Allergy to bee and wasp stings in children: state of the art

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Abstract

Hymenoptera stings are the second most common cause of anaphylaxis in children after food allergies. Identifying the culprit insect is often challenging. Venom-induced anaphylaxis occurs rapidly, within minutes of stinging, and involves multiple organ systems. Diagnosis is based on clinical history and confirmation of IgE-mediated sensitization by skin tests and determination of serum whole venom specific IgE levels. Component resolved diagnosis can provide clarity in cases of double sensitization.

The cornerstone of acute management of venom-induced anaphylaxis is intramuscular injection of adrenaline. Further management of severe hymenoptera allergy includes preventive measures to avoid accidental contact and immunotherapy. Venom-specific immunotherapy is safe and highly effective in reducing future systemic sting reactions.

Epidemiology

Wasps, bees and, to a lesser extent, hornets make up the majority of Hymenoptera responsible for allergic sting reactions in the European region (1). Hymenoptera stings are the most common cause of anaphylaxis in adults, and the second most frequent cause of anaphylaxis in children after food allergy. European epidemiologic studies report a prevalence of systemic reactions after insect stings ranging from 0.3 to 7.5%. In children, the prevalence is lower, ranging from 0.15 to 0.8% (2-3).

Identification of the culprit insect can be challenging for several reasons. Patients often fail to notice the stinging insect due to panic after the sting, and studies have shown that distinguishing between the different species can be challenging, even for professionals (4). Insects can be distinguished by their appearance and characteristics. Wasps are usually thinner with a small waist and their bodies are marked with bright yellow and black stripes, while bees tend to be rounder in shape with a thick central body, with a softer orange/brown color (Figure 1). Contrary to what we would expect, honeybees are more aggressive towards humans than wasps, especially when they feel their nest is threatened. However, wasps sting more often because they tend to hover around humans, in particular they are attracted to sugared food and drinks. Hornets are large wasps that rarely sting. The honeybee's sting apparatus is more likely to remain lodged in the skin compared to a wasp's stinger. However, whether or not the stinger remains in the skin, can be indicative of the culprit insect but is not a definitive identification factor (5).

Sting reactions: clinical features, risk factors and impact on quality of life

Fortunately, most people develop only minor local reactions after a sting. Uncomplicated local reactions consist of redness and painful swelling at the site of the sting. Most resolve within a few hours to days. In about 10% of cases, a large local reaction (LLR) can occur. This is a gradually enlarging redness and swelling that can be very extensive (up to an entire limb) and last for several days (5).

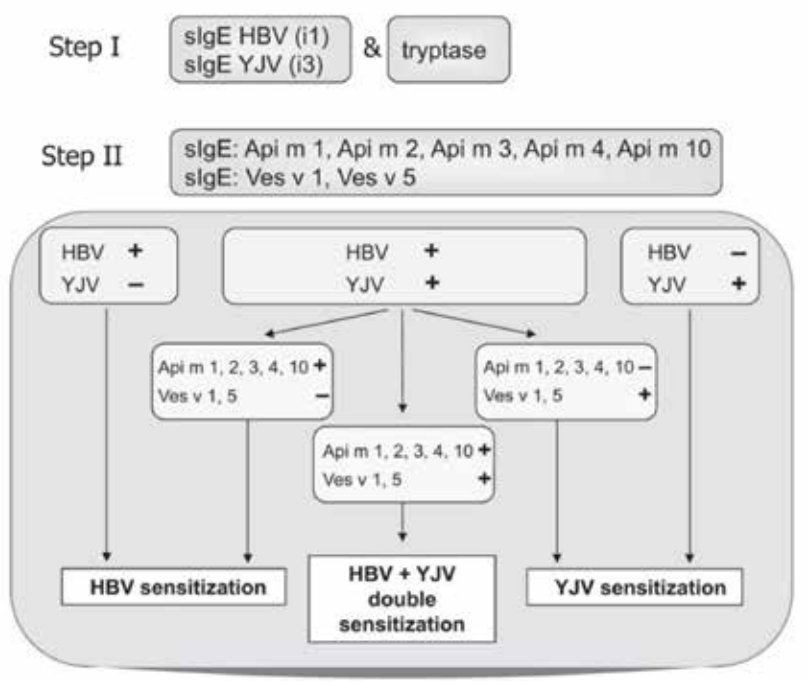
In rare cases, a systemic reaction may occur after a sting. This can range from mild cutaneous reactions (itching, urticaria, angioedema) to more severe reactions. The most dangerous systemic reaction is anaphylaxis. Venom-induced anaphylaxis occurs rapidly, usually within minutes after a sting and involves signs and symptoms in different organ systems distant from the sting site: skin (urticaria, angioedema), respiratory (dyspnea, cough, stridor), gastrointestinal (vomiting, diarrhea, nausea), cardiovascular (hypotension, tachycardia, cardiac arrest), or nervous system (dizziness, syncope, tingling sensation, sense of impending doom). Occurrence of sting-induced anaphylaxis is more common in adults and with bee stings. Adequate acute treatment results in recovery, although there is a small chance for a biphasic course, with recurrence of symptoms hours later. Fatal reactions are very rare (6-7).

Risk factors contributing to more severe reactions include: severe systemic reaction after a previous sting, older age, certain concomitant medications (beta blockers and angiotensin converting enzyme inhibitors (ACEI)), underlying cardiovascular or mast cell disease (mastocytosis and hereditary alphatryptasemia), and elevated baseline serum tryptase concentration. Beekeepers are at increased risk for more severe reactions due to repetitive exposure.

Rarely, unusual reactions occur after a sting, such as local reactions following an unusual sting location (e.g. uveitis following an eyeball sting), or reactions with atypical presentations, including toxic reactions occurring after multiple stings (e.g. rhabdomyolysis, acute kidney injury, autoimmune thrombocytopenia) (8).

Figure 1: external characteristics of bee (left) and wasp.

Figure 2: Two-step diagnostic algorithm for discriminating between wasp (Yellow Jacket YJV) and honeybee (HBV) venom. Step I: baseline sIgE measurement. Step II: component-resolved diagnostics in case of double sensitization. Reproduced from Jakob T. et al (16)



Experiencing a moderate to severe allergic sting reaction is a frightening event for both children and their parents, and can lead to significant emotional distress and anxiety during daily outdoor activities. In addition, the need to carry an adrenaline autoinjector at all times has been shown to have a negative impact on quality of life (9).

Diagnosis of insect sting allergy

Diagnosis is made based on 1/ a clinical history suggestive of anaphylaxis and 2/ confirmation of IgE-mediated sensitization. Making a correct diagnosis can be challenging for several reasons. For instance, there is a high rate of asymptomatic sensitization in the general population, with elevated levels of venom-specific IgE not associated with an increased risk of systemic reactions after stinging in 27 to 40% of individuals (10). Furthermore, identification of the culprit insect is often unreliable, and diagnostic tests are difficult to interpret or do not correlate with the clinical presentation. In addition, loss of sensitization over time can result in false negative test results.

To accurately diagnose bee or wasp allergy, the workup should begin with a thorough history including identification of offending insect and the timing and type of reaction. Only if the history is suggestive for a systemic reaction following a sting, should further diagnostic workup be performed.

The standard workup consists of skin tests and determination of serum whole venom specific IgE (sIgE) levels. A refractory period of 2-6 weeks after the sting should be taken into account, as lower sIgE levels can induce false negative results. If a test performed during this refractory period is negative, retesting at a later date is recommended (11).

Skin tests are performed with standardized whole venom preparations. Current guidelines recommend performing skin prick tests (SPTs) as a first-line diagnostic test, but sensitivity is very low compared to intradermal skin testing (IDT). Addition of IDT increases sensitivity from 49 to 94% - leading recent literature to question the utility of SPTs as a diagnostic test (12). Skin testing is generally safe. As there is a minor risk of (mild) systemic reaction following IDT, stepwise testing is recommended in patients with a history of severe anaphylaxis, although this approach is under debate (13).

The detection of whole venom sIgE antibodies in serum has a high sensitivity (98%) for bee venom allergy, but the reported sensitivity for wasp venom is lower (83-89%) (14). There is an international consensus on a cut-off level of 0.35 kU/L, but in some cases a level of 0.1 kU/L may be clinically relevant (15).

The downside of testing for sIgE to whole venom preparations is the high proportion of double sensitization to bee and wasp venoms. Since there is a high degree of asymptomatic sensitization in the general population, this double sensitization may reflect a genuine double sensitization to both venoms or may be due to cross-reactivity based on shared allergenic proteins or carbohydrate determinants. Component resolved diagnosis (CRD), the use of sIgE to single recombinant allergens, can provide clarity in these cases. Currently, commercially available allergen components are: rVes v1 and rVes v5 for wasp venom and rApi m1 - m5, and rApi m10 for honey bee venom (Figure 2). The use of CRD significantly increases sensitivity up to 95% for bee allergy and up to 98% for wasp allergy (16-17).

There is no correlation between diagnostic test results and the severity of the sting reaction. However, CRD could help predict the effectiveness of venom immunotherapy treatment. Sensitization to several recombinant bee allergens (Api m3, Api m5, and Api m10) has been shown to be a risk factor for the failure of venom immunotherapy due to insufficient allergen content in therapeutic extracts (18).

In patients with a suggestive history but negative test results, additional workup may be considered. With a basophil activation test (BAT), basophil activation is measured by flow cytometry after stimulation of whole blood with venom allergen. BAT can confirm the diagnosis in 60-80% of patients with negative test results (19). However, this test can only be performed in specialized laboratories, limiting its usefulness in routine practice.

Basal serum tryptase (BST) levels should be determined in patients with anaphylaxis after stinging. Elevated BST is associated with an increased risk of severe reactions to Hymenoptera stings and may also be indicative of a diagnosis of mast cell disease.

Finally, intentional sting challenge is used as a diagnostic test in some countries. However, this practice is controversial because it carries a significant risk of severe systemic reactions.

Management

1. Prevention

The first step in the management of severe hymenoptera allergy, as with most allergies, is prevention. Measures to avoid accidental contact with bees or wasps include:

- Maintaining a high level of vigilance during outdoor activities with a risk of exposure, such as picnic areas.
- Not waving your arms or trying to strike the insect.
- Avoid walking barefoot outside.
- Always cover food and do not leave leftover food out.

- Be careful with beverages in cans or bottles, as wasps can easily get into them; preferably use open cups/glasses with an unobstructed view of the liquid inside.

- Remove wasp nests in the near vicinity.

A common advice is to avoid wearing brightly colored clothing or strong perfumes when residing outdoors – however there is currently no evidence that these attract bees or wasps.

2. Acute treatment

After a sting, the barbed stinging apparatus is ripped from the body of the stinging insect (usually bees, but occasionally wasps), along with the venom sac. The venom is released within the first several seconds after the sting. Prompt removal of the offending insect and/or the stinger may thus help limit the amount of venom injected. In case of presentation minutes after the sting, removal of the stinger is still indicated, albeit not urgent, to prevent a local inflammatory reaction.

Management of LLR is based on symptom relief and includes topical application of cold compresses, treatment with antihistamines and topical corticosteroids to relieve pruritus, oral corticosteroids to reduce delayed swelling, and nonsteroidal anti-inflammatory drugs to relieve pain. Treatment with oral antibiotics is only rarely needed, in case of bacterial superinfection.

The cornerstone in acute management of venom-induced anaphylaxis is the administration of adrenaline by intramuscular injection (0.01 ml/kg of a 1:1000 solution; in case of an autoinjector: 0.15 mg for children from 7.5 to 25 kg, and 0.3 mg for >25 kg). All patients with a history of anaphylaxis should have at least one adrenaline autoinjector readily available. Studies have shown that patients often fail to use the autoinjector correctly. Thorough patient education on when and how to use the autoinjector, including written instructions, is therefore strongly recommended (20,21).

3. Prevention of future systemic reactions: venom immunotherapy (VIT)

The only treatment that can prevent systemic reactions in future stings is venom immunotherapy. The decision to proceed with immunotherapy, depends on the type of reaction and the risk of recurrence in case of future stings. The risk of developing a systemic allergic reaction after a LLR, is low (0.8-7%). Patients with a cutaneous systemic reaction have a 10% risk of developing a similar reaction after a future sting; however, the risk of anaphylaxis is low (<3%). In contrast, patients with anaphylaxis have a high risk of anaphylaxis recurrence with a future sting (30% in children; up to 60% in adults).

Therefore, VIT is indicated in children with a history of moderate to severe systemic reaction after a sting and documented IgE-mediated sensitization to the culprit insect by either sIgE, skin tests or BAT. Initiation and follow-up of VIT treatment should be managed by an allergologist with pediatric expertise. Special caution should be applied in individuals with underlying risk conditions, such as cardiovascular disease, use of ACE inhibitors or beta-blockers, and malignant or autoimmune diseases (VIT should not be initiated until the underlying disease is stabilized). Absolute contraindications for VIT include: asymptomatic sensitization to insect venom, sting reactions without documented sensitization, unstable malignant or autoimmune disease, and unusual (non-IgE-mediated) sting reactions.

VIT acts by inducing immunological tolerance to the culprit antigen and is the only type of allergen-specific immunotherapy for children currently reimbursed in Belgium. It is a highly effective therapy (77-84% in honeybee and 91-96% in wasp venom) and contributes to a significant improvement in quality of life (22). VIT is administered by subcutaneous injections, starting with an up-dosing phase of weekly injections in slowly increasing doses. After several weeks to months, the maintenance dose of 100 mcg of venom (equivalent to approximately 5 wasp or 2 bee stings) is reached. Faster up-dosing (rush) protocols have been shown to be safe and more efficient than conventional VIT (23-24). After the up-dosing phase, treatment continues with the maintenance phase, which involves injections every 4 weeks. With ongoing treatment, the interval between injections may be extended to 6 weeks in the second year of treatment, and to 8 weeks from year 3 on (25). The total duration of treatment is 3 to 5 years; studies show superior long-term efficacy with five years of treatment (26). Most patients maintain an adequate level of protection after discontinuation of VIT; however, a loss of efficacy over time can lead to recurrence of (mostly mild) systemic reactions. Therefore, prolonged – sometimes lifelong – therapy should be considered in several cases, such as in patients with initial life-threatening anaphylaxis, with occurrence of severe systemic reaction during VIT, in patients at high risk of re-stinging (e.g. beekeepers), and in patients with mast cell disorders (27). In these cases, extending the maintenance interval to 12 weeks may be considered, which does not appear to reduce effectiveness and is generally well tolerated.

VIT is generally safe and well tolerated. The most prevalent adverse events are local reactions (approximately 12%); there is a small risk of systemic reactions (up to 3% for wasp, and 7-14% for bee VIT). Premedication with a second-generation antihistamine 1-2 hours prior to injection can be considered, and may even positively affect treatment efficacy. However it should be noted that antihistamine treatment may mask the first symptoms of a severe reaction (28). VIT-induced anaphylactic reactions are predominantly mild to moderate reactions, and respond well to antiallergic treatment, often without the need for adrenaline administration.

Future prospects

When diagnosing and treating bee and wasp allergy, there are several issues that still raise questions.

First, in terms of diagnosis, it is not always possible to distinguish between asymptomatic and symptomatic sensitization to venom, or between cross-reactivity and true double sensitization. Further development of existing (e.g. introduction of new recombinant allergens) or new techniques is needed to address these diagnostic difficulties.

With regard to treatment with VIT, there are currently no means of assessing the efficacy of immunotherapy. Biomarkers that have been studied are skin prick tests, IgE, IgG4; however, decreasing levels during VIT show no correlation with clinical efficacy (29). BAT may be helpful in monitoring efficacy, but more research is needed (30). The only reliable test to date to estimate the efficacy of VIT is the sting challenge test, which also improves quality of life by eliminating uncertainty about possible reactions to future stings (31).

In patients who experience a systemic reaction during immunotherapy, premedication with omalizumab could be an option. More studies are needed to determine the optimal duration and dosing regimen of omalizumab (32).

Conclusion

A severe allergy to bees or wasps is a potentially life-threatening condition with a significant impact on quality of life. The diagnosis is confirmed by demonstration of IgE-mediated sensitization using skin tests or determination of specific IgE and component resolved diagnostics. Treatment with venom-specific immunotherapy is safe and highly effective in reducing future reactions

Conflict of interest

The author has no conflict of interest to declare with regard to the topic discussed in this manuscript.

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