Allergy to stings and bites from rare or locally important arthropods: worldwide distribution, available diagnostics, and treatment

Lisa Arzt-Gradwohl[1], Gunter Sturm[1], Elisa Boni[2], Dario Antolin-Amerigo[3], Bilo M.Beatrice[4], Christine Breynaert[5], Filippo Fassio[6], Kymble Spriggs[7], Arantza Vega[8], Luisa Ricciardi[9], and Wolfgang Hemmer[10]

[1]Medizinische Universitat Graz
[2]Ospedale Maggiore Carlo Alberto Pizzardi
[3]Instituto Ramon y Cajal de Investigacion Sanitaria
[4]AOU Ospedali Riuniti di Ancona SOD Clinica di Radiologia d'Urgenza e dell'Area Oncologica
[5]Katholieke Universiteit Leuven Universitaire Ziekenhuizen Leuven
[6]Ospedale San Giovanni di Dio
[7]Monash Medical Centre Clayton
[8]Hospital General Universitario de Guadalajara
[9]Universita degli Studi di Messina Dipartimento di Medicina Clinica e Sperimentale
[10]Floridsdorfer Allergiezentrum GmbH

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Abstract

Insect venom allergy is the most frequent cause of anaphylaxis in Europe and possibly worldwide. The majority of systemic allergic reactions after insect stings are caused by Hymenoptera and among these, vespid genera induce most of the systemic sting reactions (SSR). Honey bees are the second leading cause of SSR. Depending on the global region, other Hymenoptera such as different ant genera are responsible for SSR. Widely distributed hornets and bumblebees or local vespid or bee genera rarely induce SSR. Hematophagous insects such as mosquitoes and horse flies usually cause (large) local reactions while SSR occasionally occur. This position paper aims to identify either rare or locally important insects causing SSR as well as rarely occurring SSR after stings or bites of widely distributed insects. We summarized relevant venom or saliva allergens and intended to identify possible cross-reactivities between the insect allergens. Moreover, we aimed to locate diagnostic tests for research and routine diagnosis, which are sometimes only regionally available. Finally, we gathered information on disposable immunotherapies. Major allergens of most insects were identified, and cross-reactivity between insects was frequently observed. While some diagnostics and immunotherapies are locally available, standardized skin tests and immunotherapies are generally lacking in rare insect allergy.

Allergy to stings and bites from rare or locally important arthropods: worldwide distribution, available diagnostics, and treatment

Short title: Rare insect allergy

An EAACI position paper of the Working Group on Insect Venom Hypersensitivity

Gunter Johannes Sturm[1,2], Elisa Boni[3], Darío Antolín-Amérigo[4], Maria Beatrice Bilò[5,6], Christine Breynaert[7,8], Filippo Fassio[9], Kymble Spriggs[10,11,12], Arantza Vega[13,14], Luisa Ricciardi[15], Lisa Arzt-Gradwohl[1], Wolfgang Hemmer[16]

[1]Department of Dermatology and Venereology, Medical University of Graz, Graz, Austria[2]Allergy Outpatient Clinic Reumannplatz, Vienna, Austria

[3]Allergy and Immunology Department, Metropolitan Laboratory AUSL Bologna, Maggiore Hospital, Bologna, Italy[4]Allergy Department, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain.[5]Department of Clinical and Molecular Sciences, Marche Polytechnic University, Ancona, Italy[6]Allergy Unit, Department of Internal Medicine, Ospedali Riuniti Ancona University Hospital, Ancona, Italy[7]Department of General Internal Medicine - Allergy and Clinical Immunology, University Hospitals Leuven, Leuven, Belgium.[8]KU Leuven Department of Microbiology, Immunology and Transplantation, Allergy and Clinical Immunology Research Group, Leuven, Belgium.[9]Allergy and Clinical Immunology Unit, Ospedale San Giovanni di Dio, Azienda USL Toscana Centro, Florence, Italy[10]Department of Allergy & Immunology, Monash Medical Centre, Clayton, Australia[11]Department of Allergy & Immunology, The Royal Melbourne Hospital, Parkville, Australia[12]Department of Medicine, Melbourne Medical School, The University of Melbourne, Parkville, Australia.[13]Allergy Department, University Hospital of Guadalajara, Spain.[14]ARADyAL Spanish Thematic Network and Co-operative Research Centre RD16/0006/0023[15]Allergy and Clinical Immunology Unit, AOU Policlinico G.Martino, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy[16]FAZ - Floridsdorf Allergy Center, Vienna, Austria

***Correspondence to:** Prof. Gunter Sturm, MD, PhD (0000-0002-7245-121X), Department of Dermatology and Venereology, Medical University of Graz, Auenbruggerplatz 8, 8036 Graz, Austria, Phone: +43/316/385-80318; Fax: +43/316/385-12466; Email: gunter.sturm@medunigraz.at

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Abstract

Insect venom allergy is the most frequent cause of anaphylaxis in Europe and possibly worldwide. The majority of systemic allergic reactions after insect stings are caused by Hymenoptera and among these, vespid genera induce most of the systemic sting reactions (SSR). Honey bees are the second leading cause of SSR. Depending on the global region, other Hymenoptera such as different ant genera are responsible for SSR. Widely distributed hornets and bumblebees or local vespid or bee genera rarely induce SSR. Hematophagous insects such as mosquitoes and horse flies usually cause (large) local reactions while SSR occasionally occur. This position paper aims to identify either rare or locally important insects causing SSR as well as rarely occurring SSR after stings or bites of widely distributed insects. We summarized relevant venom or saliva allergens and intended to identify possible cross-reactivities between the insect allergens. Moreover, we aimed to locate diagnostic tests for research and routine diagnosis, which are sometimes only regionally available. Finally, we gathered information on disposable immunotherapies. Major allergens of most insects were identified, and cross-reactivity between insects was frequently observed. While some diagnostics and immunotherapies are locally available, standardized skin tests and immunotherapies are generally lacking in rare insect allergy.

Keywords: ants; arthropods; insects; saliva allergy; venom allergy;

Introduction Insect venom allergy is the most frequent cause of anaphylaxis in adults in Europe.[1] The majority of systemic allergic reactions after insect stings are caused by Hymenoptera and among these, vespid genera induce most of the systemic sting reactions (SSR).[1] Vespid genera are usually found in regions with temperate climate (Figure 1). Honey bees are cultivated insects and distributed worldwide except in the polar regions. They are the second leading cause of SSR.[1] Other Hymenoptera such as different ant genera are responsible for SSR mainly in Central and South America, Africa, Asia, and Australia (Figure 2). Widely distributed hornets (Figure 3) and bumblebees or local vespid or bee genera rarely induce SSR. Hematopha-

gous insects such as mosquitoes and horse flies usually cause (large) local reactions while SSR occasionally occur. Global warming, globalization, and human activity are responsible for insect redistribution, increasing the number of allergy cases caused by stinging insects worldwide.[2]

This position paper aims to identify either rare or locally important insects leading to SSR as well as rarely occurring SSR after stings or bites of widely distributed insects and other arthropods. We further summarized relevant venom or saliva allergens and intended to identify possible cross-reactivities between the arthropod allergens. Moreover, we aimed to list diagnostic tests for research and routine diagnosis and information on disposable immunotherapies.

Rare stinging Hymenoptera

Reaction types

Similar to widely distributed vespid genera and honey bees, rare stinging Hymenoptera can cause either large local reactions (LLR) or SSR; in the following overview, we focus on SSR.

Apidae family **(Table 1)**

Apis

Apis dorsata (giant honey bee) is the largest and most aggressive bee in Sri Lanka, responsible for the majority of SSR in rural areas.[3] IgE to phospholipase A2 (PLA2) of *A. dorsata* has been detected in 96.7% of patients with anaphylaxis to*A. dorsata* stings, indicating that this is the most important allergen.[4]

Bombus

Bumblebees prefer cool and temperate climates and are mainly found in Europe, Asia, and North America. It is estimated that there are about 250 different bumblebee species. In Europe, the European large earth bumblebee (*Bombus terrestris)* is the most common.[5]

Bumblebees can sting several times without attachment of the sting apparatus to the skin. The protein content per bumblebee sting is 10-31 µg depending on the species compared to 59 µg per honey bee sting.[6] As bumblebees are not aggressive, the risk of being stung is very low in the general population. The worldwide use of domesticated bumblebees as crop pollinators[7] has led to an increasing prevalence of bumblebee venom (BBV) allergy, especially in greenhouse workers and bumblebee farm employees.[5]SSR due to BBV have been consistently described, mostly in occupational settings.[8-11]

Xylocopa

Carpenter bees (*Xylocopa* spp.) are solitary bees of up to 2.5 cm closely related to honey bees and bumblebees. They have a worldwide distribution favoring warmer climates. Carpenter bee stings are rare. However, a fatal case after a *Xylocopa tranquebarica* sting has been reported in Sri Lanka.[12] Three allergens have been isolated in *Xylocopa appendiculata* ; a PLA2 similar to that of bumblebees and honey bees, and two melittin-like peptides.[13] Currently, none of the allergens is WHO/IUIS (World Health Organization and International Union of Immunological Societies) accredited.

Vespidae family **(Table 1, Figure 3)**

Vespa

Vespa crabro (*VC*) (European hornet) is widely distributed across Europe and Asia and has been introduced in the USA. Stings are rare, and systemic sting reactions usually follow previous stings from other vespids, especially *Vespula* .[14] However, one small study suggested that the risk of a life-threatening reaction after a *VC* sting was higher compared to honey bee or *Vespula* stings in Mediterranean countries.[15]

Vespa velutina (*VV*) is endemic to Southeast Asia and has rapidly spread across Europe after accidental introductions in France from China in 2004.[16] They are known for their large colonies, an extensive foraging radius, and intense predation on honey bees at the hive.[17,18] The first case of anaphylaxis due to *VV* in Spain

was reported in 2014.[19] Since then, *VV* has become the most common cause of Hymenoptera anaphylaxis in the Northwest of Spain because of their more aggressive behavior. Seventy-seven percent of patients identified *VV* as the culprit insect for the reaction; most cases report no previous *Vespula* stings. More than 47,000 nests have been identified in 2018 compared to 769 in 2014.[20]

Vespa affinis (lesser banded hornet), is a common hornet in tropical and subtropical Asia. Anaphylaxis appears to be rare[21] although a case of fatal anaphylaxis in a child has been published.[22] However, multiple stings with resulting acute renal failure occur frequently.[23] *Vespa orientalis* (VO) is located in Southwest Asia and Northeast Africa. Similar to *Vespa affinis,* anaphylaxis is rare but multiorgan dysfunction after multiple stings has been documented.[24]

Polistinae

Polybia paulista (*PP*) is a wasp in South America (Southwest Brazil, Paraguay, and north Argentina) that is largely tropical in distribution. About 10 to 15 thousand sting accidents related to bees or wasps occur annually in Brazil, most of these caused by *PP* with 35–42 deaths registered every year.[25]

Ropalidia marginata

Ropalidia marginata extends from Pakistan, India, and Sri Lanka to New Guinea, Queensland, and some eastern Pacific islands. In Sri Lanka, it has been linked to anaphylactic reactions.[3]

Scoliidae family

Scoliid wasps are solitary insects that rarely sting humans under natural conditions. They are distributed worldwide. Montagni et al[26] reported a case of anaphylaxis after a*Scolia flavifrons* sting in Italy.

Formicidae family **(Table 2, Figure 2)**

The family *Formicidae* contains all ants within the*Hymenoptera* order of stinging insects. This is divided into over 300 genera and 17 subfamilies with extant species.[27]Of these, six subfamilies and 12 genera have been reported in the literature as associated with immediate allergic-type reactions. The most important are listed in Table 2.

Similar to other Hymenoptera, ant species have been spread by humans beyond their native range, and are now "exotic" or invasive pests in many regions, and may continue to spread over time, especially with climate change.

Subfamily *Myrmeciinae*

Myrmecia ants are native to Southeastern Australia and several species have been associated with allergic reactions and anaphylaxis (Figure 2). These can be commonly divided into "jumper" ants and "bulldog" ant groups. *Myrmecia pilosula* or "jack jumper ant" is by far the most common cause of severe allergic reactions; some surveys reported a prevalence at approximately 3% for systemic allergy estimated in local populations.[28-30] They have a particularly painful sting and contain cytotoxic venom components ("pilosulins") including some thought to directly release histamine.[31] Also, unlike many ants using scent to forage, jack jumper ants use vision to hunt prey and are aggressive and will attack humans and other large animals, probably contributing to the high prevalence of allergic sensitivity and reactions. Jack jumper, with other "jumper" group ants, are estimated to make up two-thirds of ant-associated reaction in the continental Australian context.

The "bulldog" ant (*Myrmecia pyriformis*) group, although still having a painful sting, are much less aggressive towards humans, probably making up approximately 15% of ant-associated allergic reactions.

Subfamily *Myrmicinae*

Solenopsis spp. or "fire ants" are widely distributed (in both native and exotic ranges) (Figure 2) and associated with allergic reactions. Although the sting is less painful, compared to bee and wasp stings, a wheal and flare reaction usually develops at the sting site, often with a pathognomonic sterile pustule, which

may scar. This pustule effect is thought to be due to venom alkaloids, which are more potent in *S. invicta* (red imported fire ant) and *S. richteri* (black imported fire ant), compared to other species. (e.g.*S. xyloni* (southern fire ant)*, S. aurea* (desert fire ant),*S. geminata* (tropical fire ant)).[32]

Severe allergic reactions have been estimated in approximately 2% of patients seeking medical care for ant stings and, as of 1989, over 84 fatal cases had been reported in the US.[33]*Solenopsis* species are also an important cause of allergy in Asia[34] and South America perhaps exacerbated by deforestation.[32]

Pogonomyrmex , a species native to the US & Mexico, is thought to have the most painful sting of North-American ants, and the most toxic of all insect venoms based on median lethal dose in mice. At least two deaths have been attributed to stings from this species.[35]

Subfamily *Ectatomminae*

Rhytidoponera metallica (greenhead ant) is prevalent in central eastern Australia. It is a smaller, less aggressive ant, though its prevalence means that it is likely to make 11% of Australian-related allergic reactions to stings.[29]

Subfamily *Ponerinae*

Brachyponera (formerly *Pachycondyla) sennaarensis* (Samsun ant) is increasing across the Middle East (Figure 2) with multiple case reports of allergic-type reactions, and some stings previously reported to be by imported fire ants (*Solenopsis ssp.)* are actually now thought to be due to this local species.[36,37]

Brachyponera (formerly *Pachycondyla) chinensis* (Asian needle ant) was introduced to the US from Japan in the 1930s, and is now an invasive species disrupting local US native ant populations and causing allergic reactions in its native and exotic range (Figure 2).[38,39]

Odontomachus bauri (trap-jaw ant) in central and South America and *Hypoponera punctatissima* (Roger's ant) in the US have given rise to allergic reaction case reports.[35,40]

Subfamily *Pseudomyrmecinae*

Tetraponera rufonigra is another species in this family in South and Southeast Asia and appears to be one of the common causes of ant anaphylaxis along with *Solenopsis geminata* in Thailand.[41] *Pseudomyrmex ejectus* (twig or oak ant) has a highly pharmacologically active venom and has given rise to multiple case reports of anaphylactic-type reactions.[35]

Key points

- Systemic sting reactions due to rare species of the Apidae family (family of bees) are scarce. However, the giant honey bee *Apis dorsata* is locally relevant and is responsible for the majority of SSR in Sri Lanka. Furthermore, the use of domesticated bumblebees as crop pollinators has increased the prevalence of SSR.
- Stings of rare species of the Vespidae family (family of wasps) are uncommon. *Polybia paulista* is locally important in South America causing a relevant number of SSR and deaths. *Vespa velutina* is endemic to Asia and has spread within South Europe. Due to its more aggressive behavior, SSR are increasing in Europe.
- Species of the Formicidae (family of ants) are locally relevant. The most important species causing SSR are *Myrmecia pilosa* (jack jumper ant) in Australia and *Solenopsis spp* (fire ants), including but not limited to Southern America and the USA.

Cross-reactivity (see Table 4)

Bumblebee allergens and cross-reactivity with honey bee:

Bumblebee venom is similar to honey bee venom but contains some unique toxins not present in honey bee venom (Table 3).[42,43]Bumblebee PLA2 shows only 54% sequence identity (SI) with Api m 1[44] explaining the often limited cross-reactivity with honey bee venom. Serine proteases represent major allergens in bumblebee

venom. They are structurally different from the honey bee CUB serine protease Api m 7 showing only 33% identity.[45]

Seventy-three to 100% of unselected honey bee venom-allergic subjects also show IgE binding with bumblebee venom *in vitro* [43, 46, 47], and allergic reactions after bumblebee stings have been reported in subjects with primary honey bee venom allergy.[8,10,43] However, patients with occupational bumblebee exposure may react with unique epitopes or allergens (especially serine protease) in bumblebee venom that cannot be effectively inhibited by honey bee venom.[47]

Cross-reactivity between *Polybia* and other wasps:

Polybia paulista venom contains Phospholipase A1 (PLA1), hyaluronidase, antigen 5, and dipeptidyl peptidase IV as well as large amounts of serine proteases (Table 4).[48] PLA1 and antigen 5 from *Polybia* are more similar to that from *Polistes* (˜80% SI) than to that from *Vespula* (˜60% SI).

Polybia PLA1 (Poly p 1) has been found to be strongly cross-reactive with PLA1 from *Polistes* , but not with fire ant, *Vespula,* and honey bee venom.[49] In contrast, for antigen 5, substantial cross-reactivity has also been reported with *Vespula.* [50] *Polybia paulista* hyaluronidase strongly cross-reacts with *Polistes* hyaluronidase (˜95% SI) but not with honey bee Api m 2 and fire ant venom (˜50% SI).[51] *Polybia* venom reportedly lacks cross-reactive carbohydrate determinants (CCDs) and does not exhibit diagnostic interference as do *Vespinae* venoms.[52-54]

Cross-reactivity of *Vespa* venoms:

Vespa crabro venom is largely identical to *Vespula* and *Dolichovespula* venom with SIs between their PLAs1 and antigens 5 being 70-75%. Cross-reactivity between *Vespa crabro* and *Vespula* is well documented and known to be clinically relevant.[55-58]

The antigens 5 from the invasive Asian hornet (*Vespa velutina*), the Asian giant hornet (*Vespa mandarinia/magnifica*) and *Vespa affinis* are nearly identical to *Vespa crabro* Vesp c 5 (SI 90-95%) and share 65-70% SI with Ves v 5. Hornet PLAs1 share 65-70% SI with each other. Recently two new allergens (dipeptidyl peptidase IV and serin protease) have been identified in the *VV* venom.[59]

Due to the high similarity between all hornet venoms, cross-reactivity of (sub)tropical *Vespa* species with *Vespula* may be expected to be comparable to that of *Vespa crabro* .

Ant venom allergens and cross-reactivity with other Hymenoptera venoms

Allergens

Ant venom allergens have been predominantly studied in *Solenopsis* (fire ants), *Myrmecia* (jumper/bulldog ants), and *Brachyponera* (needle ants) (Table 3). While major *Myrmecia* venom allergens are toxic peptides below 10 kDa (pilosulins), other ant venoms are similar in composition to bee and wasp venoms.[60] Only a few ant venom allergens have been officially accepted by the IUIS nomenclature subcommittee thus far (Table 3).

There is limited knowledge about cross-reactions between the venoms of ants, bees, and wasps, and between different ant species.

Cross-reactivity among ants

There is substantial cross-reactivity between different fire ant species due to the high similarity of their major allergens PLA1 (Sol i 1) and antigen 5 (Sol i 3). The less conserved minor allergens Sol i 2 and Sol i 4 may harbor species-specific epitopes.[61] Strong cross-reactivity has also been reported between different *Brachyponera* species.[62] In contrast, cross-reactivity within the genus *Myrmecia* is heterogeneous and monosensitization to single species appears to be common.[29,63]

Data concerning cross-reactivity between different ant genera are scarce and controversial. SI is low between known ant venom phospholipases (30-35%), while it is 50-60% for antigens 5 from *Solenopsis* (Sol i 3), *Brachy-*

ponera (Pac c 3), and *Dinoponera* . Strong cross-reactivity between *Solenopsis invicta* and*Brachyponera sennaarensis* (samsum ant), essentially due to antigen 5, has been reported in one study[64], whereas no cross-reactivity was observed between *Solenopsis* and*Brachyponera chinensis* in another study.[62]Preliminary data revealed no evidence for cross-reactivity between*Myrmecia* and fire ant venom[65] which is consistent with the lack of antigen 5, PLA1, and Sol i 2/4-like proteins in *Myrmecia* venom.[66]

Cross-reactivity of ant allergens with bee and wasp venom

About 50% of honey bee and wasp venom-allergic patients also reacted*in vitro* with fire ant venom,[67] subsequently attributed to the venom phospholipases Ves v 1/Sol i 1 which share 31% identity.[68] No cross-reactivity was observed, however, between Sol i 1 and Poly p 1 from *Polybia paulista* despite comparable SI.[49] Cross-reactions between fire ant and honey bee venom have has been shown to be entirely due to CCDs.[68]

Recent studies using recombinant allergens reported that 37% of Ves v 5-positive sera also bind to Sol i 3.[50] Likewise,*Brachyponera chinensis* antigen 5 (Pac c 3) was found to be cross-reactive with Ves v 5.[39] In another study of*Brachyponera* allergens, however, only minimal cross-reactivity was observed with *Vespula, Polistes,* and *Solenopsis*venom.[69] Overall, available data suggest that cross-reactivity is modest or absent.

Key points

- There is limited cross-reactivity between bumblebee and honey bee venom.
- *Polypia paulista*: cross-reactivity is higher to *Polistes*compared to *Vespula* (80 versus 60% sequence identity).
- The venom of *Vespa crabro* (European hornet) and other (sub)tropical hornet species including *Vespa velutina* is largely identical to *Vespula* and *Dolichovespula.*
- There is substantial cross-reactivity between different fire ant species and within *Brachyponera* spp. In contrast, cross-reactivity within the genus *Myrmecia* is limited.
- Available data suggest that cross-reactivity between bees and wasps to ants and between different ant species is modest or absent.

Diagnosis (see Table 1)

Apidae

The 83.3–92% of patients with anaphylaxis to *A. dorsata* stings had specific IgE (sIgE) to *A. mellifera*venom.[4,70] This cross-reactivity suggests using*A. mellifera* venom for diagnosis. A similar approach can be used in patients allergic to carpenter bees.[13]

In BBV allergy skin testing can be performed,[8,11] and sIgE against BBV can be detected; no molecular allergens are commercially available. Specific IgE against HBV should be determined as well because apart from occupational exposure, primary sensitization through honey bee stings is likely.[8,10,71]

Vespidae

Vespa crabro venom is largely identical to *Vespula* venom: therefore, allergy to *Vespa* species can usually be diagnosed by determination of IgE against *Vespula* venom. Available tests for*Vespa* venoms see Table 1.

*Formicidae*Available allergen extracts are limited to only a small number of allergy-associated species

Immunotherapy (see Table 1)

Bumblebees HBV has been used for venom immunotherapy (VIT) in selected cases of BBV allergy resulting from primary sensitization to HBV.[10] Successful immunotherapy with a BBV preparation from ALK Abelló (Horsholm, Denmark) has been described, although it is not available anymore.[8,9,11,72]

Currently, only BBV from Anallergo (Scarperia e San Piero, Italy) is available in Europe. No clinical trials with this preparation have yet been published.

Vespidae

Vespa venom is available for VIT in some countries. If unavailable, *Vespula* venom appears to be effective despite only partial cross-reactivity.[73]

Vespa velutina venom is commercially available in South Europe. Otherwise, *Vespula spp* VIT appears to be an option in patients with *VV* anaphylaxis based on detectable sIgE to *Vespula* venom.[20] In patients with *VO*allergy, *Vespula spp* VIT has been effective as demonstrated by sting challenges with *VO*.[74]

Formicidae

Effective VIT against *S. invicta* was first demonstrated by case series using whole body extract in 1992 - with 98% success at preventing anaphylaxis on subsequent reported stings.[75,76]

Purified *M. pilosula* VIT proved 100% effective at preventing anaphylaxis in a double sting-challenge during a double-blind randomised-controlled trial.[77] Although highly effective, it is frequently associated with systemic adverse events depending on the up-dosing protocol.[78]

In Thailand, commercially available *S. invicta* whole body extract (WBE) VIT has been employed as a treatment for allergy to *S. geminata* , which exhibits cross-reactivity on allergen testing. [34] In a case series of children, 4 of 14 (29%) VIT-treated children still reacted to further stings. After doubling the standard dose, all children were protected.[79]

A recent case report from Saudi Arabia documented *Brachyponera sennaarensis* Samsun ant WBE immunotherapy being used successfully to treat severe symptoms.[80]

Hematophagous insects

Reaction types & epidemiology

Saliva proteins injected by hematophagous insects during the blood meal regularly induce a humoral and cellular immune response in the host frequently leading to cutaneous adverse reactions. Two main reaction patterns are commonly found in humans and in animals: (1) a short-lived immediate reaction with wheal formation, erythema, and itch occurring within 15 minutes. (2) a delayed skin reaction consisting of an indurated itchy papule of up to 10 mm in size peaking around 24 h after the bite and persisting for days.

There is evidence that the cutaneous immediate reaction represents an IgE-mediated type 1 response while the delayed papule is primarily T-cell mediated.[81,82] Both reaction patterns are ubiquitous within the general population with up to 90% showing immediate skin reactions after mosquito bites, and up to 70% delayed reactions.[81,83-86]

Epidemiological data suggest that hosts pass through different stages of hypersensitivity until acquiring secondary tolerance.

Large local reactions

Approximately 5% suffer from more severe skin reactions including large swellings of up to 10 cm in diameter as well as vesicles and blisters often proceeding to vasculitis and necrosis.[86-88] The underlying pathomechanisms are not well investigated. They might represent type 1 late phase reactions, IgG-mediated type III Arthus reactions, or pure type IV reactions.[86-88] Especially in children, skin lesions may be accompanied by fever, malaise, and lymphadenopathy.[89] Papular urticaria describes a generalized type 4 hypersensitivity characterized by chronic recurrent eruptions due to the bites from fleas and other insects.[90,91] The disease causes significant morbidity, especially in children from tropical countries.

Systemic reactions

Anaphylactic reactions are rare, presumably because of the small amounts of antigen injected during the blood meal. The most frequently reported triggers are horse flies and kissing bugs[92-96] whose salivary glands contain ˜10-30 times more protein than those of mosquitoes.[97] Anaphylaxis has also been documented after

bites from mosquitoes, tsetse flies, and louse flies.[83,98-100] Mastocytosis may be a relevant risk factor for anaphylactic reactions.[98,100]

Relevant insect species

Hematophagy has developed independently in several insect families and is also found in some non-insect arthropods such as the ticks (Table 5). Most blood-feeding insects belong to the order *Diptera* (flies and midges). Mosquitoes, black flies, and biting midges are small hematophagous midges with worldwide distribution often occurring locally in huge numbers. The horse flies, tsetse flies, stable flies, and louse flies are true flies up to 25 mm in size with a more scattered incidence parasitizing preferably big mammals including livestock. Among non-dipterans, the kissing bugs (*Triatominae*) are of local importance as an occasional cause of anaphylaxis, whereas the related bed bug (*Cimex*) is a highly synanthropic parasite with worldwide distribution.

Saliva allergens and cross-reactivity

The saliva of blood-feeding arthropods contains a complex mixture of anti-platelet, anti-clotting, vasodilatory, anti-complement, and anti-inflammatory compounds some of which have been identified as allergens (Table 6). Recent proteomic and genomic research has provided growing insight into the composition and evolution of the "sialome" (the set of salivary proteins encoded by the salivary glands) in different blood-feeding insects.[101] Some saliva proteins represent ubiquitous proteins also found in Hymenoptera venoms (e.g. antigen 5, phospholipases, hyaluronidase), while others are more unique and limited to certain insect orders, families, or even genera. As a consequence, sensitization may be limited to a narrow panel of species in some patients while involving broad cross-sensitization in others.

Mosquitoes (Culicidae)

Relevant mosquito saliva allergens have been successfully identified when using salivary gland extracts or pure saliva instead of whole-body extracts[102-105] but to date, only a few have been characterized on a molecular level. Most studies have been carried out on *Aedes* .[106-108] Four *Aedes aegypti*allergens (Aed a 1-4, (Table 6) have been cloned and well characterized in clinical studies.[109-113] Homologues have also been cloned from *Aedes albopictus* .[114] The allergens from *Culex* and *Anopheles* are less well studied.[114,115]

There is evidence from clinical and laboratory studies of cross-reactivity between different mosquito species.[108] In any case, *in vitro*cross-reactivity may be limited between less closely related mosquito species[102,116] and even between congeneric species.[117] The similarity between homologous allergens from different mosquito species may be low; for example, identity between the D7 proteins Aed a 2 and Cul q 2 is <35%.[114]

Horse flies (Tabanidae)

Three salivary allergens have been cloned from the Asian horse fly *Tabanus yao* .[94,118] All three allergens, representing apyrase (Tab y 1), hyaluronidase (Tab y 2), and antigen 5 (Tab y 5), were major allergens in patients with systemic reactions after horse fly bites. The SI between Tab y 1 and *Aedes aegypti*apyrase Aed a 1 is 36%, that of Tab y 2 with vespid and honey bee hyaluronidases ˜40%. Tab y 5 showed only low SI with Ves v 5 and other wasp antigens 5.

Black flies (Simuliidae)

Three black fly allergens, including antigen 5 (Sim vi 1) as well as serine protease inhibitor and alpha-amylase, have been identified in*Simulium vittatum* saliva using sera from horses with insect bite hypersensitivity.[119] Recent human studies identified four major salivary gland allergens of the Asian black fly *Simulium nigrogilvum* ,[120] two of them representing a D7-like and an antigen 5-like protein.

Biting midges (Ceratopoginidae)

Using sera from horses with insect bite hypersensitivity, more than 10 allergens have been identified in various *Culicoides* species, including antigen 5, hyaluronidase, and D7-like allergens.[119] Completely different proteins

have been described in human studies using whole-body extracts from the Asian biting midge *Forcipomyia taiwana* ,[84,121] but it is uncertain whether they represent relevant saliva allergens.

Tsetse flies (Glossina spp.)

An antigen 5 (Glo m 5) has been cloned and shown as a relevant allergen for patients with anaphylaxis after tsetse fly bites.[83] IgE reactivity with Glo m 5 has been seen frequently in random African serum samples suggesting that sensitization is common within the local population.

Fleas (Siphonaptera)

A 18 kDa salivary protein of unknown biochemical identity (Cte f 1) represents a major cat flea allergen for dogs with allergic dermatitis.[122] Another cat flea allergen first described from whole-body extracts (Cte f 2)[123,124]has been recently identified as an antigen 5-like protein.[91]

Kissing bugs and bed bugs (Heteroptera)

In *Triatoma protracta* , a 20 kDa protein (Tria p 1) has been identified as a major salivary allergen belonging to the lipocalin family.[125] No cross-reactivity has been observed between different *Triatoma* species.[126]Nitrophorin (Cim l NP, 32 kDa), also a lipocalin, has been shown to be a major bed bug saliva allergen.[127]

Key points

- Allergic reactions are caused by saliva allergens.
- LLR after bites of hematophagous insects occur in approximately 5% of the general population.
- SSR are rare; the most frequently reported triggers are horse flies and kissing bugs. Occasionally, SSR may occur after bites of mosquitoes, tsetse, and louse flies. Mastocytosis may be a relevant risk factor for SSR.

Diagnosis (see Table 5)

Diagnosis relies strongly on medical history. Clinical presentation of skin lesions is, in itself, rarely diagnostic of a particular insect. Flea and bedbug bites frequently display a characteristic pattern known as "breakfast, lunch, and dinner".[128]

Commercial extracts for skin testing and *in vitro* IgE determination are available only for a very limited number of species. They are, throughout, whole-body extracts with low sensitivity due to small amounts of relevant saliva allergens.[91,114,129]They also have low specificity since they contain inhalant allergens unrelated to insect bite hypersensitivity (e.g. tropomyosin).[91,129] Irrelevant IgE-binding may also occur through CCDs.[130] Several saliva allergens have been expressed as recombinant proteins, yet none of them has become commercially available for routine diagnosis.

The expected benefits of improved IgE diagnostics need to be clarified. IgE testing may be decisive in hypersensitivity to insects rarely causing sensitization but less so in, for example, mosquito allergy where up to 80% of the general population show type 1 sensitization.[85] IgE levels in "allergic" subjects and those with "normal" skin reactions substantially overlap making detection of discriminative cut-off levels difficult.[99,131] Significant morbidity in insect bite hypersensitivity is linked with delayed cell-mediated large local reactions where IgE-directed diagnostics may have limited value. Another diagnostic problem is the large number and geographic variability of relevant insect species and the uncertain cross-reactivity between them.

Treatment and prevention

Topical antihistamines are widely used for skin lesions despite low evidence from controlled studies of their effectiveness and high risk of photosensitivity.[86] Early use of topical steroids may be beneficial in preventing severe local reactions.[87]Pretreatment with oral antihistamines in normal daily doses significantly reduces wheal size and itch of mosquito bite-induced immediate reactions in adults and children.[132-135]

Bite avoidance is a key measure in the management of insect bite hypersensitivity. Among insect repellents, DEET (N,N-diethyl-3-methylbenzamide) and icaridin/picaridin are considered the most powerful, showing efficacy against a broad array of insects as well as ticks.[136] At appropriate concentrations, both may also be used in children 2 years and older. Optimal insect and tick control can be achieved by additionally treating clothing and nets with permethrin which simultaneously acts as a repellent and an insecticide.[137]

Specific immunotherapy has been carried out in a limited number of studies in adults and children with cutaneous or systemic mosquito bite allergy.[138-141] All reported a significant benefit from immunotherapy, but study quality was throughout low in terms of control subjects, patient number, or read-out parameters. All studies used whole-body extracts of unknown composition and quality.

Arachnida

Reaction types

Non-IgE-mediated reactions

Several blood-feeding *Arachnida* affect human health. Hemolytic and proteolytic enzymes in spider and scorpion venoms may have severe cytotoxic, neurotoxic or cardiotoxic effects[142] and can cause acute generalized exanthematous pustulosis (AGEP),[143-146] erythema multiforme[147], and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS).[148] Ticks are generally known as vectors of bacterial infections (e.g. Lyme disease).*Amblyomma* tick bites may cause local annular erythema of unclear pathogenesis known as Southern tick-associated rash illness (STARI).[149]

Mite and ticks bites can provoke itching and local hypersensitivity reactions such as papular urticaria and vesiculopapular eruptions thought to be due to immune reactions to salivary proteins. Also "summer penile syndrome" in children, is considered to be an immunologic hypersensitivity reaction to chigger bites.[150]

IgE-mediated reactions

Mites

Several cases of anaphylaxis after bites from *Ixodes* ticks including fatal cases have been reported from Australia, the United States, and Europe.[151,152] In Europe, bites from*Argas reflexus* (European pigeon tick), an urban pest parasitizing wild urban pigeons, have been identified as a cause of nocturnal anaphylaxis.[153]

Scorpions The scorpions include over 2200 species, of which more than 100 are considered medically relevant.[154] Systemic allergic reactions have rarely been described after stings by the slightly toxic North American Common striped scorpion *Centruroides vittatus* .[154,155] Sensitization was confirmed by intradermal skin test or western blotting. A significant cross-reactivity was described between *Centruroides vittatus* and*Solenopsis invicta* venom. [155]

Local and systemic reactions have also been reported after stings by*Androctonus australis* (North African fat-tailed scorpion) in Algeria, with less than half of patients showing a positive skin test or specific serum IgE.[156]

Ticks Bites from ticks can lead to sensitization to galactose- alpha-1, 3- galactose (α-Gal) responsible for delayed IgE-mediated anaphylaxis after meat ingestion. In the United States, *Amblyomma americanum* , also known as the lone star tick, is the primary cause of this disease, but different ticks are responsible in other countries.[157]

Allergens and cross-reactivity

The only arachnid allergen characterized so far is Arg r 1, the major allergen from the pigeon tick *Argas reflexus* (Table 6).[153,158,159] Arg r 1 is a lipocalin showing about 20% SI with lipocalins from furry animals and cockroach, and 25–35% identity with other tick lipocalins.[158]Cross-reactivity has been suggested between bee and tick allergens[152] and between scorpions and fire ants[155] based on whole venoms or WBE but has not

yet been investigated on a molecular level. Scorpion venoms contain class III PLA2s with high structural similarity to honey bee venom Api m 1 and an overall SI of 35-40%.

Diagnosis

Diagnosis of reactions to mites and scorpions is mainly based on cutaneous inspection and anamnesis. Specific IgE to *Argas reflexus* can be determined with the research ImmunoCAP U101 (ThermoFisher, Waltham, USA) or allergen macro array ALEX2 (MacroArray Diagnostics GmbH, Vienna, Austria). Specific IgE determination to α-Gal can be done with the ImmunoCAP.

Key points

- *Argas reflexus* bites may explain cases of nocturnal anaphylaxis, otherwise generally diagnosed as idiopathic anaphylaxis.
- Currently, sIgE to *Argas reflexus* can be determined with ImmunoCAP and ALEX2.
- Delayed IgE-mediated anaphylaxis to mammalian meat caused by α-Gal can be diagnosed with the ImmunoCAP.
- Cross-reactivity between fire ant venom and scorpion has been described.
- Rarely, immunologic reactions following spider bites are reported such as AGEP, erythema multiforme, and DRESS.

Cross-reactions between Hymenoptera and reptiles

Anaphylaxis to snake venoms is rare but has been described after recurrent exposure through snake bites or inhalation of dried venom in 9-10% of snake handlers.[160,161] Even regular skin contact with snake venom without a bite can lead to anaphylaxis.[162] It appears that anaphylaxis to snake venoms is IgE-mediated. However, it has also been shown that snake envenoming is characterized by significant complement activation and release of inflammatory mediators leading to non-allergic anaphylaxis (formerly called anaphylactoid reactions).[163]

Snake venoms are a complex mix of enzymatic and non-enzymatic proteins and peptides. Potential candidates for cross-reactivity are PLA2, hyaluronidase[164], and dipeptidyl peptidase IV.[165] Snake PLA2s belong to class I or II PLA2s sharing less than 19% SI with bee PLA2 (class III), indicating that there is no relevant cross-reactivity. Higher identities (>40%) are seen with the class III PLA2 from*Heloderma* (Gila monster).

Hyaluronidases and dipeptidyl peptidases of bees and wasps share about 30% of their sequence with snake homologs (Table E1; sequences of proteins were searched in the Uniprot knowledgebase[166]and compared with Clustal Omega[167]). In this light, clinically relevant cross-reactivity to snake proteins appears to be highly unlikely. Consequently, no case report of insect venom allergic patients who also reacted to snake venom has been published so far.

Key points

Anaphylaxis to snake venoms is rare and mainly seen in snake handlers.

Snake venom phospholipase, hyaluronidase, and dipeptidyl peptidase IV share only 18-35% of their sequence with their counterparts in insect venom.

To date, no case of clinically relevant cross-reactivity has been described.**References**

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Table 1: Hymenoptera rarely causing systemic allergic reactions.

Family	*Genus / Species* **Scientific name**	*Species* **Common name**	**Distribution**	**Local Morb.**	**Diagnostics**	**Venom Immunotherapy**
Apidae	*Apis dorsata*	Giant honey bee	South Asia[3,70]	+++	none; optionally with *Apis mellifera* venom[4,70]	none; optionally with *Apis mellifera* venom
	Bombus terrestris	Large earth bumblebee	Asia, Europe, North America	++	*Skin test* Anallergo* *sIgE* ImmunoCAP** optionally with *Apis mellifera* venom	Anallergo* optionally with *Apis mellifera* venom
	Xylocopa tranquebarica	Carpenter bee	South/Southeast Asia	+	none; optionally with *Apis mellifera* venom[13]	none; optionally with *Apis mellifera* venom
Vespidae	*Vespa crabro*	European hornet	Europe, North America	+	*Skin test* Anallergo * *sIgE* ImmunoCAP** Basophil activation test***	Anallergo*
	Vespa velutina	Asian hornet	Asia, Western Europe	+++	*Skin test* Roxall# *sIgE* ImmunoCAP**	Roxall#
	Vespa affinis	Lesser banded hornet	Southeast Asia, New Guinea	+	NA	NA
	Vespa orientalis	Oriental hornet	South Europe, Near-/Middle East, North Africa	+	NA	NA
	Polybia paulista		South America	+++	NA	NA
	Ropalidia marginata		Asia	+	NA	NA

*Anallergo, Scarperia e San Piero, Italy; **ThermoFisher Scientific, Waltham MA, USA**;** ***Bühlmann Laboratories AG, Schönenbuch, Switzerland; #Roxall Medicina España SA, Zamudio, Spain**;**

Local Morb.: (Apparent) local morbidity + isolated case reports; ++ case series; +++ public health concern with geographic health response

Table 2: Worldwide ant species associated with reported SSR

Subfamily	*Species* **Scientific name**	*Species* **Common name**	**Distribution**	**Local Morb.**	**Diagnostics**	**Venom Immunotherapy**
Myrmeciinae	*Myrmecia pilosula*	Jack jumper ant	Southern Australia[29]	+++	*Skin test* purified Venom: available in public specialist treatment centers* *sIgE* ImmunoCAP Nationally available non-commercial validated referred pathology test**	Standardized purified venom immunotherapy at state public treatment centers**
	Myrmecia pyriformis	Brown bulldog ant	Southern Australia[29]	++	Research only	None
Myrmicinae	*Solenopsis invicta*	Red imported fire ant	Native South America. Invasive Southern United States & Caribbean, China. Eradication programs in Northern Australia & New Zealand.[168]	+++	*Skin test* - ALK-Abello*** - Julilant Hollister Steer Allergy# - Stallergenes Greer## *sIgE* - *Solenopsis invicta WBE;* Immuno-CAP### - Immulite++ - ALEX2++++	*Whole body extract* - ALK-Abello*** - Julilant Hollister Steer Allergy# - Stallergenes Greer##
	Solenopsis richteri	Black imported fire ant	Native South America. Invasive Southern United States & Caribbean	+++	*Skin test* - Stallergenes Greer## - ALEX2++++	*Whole body extract* - Stallergenes Greer##

Subfamily	*Species* **Scientific name**	*Species* **Common name**	**Distribution**	**Local Morb.**	**Diagnostics**	**Venom Immunotherapy**
	Solenopsis geminata	Tropical fire ant	Native to southern United States, & South America. Invasive Europe, Africa, Southern & South East Asia, Australia, and Pacific Islands[169]	+++	Research only/locally available.	None (expert recommendations to use other *Solenopsis spp* venom due to cross-reactivity)
	Solenopsis xyloni	Southern fire ant	Native to southern United States[35]	++		
	Solenopsis aurea	Desert fire ant	Native to southern United States & Mexico[35]	++		
Ectatomminae	*Rhytidoponera metallica*	Greenhead ant	Eastern Australia[29]	++	Research only	None
Ponerinae	*Brachyponera sennaarensis*	Samsun ant	Native Africa, Middle East[37]	++	Non-commercial locally produced	*Whole body extract* (local production)
	Brachyponera chinensis	Asian needle ant	Native Japan and east Asia. Invasive United States range[38]	+	Research only	None
Pseudomyrmecinae	*Tetraponera rufonigra*		Native to South and South-East Asia[41,170]	++		None (but some data to use other *Solenopsis spp* venom due to cross-reactivity)[79]

Subfamily	*Species* **Scientific name**	*Species* **Common name**	Distribution	Local Morb.	Diagnostics	Venom Immunotherapy
	Pseudomyrmex ejectus	Twig or oak ant	Native to southern United States & Mexico[35]	+	None	None

WBE: whole body extract;

*Royal Hobart Hospital, Hobart TAS, Australia (non-commercial); **SA Pathology, Adelaide SA, Australia; ***ALK-Abello, Round Rock TX, USA; #Julilant Hollister Steer Allergy, Spokane WA, USA; ##Stallergenes Greer, Cambridge MA, USA; ###ThermoFisher Scientific, Waltham MA, USA; ++Siemens Healthcare, Erlangen, Germany; ++++Macro Array Diagnostics, Vienna, Austria Local Morb.: (Apparent) local morbidity + isolated case reports; ++ case series; +++ public health concern with geographic health response

Table 3: IUIS-accredited allergens from Hymenoptera rarely causing systemic allergic reactions.

Family	Species	Allergen name	MW [kDa]	Allergen family
Apidae	*Apis dorsata*	Api d 1	16	phospholipase A2
	Bombus terrestris	Bom t 1	16	phospholipase A2
		Bom t 4	27	serine protease
	Bombus pennsylvanicus	Bom p 1	16	phospholipase A2
		Bom p 4	27	serine protease
Vespidae	*Vespa crabro*	Vesp c 1	34	phospholipase A1
		Vesp c 5	23	antigen 5
	Vespa velutina	Vesp v 1	36	phospholipase A1
		Vesp v 5	23	antigen 5
	Vespa mandarinia	Vesp m 1	34	phospholipase A1
		Vesp m 5	23	antigen 5
	Vespa magnifica	Vesp ma 2	35	hyaluronidase
		Vesp ma 5	25	antigen 5
	Polybia paulista	Poly p 1	34	phospholipase A1
		Poly p 2	33	hyaluronidase
		Poly p 5	21	antigen 5
Formicidae	*Myrmecia pilosula*	Myr p 1	8	pilosulin 1
		Myr p 2	9	pilosulin 3
		Myr p 3	8	pilosulin 4.1
	*Brachyponera chinensis**	Pac c 3	23	antigen 5
	Solenopsis invicta	Sol i 1	18	phospholipase A1
		Sol i 2	14	unknown
		Sol i 3	26	antigen 5
		Sol i 4	12	unknown
	Solenopsis richteri	Sol r 2	13	unknown
		Sol r 3	24	antigen 5
	Solenopsis geminata	Sol g 2	13	unknown
		Sol g 3	24	antigen 5
		Sol g 4	12	unknown

www.allergen.org; retrieved on March 23, 2023

*formerly Pachycondyla chinensis

Table 4: Cross reactivities between allergens of rare stinging Hymenoptera.

Family	Species	Allergen name	Allergen family	Species	A
Apidae	*Bombus terrestris*	Bom t 1	phospholipase A2	*Apis mellifera*	A
		Bom t 4	protease	*Apis mellifera*	A
Vespidae	*Vespa crabro*	Vesp c 1	phospholipase A1B	*Vespula vulgaris*	V
	Vespa velutina	Vesp v 1	phospholipase A1	*Vespa crabro*	V
		Vesp v 5	venom allergen 5	*Vespa crabro*	V
	Vespa magnifica	Vesp ma 5	antigen 5, member of PR-1 family	*Vespa crabro*	V
	Polybia paulista	Poly p 1	phospholipase A1	*Polistes dominulus*	P
				Vespula vulgaris	V
		Poly p 2	hyaluronidase	*Polistes dominulus*	P
				Vespula vulgaris	V
		Poly p 5	venom group 5	*Polistes dominulus*	P
				Vespula vulgaris	V
Formicidae	*Pachycondyla chinensis*	Pac c 3	antigen 5	*Vespula vulgaris*	V
	Solenopsis invicta	Sol i 1	phospholipase A1B	*Apis mellifera*	A
				Vespula vulgaris	V
		Sol i 3	antigen 5	*Brachyponera chinensis*	P

*Amino acid sequence alignment performed on uniprot.org.

Table 5: Haematophageous arthropods causing allergic reactions.

Scientific name	Common name	Important genera/species
Culicidae	Mosquitoes	*Aedes, Culex, Anopheles*
Simuliidae	Black flies	*Simulium*
Ceratopogonidae	Biting midges, no-see-ums	*Culicoides, Forcipomyia*
Phlebotominae	Sand flies	*Phlebotomus, Lutzomyia*
Tabanidae	Horse flies, deer flies	*Tabanus, Haematopota, Chrysops*
Glossinidae	Tsetse flies	*Glossina*
Muscidae	House and stable flies	*Stomoxys calcitrans* (stable fly)
Hippoboscidae	Louse flies, keds	*Hippobosca equina* (horse louse fly), *Lipoptena cervi* (deer ked)
Siphonaptera	Fleas	*Ctenocephalides felis* (cat flea), *C. canis* (dog flea), *Pulex irritans* (
Reduviidae/ Triatominae	Kissing bugs	*Triatoma protracta, T. rubida*
Cimicidae	Bed bugs	*Cimex lectularius* (bed bug), *C. hemipterus* (tropical bed bug)

C: cutaneous; S: systemic; WBE: whole body extract; *ThermoFisher Scientific, Waltham MA, USA; **Siemens Healthcare, Erlangen, Germany

Table 6: Relevant IUIS-accredited salivary gland allergens from blood-feeding arthropods.

Family	Species	Allergen name	MW [kDa]	Allergen family
Mosquitoes (Culicidae)	*Aedes aegypti*	Aed a 1	68	Apyrase
		Aed a 2	37	D7 protein family (long form
		Aed a 3	30	30 kDa family (aegyptin)

Family	Species	Allergen name	MW [kDa]	Allergen family
		Aed a 4	67	alpha-glucosidase
	Aedes albopictus	Aed al 2	33	D7 protein family (long form
		Aed al 3	30	30 kDa family (aegyptin)
		Aed al 13	27	Antigen 5-3
		Aed al 14	34	Salivary antigen LIPS-2 / 34
	Culex quinquefasciatus	Cul q 2	33	D7 protein family (long form
		Cul q 3	35	D7 protein family (long form
	Anopheles dirus	Ano d 2	15	D7 protein family (short for
Horse flies (Tabanidae)	*Tabanus yao*	Tab y 1	70	Apyrase
		Tab y 2	35	Hyaluronidase
		Tab y 5	26	Antigen 5-like
Biting midges (*Ceratopogonidae*)	*Forcipomyia taiwana*	For t 1	24	Serin/Threonin protein kina
		For t 2	36	eukaryotic translation initiat
Tsetse flies (*Glossinidae*)	*Glossina morsitans*	Glo m 5	27	Antigen 5-like
Fleas (Siphonaptera)	*Ctenocephalides felis*	Cte f 1	18	unknown
		Cte f 2	27	Antigen 5-like
		Cte f 3	25	unknown
Kissing bugs (*Triatominae*)	*Triatoma protracta*	Tria p 1	20	Lipocalin
Soft ticks (Argasidae)	*Argas reflexus*	Arg r 1	17	Lipocalin

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Figure 1: Vespids: most important Vespula species worldwide

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`image17.emf` available at https://authorea.com/users/377221/articles/638860-allergy-to-stings-and-bites-from-rare-or-locally-important-arthropods-worldwide-distribution-available-diagnostics-and-treatment

? *Vespula vulgaris, germanica* (Eurasia) ? *Vespula pensylvanica, alascensis, squamosa, maculifrons, flavopilosa* et al. (Northern America) ? *Vespula flaviceps, koreensis, shidaii* (Asia)

Figure 2: Ants: most important genera worldwide

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`image18.emf` available at https://authorea.com/users/377221/articles/638860-allergy-to-stings-and-bites-from-rare-or-locally-important-arthropods-worldwide-distribution-available-diagnostics-and-treatment

? *Solenopsis invicta*

? *Solenopsis geminata*

? *Solenopsis xyloni* & *aureus* (northern limit of distribution)

? *Myrmecia pilosula, pyriformis* & *forficata*

? *Brachyponera chinensis*

? *Brachyponera sennaarensis*

Figure 3: Hornets: most important species worldwide

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image19.emf available at https://authorea.com/users/377221/articles/638860-allergy-to-stings-and-bites-from-rare-or-locally-important-arthropods-worldwide-distribution-available-diagnostics-and-treatment

? *Vespa crabro* (European hornet)

? *Vespa orientalis* (Oriental hornet) ? *Vespa velutina* (Asian hornet)