challenge is performed in an ICU setting, but this facility is not available in South Africa.

Table I. Grades of reactions to hymenoptera.³

Grade I	Localised reaction
Grade II	Angioedema and/or diffuse urticaria
Grade III	Bronchospasm and/or involvement of the throat
Grade IV	Anaphylaxis, hypotension, multi-organ involvement, shock

MANAGEMENT OF THE BEE-SENSITIVE PATIENT

A detailed clinical history

This should include the following:

- circumstances surrounding the sting
- location of the sting

- type of stinging insect observed
- presence of a 'stinger'
- previous reactions to 'stings'
- history of asthma
- history of anxiety or hyperventilation disorders
- history of current medications
- concomitant diseases (hypertension, thyroid or autoimmune disease).

First aid

Let the patient lie down. Do not squeeze the venom sac but remove it carefully using a fingernail, knife or credit card. Apply ice to the lesion to soothe the pain and to delay absorption of any toxin. Give the patient an oral antihistamine. A large localised reaction can be treated by a short course of prednisone 1 mg/kg/day for 3 days.

Intramuscular adrenaline

In patients known to be hypersensitive to bees who are developing a systemic reaction (Grade III or IV), adrenaline should be given early rather than late: 0.3-0.5 ml 1:1000 IMI stat and repeated after 8-10 minutes if the patient is not responding to the first dose. The dose must be given truly intramuscularly in such patients. Severely sensitive patients should be taught to self-administer adrenaline and should carry an Epipen (Merck) on standby. For children the dose of adrenaline is 0.01 ml/kg IMI (maximum 0.3 ml).

Further resuscitation

If the patient has a severe reaction full treatment for anaphylaxis must be instituted immediately. Intravenous adrenaline should be administered slowly via an IV line (using a crystalloid solution), adrenaline 1:10 000 (0.25-0.5 ml in adults and 0.01 ml/kg in children) at 5-15-minute intervals.

Subcutaneous adrenaline is not suitable for the treatment of anaphylaxis. In addition to adrenaline and IV fluids (crystalloids) it may be useful to place a BP cuff above the site of the sting and necessary to include other sympathomimetic drugs (dopamine 5-20 µg/kg/min, levophed 3-10 µg/min, glucagon 1 mg IVI and IVI cimetidine).

IMMUNOTHERAPY FOR BEE-VENOM HYPERSENSITIVITY

Patients who are hypersensitive and have Grade III or IV reactions should be offered bee-venom specific immunotherapy if they have no contraindications. Immunotherapy is highly effective in over 80% of cases and accompanied by significant immunological changes. Specific IgG₄ and interleukin (IL)-10 rise early, followed by the induction of CD25+ T-regulatory suppressions and reduction in end-organ sensitivity. Although specific IgE levels eventually do fall, this may take years and skin-prick tests may remain positive when patients are fully protected.

Contraindications to commencing immunotherapy include coronary artery disease, old age (over 70 years), pregnancy, moderate to severe hypertension, patients on beta-blockers, hyperthyroidism, auto-immune disease and severe uncontrolled asthma.

If patients have been taking beta-blockers, care should be exercised when prescribing alternative antihypertensives; ensure that they are stabilised on their new treatment.

Precautions

Immunotherapy must be conducted by trained personnel in a facility where full resuscitation equipment is at hand. Patients must be carefully selected and the risks and procedures explained in detail. Written consent should be obtained with a commitment to at least 3 years of treatment.

Premedication with antihistamines is helpful in preventing unpleasant localised itching but will not prevent anaphylaxis.

For patients with exquisite sensitivity a slower up dosing protocol is recommended.

Great care should be taken to give the correct dose to the correct patient with the correct antigen at each visit. The injection should be given truly subcutaneously and a good site is on the upper outer fatty part of the upper arm (and not over the deltoid muscle which lies rather superficially). Injections in the forearm are not recommended. Use a tuberculin syringe, avoid blood vessels and do not rub the injection site.

Prior to injection, a safety questionnaire should be com-

pleted to obtain details of the patient's current medical status (asthma, medications, pregnancy and their early or delayed reactions to previous injections).

After the injection the physician should observe the patient carefully, watch out for early signs of a reaction (e.g. clearing of the throat, scratching of palms or soles, or the development of urticaria). Pulse, BP, skin colour and PEFR should be monitored after 30 minutes or if any untouched reaction seems to be occurring.

The patient must also be made aware of the early signs of a systemic adverse reaction especially tingling of the soles of the foot or palms and itching of the throat and generalised skin. Systemic adverse reactions can be expected in 2% of patients during the up dosing phase and in 0.5% of patients during the maintenance phase of treatment.

In a survey of 840 patients who received venom immunotherapy in Europe 205 had side-effects and 33% of these required medical treatment.³

However in a study of 657 patients by Møllerup *et al.*,⁴ only 28% of 117 venom-sensitive patients had side-effects compared with 53% of 272 grass-sensitive and 57% of 54 mite-sensitive patients.

After completing a course of immunotherapy there is only a 5-10% risk of a systemic reaction and a 2% risk of a reaction requiring epinephrine.⁵

Dosing and up dosing

Immunotherapy vaccines should be given according to the manufacturer's instructions. Some protocols provide for a fairly rapid up dosing schedule to achieve maintenance doses in about 8 weeks, whereas others provide slow up dosing protocols taking up to 16 weeks to reach maintenance therapy. Once on maintenance, patients can be given injections at monthly intervals and then every 8 weeks for 3-5 years.

It is important to keep strict records of all injections given and any reactions to the injections. This includes patient ID, date, vial strength and vaccine used.

Prior to injection PEFR, pulse and blood pressure should be measured and this should be repeated after a compulsory 30-minute waiting period. If patients have had systemic reactions to any previous dose a 1-hour waiting period post injection is recommended.

Table II. Safety questionnaire

1. Bronchospasm, infection, fever	Postpone
2. Previous immediate local reaction	<5 cm diameter continue 5-10 cm repeat dose >10 cm reduce to last tolerated dose
3. Previous delayed local reaction	< 10 cm repeat same dose
4. Any signs of general reaction, immediate or delayed	Reduce injection to last tolerated dose
5. Lapse in injections	Initial <3 w continue 3-4 repeat last dose >4 w start again Maintenance <6 w repeat last dose <6-12 w 10% of last dose >3 mo. reinitiate it

The target dose is usually 100 µg hymenoptera venom for maintenance treatment but recently it has been recommended that patients should receive the highest tolerated dose, up to 250 µg /dose for treatment failures.⁶ Doses can be adjusted according to Table II.

Discontinuing treatment

Patients with historically mild systemic reactions have a lower risk of reaction before and after venom immunotherapy.

Even when skin-prick test remains positive, venom immunotherapy may be stopped after 5 years. However protection is better when a 5-year course of immunotherapy is compared with a 3-year period.

In children insect allergy has a more benign and transient course than in adults.

Venom immunotherapy in children provides prolonged protection even 20 years after stopping treatment.

QUALITY OF LIFE AND EDUCATION

Patients who are highly sensitive to honeybees have significantly impaired quality of life and may develop severe anxiety disorders. The effects on other members of the family may also be significant.

It is essential to spend time with the patient to discuss

avoidance measures in detail – avoid exposure, avoid brightly coloured clothes, scented perfumes and high-risk areas (e.g. rubbish bins are often filled with sticky cooldrink cans).

Teach patients how to remove a stinger and how to self-inject with adrenaline if necessary. Encourage them to wear a *MedicAlert* disc and reassure them about the safety of receiving their injections in a well-equipped facility where careful monitoring and early treatment will prevent a serious reaction.

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