

Insect Venoms

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Abstract

Insect venoms applied by stings of social Hymenoptera, like honey bees, vespids or ants are – together with foods and drugs – the most frequent elicitors of anaphylaxis in humans. Besides taxonomy, the biology of the responsible social Hymenoptera is important: guidelines based upon its knowledge allow to reduce the risk of further stings in patients with a history of venom anaphylaxis. Epidemiology of venom anaphylaxis has special aspects with regard to prevalence, fatality and natural history. An estimated 200 individuals die every year in Europe from anaphylaxis following Hymenoptera stings. Most of the relevant venom protein allergens have been identified and many of them have been expressed in recombinant form. Proof of venom sensitization is based on skin tests with venoms and serum venom-specific IgE antibodies as standard diagnostic tests. Allergen-specific immunotherapy with Hymenoptera venoms is highly effective and therefore recommended for all patients with a history of Hymenoptera sting anaphylaxis and positive diagnostic tests with the respective venom. Frequent cross-reactions to venoms of different Hymenoptera species may cause difficulties in identifying the responsible species and the selection of the respective venom for immunotherapy.

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Insect venoms, together with foods and drugs, are the most frequent elicitors of anaphylaxis in men. The insect venom is applied by stings which must have occurred for more than 100,000 years, since human beings exist. Conflicts between stinging insects and humans occur while fighting for food, like honey or foods consumed outdoors, or while venomous insects feel threatened by human beings, most often near their nests.

Taxonomy and Biology of Responsible Insects

Venoms causing anaphylaxis or other allergic reactions originate almost exclusively from social Hymenoptera, most often honey bees and vespids (fig. 1) [1], occasionally from bumble bees [2], in America [3] and in Australia [4], also from ants. Stings by other insects like mosquitoes, bedbugs, fleas, horse flies and midges can very rarely also cause systemic allergic reactions. These are however not due to venoms but to

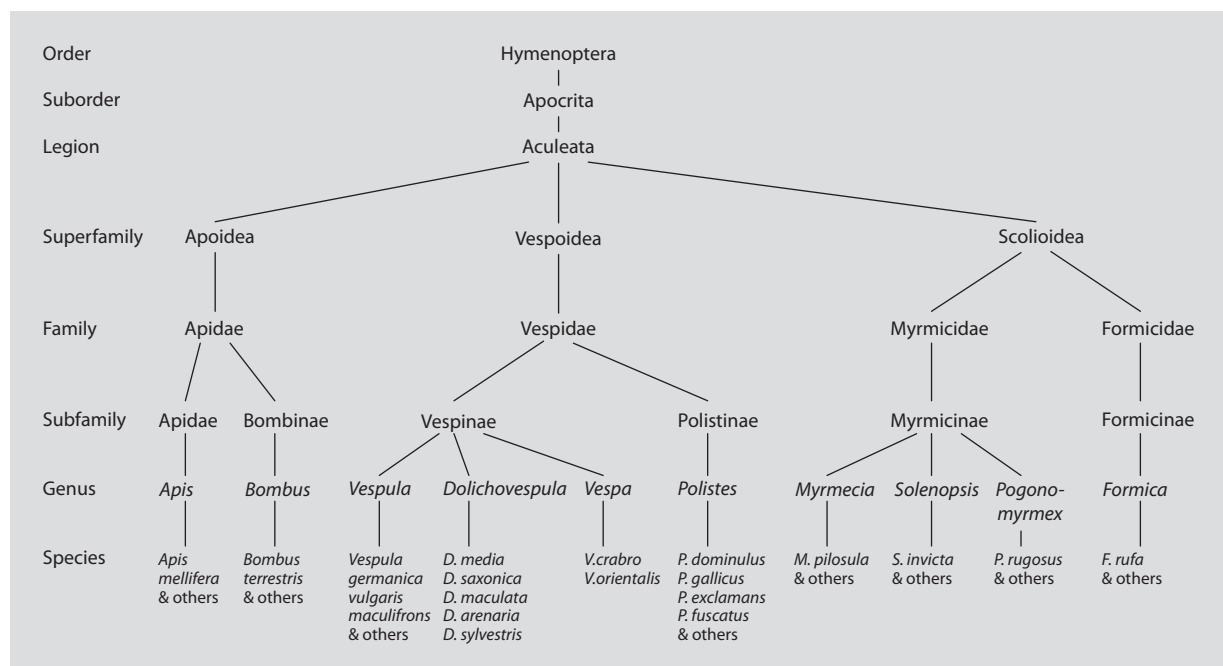


Fig. 1. Taxonomy of Hymenoptera.

salivary proteins, since these insects sting, or better bite, to suck blood and not to defend themselves [5]. Exceptionally, anaphylaxis has also been reported following stings by venomous arthropods like scorpions or arachnids and bites by ticks, which all are of course not insects.

We will concentrate in this chapter on venoms of social Hymenoptera which are certainly responsible for more than 99% of insect sting-induced anaphylaxis.

Apidae

The domesticated honey bee (*Apis mellifera*) (fig. 2a) is the most important species of this family. It is cultured by man all over the world for production of honey and pollination of fruit trees. In contrast to bumble bees and vespids, not only the queen, but the whole bee hive survives during winter. Stings may therefore occur exceptionally also on warm sunny winter days, but are most frequent in spring and early summer. The risk of exposure is highest near bee hives, while gardening, or when walking barefoot on a lawn. After stinging, the sting usually stays in the skin. Bumble bees (*Bombus* spp.) (fig. 2b) are also social Hymenoptera and usually build their nests in the ground. They are increasingly used as pollinators in greenhouses and occasionally cause anaphylaxis in greenhouse workers [2]. Bumble bees are much larger than honey bees, more hairy and most species have distinct yellow or white bands on their abdomen. After stinging, the sting usually does not stay in the skin.

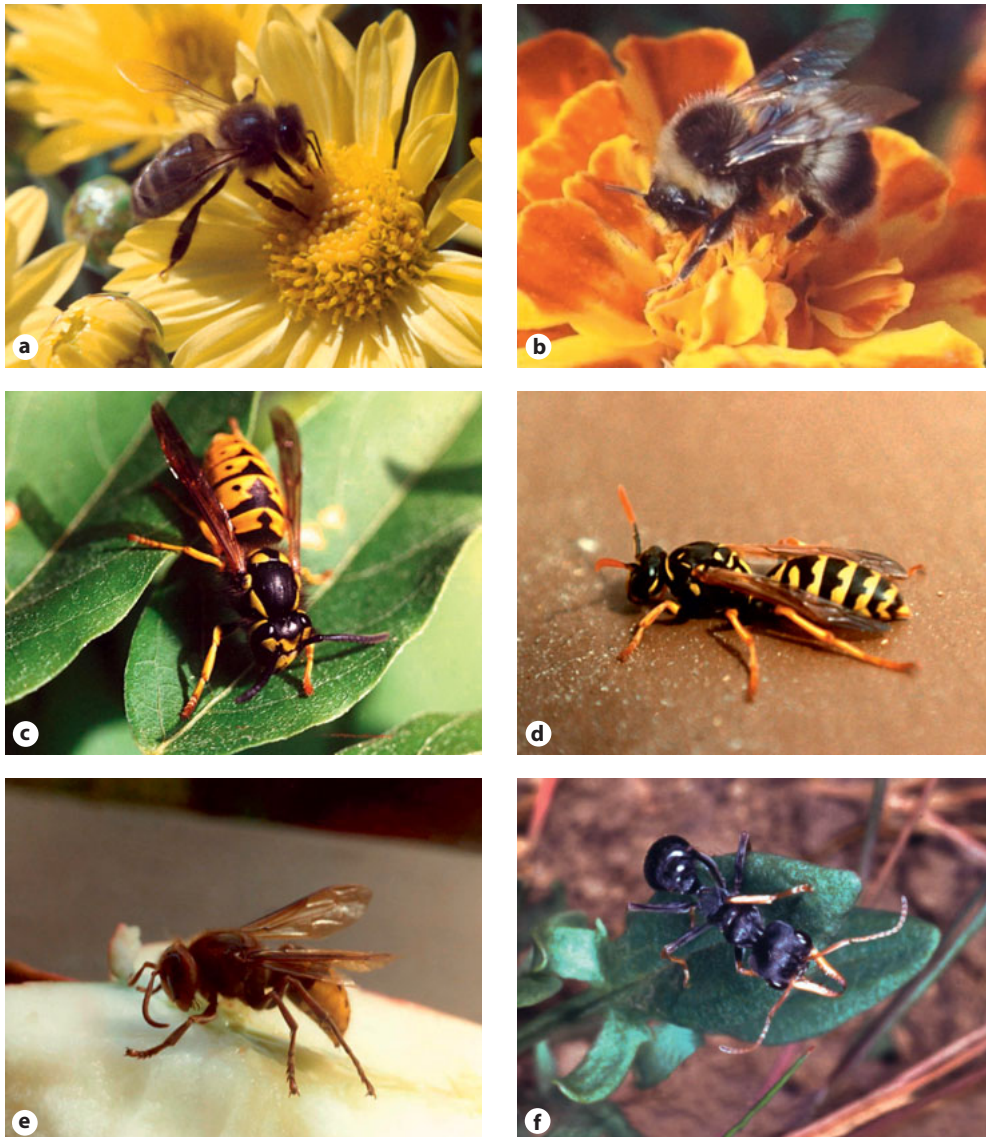


Fig. 2. Species of Hymenoptera responsible for systemic allergic reactions: (a) honey bee (*A. mellifera*), (b) bumble bee (*Bombus* spp.), (c) wasp, in the USA yellow jacket (*Vespula* spp.), (d) European paper wasp (*P. gallicus*), (e) European hornet (*V. crabro*), and (f) Australian jack jumper ant (*M. pilosula*) [by courtesy of Dr. S.G. Brown, Perth, Australia].

Vespidae

The family Vespidae is divided in subfamilies *Vespinae* and *Polistinae*, which are distinguishable by differences at the junction of thorax and abdomen: The abdomen becomes thicker rapidly after the waist in *Vespinae* but only gradually in *Polistinae*

(fig. 2c, d). *Vespinae* include the genera *Vespula*, *Dolichovespula* and *Vespa* (fig. 1). While only the queen survives winter, vespids populations reach their maximal size only in summer and stings occur most often in summer and fall. After vespids sting, the sting does not stay in the skin as a rule. It may however stay when the insect is crushed during stinging, and according to one report more often in *Vespula maculifrons* than in other vespids [6].

The most important species of the genus *Vespula*, in Europe called wasps, are *Vespula vulgaris* and *V. germanica* (fig. 2c). In America they are called yellow jackets and besides *V. vulgaris* and *V. germanica* also *V. maculifrons*, *V. squamosa* and *V. pennsylvanica* are of importance. *Vespula* build their nests most often underground, but also under the roofs or in attics or window shutters. In contrast to honey bees, *Vespula* are prevalent also in urban areas. They like human food and stings most often occur while eating outdoors, under trees with fallen fruits, around garbage bins and of course near their nests.

In the genera *Dolichovespula*, *D. maculata* and *D. arenaria*, the American hornets, are the most prevalent species in the USA; in Europe, *D. saxonica*, *D. media* and *D. sylvestris* are important. *Dolichovespula* usually build their nests above ground, either hanging freely in tree branches, or in attics or window shutters. In contrast to *Vespula*, *Dolichovespula* has not much interest in human foods and stings therefore occur mainly near their nests.

Vespa crabro, the European hornet, and *V. orientalis* are the most important species of the genus *Vespa* in Europe, Asia and Africa, and *V. crabro* has also been imported in the USA. These species are much larger than other vespids (fig. 2e). They build their nest mostly above ground, in hollow tree trunks or in birds' nest boxes. Stings occur almost exclusively near the nests.

Among the subfamily *Polistinae*, *P. annularis*, *P. exclamans* and *P. fuscatus* are the most important species in southern US states, *P. dominulus* and *P. gallicus* (fig. 2d) in southern and Mediterranean areas of Europe. Occasional members of these species are however also observed in regions with a temperate climate. Because *Polistes* build their nest mostly around or on human buildings, stings may occur frequently, especially in southern countries of Europe and southern US states.

Ants (Formicidae, Myrmecidae)

In South and Central America as well as in southern US states, the fire ants (*Solenopsis invicta*) are often responsible for allergic sting reactions [7]. Fire ants build their mounds in playgrounds, gardens and fields. The sting does not stay in the skin of the victim. Besides local wheal-and-flare reactions, later pustule formation is characteristic of fire ant stings. Occasional allergic reactions have also been reported on stings by *Pogonomyrmex*, the harvester ant, and to other ant species all over the world [7]. In Southern Australia several species of Myrmecinae, especially the jack jumper ant *Myrmecia pilosula* (fig. 2f), are an important cause of allergic sting reactions [4].

Table 1. Allergens of Hymenoptera venoms

Venom	Allergen	Function/ name	MW kDa	Major/ minor	Cloned and sequenced	Expressed as recombinant	Glycosylated (n sites)
<i>A. mellifera</i>	Api m1	phospholipase A ₂	16	major	yes	yes	yes (1)
	Api m2	hyaluronidase	43	major	yes	yes	yes (4)
	Api m3	acid phosphatase	45	major?	yes	yes	yes (4)
	Api m4	melittin	2.9	minor	available as synthetic peptide		no
	Api m5	dipeptidylpeptidase*	102	minor	yes	yes	yes
	Api m6		7.9	minor	yes	yes	no
	Api m7	CUB serine protease	39	major?	partly	partly	yes
<i>V. vulgaris</i> (similar for <i>V. germanica</i> , <i>V. maculifrons</i>)	Ves v1	phospholipase A ₁	33.5	major	yes	yes	no
	Ves v2	hyaluronidase	45	minor	yes	yes	yes (4)
	Ves v3	dipeptidylpeptidase**	100	minor	yes	yes	yes
	Ves v5	antigen 5	23	major	yes	yes	no
<i>S. invicta</i>	Sol i1	phospholipase A ₁	37	major	yes		
	Sol i2		14	minor	yes		
	Sol i3	antigen 5	24	major	yes		
	Sol i4		13.4	minor			
<i>M. pilosula</i>	Myr p1	pilosulin 1	6.1	major			
	Myr p2	pilosulin 3	5.6	minor			
	Myr p3	pilosulin 4.1	8.2	minor			
			25.6	major?			
			89.8	major?			

* allergen C; ** Vmac 3.

Allergens in Hymenoptera Venoms (table 1)

Hymenoptera venoms are composed of biogenic amines and other low molecular weight substances, of basic peptides and of proteins. Injection of venom by Hymenoptera stings has toxic effects, due to biogenic amines, peptides and proteins: biogenic amines such as histamine cause pain, are vasodilatory and increase

vascular permeability, allowing the spread of the venom through the body of the victim, as do some of the enzymes, like hyaluronidase. Biogenic amines and peptides are mainly responsible for the local wheal-and-flare reaction after Hymenoptera stings. Cytotoxic and hemolytic effects after multiple, several hundred to over 1,000 stings, with systemic tissue damage, especially renal failure, are caused by basic peptides and phospholipases and responsible for severe toxic and sometimes fatal reactions. Allergic reactions on the other hand can occur after a single sting and are due to specific IgE antibodies, mainly to proteins, occasionally also to peptides. Major allergens are defined as inducing specific IgE antibodies in at least 50% of patients with allergy to the respective venom [1].

Venom collection is done by electrostimulation in honey bees [8] and by venom sac extraction in vespids [9]. While electrostimulation results in pure venom, venom sac extracts may be contaminated by some body proteins. The amount of venom injected by a sting varies from 50 to 140 µg dry weight for the honey bee, but was estimated to be much lower in vespids: 1.7–3.1 µg for *Vespula*, 2.4–5 µg for *Dolichovespula*, and 4.2–17 µg for *Polistes* [10].

Allergens in Apid Venoms (table 1)

Definite major allergens in bee venom are phospholipase A₂ (Api m1), a 16-kDa glycosylated enzyme which cleaves fatty acids at the 2 position of phosphatidylcholine and makes up for 10–15% of dry weight of bee venom [9, 11], and hyaluronidase (Api m2) a 43-kDa glycoprotein, which by cleaving hyaluronic acid increases permeability of connective tissue and makes up for about 1% of dry weight [12]. Specific IgE antibodies have also been identified against acid phosphatase (Api m3) [13], the peptide melittin (Api m4), a 39-kDa-serine protease (Api m7) [9], a 7.9-kDa protein (Api m6) [14], and the high molecular weight protein allergen C (Api m5), recently identified as dipeptidylpeptidase of 102 kDa [15, 16]. Except for melittin and Api m6, all these allergens are glycosylated. Part of the specific IgE antibodies to bee venom are directed to carbohydrate epitopes, so-called cross-reacting carbohydrate determinants, which are not species-specific, occur also in vespids, other insects and in plants, but not in mammals, and probably are of little clinical relevance [17, 18]. The significance of the heavily glycosylated higher molecular weight proteins protease, hyaluronidase, acid phosphatase and allergen C may therefore be overestimated.

Bumble bee venom contains also a phospholipase A₂ with partial identity to bee venom phospholipase A₂ and a protease, but no melittin. Instead there are several small peptides called bombolitins [9]. There is limited cross-reactivity between honey bee and bumblebee venoms [2].

Allergens in Vespid Venoms (table 1)

Major allergens in all vespid venoms are phospholipase A₁, a 33.5-kDa enzyme which digests cell membranes (Ves v1 for *V. vulgaris*) and antigen 5 (Ves v5), a 23-kDa

protein, maybe a neurotoxin. While antigen 5 is non-glycosylated, the situation is unclear for phospholipase A₁, which is not related to phospholipase A₂ of bee venom. Hyaluronidase is also present in vespid venoms but most likely is not a major allergen in the family of *Vespidae*. A dipeptidylpeptidase of 100 kDa (Ves v3), earlier called Vmac 3, with partial identity to Api m5, has been described recently [15, 16]. Sequence identity between different species of the major allergens antigen 5 and phospholipase A₁ is high (above 80–90%) within the genera *Vespula*, *Dolichovespula* and *Vespa*, but lower (around 70%) between these genera. It is even lower between these three genera and *Polistes*. Within the genus *Polistes* there is limited sequence identity and cross-reactivity between the European (*P. dominulus*, *P. gallicus*) and the American species (*P. fuscatus*, *P. exclamans*), because a protease, rather than phospholipase A₁ and antigen 5, seems to be the major allergen in European *Polistes* venoms [9]. Hyaluronidase (Ves v2) is a minor allergen in vespids, is glycosylated and shows considerable sequence identity with bee venom hyaluronidase. Part of the cross-reactivity between bee and vespid hyaluronidase is however also due to specific IgE to carbohydrate epitopes [17, 18].

Allergens in Ant Venoms (table 1)

The venom of the American fire ant *S. invicta* consists of 90–95% water-insoluble *n*-alkyl and *n*-alkenyl piperidine alkaloids, which are responsible for early wheal-and-flare and later pustule formation characteristic of fire ant stings, but are not allergenic [5]. The allergens are present in the aqueous phase which contains 10–100 ng/sting of a mixture of four proteins: Sol i1, a 37-kDa phospholipase A₁, cross-reacting with specific IgE from vespid venom-sensitive patients; Sol i2, a 14-kDa protein, is not related to other known Hymenoptera venom allergens; Sol i3, a 24-kDa protein, is a member of the antigen 5 family of vespid venom proteins, but in spite of a 40–50% sequence identity does not exhibit significant cross-reactivity with these, and Sol i4 is a 13.4-kDa protein. Sol i1 and Sol i3 are major allergens [9].

The venom of the Australian jack jumper ant *M. pilosula* has only been analyzed for its allergen composition in recent years. Besides three low molecular weight allergens, Myr p1, Myr p2 and Myr p3 (table 1), six higher molecular weight allergens of 22.8–89.9 kDa have been identified by Western blot [19]. Myr p1, a 25.6- and a 89.9-kDa protein could be major allergens.

Recombinant Venom Allergens

A number of allergens from both honey bee and vespid venoms have been cloned and expressed by either *Escherichia coli* or baculovirus-infected insect cells (table 1): phospholipase A₂ [20], hyaluronidase [21], acid phosphatase [13] and Api m6 [14] from honey bee venom, as well as antigen 5 [22], phospholipase A₁ and hyaluronidase [23] from vespid venom, and dipeptidylpeptidases from both bee and *Vespula* venoms [15, 16]. Their reactivity with human-specific IgE antibodies to the respective allergens has been documented [11–16, 22, 23] and their specificity is superior

to natural purified venom proteins or whole venoms. Recombinant species-specific non-glycosylated major allergens like Api m1 and Ves v5 are helpful in distinguishing between cross-reactivity and true double sensitization in the frequent Hymenoptera venom-allergic patients with double positivity to both honey bee and *Vespula* venoms [24].

Clinical Presentation of Anaphylaxis to Hymenoptera Venoms

The symptoms of anaphylaxis following Hymenoptera stings are the same as in anaphylaxis from other causes: cutaneous involvement with flush, urticaria and angioedema; respiratory symptoms include dyspnea, wheezing, cough, hoarseness; gastrointestinal tract involvement is characterized by abdominal pain, vomiting and diarrhea, and cardiovascular symptoms are dizziness, palpitations, arrhythmia, drop in blood pressure, collapse and unconsciousness. The interval between sting and symptoms lies between minutes and half an hour as a rule and is thus usually shorter than in anaphylaxis induced by food or oral medication [1, 25].

Severe or even fatal anaphylaxis to Hymenoptera stings occur most often in elderly patients with preexisting cardiovascular disease [26], not in children or young adults with preexisting asthma, as in food allergy [27]. This is partly explained by the fact that atopy is not more frequent in Hymenoptera venom-allergic patients than in the whole population [1, 25], whereas most patients with severe food-induced anaphylaxis are atopic and suffering from asthma. Interestingly, venom allergy is associated with atopy more frequent in venom-allergic beekeepers, where it was found in about 50% as compared to only 13% in non-venom-allergic beekeepers. It is suggested that during work in bee hives, sensitization may often occur by inhalation of bee dust containing venom proteins in atopic, but not in non-atopic beekeepers [28].

Epidemiologic Aspects

Prevalence of anaphylaxis from Hymenoptera stings in various countries and areas is dependent on climatic and environmental factors and may vary considerably (table 2). A warm and dry climate favors the development of most Hymenoptera species resulting in a higher risk of stings and thus a higher lifetime prevalence, as found e.g. in Mediterranean countries as compared to Great Britain or Scandinavia [25]. In large urban areas, vespid venom anaphylaxis – especially caused by *Vespula* spp. – is definitely more frequent than bee venom anaphylaxis, while the latter prevails in agricultural, especially fruit-growing areas, like in California or in Switzerland [1]. Lifetime prevalence of venom anaphylaxis is of course increasing with age and thus significantly higher in adults [29] than in children [30].

Table 2. Prevalence of anaphylaxis to Hymenoptera stings [1, 25]

Author	Country	Population age	Number questioned	Percent with history of anaphylaxis to venoms
Settipane 1972	USA	boy scouts 11–16 years	2,964	0.8
Golden 1989	USA	adult	269	3.3
Björnsson 1995	Sweden	adult	1,815	1.5
Strupler 1995	Switzerland	adult	8,322	3.5
Kalyoncu 1996	Turkey	mostly adult	786	7.5
Grigoreas 1997	Greece	soldiers	480	3.1
Incorvaia 1997	Italy	conscripts	701	2.7

Fatal reactions to Hymenoptera stings are rare: they range from 0.09 to 0.48 per million inhabitants and year [31, 32]. However, the true number may be underestimated: in one study, specific IgE antibodies to Hymenoptera venoms were detected in 23% of postmortem serum samples from patients who died outdoors from unknown reasons [33]. Between 1961 and 2004, 140 fatal Hymenoptera sting reactions were registered by the federal administration for statistics in Switzerland with about 7.5 million inhabitants, resulting in an average annual fatality rate of 3.18. If these data are extrapolated to Europe with a population of around 500 million, the annual death rate in Europe would amount to about 200.

The *natural history* of Hymenoptera venom anaphylaxis, that is the risk to develop anaphylaxis again when re-stung, has been analyzed in several prospective studies (table 3) [35–37], and in placebo or whole-body extract treated controls of prospective studies on venom immunotherapy [38–40]. It is higher in patients with a history of severe as compared to mild systemic anaphylactic reactions, and in honey bee than in vespid venom-allergic patients – most likely because of the smaller and less constant amount of venom applied by vespids [10, 41]. A short interval between two stings increases the risk of anaphylaxis [25], but severe anaphylaxis may occur again even after intervals of 10–20 years or more.

Diagnosis

History

After a painful sting the elicitor of Hymenoptera venom-induced anaphylaxis is usually clear. However the identification of the responsible species is often difficult.

Table 3. Natural history of Hymenoptera venom allergy

Author	Previous reaction	Patients n	Re-exposure	Percent with systemic reaction to re-exposure			
				bee or vespid	bee	vespid	ant
Re-exposures in untreated patients							
Blaauw 1985 [35]	any systemic	88	challenge	35	50	23	
	mild	30			31	10	
	severe	58			60	33	
Van der Linden 1994 [36]	any systemic	324	challenge		51	25	
	mild						
	bee	17			53 (0% severe)		
	vespid	94				20 (0% severe)	
	severe						
	bee	35			51 (40% severe)		
	vespid	178				28 (14% severe)	
Re-exposures in control groups of controlled studies							
Hunt 1978 [38]	severe systemic	23	challenge	61			
Müller 1979 [39]	severe systemic	12	field sting		75		
Brown 2003 [40]	severe systemic	29	challenge				72

Photos as shown in figure 1, the season and the environment of the sting, as well as whether the sting stayed in the skin may be helpful (see section: Taxonomy and Biology of Responsible Insects).

Skin Tests and Specific IgE Antibodies

The sensitivity of these tests is very high: in the first year after sting anaphylaxis more than 90% of patients have a positive result with both tests; with an increasing interval from the last sting reaction the positivity rate decreases, more rapidly for specific IgE than for intracutaneous skin tests, but even 5 years after the reaction the majority of patients still have positive results [1, 24, 25]. The specificity of both skin tests and

serum venom-specific IgE is however limited: 10–20% of patients without a history of systemic sting reactions have positive tests. Of course they may have been sensitized after the last sting. However, according to one study, only 17% of these history-negative test-positive individuals reacted when re-stung [29]. Moreover, more than 50% may have double positive tests with honey bee and vespid venoms [24]. As mentioned above, cross-reactivity based on the protein structure of venom allergens is limited, but cross-reacting carbohydrate determinants of plant origin may well be responsible for part of these false-positive results.

Other Tests

Cellular tests like the CAST (cellular antigen stimulation test), measuring the leukotriene mediator release from basophils after allergen exposure [42], or the BAT (basophil activation test), analyzing the appearance of activation markers like CD63 on the surface of basophils following allergen exposure [43], may be more specific. However, convincing data in relation to re-exposures are still missing, and these tests are expensive.

Sting provocation tests are often considered to be the gold standard, although they are less reliable in vespids than in honey bees [35–37, 41, 43]. They are commonly used to assure the efficacy of venom immunotherapy, but are generally considered as unethical in untreated patients with a history of venom anaphylaxis.

Prevention and Emergency Treatment

All patients with Hymenoptera venom anaphylaxis should receive oral and written information about the biology of the responsible insects and how to avoid further stings [1, 45]. During the flying season of Hymenoptera they must carry emergency medications, including an adrenaline autoinjector for self-application, and must be instructed about their use in case of a re-sting. Emergency treatment of anaphylaxis to Hymenoptera stings is the same as for anaphylaxis to other elicitors and is discussed in more detail by Ring et al. (see section: Treatment and Prevention).

Immunotherapy

Efficacy and Safety

While in anaphylaxis caused by other frequent elicitors like food and drugs, allergen-specific immunotherapy is not established, immunotherapy with Hymenoptera venoms has been shown to be effective in three prospective controlled trials (table 4) [38–40] and also in a number of studies where patients were submitted to a sting challenge with the responsible insect during venom immunotherapy (table 5) [44]. While over 90% of vespid venom-allergic patients are fully protected and do not develop any

Table 4. Efficacy of venom immunotherapy: controlled prospective studies

Author, year	Immunotherapy with	Number re-exposed	Re-exposure by	Systemic reaction at re-exposure (%)	p verum vs. control
Hunt 1978 [38]	venom (bee or <i>Vespula</i>)	19	challenge	1 (5)	
	whole-body extract	11	challenge	7 (64)	<0.01
	placebo	12	challenge	7 (58)	<0.01
Müller 1979 [39]	bee venom	12	field sting	3 (25)	
	whole-body extract	12	field sting	9 (75)	<0.03
Brown 2003 [40]	ant venom	35	challenge	1 (3)	
	placebo	29	challenge	21 (72)	<0.0001

Table 5. Efficacy of venom immunotherapy: Result of sting challenge on maintenance immunotherapy [1, 41, 44]

Author, year	Immunotherapy with venom of	Number challenged	Systemic reaction after challenge (%)
Hoffman, 1981	honey bee, adults	25	5 (20)
Urbanek, 1985	honey bee, children	66	4 (6)
Müller, 1992	honey bee, adults	148	34 (23)
	<i>Vespula</i> , adults	57	5 (9)
Chipps, 1980	mostly <i>Vespula</i> , children	42	1 (2)
Golden, 1981	mostly <i>Vespula</i> , adults	147	4 (3)

systemic allergic symptoms when re-stung, the full protection rate lies only between 75 and 90% in bee venom-allergic patients. Most of the not fully protected patients do however develop only minor systemic allergic symptoms which are definitely less severe than before treatment. Moreover, an increase of the maintenance dose from the usual 100 µg per injection to 200 µg leads to full protection in most of these patients [46]. Allergic side effects to immunotherapy injections may occur and are more frequent in honey bee than in *Vespula* venom-allergic patients [41–45]. Antihistamine

Table 6. Protocols for venom immunotherapy [51]

Conventional		Ultra-rush		
week	amount of venom, µg	day	min	amount of venom, µg
1	0.01	1	0	0.1
2	0.1		30	1
3	1		60	10
4	2		90	20
5	4		150	30
6	8		210	50
7	10			
8	20	8	0	50
9	40			50
10	60			
11	80	21	0	100
12	100	49	0	100

Afterwards 100 µg monthly for 1 year, then every 6 weeks from year 2 to 5.

premedication during the dose increase phase of venom immunotherapy has been shown to reduce local and systemic allergic side effects significantly in a number of placebo-controlled double-blind studies [47, 48].

Indications

The indication for venom immunotherapy is based on a history of systemic allergic reactions to Hymenoptera stings and positive diagnostic tests, skin tests and/or venom-specific serum IgE antibodies [45, 49]. In the presence of only mild systemic allergic reactions, limited to the skin, immunotherapy is not generally recommended: in the USA not for children, in Europe not for children and adults, unless they are heavily exposed and had repeated such reactions.

Contraindications are the same as for immunotherapy for inhalant allergy, but are relative in nature because of the life-saving potential of venom immunotherapy. Elderly patients, especially with preexisting cardiovascular disease, are at a high risk to develop severe or even fatal anaphylaxis [26]. Therefore, venom immunotherapy is often recommended in patients over 50–60 years of age. Since β -blocker treatment is associated with a significantly increased survival rate in patients with coronary heart

disease and chronic heart failure, venom immunotherapy on β -blockers may be indicated for venom anaphylaxis in such patients [50].

Immunotherapy Protocols and Duration

The usual starting dose lies between 0.01 and 0.1 μg of the venom, the usual maintenance dose is 100 μg . The dose may be increased according to conventional protocols with weekly injection, or with rush or ultra-rush protocols [45, 49, 51] (table 6). Rush and especially ultra-rush protocols have the advantage of providing rapid protection, but may be associated with more frequent allergic side effects. After reaching maintenance dose, the recommended interval between injections is 4 weeks in the first year and 6 weeks from the second year. An increase of the maintenance dose to 200 μg or even more is recommended in beekeepers, who often are stung by more than one bee at the time, and in patients with incomplete protection when re-stung during venom immunotherapy [46]. The recommended treatment duration is at least 3–5 years. Even longer treatment is indicated in patients with a history of very severe reactions [26, 50], and in those with concurrent mastocytosis or elevated baseline serum tryptase levels [51, 52].

After stopping venom immunotherapy, most patients remain protected, but relapses may occur, especially after repeated re-exposures [45, 49].

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