



Long-term follow-up of Hymenoptera allergy

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Insects responsible for allergic reactions

- ▶ Order Coleoptera—beetles
- ▶ Order Diptera—flies, mosquitos, midges
- ▶ Order Ephemeroptera—mayflies
- ▶ Order Hemiptera—aphids, bed bugs, and kissing bugs
- ▶ **Order Hymenoptera—ants, bees, and vespids**
- ▶ Order Lepidoptera—moths and caterpillars
- ▶ Order Orthoptera—cockroaches
- ▶ Order Siphonaptera—fleas
- ▶ Order Trichoptera—caddis flies

History

- ▶ Insect allergy has been described since antiquity, with King Meneses of Egypt purportedly dying of wasp anaphylaxis in 2641 BC
- ▶ The culprit was wasp

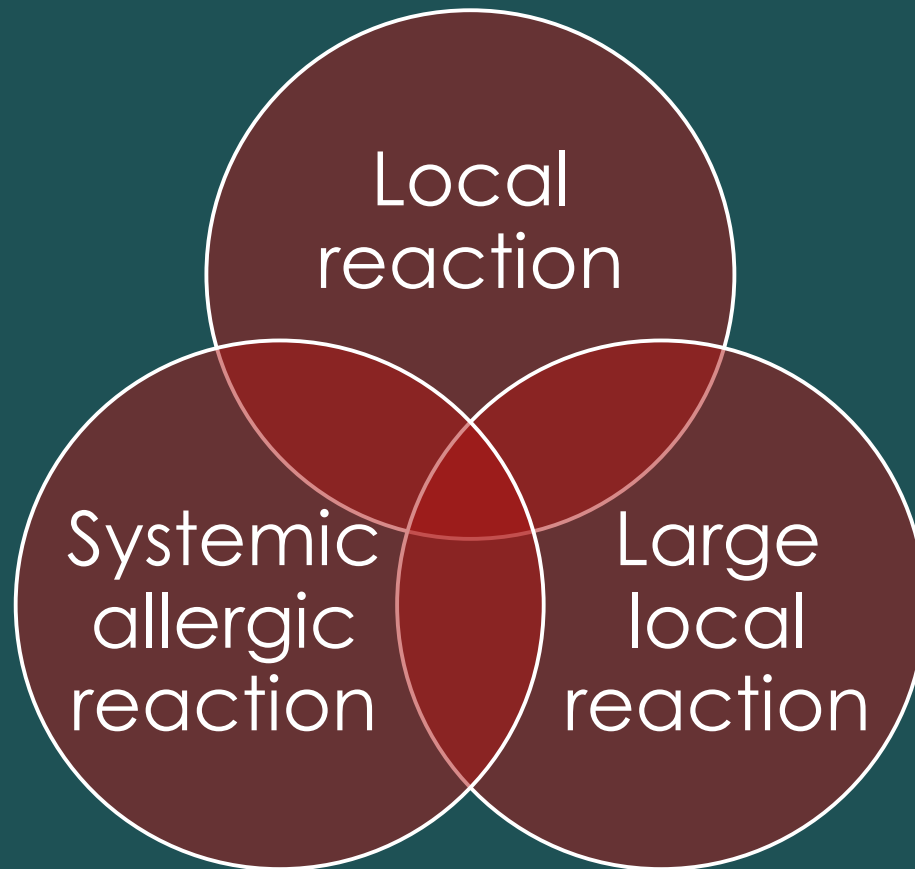
Pharaoh comes from the words that mean “great house”

- Menes is the first ruler of Ancient Egypt to leave a written record.



- The people of ancient Egypt believed their kings were also [gods](#).
- Modern people refer to ancient Egyptian rulers as pharaohs, but pharaoh originally referred to the palace where the king lived.
- Pharaoh was not used as a title for the Egyptian ruler until the later part of ancient Egyptian history, but today we use the term to describe all of the rulers of ancient Egypt.
- They were believed to be descended from the sun god Re and held absolute power

Insect sting or bite



Epidemiology

- ▶ Population-based studies suggest that about 3% of the U.S. population
- ▶ 7% of adult Europeans may be prone to SARs after a Hymenoptera sting.

Among patients needing an anaphylaxis treatment in an emergency care unit, 24%–30% of adults and 4%–11% of children suffer from a Hymenoptera venom-induced anaphylaxis

Epidemiology

- ▶ 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
- ▶ Fatal anaphylactic sting reactions are probably very rare (**0.05 to 0.1 cases per one million** inhabitants per year) , but this frequency may be falsely low because of an under-diagnosis of anaphylaxis

Recent findings

- ▶ The frequency of self-reported 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 incidence of anaphylaxis in Gorgan study is reported to be equal to 1 in every 700 people

Indication for venom immunotherapy

symptoms	Age	Skin test/RAST	VIT
Local or large local reactions	All	+ or -	No
Systemic reactions limited to skin	< 16y/o	+ or -	No
Systemic reactions beyond the skin	> 17y/o	+	Yes
	All	+	Yes
		-	No

Whether all anaphylactic patients need immunotherapy?

- ▶ It should be based on an individual risk assessment.
- ▶ Indication for an urgent VIT, or for preventive measures only (including an emergency kit for self-administration)

RISK FACTORS FOR NEXT ANAPHYLAXIS

- ▶ The risk varies between 36% and 51% in patients suffering from honeybee venom allergy
- ▶ Between 9% and 30% in those with *Vespula* venom allergy
- ▶ 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

A- Spontaneous remission

B- The presence/absence of a specific trigger, such as for example, concomitant diseases or medication.

NATURAL HISTORY OF LARGE LOCAL REACTIONS

- ▶ 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.

NATURAL HISTORY OF LARGE LOCAL REACTIONS

- ▶ On average, subsidence of LLR requires about 7 days (1–21 days).
- ▶ Because LLR commonly represents a late-phase IgE-mediated reaction, positive test results (in-vitro and/or skin tests) do not justify VIT

Whether LLR may a risk for a subsequent anaphylaxis?

- ▶ 4%–10% of the patients are at risk to develop a SAR after a subsequent sting
- ▶ Even without a preceding LLR, 5% of sensitized but asymptomatic patients will develop a SAR to insect stings when undergoing a diagnostic sting challenge

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

Severity of SAR

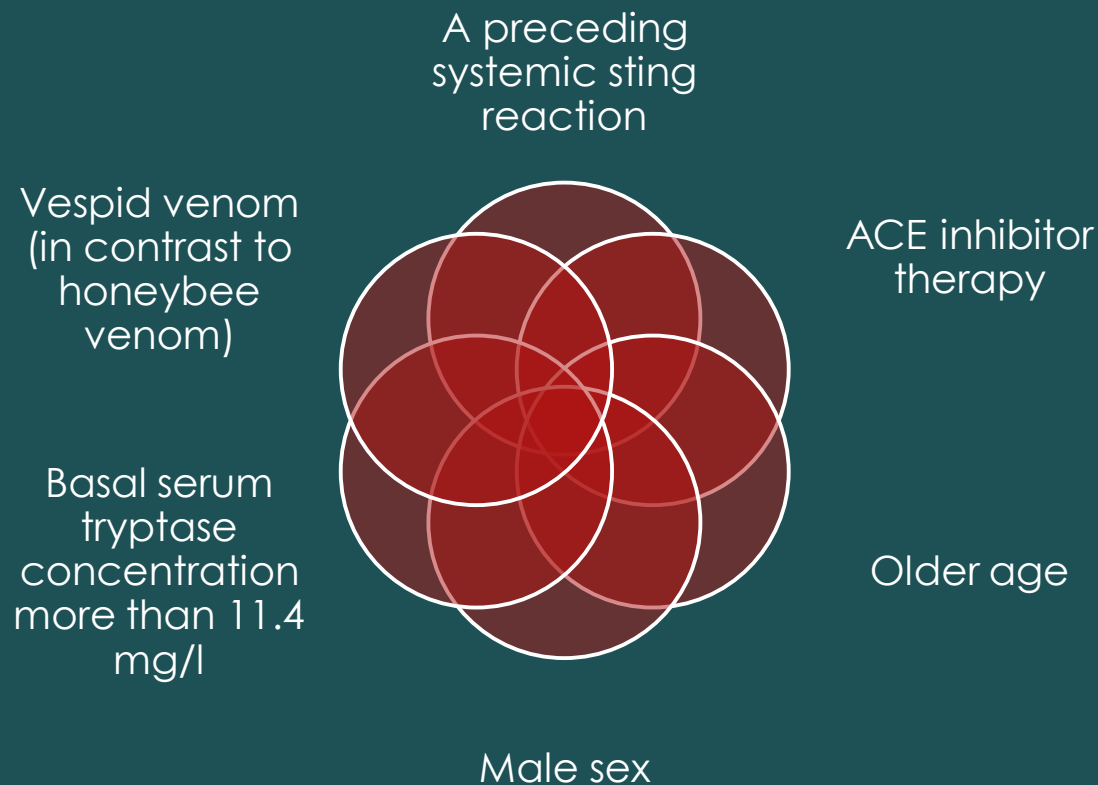
- ▶ The severity grade of SARs ranges from mild systemic sting reactions to anaphylactic shock with near-fatal and even fatal outcome.
- ▶ Approximately one quarter (18%–42%) of venom-induced reactions are severe

Gorgan study:

1- Seven (9.5%) children and sixty seven (39.6%) adults had hypotensive symptoms ($P=0.05$).

2- Ninety five percent of cases have been stung less than 10 times, and 80% of those who have experienced more than 10 stings had severe anaphylactic attacks ($P = 0.003$).

Increased risk for a severe SAR after an insect sting



Boosting action

- ▶ Repeated stings will increase likelihood and severity of insect sting anaphylaxis.
- ▶ 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

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

Mast cell diseases and severe anaphylaxis with insect venom

- ▶ Hymenoptera venoms are potent releasers of mast cell compounds via IgE-mediated and non-IgE mediated mechanisms.
- ▶ A controlled mast cell activation and degranulation is of central importance for mediating the antivenom 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 severe or even fatal sting anaphylaxis

Higher age

- ▶ Patient at higher age are at risk for a more severe sting anaphylaxis even fatal sting reaction .
- ▶ 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

Higher age

- ▶ At a follow-up examination, about 18 years (mean) after anaphylaxis during childhood, 17% of adults again developed anaphylaxis after an insect sting .
- ▶ In those patients who had received VIT during childhood systemic reactions occurred significantly less frequently (3%)
- ▶ 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.

ACE inhibitors and beta blocker

- ▶ 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

Type of venom

- ▶ Vespid venom being markedly more dangerous than the bee.
- ▶ This difference is also evident during immunotherapy by the respective venom
- ▶ The association is inverse. Vespid VIT is safer and more effective than bee VIT

Male gender

- ▶ Male sex is a risk factor for more severe and even fatal anaphylactic reactions.
- ▶ It is a gender-dependent intensity of exposure.
- ▶ 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

Change in life-style

- ▶ 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.

FOLLOW-UP: GENERAL RECOMENDATIONS

Job/workplace

- ▶ 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

Periodic appointments

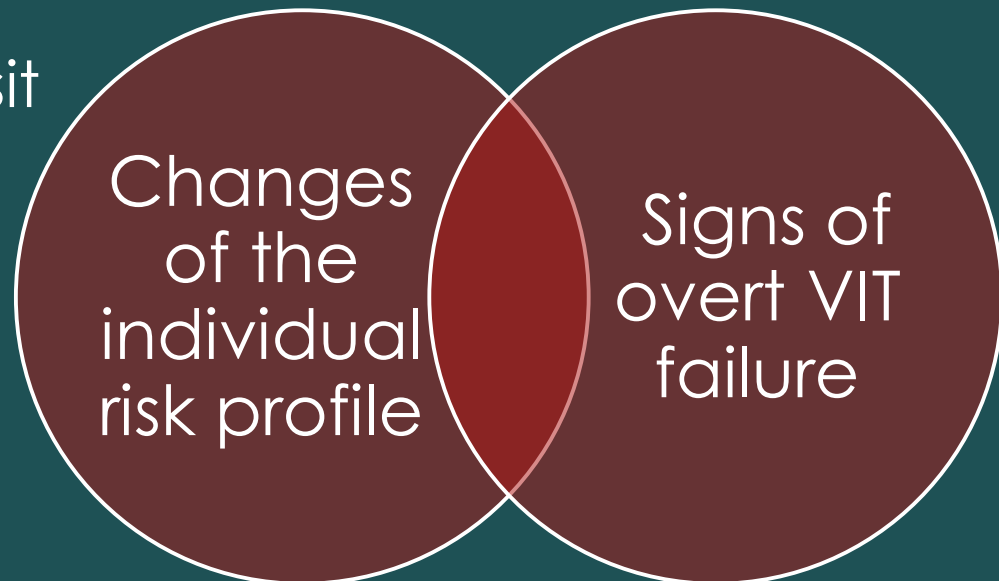
- ▶ Not using epinephrine auto-injectors, or using them too late will significantly increase the percentage of anaphylaxis-related fatalities
- ▶ To check the expiry dates of the various drugs incorporated into the emergency kit, all patients should make periodic appointments (1–1.5 years) with their treating physicians.

Empty ventricle syndrome

- ▶ How to correctly position an unconscious patient.
- ▶ Upright position during a severe anaphylactic reaction resulted in sudden death.
- ▶ 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



Sting challenge

treatment 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.

Accidental Field stings

- ▶ 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.
- ▶ 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.

Poor identification of the stinging Hymenoptera

Small amounts of venom, since patients are advised to remove the stinger

VIT failure

- ▶ When using a standard regimen (100 mg 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.
- ▶ 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

VIT Failure

Api m 10

- ▶ 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
- ▶ 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

When recommend termination of VIT?

- ▶ 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

Relapse after VIT

10–15% of patients will again develop an anaphylactic reaction if re-stung by the culprit insect.

- ▶ Mast cell disease
- ▶ Honeybee venom allergy
- ▶ if they had experienced side effects during VIT
- ▶ If they had had VIT for less than 4 years

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
- ▶ So, VIT can only prevent a small portion of fatal or near-fatal SAR.

QUALITY OF LIFE ASPECTS

- ▶ 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.

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.

Summary

- ▶ 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.

CONCLUSION

- ▶ Children, who have experienced only mild reactions in the absence of the above mentioned additional risk factors, or whose QOL 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.

Conclusion

- ▶ 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.

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End