



Natural history and long-term follow-up of Hymenoptera allergy

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Purpose of review

Information on the natural history of hypersensitivity reactions is helpful for deciding which patient urgently needs a venom immunotherapy (VIT).

Recent findings

The frequency of self-reported systemic allergic reactions (SAR) to Hymenoptera stings is approximately 3–7% in the Northern Hemisphere. About 25% of SAR are severe (anaphylactic shock). Fatal sting reactions are very rare. The most important risk factor for severe insect sting anaphylaxis is mast cell disease. Other risk factors are higher age, vespid venom allergy (in contrast to honeybee venom allergy), repeated stings, male sex, and treatment with ACE inhibitors. Preceding large local reactions seem not to play a risk factor for subsequent SAR.

Summary

The majority of risk factors for severe anaphylaxis are not modifiable. For patients presenting with well defined risk factors for a very severe or even fatal anaphylaxis, VIT is of utmost importance, and they should be performed for the rest of their life. Sting challenge tests are required to identify patients in whom treatment was ineffective. Those patients, who did not receive VIT although presenting with a firm indication, or in whom VIT was stopped, require yearly monitoring to teach preventive measures and to renew the emergency kit.

Keywords

allergy, hymenoptera venom, immunotherapy, large local reaction, systemic allergic reaction

INTRODUCTION

The frequency of systemic allergic reactions (SAR) to Hymenoptera stings is not exactly known. Epidemiological data from population-based studies suggest that about 3% of the U.S. population [1] and about 7% of adult Europeans [2] may be prone to SARs after a Hymenoptera sting. SAR occur less frequently in children.

Among patients needing an anaphylaxis treatment in an emergency care unit, 24%–30% of adults [3,4] and 4%–11% of children suffer from a Hymenoptera venom-induced anaphylaxis [3,5]. Among patients seen by an allergist for anaphylaxis work-up, Hymenoptera venom allergy accounts for the majority of anaphylactic reactions in adults, and is second as elicitor of anaphylaxis in children (European Anaphylaxis Registry) [6].

It is still uncertain whether all patients with a history of a systemic allergic Hymenoptera sting reaction and sensitization to the culprit venom, in fact need a venom immunotherapy (VIT). Indication for an urgent VIT, or for preventive measures only

(including an emergency kit for self-administration) should be based on an individual risk assessment.

This risk assessment requires information on the probability of future stings and of specific risk factors associated with a life-threatening sting reaction. Fatal anaphylactic sting reactions are probably very rare (0.05 to 0.1 cases per one million inhabitants per year) [7,8], but this frequency may be falsely low because of an under-diagnosis of anaphylaxis.

The current review wants to discuss risk factors increasing the chance of a very severe sting

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Curr Opin Allergy Clin Immunol 2020, 20:445–451

DOI:10.1097/ACI.0000000000000671

KEY POINTS

- In patients who present for work-up of anaphylaxis Hymenoptera venom allergy accounts for the majority of anaphylactic reactions in adults, and is second as elicitor of anaphylaxis in children.
- For the decision to whom VIT should urgently be recommended or for whom prevention measures and an emergency kit for self-administration might be sufficient, an individual risk calculation should be done.
- The most important risk factor for severe insect sting anaphylaxis (anaphylactic shock or fatal / near fatal reactions) is mast cell disease (mastocytosis or monoclonal mast cell activation syndrome).
- Other risk factors for severe systemic sting reactions are higher age, repeated stings, vespid venom allergy (in contrast to honeybee venom allergy), male sex, and treatment with ACE inhibitors.
- All patients with prior systemic allergic sting reactions should receive an emergency medication kit for self-treatment, and should take part in a structured training on how to use this kit, and other precaution measures.

anaphylaxis, and to provide information on how to manage patients before, during or after VIT.

NATURAL HISTORY OF LARGE LOCAL REACTIONS

Stinging Hymenoptera inject venom into the skin thereby provoking, at least to a certain degree, physiological local reactions. Large local reactions (LLR) are defined as commonly painful reddish swellings to be seen mostly after stings at the extremities. In about 80% of LLR, the diameter of the swelling varies between 10 and 20 cm, in about 20%, it exceeds more than 20 cm. The diameter of the swelling depends on the time passed by after the sting increasing rapidly within the first hours or more; usually, a further progress is evident for 1 to 2 days. On average, subsidence of LLR requires about 7 days (1–21 days) [9[¶]]. Routine work-up (testing for a sensitization) is not recommended, because about 85% of the patients with LLR demonstrate specific IgE [9[¶]]. Because LLR commonly represents a late-phase IgE-mediated reaction, positive test results (in-vitro and/or skin tests) do not justify VIT.

Still, in individual patients such severe LLR may cause an enormous distress. Because many patients will again develop a LLR upon the next sting [10], they may benefit from specific therapeutic measures. Patients should apply cold compresses at the site of the reaction, take oral antihistamines

to reduce itching, and – in case of severe large local reactions – start taking oral corticosteroids for a few days as soon as possible after the sting to prevent the late-phase inflammatory response.

Although a LLR is not dangerous per se (unless the sting occurs in the upper airways), many patients and their physicians are concerned by the question whether this event may indicate a risk for a subsequent, SAR. Observational evidence suggests that after a LLR 4%–10% of the patients are at risk to develop a SAR after a subsequent sting [10]. This frequency is probably too high: first, retrospective studies on the subject are flawed by specific limitations, among which the most important one is the so-called ‘re-call bias’. When asked for preceding events, a patient emotionally presenting with a new SAR will be prone to overemphasize the magnitude of a previous sting reaction describing it as larger as in reality. Second, the majority of patients with a history of a LLR also show an IgE-mediated sensitization. Even without a preceding LLR, 5% of sensitized but asymptomatic patients will develop a SAR to insect stings when undergoing a diagnostic sting challenge [11]. A recent small prospective study found that, after a second sting, none of 31 patients who had a history of a LLR actually developed a SAR [12]. A definitive answer to this question will only come from well designed prospective studies observing a far greater number of patients.

RISK FACTORS FOR AN ADVERSE OUTCOME AFTER A SYSTEMIC ALLERGIC REACTION

The overall risk of patients to develop a repeated systemic sting reaction after a preceding anaphylactic event depends on the insect species. The risk varies between 36% and 51% in patients suffering from honeybee venom allergy, and between 9% and 30% in those with *Vespula* venom allergy [13]. This variation may be the result of a spontaneous remission of the allergic disease, or of the presence/absence of a specific trigger, such as for example, concomitant diseases or medication. If a patient with a history of a SAR did not develop a repeated SAR to a new sting by the culprit insect, this will not indicate that there is now a permanent cure from insect venom allergy.

The severity grade of SARs ranges from mild systemic sting reactions to anaphylactic shock with near-fatal and even fatal outcome. Approximately one quarter (18%–42%) of venom-induced reactions are severe [14]. Several factors may modify the outcome of a subsequent insect sting reaction.

A recent study analyzed the relative importance of specific variables to predict the risk of a severe

anaphylaxis [15²²]. The study examined more than 8000 patients collected over a period of 10 years in the European Anaphylaxis Registry. For the combined group of elicitors (insect venom, food, and drugs), high age, mastocytosis, and male sex were the most important risk factors for SAR [15²²]. Additional risk factors were specific drugs such as ACE inhibitors and β -blockers.

It is, however, very likely that the importance of a specific risk factor for a severe anaphylaxis varies by the type of elicitor, that is insect venom, drugs, or food. Some risk factors may only become effective, when the allergen is absorbed from the gastrointestinal tract, but may be unimportant after an insect sting. For example, physical exercise may be only a risk factor in food allergy. Strenuous exercise causes mucosal microlesions, which facilitate the absorption of allergens thereby increasing the severity of SAR. It is highly unlikely that such a mechanism is involved in SAR observed after a parenteral allergen exposure (e.g. insect venom). Therefore, when analyzing the relative importance of risk factors for SAR, it is important to differentiate between various types of elicitors (food, insect venom, drugs).

So far, several variables have been identified which are associated with an increased risk for a severe SAR after an insect sting: a preceding systemic sting reaction, ACE inhibitor therapy, older age, male sex, basal serum tryptase concentration more than 11.4 $\mu\text{g/l}$ and vespid venom (in contrast to honeybee venom) [16].

- (1) Repeated stings: in certain professions, intense repeated exposure will increase likelihood and severity of insect sting anaphylaxis [17]. Such a boosting action is well established and typical for insect venom (particularly seen in adults): a mild sting reaction or even an asymptomatic sting in the past significantly increases the likelihood for a more severe SAR after a subsequent sting [16]. Therefore, there is no guarantee that a sting reaction, which has been only mild after a preceding sting, will be of the same intensity after a subsequent sting.
- (2) Several observational studies have impressively documented the particular importance of mastocytosis and other mast cell diseases for eliciting severe symptoms in patients with insect venom allergy [18,19]. According to careful analyses of data from the European Anaphylaxis Registry, there is now strong evidence that mast cell disease is an independent risk factor [6,20²³]. The association between mast cell diseases and insect venom allergy probably results from the specific physiologic role of mast cells. Mast cells are part of the innate immune system, and are

important for detoxifying specific venoms, for example those produced by snakes [21]. Hymenoptera venoms are potent releasers of mast cell compounds via IgE-mediated and non-IgE-mediated mechanisms [22,23]. A controlled mast cell activation and degranulation is of central importance for mediating the anti-venom effect, and these mast cell functions must be regarded by nature as protective. In patients with mastocytosis, however, this protection turns into a detrimental risk for very a severe or even fatal sting anaphylaxis.

- (3) Patient at higher age are at risk for a more severe sting anaphylaxis [16] or even fatal sting reaction [24]. In contrast, children and adolescents have a more favorable outcome of insect venom allergy. Many children under the age of 16 outgrow their allergic reactivity to insect stings, or at least do not develop more severe sting reactions after repeated stings [25,26]. In individual children, however, severe systemic reactions may still occur [26]. Children will become adults and some of them remain venom-allergic in adulthood. At a follow-up examination, about 18 years (mean) after a systemic sting reaction during childhood, 17% of adults again developed a SAR after an insect sting [27]. In those patients who had received VIT during childhood systemic reactions occurred significantly less frequently (3%) during adulthood than in untreated patients (17%, $P=0.007$). Furthermore, the magnitude of a SAR was greater in untreated patients with a history of a moderate-to-severe reaction during childhood than in patients who had had a VIT. Protective effects of VIT during childhood appear to be long-lasting, and may persist for even 10 to 20 years after treatment has been stopped.
- (4) It is still controversial whether ACE inhibitors and β -blockers increase the risk for severe SAR after an insect sting. Currently, the number of reviews, opinion papers and guidelines focusing on this particular issue significantly surmounts that of original publications. That ACE inhibitors may act as risk factors can be explained on theoretical grounds since these compounds inhibit degradation of kinins, which are potent vasodilators presumably potentiating the magnitude of circulatory allergic reactions. Experimental data (mouse model) suggest that the combination of an ACE inhibitor and Beta Blocker medication may be particularly unfavorable enhancing anaphylactic symptoms by the accelerated release of mast cell mediators during an anaphylactic reaction [28]. Observational studies in allergic patients prior to VIT

found a significant independent association between an ACE inhibitor therapy and a worse outcome of an anaphylactic sting reaction [16,20²²]. Studies unable to reproduce these results, were flawed by their monocentric design, ignorance of additional risk factors, and absence of adjustment to confounders [29].

- (5) Type of venom: Throughout the last three decades, numerous observational studies have established a significant difference between the anaphylactic potential of bee and vespid venom, with the latter being markedly more dangerous than the former [15²³,16,30,31]. This difference is also evident during immunotherapy by the respective venom; there, however, the association is inverse. Vespid VIT is safer and more effective than bee VIT [32,33].
- (6) Male sex is a risk factor for more severe [16] and even fatal anaphylactic reactions [24]. It is, however, likely that the association is not because of sex itself, but to secondary behavioral mechanisms having their counterpart in a gender-dependent intensity of exposure. Presumably, for professional reasons (outdoor workers) men are stung more frequently than women, and might therefore be at a higher risk for sensitization, boosting, and, consecutively, allergic reactions which are more severe.

FOLLOW-UP: GENERAL RECOMENDATIONS

The general risk of insect venom allergic patients varies depending on whether they have undergone VIT, whether attempts have been made to proof the efficacy of VIT, and whether VIT has already been stopped. To protect patients adequately, the magnitude of the individual risk should determine the intensity of safety measures.

- (1) For all patients, protective measures should routinely include an education on how to prevent stings. Insect stings, however, cannot reliably be avoided unless patients are willing to accept a significant change in life-style, or sometimes even in their profession. Highly exposed individuals, such as beekeepers, should routinely wear protective clothing, at least during hazardous activities. Patients with a history of insect venom anaphylaxis should not work in an environment, which puts them at an increased risk to be stung, or to suffer a severe injury in case of an anaphylactic reaction causing a loss of consciousness (e.g. a fall from high height) [17].

- (2) Active guidelines recommend to all patients suffering from Hymenoptera venom allergy to carry an emergency medication for self-treatment before, during, and with some exceptions also after VIT [2,34]. There are, however, no controlled studies proofing that just prescribing an emergency kit will be sufficient to prevent a fatal outcome during a very severe anaphylactic reaction. Furthermore, if management is poor, anaphylactic symptoms will even aggravate. Not using epinephrine auto-injectors, or using them too late will significantly increase the percentage of anaphylaxis-related fatalities [35,36]. To check the expiry dates of the various drugs incorporated into the emergency kit, all patients should make periodic appointments (1–1.5 years) with their treating physicians.
- (3) Self-management of anaphylaxis includes the instruction of patients and their relatives on how to correctly position an unconscious patient [37]. There are case reports on fatal anaphylactic reactions describing how an upright position during a severe anaphylactic reaction resulted in sudden death [35,36]. Elevating the upper part of the body in shock states will further aggravate circulatory failure by reducing right cardiac preload via a decreased central venous blood return.

FOLLOW-UP OF PATIENTS DURING VENOM IMMUNOTHERAPY

Patients on VIT should be seen regularly in outpatient clinics for follow-up even if these patients only had a low risk in the beginning to develop severe adverse reactions. During this visit, physicians should look for changes of the individual risk profile, and for signs of overt VIT failure.

Sting challenge tests have the highest diagnostic power to detect treatment failure in patients on VIT, and are highly reliable to predict the reaction to future stings after a stopping of VIT. Field stings may also evoke a SAR, and may serve as indicators of VIT failure. If, however, a patient has tolerated a field sting, this is by no means a reliable sign of future venom tolerance. Accidental field stings may only inject comparably small amounts of venom, since patients are advised to remove the stinger without squeezing it. Tolerance of a very small amount of venom does not allow a reliable prediction of the outcome after the injection of a markedly larger venom dose. Another problem of accidental field stings consists in the poor identification of the stinging Hymenoptera species.

When using a standard regimen (100 µg venom every 4–6 weeks) VIT failure occurs in about 4% of patients allergic to *Vespula* venom, and in about 11% of patients allergic to honeybee venom [33]. The reasons for this varying efficacy remain unclear, and are hypothetical. Thus, composition and amount of molecular allergens may differ between natural venom and treatment extracts.

In general, honeybee stings release a greater amount of venom than *Vespula* stings. On the other hand, some extracts used to treat honeybee venom allergy lack some major allergens such as Api m 10 [38]. It is still unclear to which extent Api m 10-sensitization contributes to honeybee venom allergy. The majority of patients, in whom a standard venom dose did not lead to protection, will achieve full protection after application of an increased dose irrespective from the type of venom extract (own unpublished data).

Sting challenge tests, however, are only performed at some specialized centers, and the majority of allergists have to rely on the patient's history and individual risk profile when deciding on whether to stop or to continue VIT (possibly for the rest of the patient's life). The decision to continue VIT indefinitely is easy in patients presenting with a history of a near fatal reaction and/or of treatment failure, and with important risk factors for future treatment failure. It will be also easy to recommend a stop of VIT if a patient has only had mild reactions in the past, and/or is lacking significant risk factors for treatment failure. There is no need to perform diagnostic tests (venom-specific IgE antibodies, skin test reactivity) in those patients whose individual characteristics markedly facilitate decisions on a continuation of VIT.

According to results of diagnostic in-vitro tests, the degree of sensitization usually increases during the first years of exposure, and will decrease later on. Diagnostic in-vitro tests will rarely yield completely negative results, because test sensitivity has improved significantly throughout the last years. Therefore, test results do not allow a precise prediction of a patient's individual clinical reaction after a sting by the culprit insect. Nevertheless, results of in-vitro tests are an integral part of a larger puzzle used to identify patients at risk for a relapse, or tolerating a stop of VIT.

FOLLOW-UP OF PATIENTS AFTER VENOM IMMUNOTHERAPY

After termination of VIT, and despite its initial effectiveness, 10–15% of patients will again develop an anaphylactic reaction if re-stung by the culprit insect. Only a few studies including small numbers

of patients examined the outcome of field stings or sting challenges after a stop of VIT [13]. A major limitation of these studies was the small number of outcome events (e.g. an allergic sting reaction) preventing a reliable identification of independent risk factors for a relapse of Hymenoptera venom allergy. A recent study found that the majority of patients experiencing such a relapse were suffering from a mast cell disease [39]. Because a mast cell disease is a particular risk factor for a relapse after treatment stop, these patients should remain on VIT for the rest of their lives.

Current evidence suggests that protection by VIT will last for a shorter period, if patients were suffering from honeybee venom allergy [40], if they had experienced side effects during VIT [41,42], or if they had had VIT for less than 4 years [40,43]. Repeated stings may resensitize the patient even after an initially successful VIT [43,44]. Therefore, avoiding subsequent stings after VIT will be beneficial in two ways. First, even if protection is being lost over time, a new allergic reaction will not materialize. Second, even if protection is not being lost, boosting by subsequent stings will not occur.

QUALITY OF LIFE ASPECTS

The majority of fatal or near-fatal outcomes after a Hymenoptera sting is a sequelae of the first anaphylactic sting reaction when patients are not protected yet. The frequency of fatal reactions after a preceding moderate SAR is comparably low. Because of this low frequency, and because therapy will only start after the first SAR, VIT can only prevent a small portion of fatal or near-fatal SAR.

VIT, however, significantly improves the quality of life in patients who have experienced a SAR [45]. Those patients usually are afraid of a subsequent severe SAR even if it may not be life-threatening, and this fear significantly affects the patient's quality of life. Interestingly, the magnitude of this fear does not depend on the severity grade of the preceding SAR [46].

VIT ameliorates the fear of the patient thereby improving his quality of life, and is highly effective in terms of a prevention of future SAR. Such a prevention may also be economically important by reducing the number of patients calling for an emergency treatment either outside the hospital or presenting in emergency units.

CONCLUSION

Children, who have experienced only mild reactions in the absence of the above mentioned additional risk factors, or whose quality of life is not

impaired, usually do not require VIT. In contrast, adults usually will benefit from VIT, even if sting reactions have been only mild. VIT will be also useful, if patients most probably cannot avoid future stings by the culprit insect. The most important risk factors for a severe insect sting anaphylaxis (age, mast cell disease, sex, or type of culprit venom) cannot be modified. It is only possible to discontinue an ACE inhibitor medication. Alternative antihypertensive drugs should replace ACE inhibitors until VIT has most likely become protective, or until a sting challenge has demonstrated the effectivity of VIT.

All patients should receive an emergency medication kit for self-treatment, and should take part in a structured training on how to use this kit, and other precaution measures. A regular follow-up can help to identify those patients whose risk profile has changed over time requiring an adjustment of treatment. Patients with a history of a LLR usually do not require routine follow-up examinations, since such reactions are unlikely to develop to systemic allergic sting reactions. On an individual basis, however, exceptions from this rule are possible.

Acknowledgements

The author thanks W. Hartl, M.D., for the critical revision of the manuscript.

Financial support and sponsorship

None.

Conflicts of interest

F.R. has worked within the last 3 years as adviser for or has received speaker's honorarium from Abbvie, ALK-Abelló, Allergopharma, Bencard, HAL, LEO-Pharma, MEDA Pharma, MYLAN, Novartis, and UCB.

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