Part I: Insect stings and bites—Beyond the realm of bee and wasp allergies: A survey of the literature and our own cases

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Part I: Insect stings and bites—Beyond the realm of bee and wasp allergies

A survey of the literature and our own cases

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Summary

Background Insects are a very diverse group of animals and valuable members of any ecosystem. Allergies to bees and wasps (order: Hymenoptera) are well known in Europe. Allergies, toxicities, and the spread of diseases by other insects are also possible but quite frequently are not diagnosed.

Sources A MEDLINE search on allergy caused by stinging and biting insects apart from bees and wasps was conducted. All relevant articles were evaluated, and a selection of relevant publications and cases from our outpatient units are used to illustrate our arguments.

Content and implications Allergies to insects following bites and stings are common. Ant stings, mainly from imported fire ants, frequently lead to severe anaphylaxis, and their venom can elicit systemic toxic effects. Stings and bites of various other ant species can also lead to severe allergic reactions. Mosquito stings and horsefly or other Diptera stings may elicit severe local and IgE-mediated systemic reactions. True bugs (Hemiptera) are hematophagous insects and can also cause severe allergic reactions, in addition to being feared for transmitting diseases.

Introduction

Arthropods are a phylum of invertebrate animals, including insects, crustaceans, spiders, mites, ticks, and others. Fig. 1 provides a summary of the phylogenetic relationships within arthropods [1].

Insects are invertebrates with three pairs of legs and form the largest group within the arthropod phylum. In fact, insects are the most diverse animals on the planet, encompassing more than a million described species, thus representing over 90% of animal life forms on earth [2]. Their stings, bites, and excrements can cause mild to life-threatening allergic reactions, illicit toxic effects, lead to various skin changes and act as vectors of disease transmission. Diagnosing illness following insect stings, bites, inhalation, or ingestion can be challenging due to their often hidden character and because of mimicry of other conditions [3]. Table 1 provides an overview of allergologically relevant insects, allergy mechanisms, and typical clinical findings.

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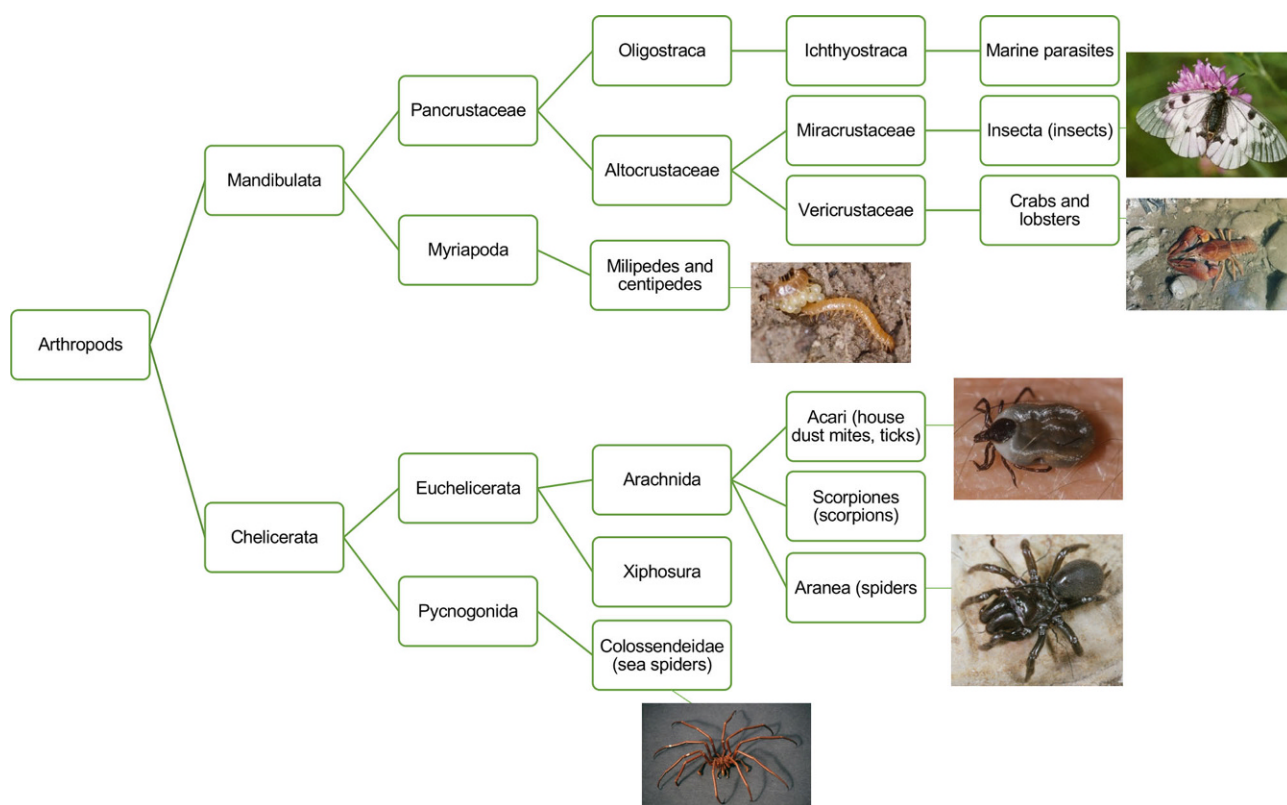CK-CARE, Davos, Switzerland

Fig. 1 Phylogenetic relationships within the arthropods. (Adapted from: Regier JC et al., *Nature* 2010 [1]. Images: Insecta: Clouded Apollo [*Parnassius mnemosyne*], Entomologie/Botanik, ETH Zürich/Photographer: Albert Krebs, CC BY-SA 4.0. Crabs and lobsters: European crayfish [*Astacus astacus*], Entomologie/Botanik, ETH Zürich/Photographer/Albert Krebs, CC BY-SA 4.0. Millipede [*Geophilus flavus*]. ETH-Bibliothek Zürich, Bildarchiv/Photographer: Keller, Siegfried, CC BY-SA 4.0. Acari: Hard bodied tick [*Ixodes* sp.], ETH-Bibliothek Zürich, Bildarchiv/Photographer/Keller, Siegfried, CC BY-SA 4.0. Aranea: Purseweb spider [*Atypus* sp.], Entomologie/Botanik, ETH Zürich/Photographer/Albert Krebs, CC BY-SA 4.0. Colosseneidae: Sea spider [Pycnogonida]. Joy Viola, Northeastern University, Bugwood.org, with permission)

Methods

Search methods A literature search was conducted in PubMed in May 2021. The search terms included "Insect, allergy and/or Hymenoptera, ant, imported fire ant, *Solenopsis invicta*, red wood ant *Formica rufa*, Chinese needle ant, *Pachycondyla* spp., Jack jumper ant, *Myrmecia* spp., green-head ant, *Rhytidoponera metallica*, harvester ant, *Pogonomyrmex* spp., *Solenopsis geminata*, Solenopsis richteri, *Solenopsis saevissima*, Diptera, true flies, Neoptera, Tabanidae, *Haematopoda, Chrysops, Chrysops vittatus*, mosquito, *Aedes aegypti, Aedes vexans, Anopheles, Plasmodium*, Hemiptera, true bug, bed bug *Cimex lectularis, Cimex hemipterus*, Triatominnae, kissing bug, Mexican bed bug, *Trypanosoma cruzii*, Chagas disease, sucking lice, Pediculidae, Phthiraptera, fleas, Siphonaptera". Pivotal papers describing initial descriptions of allergies to above-mentioned insect orders, families or species, newest insights, papers by key opinion leaders, and society guidelines were considered. Additional studies were identified using bibliographical information contained in selected articles. Articles regarding bee and wasp allergies were deliberately not covered in detail in this article.

Case description Illustrative cases from our outpatient clinics are also included.

Results

Hymenoptera—Bees, wasps, and ants

Allergic reactions to hymenopteran venoms after stings or bites, especially bee and wasp stings, are common and a leading cause of anaphylaxis in Europe [4]. The order Hymenoptera also includes the family Formicidae, e.g., the imported fire ant (*Solenopsis invicta*; IFA) or the red wood ant (*Formica rufa*). Ants are a very diverse family, consisting of 22 subfamilies encompassing more than 14,000 species [5]. A comparatively small number of ants have been identified to cause allergic reactions, including specific IgE-mediated allergies to various venom proteins [6].

Like many ant species, the red wood ant (*Formica rufa*) has lost its stinging ability during evolution. However, it has a powerful chewing apparatus and can inject its venom directly into the bite wound [7].

Native to South America and introduced in North America from the middle of the 20th century, the IFA is known for its excruciating sting and the ability to

Table 1 Overview of allergologically relevant insects and clinical findings presented in this article

Order and family	Genus or species	Route of allergen exposure	Clinical manifestation	Disease transmission	Molecular allergen (WHO/IUIS) [99]	Distribution	Reference
Hymenoptera: Formicidae	Imported fire ant, IFA (*Solenopsis invicta*)	Sting, injection of venom	Painful sting, large LR, sterile pustule formation, Ven_tox, IgE-Anaphylaxis	No	Sol i 1-4	Native to South America, spreading to USA, Australia, Asia since mid-1950s	Tankersley (2015) [5]
	Red harvester ant (*Pogonomyrmex barbatus*)	Sting, injection of venom	Painful sting, large LR, Ven_tox, IgE-Anaphylaxis	No	NA	Southern USA, Mexico	Klotz (2009) [11], Pinnas (1986) [81]
	Red wood ant (*Formica rufa*)	Bite, spray with venom	Mild LR, IgE-Anaphylaxis rare	No	NA	Europe, North America	Schmid-Grendelmeier (1997) [23], Seebach (2000) [7]
	Chinese needle ants (*Pachycondyla chinensis*)	Sting, injection of venom	Mild to large LR, IgE-Anaphylaxis	No	Pac c3	East Asia, North America	Nelder (2006) [9]
	Samsum ant (*Brachyponera sennaarensis*)	Sting, injection of venom	Mild to large LR, IgE-Anaphylaxis	No	NA	Middle East, Asia	Alsharani (2009) [21]
	Jack jumper ant (*Myrmecia pilosula*)	Sting, injection of venom	Very aggressive, large LR, IgE-Anaphylaxis, Ven_tox	No	Myr p1-3	Tasmania, Australia	Street (1994) [10], Brown (2003) [22]
Diptera: Tabanidae	Horse and deer flies (*Tabanus, Chrysops, Haematopota*)	Blood-sucking ectoparasite, allergen-containing saliva	Mild to large LR, IgE-Anaphylaxis	Transmission of diverse pathogens to humans is possible as an intermediate host or mechanically (contaminated blood on the mouth part of the fly)	NA	Global distribution	Whyte (2020) [28], Hemmer (1998) [30]
Diptera: Culicidae	Yellow fever mosquito (*Aedes aegypti*)	Blood-sucking ectoparasite, allergen-containing saliva	Mild to severe immediate and delayed type LR (wheals and flares, itchy papules, papular urticaria, bullae, ecchymosis, Skeeter syndrome); IgE-Anaphylaxis possible but rare	Yellow fever, dengue fever, Zika fever, several other viral diseases	Aed a 1-11	South America, Middle America, Southern USA, Africa, Southeast Asia, India, Australia	Simons (1999) [44], Reunala (1990) [45], Peng (2004) [42], Galindo (1998) [47], McCormack (1995) [48]
Hemiptera: Reduviidae	Kissing bugs (*Triatoma* spp.)	Blood-sucking ectoparasite, allergen-containing saliva, parasite-laden (*T. cruz*) feces	First bites: Little to no reaction, repeated exposure: cutaneous manifestations (erythema, papules, vesicles, hemorrhagic bullae). IgE-Anaphylaxis common	Chagas disease	Tria p 1	South America, Middle America, Southern USA, Africa, Southeast Asia, India, Australia	Pinnas (1986) [81], Marshall (1986) [77, 78], Moffitt (2003) [79], Paddock (2001) [80]
Hemiptera: Cimicidae	Bed bugs (*Cimex lectularis, Cimex hemipterus*)	Blood-sucking ectoparasite, allergen-containing saliva	Usual, common and complex local reactions; anaphylaxis not certain	No	NA	Worldwide	de Shazo (2012) [68]

Table 1 (Continued)

Order and family	Genus or species	Route of allergen exposure	Clinical manifestation	Disease transmission	Molecular allergen (WHO/IUIS) [99]	Distribution	Reference
Phthiraptera/ Pediculidae	Lice (*Pediculus humanus capitis, corporis, pubis*)	Blood sucking ectoparasite, allergen-containing saliva, airborne	Itch, dermatitis due to saliva, IgE-mediated reactions (asthma, nasal and ocular allergy) rare	*Pediculus corporis*: Transmission via feces of epidemic typhus (*Rickettsia prowazekii*), relapsing fever (*Borrelia recurrentis*), five-day fever (*Bartonella quintana*). *Pediculus capitis and pubis*: Not known to transmit disease	NA	Worldwide	Lafeber (1984) [86], Fernández (2006) [87], de las Marinas (2019) [88]
Siphonaptera/ Pulicidae	Common cat flea (*Ctenocephalides felis felis*)	Blood sucking ectoparasite, allergen-containing saliva	Intense pruritus and allergic dermatitis (especially in cats), papular urticaria	Cat scratch disease (*Bartonella henselae*), tapeworms, Flea-borne (murine) typhus (*Rickettsia typhi*)	Cte f 1-2	Worldwide	Benjamini (1963) [92], Bruet (2012) [93], Mc Dermott (2000) [94], Sabogal (2019) [95]

WHO/IUIS World Health Organization/International Union of Immunological Societies Allergen Nomenclature Sub-committee, http://www.allergen.org, *NA* not available, *IgE-Anaphylaxis (I–IV)* IgE-mediated anaphylaxis grade I–IV, *Ven_tox* Direct toxicity of venom, *LR* Local reaction

cause severe, IgE-mediated anaphylaxis. Due to the effects of global warming, which increases climatic suitability for the IFA and reduces the resistance of native ant communities, this invasive species has spread to the United States, the Caribbean, and some Asian countries and is also invading Australia and parts of New Zealand. IFA is the most common cause of ant-induced allergic reactions worldwide [8]. Allergies to ants other than IFA are less common.

In Southeast Asia, imported fire ants and Chinese needle ants (*Pachycondyla* spp.), in Australia, Jack jumper ants (*Myrmecia* spp.) and Green-head ants (*Rhytidoponera metallica*), and in the USA, the harvester ant (*Pogonomyrmex* spp.) can also cause allergies [9–11]. Some cases of allergies induced by the red wood ant (*Formica rufa*), endemic in Europe and North America, have also been reported [7].

After an IFA sting, a dermal flare with wheal, a small vesicle, or a sterile pustule develops within minutes to hours due to direct toxic effects of the ant venom and tissue inflammation caused by the venom ([12]; Fig. 2). The IFA venom is composed of alkaloids, which explains sterile pustule formation after stings [5]. Some patients (17 to 56%) develop a large local reaction consisting of an extremely large and pruritic lesion persisting for up to 72 h [13]. IgE-mediated severe allergic reactions following IFA stings are well documented and sometimes even lead to severe end-organ damage, including rhabdomyolysis, renal failure, and neurotoxic effects, which can also be induced by direct toxic effects of multiple ant stings [14–17].

The diagnosis of immediate-type hypersensitivity to ants is made by correlating the clinical manifestations of the sting reactions with ant-specific IgE determined by skin testing and/or radioallergosorbent test. Major protein allergens were isolated from IFA venoms (Sol I 1-4) and several allergens from other *Solenopsis* species (Sol g2-4 from *Solenopsis geminata*, Sol r2-3 from *Solenopsis richteri,* and Sol s2-3 from *Solenopsis saevissim*a), the Australian jack jumper ant (Myr p1-3, *Myrmecia pilosula*) and the Asian needle ant (Pac c3, *Pachycondyla chinensis*) [8]. Whole-body extracts contain relevant venom allergens and can be used for skin testing and immunotherapy for IFA allergy, Jack jumper ant allergy, Chinese needle ant allergy, and Samsum ant allergy ([18–22].

Fig. 2 Sterile pustules on hand (**a**) and leg (**b**) after fire ant sting. (Sanford Porter, with permission)

Fig. 3 Red wood ant (*Formica rufa*). (Beat Wermelinger, WSL, with permission)

Fig. 4 Red fire ant (*Solenopsis invicta*). (Sanford Porter, with permission)

The following two cases of ant allergy stem from the outpatient department in Zurich [7, 23]:

Case 1: Anaphylaxis due to a redwood ant (*Formica rufa*) bite *A 12-year-old boy sustained an ant bite during a in the forest in September. Prior ant bites and bee and wasp stings had been tolerated well. The boy developed flushing, generalized urticaria, and severe dyspnea only minutes after being bitten. He required treatment with bronchodilators and corticosteroids. Subsequently, the ant that patient had preserved after being stung was identified as a redwood ant (Formica rufa) by an entomologist. A skin prick test with a whole-body extract of red wood ant produced a large wheal and flare. Specific IgE against red wood ant was positive (1.8 U/ml) and thus, anaphylaxis to a red wood ant bite was diagnosed* (Fig. 3).

Case 2: Anaphylaxis due to a red fire ant (*Solenopsis invicta*) sting *A 56-year-old woman developed generalized urticaria and angioedema after being stung by an ant during a holiday in Florida. We strongly suspected a red fire ant venom allergy, as these ants are endemic to Florida and the patient could identify the ants from photos. Diagnostic testing performed in Switzerland showed sensitizations to wasp and hornet allergens measured by ImmunoCAP. Specific IgE to fire ant (i70) was negative. One year after this episode, another sting occurred in Florida, causing more severe anaphylaxis (grade III according to Ring & Messmer; [24]). The consecutively performed skin prick test with commercially available whole-body extract was strongly positive, and specific IgE to Sol i 1 was now positive. However, it remains unclear why IFA-specific IgE and skin testing were negative at the first presentation. Specific venom immunotherapy was initiated following a rush protocol. A sting was well tolerated after the immunotherapy was stopped after five years of continuous treatment* (Fig. 4).

Diptera—True flies

Diptera, or true flies, occur in numerous habitats and have spread to all continents [25]. Numerous hematophagous insects belong to this order, with representatives of the Tabanidae and mosquitoes being particularly relevant in medicine. Respiratory and occupational allergies to Diptera, e.g., common houseflies or fruit flies, are rare [26, 27].

Tabanidae—Horse flies and deer flies

The family Tabanidae contains about 4500 species and subspecies and has a worldwide distribution [27]. The clinically most relevant representatives of the Tabanidae family belong to the genera *Tabanus* and *Chrysops*, all of which occur in Central Europe ([28]; Fig. 5). Local reactions after a tabanid bite are common, but anaphylaxis and systemic symptoms are rare [28, 29]. There are only single cases and small case series describing allergies to Tabanidae [28, 30–35]. Tabanid allergens in saliva are still incompletely characterized. Only three allergens have been identified so far, some of which overlap with mosquito and wasp venom allergens [36]. The diagnosis of an allergy to tabanids is therefore difficult. In cases with significant local reactions, no further investigation is necessary. In patients with anaphylaxis, prick tests are possible, albeit not standardized. A whole-body extract for *Chrysops vittatus* is commercially available (Stallergenes Greer, London, UK). The same limitation applies to in vitro tests, where sensitivity and specificity remain unclear. Although specific immunotherapy was performed in individual cases [37, 38], extracts are not commercially available or standardized and are usually performed using whole-body extracts.

Case 3: Anaphylaxis due to a horsefly (*Tabanus eggeri*) sting *A 35-year-old woman was stung on the*
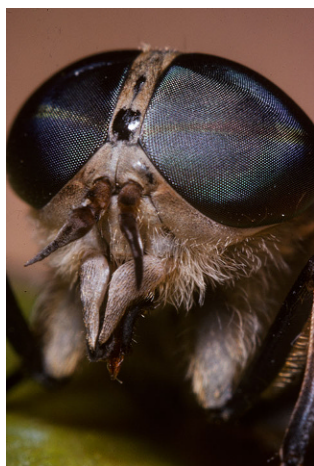
Fig. 5 Pale giant horse-fly (*Tabanus bovinus*). (ETH-Bibliothek Zürich, Bildarchiv/Fotograf: Keller, Siegfried, CC BY-SA 4.0)

back of the head by an insect while bathing in a lake in Switzerland. She identified the insect herself as a horsefly. Minutes after the sting, severe itching occurred on the head, spreading rapidly to the whole body. Generalized urticaria and angioedema in the facial region quickly appeared, followed by hypotension (80 mm Hg, systolic) and bradycardia. Emergency treatment consisted of intravenously administered epinephrine, volume administration, antihistamines, and systemic steroids. The tryptase in the acute event was 14.4 μg/l, the basal value measured later was 4.6 μg/l. Skin test solution for tabanids was not available, specific IgE against horsefly (0.45 kU/L) was positive, and thus the diagnosis of anaphylaxis following a horsefly sting was made.

Culicidae—Mosquitoes

Mosquitoes (Nematocera) are insects within the Diptera order and encompass more than 3500 species worldwide [39, 40]. In allergology, the most important mosquito species are *Aedes aegypti* and *Aedes vexans* [41]. Allergic reactions to mosquito bites are caused by sensitization to mosquito salivary antigens [40, 42]. Specific IgE and IgG antibodies and T-cell mediated delayed-type hypersensitivity reactions are involved in the pathogenesis of mosquito allergy [43]. Common reactions to mosquito stings include immediate-type reactions minutes after the sting, consisting of wheals and flares and delayed reactions manifesting 24 to 36 h after the sting as itchy papules. Late type reactions manifest as vesicles, bullae, ecchymosis, and even Skeeter syndrome and Arthus-type local and systemic reactions [44, 45]. Albeit rare, severe anaphylaxis to mosquito stings is also possible [46–48].

Different mosquito saliva proteins were identified as potential allergens. A correlation of immediate type reactions and mosquito bite-induced anaphylaxis with elevations of serum-specific IgE levels was shown [43]. Immunoassays using recombinant mosquito salivary allergens (rAed a one and rAed a 3) are sensitive and specific for the diagnosis of mosquito allergy [42].

Nevertheless, diagnosing mosquito allergy remains challenging. Skin prick reagents commercially used for diagnosing mosquito allergy contain whole body parts of mosquito and small concentrations of allergenic saliva proteins [49]. To date, no robust studies could prove the effect of desensitization with whole-body extract in treating mosquito allergic patients. Therefore, the most important treatment of mosquito allergy remains prevention from being stung using repellents and mosquito nets. Studies suggest that natural desensitization in mosquito-allergic children may occur during adolescence [46].

In addition to mosquito allergies, bacterial superinfections resulting from scratching itchy lesions after a bite, and transmission of pathogens such as *Plasmodium* (malaria) transmitted by *Anopheles* spp. mosquitoes or Flaviviridae (the causes of yellow fever or dengue fever) are of global health importance [50, 51].

Other Nematocera families like Ceratopogonidae (e.g., biting midges) and Chironomidae have been shown to have allergenic potential both after stinging humans and also as airborne allergens [52, 53].

Hemiptera—True bugs

Hemiptera, or true bugs, are an insect order within the Neoptera. In 2008, there were 82,000 described species, and the total number of species worldwide was estimated to be over 200,000 [54]. Allergic reactions following bed bug (*Cimex lectularius*) and kissing bug (subfamily Triatominae) bites are common, but lesser-known true bugs can also cause allergies when used as food additives, such as cochineal lice (*Dactylopius coccus*) or lac bugs (*Kerria lacca*) [55–58]. Reactions to insects and insect compounds as food will be further discussed in part II of this article. Hemiptera are also important vectors of diseases such as Chagas disease, where kissing bugs transmit the parasite *Trypanosoma cruzi* [59].

Cimicidae—Bed bugs

Bed bugs such as *Cimex lectularis* or *C. hemipterus* were nearly eradicated in Western countries in the 1940s due to pesticides. However, a re-emergence of bed bugs began in the mid-1990s, and their infestation is currently increasing and spreading worldwide [60–62]. Partially, their re-emergence may be due to a resistance to pesticides [63].

Bed bugs are nocturnal bloodsuckers that can live up to 1 year without feeding. The primary hosts are humans and other mammals. Bed bugs are insensitive to cold and die only at temperatures above 41 °C [64]. Due to their small size and adjustability, bed bugs can hide in small loopholes in mattresses or wallpaper and

Fig. 6 Bed bugs (*Cimex lectularis*). (Photo by Stephen Ausmus, USDA Agricultural Research Service, with permission)

Fig. 7 Assassin bug (*Triatoma gerstaeckeri*). (Gabriel Hamer, Texas A&M University, with permission)

travel long distances, for example, in suitcases [65]. The bed bug's bite usually occurs at night and is not noticed at first due to the anesthetic effect of its saliva.

A bed bug bite may give rise to localized cutaneous responses of various manifestations and anaphylactic reactions of different grades [64, 66, 67]. Classification of cutaneous reactions after bed bug bites has been proposed (i.e., usual, common, and complex reactions) [68]. "Usual reactions" occur within one hour and consist of pruritus and no local reaction save for punctiform visibility of the bite site. "Common reactions" occur within hours and manifest as pruritic macules or papules resembling papular urticaria. "Complex reactions" are bullous, pruritic, and may be painful and persist for several days [68–72].

Bullous rashes occurring days after stings could represent late-phase responses of IgE-mediated hypersensitivity [66, 73]. However, severe immediate-type anaphylactic reactions have not been documented with certainty, but sometimes multiple stings can imitate the picture of generalized urticaria, and one case of severe anaphylaxis following bed bug bite mimicking acute coronary syndrome was reported in 2006 [69]. Salivary proteins of bed bugs (nitrophorin, factor X, apyrase-like nucleotide-binding enzymes) are of immunological importance, and specific IgEs to *C. lectularis* crude extract and *C. lectularius* nitrophorin recombinant protein can be present in individuals with a history of bed bug bites [55, 74–76]. The use of high-potency topical corticosteroids and oral antihistamines is the treatment of choice in local bullous reactions, and severe reactions may even require systemic corticosteroids ([68]; Fig. 6).

Triatominae—Kissing bugs

Triatomine insects (also called: kissing bugs, Mexican bed bugs, and cone-nosed bugs) are found mainly in the western and southern United States, Central

and South America, and Mexico (Fig. 7). They are ectoparasites on small mammals and feed on their blood. Bites usually occur on exposed body parts (face, hands, feet) at night and are painless. Kissing bug bites are among the common causes of insect-bite-related allergies [77, 78]. Initial bites produce little to no reaction, and repeated exposure leads to a range of local reactions with variable presentation (erythema, papules, vesicles, hemorrhagic bullae). In addition to cutaneous hypersensitivity reactions, life-threatening immediate-type reactions have been described ("nocturnal anaphylaxis") [79].

The primary allergen identified in triatomine saliva is a 20 kDa protein, which interestingly belongs to the same protein family (lipocalins) as known of inhalation allergens of dogs, cats, and other mammals [80]. Reactivity to two salivary gland extracts of two Triatominae species was demonstrated and immunotherapy using a salivary gland extract showed benefits in a small patient cohort. No commercial testing or treatment allergen is available [81, 82]. While feeding, triatomines defecate parasite-laden feces and can transmit *Trypanosoma cruzii*, the causative organism of Chagas disease [56].

Phthiraptera—Sucking lice

Body lice and head lice (*Pediculus humanus humanus* and *Pediculus humanus capitis*) and pubic lice (*Pthirus pubis*) are hematophagous ectoparasites of humans living on the scalp, body, and pubic or on other areas with coarse hair ([83–85]; Fig. 8). They feed on mammalian blood and cause pediculosis capitis, pediculosis corporis, or pediculosis pubis in humans. Infestation with lice leads to itching, with sometimes eczema caused by the saliva of the parasites. Head lice spend their entire life cycle on their hosts and are not transmitted by pets as vectors. Head lice are

Fig. 8 Head louse (*Pediculus humanus capitis*). (ETH-Bibliothek Zürich, Bildarchiv/Photographer: Keller, Siegfried, CC BY-SA 4.0)

a widespread infestation, especially in children. Few allergic reactions to head lice have been described, including one case of allergic asthma and one case of nasal and ocular allergy induced by a specific IgE-mediated reaction to louse body proteins [86–88]. To date, no allergic reactions to the body or pubic lice have been reported.

Siphonaptera—Fleas

Fleas are small blood-sucking ectoparasites [89] and include more than 2500 species. Fleas play an essential role in veterinary medicine since they frequently lead to allergic flea dermatitis in cats and dogs (FAD) [89]. The common cat flea (*Ctenocephalides felis felis*) is mainly responsible for the development of allergic flea dermatitis ([90]; Fig 9). Albeit rarer, flea allergic dermatitis can also manifest in humans, especially those more commonly exposed to ectoparasites, e.g., homeless people [91]. After a flea bite, the components of flea saliva (polypeptides, phosphorus, amino acids, aromatic amines) cause severe pruritus and papules, crusts, and excoriations [92]. In veteri-

Fig. 9 Cat flea *(Ctenocephalides felis).* (ETH-Bibliothek Zürich, Bildarchiv/Phottographer: Keller, Siegfried, CC BY-SA 4.0)

nary medicine, an intradermal skin test with glycerinated flea antigens can be used to diagnose FAD [93]. Cte f 1 and Cte f 2 are the major allergens described from *Ctenocephalides felis* [94].

In humans, papular urticaria after a flea bite is common [95–97]. In children living in areas where flea bites frequently induce papular urticaria, like in South America, Cte f 2 induces both IgE and IgG production as well as T-cell proliferation [95]. Furthermore, disease transmission by fleas is possible in humans, cats, and dogs, e.g., flea-borne murine typhus [98].

Conclusion

Allergic reactions and direct poisoning following insect stings or bites are common, occur worldwide, and are associated with significant morbidity. Ant stings and bites, especially from imported fire ants, can cause severe anaphylaxis, and their venom can lead to systemic poisoning and end-organ damage. Mosquito and tabanid stings but also as inhaled allergens rarely trigger IgE-mediated reactions. True bugs, such as bed bugs or kissing bugs, are nuisance pests that can cause allergies but can also be a vector for disease transmission, such as kissing bugs causing Chagas disease. Other blood-sucking insects like lice and fleas often cause dermatitis, papular urticaria, whereas severe IgE-mediated reactions are infrequent. Allergic reactions following insect stings or bites may not be detected or diagnosed if the causative insect cannot be identified. For this reason, patients should be encouraged to keep causative insects for identification and diagnostic testing. In uncertain cases, an entomologist should be consulted.

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