

Insect Allergy



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KEYWORDS

- Insect bites • Insect stings • Diagnosis • Treatment • Allergic reaction
- Anaphylaxis • Venom immunotherapy

KEY POINTS

- Insect bites and stings are common and mostly clinically mild, but providers should be aware of potential systemic reactions, including anaphylaxis.
- Common insects that bite or sting include mosquitoes, ticks, flies, fleas, biting midges, bees, and wasps; immunocompromised patients or patients with hypersensitivity reactions may experience large local reactions or papular urticaria.
- The key to diagnosis is a thorough clinical history and identification of the insect when possible; skin testing and serum immunoglobulin E levels are indicated for certain high risk patients.
- Management of insect bites or stings is usually supportive care with antihistamines, pain medications, and cold compresses; patient with anaphylaxis should be given epinephrine and transported to the emergency department.
- Venom immunotherapy (VIT) can be helpful for patients with anaphylaxis or risk for severe reactions; VIT is highly effective in reducing the risk of future reactions.

INTRODUCTION

The purpose of this article is to review the current available material pertaining to insect bites and stings. It will review the development, presentation, and treatment of both common insect bites and insect stings. Although the clinical presentation may be similar between insect bites and insect stings, the evaluation and treatment can differ considerably. The proper diagnosis and treatment can decrease the risk of complications, which can include life-threatening anaphylaxis.

BACKGROUND

Insects are arthropod invertebrates characterized by an exoskeleton and a 3-part body with 3 pairs of jointed legs. There are an estimated 4 to 6 million species of insects,¹ which represent over 50% of all living organisms on earth.² Insect bites and

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stings are common and generally clinically mild, but can lead to serious medical conditions, including life-threatening complications. Common insects that bite include: bedbugs, chiggers, fleas, flies, mosquitoes, and ticks. Common insect stings, involving in the introduction of venom into people, include ants, bees, and centipedes.

EPIDEMIOLOGY

Exact incidence statistics on insect bites or stings is unknown, as most people bitten or stung have mild local reactions that are not reported or tracked. In Europe, between 56% and 94% of people report being stung by a Hymenoptera insect.³ The prevalence of systemic reactions to Hymenoptera stings is reported to be 0.5% to 3.3% in adults and 0.15% to .8% in children.⁴ In Florida, review of emergency department billing codes suggests that 42% of pediatric patients experienced systemic reactions to Hymenoptera stings.⁵

Among stinging ant endemic areas of the United States, 55% of people reported being stung within a 3-week period.³ The prevalence, however, of systemic anaphylaxis to ant stings is reported to be less than 1%.⁶

Approximately 40 to 100 Americans die annually from insect bites or stings, although many experts believe the true mortality is higher.⁷

RISK FACTORS

Risk factors for insect bites and stings are related strongly to environmental exposure. People who live next to bodies of water or wetlands are at risk for mosquitoes, biting midges, or other insects that require nearby water to reproduce. Living near wooded or grassy areas is a risk factor for tick bites. People who work with or live with animals, particularly horses, dogs, or cats are at risk for fly or flea bites. Finally, occupational hazards like gardening or beekeeping increase the risk for insect-specific bites or stings. Seasonal exacerbation of papular urticaria may occur, related to the re-exposure of the insect.⁸

CLINICAL PRESENTATION

Insect bites and stings typically result in mild, local, allergic reactions. Delayed hypersensitivity and systemic reactions including anaphylaxis are rare but may occur. Most insect bites and stings result in a local inflammatory response at the specific site. Large areas of redness, itching, and swelling mimicking cellulitis may occur.⁹ Vesicular or bullous lesions may also arise (**Fig. 1**).¹⁰

One common response to insect bite or stings is papular urticaria (**Table 1**). This insect bite-induced hypersensitivity reaction is common in children ages 2 to 10, but can occur in adolescents and adults. Common insect culprits include mites, ticks, fleas, mosquitoes, and flies. Typically, papular urticaria presents as recurrent erythematous, pruritic papules from 3 to 10 mm in size, with possible vesicles and wheals. Papular urticaria often occurs in a line or grouped in clusters. Extremities and clothing-constricted areas like ankles and waistbands are common presenting areas for papular urticaria. Genital, perianal, and axillary regions are not usually involved.^{8,11}

Immunocompromised patients, including those with human immunodeficiency virus (HIV) or cancer, may develop more severe local allergic reactions and systemic signs, including fever, malaise, headache, and lymphadenopathy (**Fig. 2**).^{12,13} Some patients may develop these systematic symptoms and signs without being immunocompromised. In severe cases, insect bites and stings may cause anaphylaxis, “a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with



Fig. 1. A large bullous reaction to a fire ant bite on the arm. (Courtesy of Mark Lebwohl, MD, Mount Sinai Hospital, New York, NY.)

Table 1 Distribution of papular urticaria as a diagnostic tool				
Arthropod	Exposed Area	Ventral Surfaces	Constricting Band (Waist, Sock)	Generalized
Mosquito	Yes	No	No	No
Flies	Yes	No	No	No
Gnats	Yes	No	No	No
Scabies	Yes	No	No	No
Other mites	Yes	Yes	Yes	No
Ticks	No	No	Yes	No
Lepidoptera	Yes	No	Yes	No

(From Demain JG. Papular urticaria and things that bite in the night. *Curr Allergy Asthma Rep* 2003;3(4):291–303; with permission.)

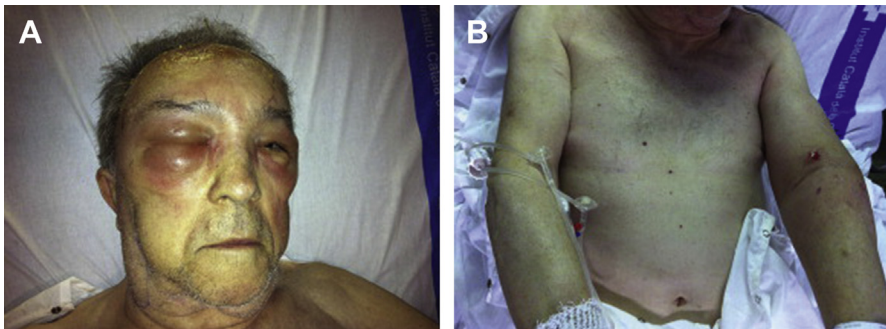


Fig. 2. An exaggerated insect bite reaction on the eye, forehead (A), and arm (B) of a chronic lymphatic leukemia patient. (From Royo-Cebrecos C, Garcia-Vidal C. Exaggerated insect bite reaction related to chronic leukemia. *Mayo Clin Proc* 2013;88(4):e37; with permission.)

an allergy-causing substance.”¹⁴ Criteria for diagnosing anaphylaxis can be found in **Box 1**. The key clinical symptoms include rapid onset, involvement of skin or mucosa, along with cardiovascular or respiratory symptoms. Patients with mast cell disease must be carefully assessed for anaphylaxis after insect bites and stings, especially after bee or wasp stings.¹⁵

MOSQUITOES

Mosquitoes belong to the order Diptera and family Culicidae. They are among the most common insect bites. Symptoms include local swelling, warmth, erythema, pain, and pruritis with accompanying papules and wheals. Some patients may experience larger local reactions with ecchymosis or vesicular lesions accompanied by systemic symptoms including fever, generalized urticaria, wheezing, and angioedema (**Fig. 3**). A serum sickness-like condition and anaphylaxis have also been reported.^{9,16,17}

TICKS

Tick bites without secondary infection typically cause a local allergic reaction characterized by erythematous, papular lesions accompanied by pain and pruritis, which can persist up to weeks after the initial bite. Hard ticks are found in brush fields and tall

Box 1
Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) and at least 1 of the following
 - a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia)
 - b. Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. At least 2 of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
 - a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
 - b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
 - d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):
 - a. Infants and children: low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure^a
 - b. Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

^a Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than 70 mm Hg + (2 × age) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

From Sampson HA, Munoz-Fulong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report: Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol 2006;117:393; with permission.

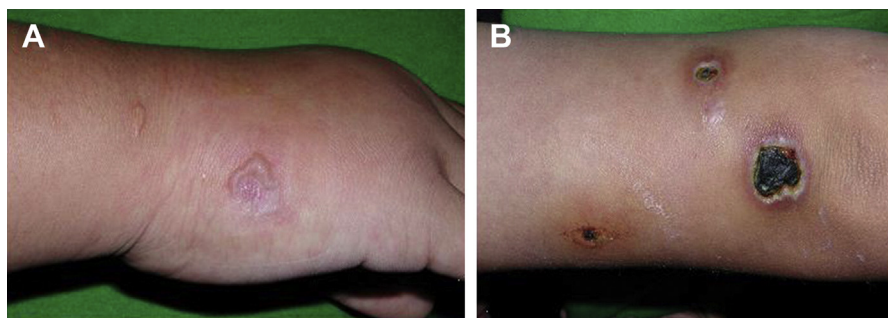


Fig. 3. Typical skin lesions in a patient with hypersensitivity to mosquito bites. (A) erythema and swelling with blister formation 2 days after the mosquito bites. (B) skin necrosis and ulcer formation after 10 days. (From Asada H. Hypersensitivity to mosquito bites: a unique pathogenic mechanism linking Epstein-Barr virus infection, allergy and oncogenesis. *J Dermatol Sci* 2007;45(3):154; with permission.)

grass and then attach to people and can feed for days (**Fig. 4**).¹⁸ Eight percent to 16% of patients can experience anaphylactic symptoms depending on the type of tick and previous tick exposure.^{19–21}

FLIES

Several fly species are able to bite people and cause local inflammatory reactions (**Fig. 5**). These include black flies, deer flies, horse flies, and sand flies. Most patients will complain of painful bites with local inflammatory reactions similar to other insect bites described previously. Case reports of anaphylaxis have been reported with horse fly bites.^{22,23}

FLEAS

Flea bites create erythematous papules and can also lead to papular urticaria,²⁴ because the bites are pruritic and excoriation of the papules or vesicles are common. Large bullae have been reported as well.²⁵ Fleas usually transfer from animals such as dog or cats.¹⁸

BITING MIDGES

Biting midges are tiny biting flies. Due to their small size and painful bite, they go by other colloquial names, including, punkies, no-see-ums, flying teeth, and no-nos. Midges prefer low light, and females feed at sunrise and sunset. Water is necessary for their life cycle, so oceans and wetlands are common areas to find biting midges. Their bites can create papules, wheals from 2 to 10 cm in size, or honey-crusted lesions due to excoriations, which can persist from weeks to months.^{26,27}

BEE AND WASP STINGS

Bees belong to the order Hymenoptera, including bees, yellow jackets, hornets, wasps, and stinging ants (**Figs. 6 and 7**). The most common local reactions include pain, erythema, swelling and pruritis. Large swelling over 10 cm is possible, and is associated with an increased risk for systemic reactions upon repeat exposure. Moderate systematic symptoms include mild asthma, moderate angioedema, and



Fig. 4. Dermacentor tick feeding on skin. (From Steen CJ, Carbonaro PA, Schwartz RA. Arthropods in dermatology. *J Am Acad Dermatol* 2004;50(6):828; with permission.)

abdominal pain with vomiting, diarrhea, and dizziness. More severe systemic symptoms include respiratory difficulty, hypotension, loss of consciousness, or seizures.²⁸

DIAGNOSIS

The accurate diagnosis of insect allergy requires a careful and detailed history, including prior exposure to bites and stings and potential venom allergy. The 1



Fig. 5. Wound myiasis from a botfly. (From Demain JG. Papular urticaria and things that bite in the night. *Curr Allergy Asthma Rep* 2003;3(4):298; with permission.)



Fig. 6. Female winged reproductive *Hypoponera* genus. Females are approximately 2.7 to 2.9 mm in length. (From Klotz JH, deShazo RD, Pinnaas JL, et al. Adverse reactions to ants other than imported fire ants. *Ann Allergy Asthma Immunol* 2005;95(5):422; with permission.)

exception to a clinical diagnosis is the specific diagnosis of Hymenoptera allergy, which is based upon the clinical history and the presence of venom-specific immunoglobulin E (IgE) antibodies.^{29–32}

MEDICAL HISTORY

A detailed medical history is the most important and key to a proper diagnosis. Usually the sting or bite is painful, and patients are aware of the onset.³¹

Questions to consider include:

- When did the bite or sting episode happen?
- How many bites or stings did you get?
- Where did you get bitten or stung?



Fig. 7. Worker ant from *Pseudomyrmex ejectus*. (From Klotz JH, deShazo RD, Pinnaas JL, et al. Adverse reactions to ants other than imported fire ants. *Ann Allergy Asthma Immunol* 2005;95(5):423; with permission.)

- After the bite or sting, how long before other symptoms appeared? Did you have any symptoms that appeared later on?
- How did you treat the bite or sting?
- Have you ever been bitten or stung before? What was the reaction to those prior episodes? (a large local reaction is an area of redness or swelling that enlarges over 2 days, is usually >10 cm in size, and resolves in 5–10 days)
- Do you have a regular exposure to insects from either your occupation or recreational activities?

A thorough review of symptoms should be done, including assessing for shortness of breath, palpitations, dizziness, or lightheadedness. Medications that can exaggerate the immune response, such as angiotensin-converting enzyme (ACE) inhibitors, or beta-blockers, should be assessed. If the patient accessed emergency services, medical records should be obtained for review. Patients with systemic reactions should be graded by severity (Boxes 2 and 3).

IDENTIFICATION OF INSECT

The history can provide important clues to identifying the possible insect. For example, yellow jackets tend to be found near garbage or food. The season of year can also be helpful: honey bee stings tend to occur in the spring and summer, while vespid stings occur more frequently in late summer and fall. If the patient cannot describe the insect in question, it can sometimes be identified based on the patient's geographic location or setting where the bite or sting occurred.

Patients should be encouraged to bring in the insect, when available, for physician identification.²⁸ Physicians can use a reference book or internet resources (<http://www.cdc.gov/niosh/topics/insects/>) to help identify the insect.

Some key distinguishing factors include³³ bumble bees, honey bees, hornets, and wasps.

Bumble bees (*Bombus* spp) have abundant feathering and yellow, orange, or white stripes on the thorax and abdomen. They are slow, fly low to the ground, and make a characteristic loud buzzing sound. Ordinarily, bumble bees are calm insects and only sting in extreme situations like when their nest is attacked.

Box 2
Classification of systemic reactions to insect stings according to Mueller
<i>Grade I</i>
Generalized urticaria, itching, malaise, and anxiety
<i>Grade II</i>
Any of the previously mentioned symptoms plus at least 2 of the following: angioedema, chest constriction, nausea, vomiting, diarrhea, abdominal pain, dizziness
<i>Grade III</i>
Any of the previously mentioned symptoms plus at least 2 of the following: dyspnea, wheezing, stridor, dysarthria, hoarseness, weakness, confusion, feeling of impending disaster
<i>Grade IV</i>
Any of the previously described symptoms plus at least 2 of the following: fall in blood pressure, collapse, loss of consciousness, incontinence, cyanosis
<i>From Mueller HL. Diagnosis and treatment of insect sensitivity. J Asthma Res 1966;3(4):331–3.</i>

Box 3**Classification of systemic reactions modified according to Ring and Messmer***Grade I*

Generalized skin symptoms (eg, flush, generalized urticaria, angioedema)

Grade II

Mild-to-moderate pulmonary, cardiovascular, and/or gastrointestinal symptoms

Grade III

Anaphylactic shock, loss of consciousness

Grade IV

Cardiac arrest, apnea

From Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. Lancet 1977;1(8009):466–9.

Honey bees (*Apis mellifera*) are nearly uniform dark brown color. After a bee sting, the bee leaves the entire stinging apparatus with venom reservoir in the skin (**Fig. 8**). This kind of sting often happens near beehives or orchards (**Fig. 9**).

Hornets (*Vespa*) build their nests in hollow attics and trees. In contrast to honey bees, they do not leave their stinger in the skin.

Wasps (*Vespidae*) have a black-yellow or dark brown-yellow color. Some wasps build their nests in the ground, and others build them in tree branches or attics. Like hornets, they do not leave the venom apparatus in the skin. Wasps are attracted to sweet food and drinks in open-air environments (see **Fig. 9**).

DIAGNOSTIC TESTS

The 2011 stinging insect hypersensitivity practice parameters provide guidance on when to perform diagnostic tests.²⁸ Patients who experience a systemic allergic reaction after an insect bite or sting are at increased risk for subsequent systemic reaction,

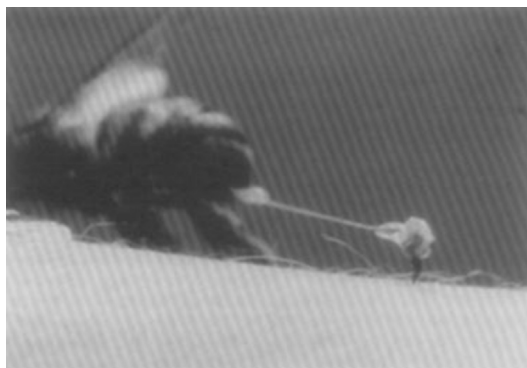


Fig. 8. Honeybee sting embedded in human skin. (From Schumacher MJ, Tveten MS, Egen NB. Rate and quantity of delivery of venom from honeybee stings. *J Allergy Clin Immunol* 1994;93(5):832; with permission.)

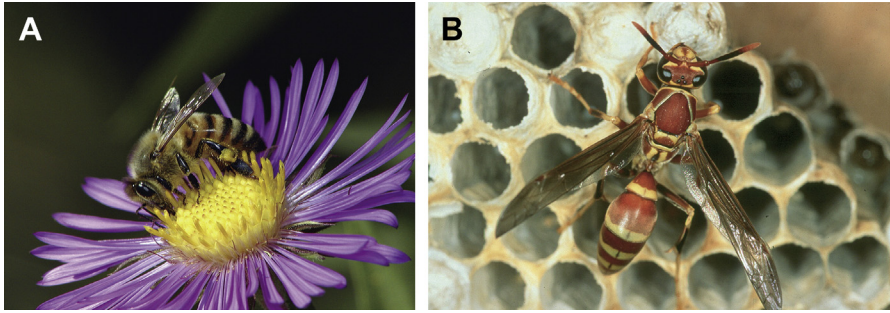


Fig. 9. (A) the honeybee (*Apis mellifera*); and (B) a common species of wasp (*Polistes exclamans*). (From Golden DB. Insect sting allergy and venom immunotherapy: a model and a mystery. J Allergy Clin Immunol 2005;115(3):441; with permission.)

and diagnostic testing should be performed.³³ A referral to an allergist-immunologist is recommended when a person:

- Experiences a systemic allergic reaction to an insect sting
- Develops a systemic allergic reaction in which an insect sting could be the cause
- Needs education regarding stinging avoidance or treatment in case of emergency
- Might be candidate for venom immunotherapy (VIT)
- Has a coexisting situation that may complicate the treatment of the allergic reaction (eg, epinephrine in patients with cardiac disease)

Diagnosis usually starts with hypersensitivity skin testing, indicated for people who are candidates for VIT.

Skin testing should be used for initial measurement of the venom-specific IgE. If the skin test response is negative and the patient has had a severe allergic reaction, further testing, such as repeat skin testing or in vivo testing, can be done.

In patients with severe skin disease or dermatographism or in patients who cannot undergo skin testing, in vitro testing using enzyme-linked immunosorbent assay (ELISA) or radioallergosorbent test (RAST) techniques can detect venom-specific IgE antibodies. The sensitivity of in vitro tests was 88.5% for wasps and 94% for bee venom.³³

Recent studies have shown that elevated levels of serum tryptase are associated with a high risk of severe anaphylaxis following a subsequent sting. Tryptase is an enzyme present in mast cell granules and basophils. Elevated tryptase levels can be useful in confirming a diagnosis of anaphylaxis that is not food related. It is recommended to determine serum tryptase in patients with a severe anaphylactic reaction after a bite or sting.^{28,33}

DIFFERENTIAL DIAGNOSIS

Although not covered in this article, several important diseases are transmitted through insect bites and stings. Mosquitos serve as vectors for several diseases, including chikungunya, dengue hemorrhagic fever, malaria, LaCrosse encephalitis and St. Louis encephalitis, West Nile virus, and yellow fever. Tick bites can transmit babesiosis, human ehrlichiosis, Lyme disease, Rocky Mountain spotted fever, and tularemia. Fly bites can lead to bartonellosis, leishmaniasis, myiasis, and onchocerciasis. Fleas can transmit bartonellosis, the plague, tungiasis, and typhus. Biting midges can lead to filarial worm infections. It is important to assess for these secondary infections when indicated.

An allergic reaction and anaphylaxis can be triggered in numerous ways, but the 3 most common triggers are insect bites or stings, food, and medication. Some other entities causing skin allergic reaction with or without systemic involvement can resemble insect allergic reaction. Other common diagnoses that can mimic an insect bite or sting include angioedema, cellulitis, cat scratch disease, and animal bites.

MANAGEMENT/TREATMENT

An overview algorithm for management of an insect bite or sting is found in [Fig. 10](#). For local insect bite or sting reactions (eg, redness, swelling, itching, and pain), symptomatic treatment with oral antihistamines, pain medications, and cold compresses is recommended. Early removal of the stinger might decrease additional injection of venom. Ninety percent of venom delivery is complete within 20 seconds, so intervention is only helpful if it occurs immediately.^{28,34}

Large local reactions increase in size over 24 to 48 hours, cause swelling beyond the immediate sting area, and can take 5 to 10 days to resolve. Up to 10% of patients with large local reactions may have future systemic reactions, and providers should consider prescribing injectable epinephrine as a precaution. Oral corticosteroids are also sometimes used to decrease swelling. Antibiotics are not helpful for these allergic reactions. VIT is not recommended for large local reactions unless these reactions become a frequent occurrence and the patient has detectable immediate hypersensitivity skin test or in vitro tests for serum-specific IgE.²⁸

Systemic reactions can include almost any body system. When anaphylaxis is present, the patient should be treated immediately with injectable epinephrine and transported to the emergency department. Once in the emergency department, a patient not responding to epinephrine injection should be given an intravenous infusion of epinephrine. Patients should be kept supine, and adjunctive antihistamines and corticosteroids can also be given, but never as substitute for epinephrine. Airway and blood pressure support should be given; patients should be observed for at least 4 to 8 hours, longer if any history of risk factors for severe anaphylaxis such as asthma, biphasic reactions, or protracted anaphylaxis exists. Elevated tryptase levels have also been associated with systemic reactions to VIT and greater failure rates with more frequent relapse after immunotherapy has been stopped. After discharge from the emergency department, patients with anaphylaxis should be seen by an allergist-immunologist.^{28,35–37}

A rare allergic reaction is serum sickness, which involves fever, malaise, urticarial, and arthralgia starting several days after an insect sting. This can increase risk of future anaphylaxis, so VIT is appropriate in these patients.^{38,39}

Besides venom injection from stinging insects, other insect-related allergic reactions, exist including a severe reaction to mosquito bites called skeeter syndrome, a large local reaction or systemic reaction with low-grade fever that can require both supportive treatment and possibly oral glucocorticoids and epinephrine and transport to the emergency department when anaphylaxis is present.^{9,34}

A more unusual source of insect allergy has been reported in cases of hymenoptera venom exposure via ingestion of wine or grape juice causing systemic symptoms.⁴⁰

PREVENTION: VENOM IMMUNOTHERAPY

For patients who have had systemic reactions to a stinging insect or fire ant, VIT may be an option to help decrease the risk of future severe reactions. The criteria for immunotherapy include evidence of specific IgE antibodies to the offending insect in a patient who has had a systemic reaction. Patients under the age of 16 with only

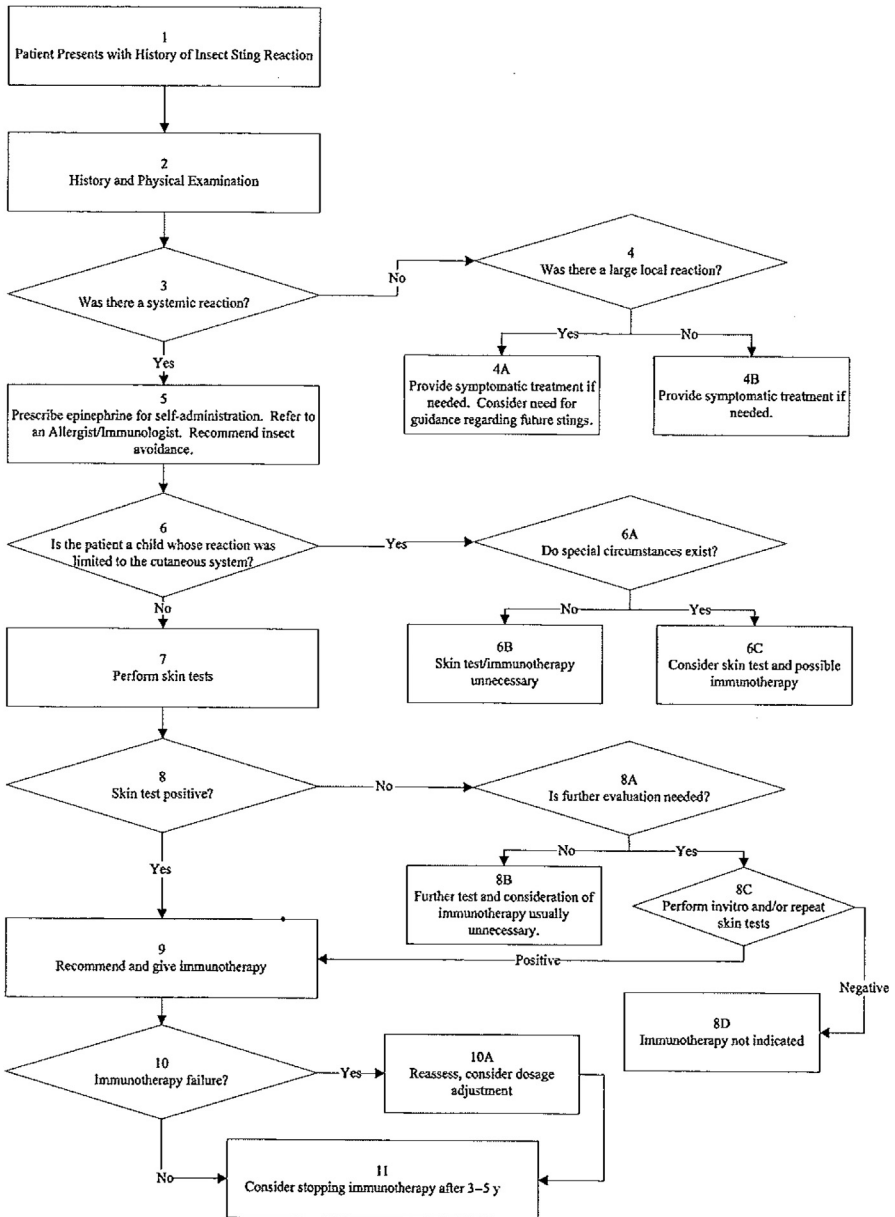


Fig. 10. Algorithm for management of stinging insect reactions. (From Golden DB, Moffitt J, Nicklas RA, et al. Stinging insect hypersensitivity: a practice parameter update 2011. *J Allergy Clin Immunol* 2011;127(4):854.e20; with permission.)

cutaneous symptoms do not need immunotherapy.³⁵ High-risk pregnant patients may be considered for VIT.⁴

Protocols vary depending on inciting insect (honeybee vs vespid vs fire ant) and how quickly to reach maintenance dosing. Initial doses are given 1 to 2 times per week, and the standard (slow) protocol recommends reaching maintenance dosing in 8 to 15 weeks.

Ultrarush protocols with possible hospitalization (1–2 days) may be used but also increase the risk of an adverse reaction.^{4,28} VIT is highly effective in reducing the risk of large local reactions or systematic reactions with a number needed to treat 2–4 patients.⁴¹ ACE inhibitor use, honeybee VIT, adverse reactions during VIT, and increased tryptase levels are all associated with risk of VIT failure.⁴² Large local reactions, serum sickness, and anaphylaxis are all reported adverse effects from VIT.^{4,28} Premedication with antihistamines may reduce local and mild systemic adverse reactions. Patients should be kept in the office at least 30 minutes to be observed after an immunotherapy injection. The risk of systemic reaction per injection is about 0.2%.⁴³ Life-threatening anaphylaxis is rarely seen after 30 minutes. VIT is recommended for 3 to 5 years or sooner if skin testing becomes negative or IgE levels return to normal. Some experts recommend indefinite treatment for certain patients.²⁸

REFERENCES

1. Novotny V, Basset Y, Miller SE, et al. Low host specificity of herbivorous insects in a tropical forest. *Nature* 2002;416(6883):841–4.
2. Threats to global diversity. Available at: <http://www.globalchange.umich.edu/globalchange2/current/lectures/biodiversity/biodiversity.html>. Accessed October 11, 2015.
3. Antonicelli L, Bilò MB, Bonifazi F. Epidemiology of hymenoptera allergy. *Curr Opin Allergy Clin Immunol* 2002;2(4):341–6.
4. Pesek RD, Lockey RF. Treatment of Hymenoptera venom allergy: an update. *Curr Opin Allergy Clin Immunol* 2014;14(4):340–6.
5. Bilò BM, Bonifazi F. Epidemiology of insect-venom anaphylaxis. *Curr Opin Allergy Clin Immunol* 2008;8(4):330–7.
6. deShazo RD, Butcher BT, Banks WA. Reactions to the stings of the imported fire ant. *N Engl J Med* 1990;323:462–6.
7. Clark S, Camargo CA Jr. Emergency treatment and prevention of insect-sting anaphylaxis. *Curr Opin Allergy Clin Immunol* 2006;6(4):279–83.
8. Demain JG. Papular urticaria and things that bite in the night. *Curr Allergy Asthma Rep* 2003;3(4):291–303.
9. Simons FE, Peng Z. Skeeter syndrome. *J Allergy Clin Immunol* 1999;104(3):705–7.
10. Vassallo C, Passamonti F, Cananzi R, et al. Exaggerated insect bite-like reaction in patients affected by oncohaematological diseases. *Acta Derm Venereol* 2005;85(1):76–7.
11. Hernandez RG, Cohen BA. Insect bite-induced hypersensitivity and the SCRATCH principles: a new approach to papular urticaria. *Pediatrics* 2006;118(1):e189–96.
12. Royo-Cebrecos C, Garcia-Vidal C. Exaggerated insect bite reaction related to chronic leukemia. *Mayo Clin Proc* 2013;88(4):e37.
13. Smith KJ, Skelton HG 3rd, Vogel P, et al. Exaggerated insect bite reactions in patients positive for HIV. Military Medical Consortium for the Advancement of Retroviral Research. *J Am Acad Dermatol* 1993;29(2):269–72.
14. Sampson HA, Munoz-Fulong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report: Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. *J Allergy Clin Immunol* 2006;117:391–7.

15. Bonadonna P, Perbellini O, Passalacqua G, et al. Clonal mast cell disorders in patients with systemic reactions to Hymenoptera stings and increased serum tryptase levels. *J Allergy Clin Immunol* 2009;123(3):680–6.
16. Przybilla B, Ruëff F. Insect stings: clinical features and management. *Dtsch Arztebl Int* 2012;109(13):238–48.
17. Peng Z, Ho MK, Li C, et al. Evidence for natural desensitization to mosquito salivary allergens: mosquito saliva specific IgE and IgG levels in children. *Ann Allergy Asthma Immunol* 2004;93(6):553–6.
18. Juckett G. Arthropod Bites. *Am Fam Physician* 2013;88(12):841–7.
19. Kleine-Tebbe J, Heinatz A, Gräser I, et al. Bites of the European pigeon tick (*Argas reflexus*): risk of IgE-mediated sensitizations and anaphylactic reactions. *J Allergy Clin Immunol* 2006;117(1):190–5.
20. Gauci M, Loh RK, Stone BF, et al. Allergic reactions to the Australian paralysis tick, *Ixodes holocyclus*: diagnostic evaluation by skin test and radioimmunoassay. *Clin Exp Allergy* 1989;19(3):279–83.
21. Moneret-Vautrin DA, Beaudouin E, Kanny G, et al. Anaphylactic shock caused by ticks (*Ixodes ricinus*). *J Allergy Clin Immunol* 1998;101(1):144–5.
22. Hemmer W, Focke M, Vieluf D, et al. Anaphylaxis induced by horsefly bites: identification of a 69 kd IgE-binding salivary gland protein from *Chrysops* spp. (Diptera, Tabanidae) by western blot analysis. *J Allergy Clin Immunol* 1998;101(1):134–6.
23. Freye HB, Litwin C. Coexistent anaphylaxis to diptera and hymenoptera. *Ann Allergy Asthma Immunol* 1996;76(3):270–2.
24. Naimer SA, Cohen AD, Mumcuoglu KY, et al. Household papular urticaria. *Isr Med Assoc J* 2002;4(11):911–3.
25. Golomb MR, Golomb HS. What's eating you? Cat flea (*Ctenocephalides felis*). *Cutis* 2010;85(1):10–1.
26. Cohn BA. Biting midges—those marauding “no-see-ums”. *Int J Dermatol* 2003;42(6):459–60.
27. Chen YH, Lee MF, Lan JL, et al. Hypersensitivity to *Forcipomyia taiwana* (biting midge): clinical analysis and identification of major For t 1, For t 2 and For t 3 allergens. *Allergy* 2005;60:1518–23.
28. Golden DB, Moffitt J, Nicklas RA, et al. Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma & Immunology (AAAAI), American College of Allergy, Asthma & Immunology (ACAAI), Joint Council of Allergy, Asthma and Immunology. Stinging insect hypersensitivity: a practice parameter update 2011. *J Allergy Clin Immunol* 2011;127(4):852–4.e1–23.
29. Demain JG, Minaei AA, Tracy JM. Anaphylaxis and insect allergy. *Curr Opin Allergy Clin Immunol* 2010;10(4):318–22.
30. Scherer K, Bircher AJ, Heijnen IA. Diagnosis of stinging insect allergy: utility of cellular in-vitro tests. *Curr Opin Allergy Clin Immunol* 2009;9(4):343–50.
31. Biló BM, Rueff F, Mosbech H, et al. Diagnosis of Hymenoptera venom allergy. *Allergy* 2005;60(11):1339–49.
32. Tracy JM, Khan FS, Demain JG. Insect anaphylaxis: where are we? The stinging facts 2012. *Curr Opin Allergy Clin Immunol* 2012;12(4):400–5.
33. Matysiak J, Matysiak J, Bręborowicz A, et al. Diagnosis of hymenoptera venom allergy—with special emphasis on honeybee (*Apis mellifera*) venom allergy. *Ann Agric Environ Med* 2013;20(4):875–9.
34. Schumacher MJ, Tveten MS, Egen NB. Rate and quantity of delivery of venom from honeybee stings. *J Allergy Clin Immunol* 1994;93(5):831–5.

35. Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol* 2011;127(1 Suppl):S1–55.
36. Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol* 2010; 126(3):477–80.e1–42.
37. Campbell RL, Li JT, Nicklas RA, et al. Emergency department diagnosis and treatment of anaphylaxis: a practice parameter. *Ann Allergy Asthma Immunol* 2014;113(6):599–608.
38. Reisman RE, Livingston A. Late-onset allergic reactions, including serum sickness, after insect stings. *J Allergy Clin Immunol* 1989;84(3):331–7.
39. Peng Z, Simons FE. Advances in mosquito allergy. *Curr Opin Allergy Clin Immunol* 2007;7(4):350–4.
40. Armentia A, Pineda F, Fernández S. Wine-induced anaphylaxis and sensitization to hymenoptera venom. *N Engl J Med* 2007;357(7):719–20.
41. Boyle RJ, Elremeli M, Hockenhull J, et al. Venom immunotherapy for preventing allergic reactions to insect stings. *Cochrane Database Syst Rev* 2012;(10): CD008838.
42. Ruëff F, Vos B, Oude Elberink J, et al. Predictors of clinical effectiveness of Hymenoptera venom immunotherapy. *Clin Exp Allergy* 2014;44(5):736–46.
43. Cox L, Larenas-Linnemann D, Lockey RF, et al. Speaking the same language: The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. *J Allergy Clin Immunol* 2010;125(3):569–74, 574.e1–574.e7.