Insect Allergy: A Review of Diagnosis and Treatment

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Contents

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Abstract

Insect allergy is the third most common cause of the life-threatening condition anaphylaxis, following food and medications. Insect allergy anaphylaxis poses risk of considerable morbidity and mortality. Avoidance of the offending agent is the cornerstone to the management anaphylaxis regardless of the cause. However, unlike food and medication allergy, insect allergy has been effectively treated, using well-established protocols for many years. Hymenoptera are the insects most associated with allergy and anaphylaxis with at least 40 deaths per year attributed to

insect stings in the United States. It is critical that healthcare professionals and the public understand the proper diagnosis as well as the long-term treatment of this potentially life-threatening allergy. Insect allergy from Hymenoptera, managed *prospectively* using venom immunotherapy, conveys up to 98% protection of anaphylaxis with future stings. Insects of the order Hymenoptera include bees, wasps, hornets, yellow jackets, and stinging ants. Stinging ant allergy will not be reviewed in this chapter. An understanding of the biology and habitat of the various Hymenoptera species is helpful in recommending insect avoidance strategies. The diagnosis of insect allergy relies on a history of a systemic allergic reaction followed by appropriate testing for venom-specific IgE. If the history of a generalized anaphylactic reaction to an insect sting and the presence of venom-specific IgE are confirmed, venom immunotherapy is indicated. It is venom immunotherapy, a disease modifying therapy, that provides the most effective protection against future sting reactions. Ultimately, recognition and lifesaving management is critical. Subsequently, evaluation and potentially long-term management of insect allergy include appropriate referral to an allergist familiar with insect allergy and, if indicated, venom immunotherapy.

Keywords
Insect · Hymenoptera · Anaphylaxis · Epinephrine

Insects are one of the three most common allergic triggers for anaphylaxis, the others being foods and medications (Simons 2008; Simons et al. 2007; Sampson et al. 1992; Simons and Sampson 2008). Insect allergy results in significant morbidity and mortality, with potentially life-threatening systemic reactions occurring in 0.4% to 0.8% of children and up to 3% of adults, and accounts for at least 40 deaths annually in the United States (Graft 2006; Schwartz et al. 1995). Under recognition and treatment may actually underestimate the true mortality from insect anaphylaxis (Graft 2006; Schwartz et al. 1995; Golden et al. 2011). With proper evaluation and treatment, the risk of a severe event with a subsequent sting can be dramatically diminished. Venom immunotherapy (VIT) can provide up to a 98% level of protection from future insect-related anaphylactic events (Golden et al. 2011; Valentine 1984; Hunt et al. 1978; Reisman and Livingston 1992). This chapter will address the current state of knowledge about insect allergy, including insect identification, diagnosis, and evaluation, as well as long- and short-term evaluation and treatment.

30.1 Introduction: Terminology, Types of Reactions, and History

Insects belonging to the order Hymenoptera account for the majority of serious sting-related reactions. Within this order, three families are medically relevant. These include the Apidae, Vespidae, and Formicidae families. The Apidae family includes honeybees and bumblebees; the Vespidae family includes yellow jackets, white-faced hornets, yellow hornets, and wasps; the Formicidae family includes primarily imported fire ants and harvester ants (Gurlanick and Benton 2003; Goddard 2003). The family Vespidae includes the genus *Polistes* or wasps. In North America *P. annularis*, *P. fuscatus*, *P. metricus*, and *P. exclamans* are the predominant species. In Europe *P. dominulus*, *P. gallicus*, and *P. nimphus* are widespread. Although there is some cross-reactivity between American and European *Polistes* species, there are significant differences to warrant different testing and treatment venoms (Severino et al. 2006).

Anaphylaxis to stings of the imported fire ant and to bites from reduviids and mosquitos is reviewed in a separate chapter. Non-Hymenoptera stinging and biting arthropods, such as scorpions and spiders, are more extensively reviewed elsewhere and will not be the focus of this work (Demain 2003; More et al. 2004).

30.2 Insect Biology, Terminology, and Identification

Knowledge of these Hymenoptera insects, their biology, habits, and dwellings, can assist in recognition of the insect and circumstance of sting,

though this information should not be relied upon solely in identification of the offending insect. This knowledge of the circumstance and the suspect insect can be helpful for the diagnosis and treatment of insect allergy (Gurlanick and Benton 2003; Goddard 2003).

Yellow jackets can be either ground dwelling or in nests above ground. *Vespula vulgaris* are generally ground-dwelling yellow jackets, commonly encountered during outdoor activities. *V. vulgaris* can be very aggressive after even minimal provocation, particularly with vibration, such as a leaf blower or weed whacker (Fig. 1). A second species of yellow jacket (*Dolichovespula arenaria*) nests above ground, usually in shrubs and trees. Yellow jackets are carnivorous, have smooth bodies with straight barbless stingers, and can sting multiple times.

Wasps (*Polistes*) are also carnivorous and smooth bodied. The nests of wasps can be distinguished from yellow jackets by the triangular, open-celled configuration without the outer paper encasement typical of other vespids (Fig. 2). Wasp nets are frequently found under the eaves of houses and barns.

Domestic or European honeybees are herbivorous with hairy bodies and have a barbed stinger that results in evisceration and their death after the sting. Typically, they are nonaggressive unless protecting their hives; as a result, honeybee stings are often accidental and occur in children and adults who, while barefoot, inadvertently step on them in the grass (Fig. 3). Africanized honeybees were imported to South America from Africa and have been migrating north to the United States. Unlike their domestic counterparts, they are very aggressive. The venom from Africanized honeybees is identical to their domestic cousins, and the venom volume per sting is similar. However, unlike the single sting of a domestic honeybee, Africanized honeybees often sting in large numbers and will pursue their victim for much longer distances. The domain of the Africanized honeybee is currently limited in the United States to Texas, New Mexico, Arizona, Nevada, and California (Golden et al. 2011) (Fig. 4). Imported fire ants (Formicidae), which are discussed in other chapters, also have limited, but similar domains in the Southern United States (Golden et al. 2011) (Fig. 5).

Fig. 1 Yellow jacket (Photograph courtesy of Dr. Jeffrey G. Demain)

Fig. 2 Wasp (Photograph courtesy of Dr. Jeffrey G. Demain)

Fig. 3 Honeybee (Photograph courtesy of Dr. Jeffrey G. Demain)

Unfortunately, the absolute identification of the culprit insect usually cannot be confirmed, so testing with each of the common venoms is

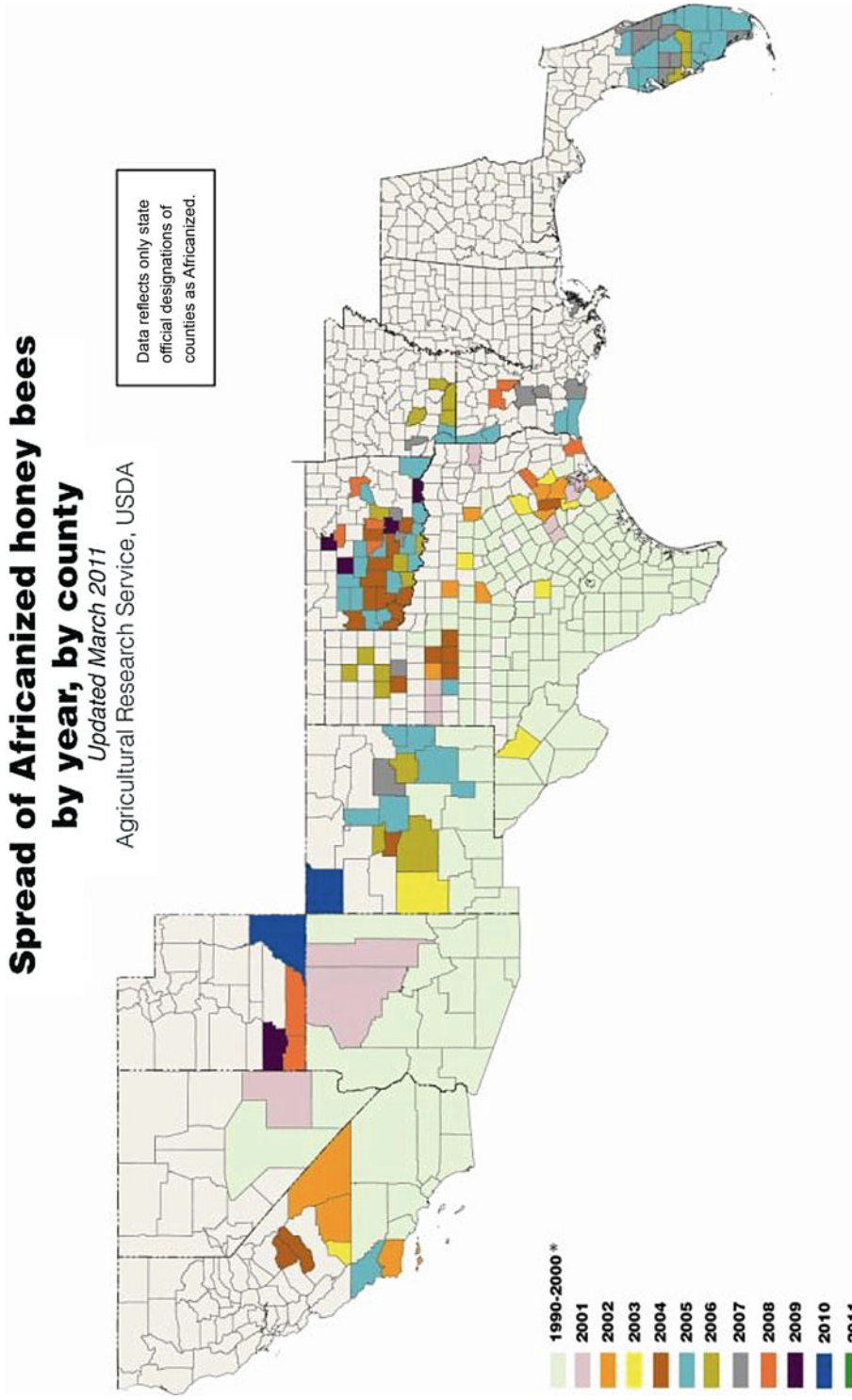

Fig. 4 Spread of Africanized honeybees (www.ars.usda.gov/SP2UserFiles/Place/53420300/New Bee Map09 compressed.jpg)

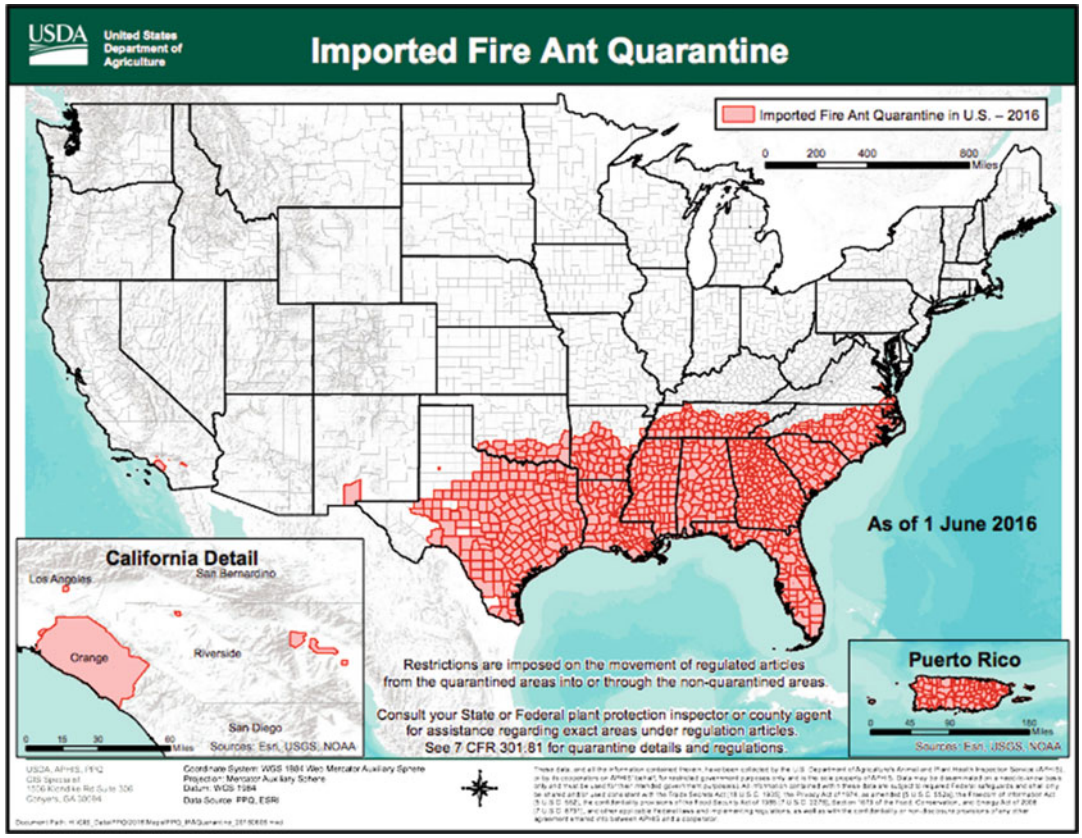

Fig. 5 Imported fire ant quarantine. (Regularly updated maps of the fire ant range and agriculture quarantine areas within the United States (Golden et al. 1989))

warranted in almost all cases, which will be discussed later. There are some circumstances where the offending insect is more obvious. As mentioned, honeybees have barbed stingers, and usually their venom sac can become lodged in the skin following a sting event. While this can be helpful in identification, it is important to note that yellow jackets may also leave the stinger embedded in the skin. In the case of imported fire ants, the presence of a pseudo-pustule up to 24 h later is virtually diagnostic of a fire ant sting (Golden et al. 2011; Moffitt 2003). When taking a history, it is important to take into account historical elements such as the person's activity at the time of the sting, insect activity in the area where the patient was stung, time of the year, and/or geographical considerations (Moffitt 2003).

The amount of venom delivered with a single sting varies between species. A single imported fire ant sting may contain up to 100 ng of venom, while in the case of honeybees, yellow jackets, hornets, and wasps, each sting can range from 20 to 50 mcg (Hoffman and Jacobson 1984). Hymenoptera venoms contain a variety of peptide and protein components. It is these components that cause the characteristic local reactions consisting of redness, swelling, and pain. Individuals having been previously stung may have generated venom-specific IgE antibodies, placing that individual at risk for a potential life-threatening anaphylaxis with subsequent stings. Individual Hymenoptera species contain some shared venom antigenic components. There is considerable immunologic cross-reactivity and sensitization between hornet and yellow jacket venoms, though there is much less between yellow jacket and hornet with wasp venoms. The immunogenic cross-reactivity and sensitization are even less

common between honeybee and the other venoms (Hoffman 1993; King et al. 1985; Reisman et al. 1982). Bumblebee (*Bombus terrestris*) venom has variable cross-reactivity and sensitization with honeybee venom, though at least two antigens are unique. Because bumblebees are non-aggressive, allergic reactions to bumblebee field stings are rare in the United States compared to other Hymenoptera stings. In Europe, bumblebees are used for pollination in greenhouses; therefore more frequent allergic reactions have been reported, particularly among greenhouse workers. Specific venom to bumblebee would be optimal for skin testing and immunotherapy but is currently not available in the United States (Franken et al. 1994; Hoffman et al. 2001; Freeman 2004; De Root 2006) (Table 1).

30.3 Diagnosis

Diagnosis of Hymenoptera allergy is based upon a comprehensive clinical history, the presence of allergic symptoms consistent with anaphylaxis, and objective evidence of venom-specific IgE antibodies. Accurate diagnosis is critical as once the thorough history supports that a generalized systemic reaction to a sting occurred, and the presence of venom-specific IgE is confirmed, the patient becomes a candidate for venom-specific immunotherapy (VIT) (Franken et al. 1994; Hoffman et al. 2001; Freeman 2004; De Root 2006). Proper treatment with VIT can result in up to 98% protection from future life-threatening sting events.

In the majority of cases, the insect sting is reported by the patient; however, it is important to know that there are reports of systemic events occurring without the patient realizing they have been stung. Following an insect sting, the initial diagnostic question is to determine whether the sting reaction is localized, cutaneous such as hives or angioedema, or a more severe systemic reaction (Golden et al. 2006). After a sting, most people develop only minor local symptoms, limited to local pain, tenderness, and swelling; these reactions are self-limited, lasting between 48 and 72 h. A local reaction is defined as a reaction in which the swelling and redness are confined to the tissues contiguous to the sting site. Large local reactions are based on size and vary from 5 to 8 cm to greater than10–16 cm. It is estimated that large local reactions make up 5–15% of sting events

Table 1 Hymenoptera biology and habitat

Common names	Taxonomic classification	Nesting habits	Feeding habit	Avoidance strategies
Honeybee[a]	Family Apidae	Commercial hives	Herbivorous. Nectar and pollen flowering trees and plants	Avoid dark or flower-print clothing and wearing floral scents; wear shoes and socks
Yellow jacket	Family Vespidae *Vespula* species	Multilayered, usually underground; although there is also an aerial yellow jacket: *Dolichovespula arenaria*[b]	Scavengers, aggressive Carnivorous	Avoid open food sources, picnic areas, garbage; destroy in-ground nests
Paper wasp	Family Vespidae *Polistes* species	Hangs from eaves and porches	Nectar and arthropods	Avoid flower-print clothing and wearing floral scents; remove nests when possible
White-faced hornet	Family Vespidae *Dolichovespula* species	Multilayered, open areas	Nectar and arthropods	Avoid flower-print clothing and wearing floral scents; remove nests when possible
Fire ant	Family Formicidae	Earthen mounds in Southern United States	Omnivorous	Avoid mounds; wear shoes, sock, and gloves

[a]A subspecies of honeybee exists in South Texas, Central and South America called "Africanized." It is more aggressive than local species and is clinically relevant in regions of infestation
[b]European species include *P. dominulus*, *P. gallicus*, and *P. nimphus*

(Golden et al. 2011). By contrast, systemic reactions, though occasionally delayed, are generally immediate-type hypersensitivity, mediated by venom-specific IgE. Systemic reactions involve signs and symptoms distant from the immediate sting site; the symptoms may range from mild to life-threatening. Mild systemic reactions, also termed cutaneous reactions, are typically limited to minimal flushing, urticaria, or angioedema. While some serious reactions may begin 15–30 min or longer after the sting, most serious reactions occur within minutes of the sting event. Generalized systemic reactions may include bronchospasm, gastrointestinal symptoms, hypotension, diaphoresis, shock, and – the most common cause of fatalities – laryngeal edema.

30.4 Diagnostic Testing

Once the history of a systemic reaction to an insect sting has been established, the next step is to discern the presence of venom-specific IgE. It is important to note that up to 27% of the general population may have detectable levels of venom-specific IgE, so the presence of venom-specific IgE *without* a history of a systemic reaction may not be predictive of a future insect-related anaphylactic event (Golden et al. 1989). As a result, skin testing is not indicated unless the patient has a history of a systemic allergic reaction other than hives to an insect sting. All individuals, regardless of age, with a history of a systemic or anaphylactic reaction, beyond hives and/or angioedema, following an insect sting should be tested (Golden et al. 2006, 2011; Light et al. 1977; Reisman 2005). Recently new guidance has emerged regarding testing and VIT in individuals with systemic anaphylactic reactions limited to cutaneous involvement (Golden et al. 2011). In the 2017, Golden et al. outlined changes for individuals with limited cutaneous systemic reactions to stinging insects and who required testing and ultimately therapy. Adults and children who have reactions limited to the skin, such as hives and angioedema, appear not to have a significant risk for more severe reactions in the future, and therefore testing is not warranted (Georgitis and Reisman 1985; Golden et al. 2017). This is a change from the previous recommendations, where adults, but not children younger than 16 years, warranted testing for hives and/or angioedema (Golden et al. 1997, 2011, 2017; Georgitis and Reisman 1985). Sensitivity can persist for many years, even in cases of an intervening sting without a reaction; as a result, testing should be performed regardless of when the systemic sting event occurred.

30.4.1 Methods

The next consideration is the selection of the method for allergy testing. Skin testing to specific venom is the gold standard for identifying venom-specific IgE. In general, skin testing is preferred over in vitro methods for initial assessment because skin testing is more sensitive and usually less costly (Hamilton 2001, 2004) and should be performed by an allergist/immunologist who has training and experience in the diagnosis and treatment of insect allergy (Golden et al. 2011). Skin testing for Hymenoptera venom is most commonly performed using a combination of epicutaneous (prick/puncture) and intracutaneous (intradermal) methods accompanied by appropriate positive and negative controls. Testing for Hymenoptera venoms usually begins with skin prick testing at 100mcg/ml concentrations and if negative followed by intracutaneous testing starting at venom concentration of between 0.001 and 0.01 mcg/ml. At intervals of 20–30 min, the skin tests are preformed using tenfold increase in concentration until a positive skin test response occurs – or a maximum concentration of 1.0 mcg/ml is administered. Venom concentrations greater than 1.0 mcg/ml are associated with an increase in irritant skin reactions or falsely positive results. A positive skin test reaction at a concentration $\leq$1.0 mcg/ml confirms the presence of venom-specific IgE antibodies (Georgitis and Reisman 1985; Golden et al. 2017). Whole-body extract is the only reagent available for testing in imported fire ant patients suspected of having fire ant hypersensitivity and is discussed in later chapters. Venom skin testing is

positive in 70–90% of patients with a significant history of a systemic reaction (Valentine 1984; Hunt et al. 1978; Reisman 2005; Golden et al. 1997; Parker et al. 1982). Since the stinging insect cannot always be reliably identified, physicians should test all relevant insects for the geographic area in question. For most areas in the United States, skin testing should include testing for honeybee, yellow jacket, yellow hornet, white-faced hornet, and wasp. Discussed in detail elsewhere, in areas of the Southern United States, testing for venomous ants including the imported fire ants should be considered. Many individuals experience reduced sensitivity to venom testing in the first few weeks after a systemic sting reaction; therefore testing should be deferred for 4 to 6 weeks, as the potential of a false-negative reaction may be greater within 4–6 weeks of anaphylaxis (Goldberg and Confino-Cohen 1997).

A negative skin test result with a convincing history of sting reaction should be interpreted with caution (Golden et al. 2001; Reisman 2001). If the initial percutaneous and intradermal tests are negative, an in vitro test, measuring sIgE for venoms, such as Immunocap Assay®, is indicated. A serum basal tryptase level should also be ordered to assess for possible underlying mast cell disease (discussed later) (Georgitis and Reisman 1985; Golden et al. 2017). If both initial skin testing and in vitro testing are negative, then the testing should be repeated in 6–12 weeks (Georgitis and Reisman 1985; Golden et al. 2017).

As previously noted, there is some antigen cross-reactivity between the various Hymenoptera species. This could be secondary to cross-reacting carbohydrate determinants, which not thought to be clinically relevant (Hoffman 1993; King et al. 1985; Reisman et al. 1982). Neither the size of the skin test reaction nor the measured level of venom-specific IgE antibodies is reliable indicators of future sting reaction severity (Hoffman 1993; Golden et al. 2001; Reisman 2001).

Periodically, falsely positive and falsely negative reactions may occur. False-positive reactions are usually caused by the inherent, nonspecific irritant effect of the venom, usually at concentrations above 1 mcg/ml (Hoffman 1993). The combination of venom skin testing and complementary in vitro testing detects 98% of sensitized individuals (Hamilton 2001, 2004). However, occasionally, an individual with a convincing history of a systemic Hymenoptera sting reaction has both negative skin and in vitro testing (Golden et al. 2001, 2003; Reisman 2001). Again, a negative venom test should be interpreted with caution. Occurrences of anaphylaxis have been reported in individuals who tested negative to both venom skin testing and in vitro methods (Hamilton 2004; Golden et al. 2001; Reisman 2001). In such cases, mast cell disorders, such as occult or indolent mastocytosis or mast cell activation syndromes, should be considered. A basal serum tryptase level is recommended in subjects with negative testing and convincing history. The role and utility of serum tryptase in the evaluation of Hymenoptera allergy and occult or indolent mast cell disorders is evolving. A baseline serum tryptase level of >11.4 ng/ml after a fully subsided reaction suggests an underlying mast cell disorder (Bonadonna et al. 2010). Serum tryptase levels of greater than 20 ng/ml would warrant consideration of additional testing, including bone marrow biopsy (González de Olano et al. 2008; Brockow et al. 2008; Rueff et al. 2009; Bonadonna et al. 2010). Individuals with underlying or occult mast cell disorders are at greater risk for anaphylaxis, particularly insect anaphylaxis (Rueff et al. 2009; Bonadonna et al. 2009, 2010). The protective level of VIT may be lower than that in the general population, and the safety of VIT may also be lower in individuals with mast cell disorders (Oude Elberink et al. 1997; Niedoszytko et al. 2009). However, VIT is recommended as affected subjects are at greater risk without treatment.

30.5 Treatment

Hymenoptera stings are usually acutely painful and the event is obvious. Local reactions – those that are limited to the area contiguous to the sting site – are treated symptomatically. If a stinger is embedded, it should be removed by flicking it out and not squeezing the attached venom sac. The rate of venom delivery can be very rapid. In honeybees 90% of the venom is delivered in 20 s, and by 1 min nearly the entire venom sac has been

emptied suggesting that the removal of the venom sac must occur within seconds to reduce the potential of anaphylaxis. Otherwise, icing the affected area, using age-appropriate analgesia and oral antihistamines, is the mainstay of treatment. Although considerable pain, erythema, and swelling may exist, even in the case of large local reactions, secondary infection is rare (Schumacher et al. 1994a).

Anaphylaxis due to insect venom is managed the same as anaphylaxis caused by any other allergen (Kosnik and Korosec 2011). Initial treatment of choice is an intramuscular injection of epinephrine, preferably into the anterior, upper, and outer aspect of the thigh. Other medications, such as oral or intravenous corticosteroids and/or H-1 and H-2 histamine receptor blockers, are secondary medications that do not substitute for epinephrine. These are secondary therapies and should be administered only after epinephrine. This is regardless of the patients' age, health status, or comorbid medical conditions (Golden et al. 2011). The time interval between the onset of anaphylactic symptoms and the first dose of epinephrine is the best indicator of a successful outcome, and delayed use is a risk factor for death. Regrettably, underuse of epinephrine in the outpatient and emergency department settings remains problematic (Simons 2008; Manivannan et al. 2009; Bilò and Bonifazi 2008; Demain et al. 2010).

Once the patient is stabilized and the effects of the initial sting event are addressed, further intervention may be necessary. If the reaction is limited to a local reaction, regardless of how large, the patient should be reassured that the risk of a more severe future reaction is small (5–10%) (Graft et al. 1984; Mauriello et al. 1984). Generally, in cases where the sting event reaction was limited to local signs and symptoms, an epinephrine auto-injector is not warranted. In rare cases, where the patient has significant anxiety about a future sting event, an epinephrine auto-injector may contribute to an improved quality of life. This requires careful consideration and should be evaluated on a case-by-case basis. If the reaction included more generalized symptoms, such as bronchospasm, gastrointestinal symptoms, hypotension, or laryngeal edema, provision of and detailed training on the utilization of an epinephrine auto-injector is recommended. The patient and/or family should be able to demonstrate understanding of appropriate utilization. Avoidance is the mainstay of the management of all allergic diseases. This is certainly true of Hymenoptera allergy, regardless whether the reaction was local or systemic. The individual or family should be counseled on the insect-appropriate avoidance strategies and the benefits of following these strategies. If the sting event resulted in systemic signs and symptoms, the appropriate next step is to refer the patient to an allergy specialist for further evaluation, where the insect allergy will be evaluated and VIT considered (Golden et al. 2011).

VIT should be considered and offered to any patient with a history of a systemic allergic reaction to a Hymenoptera sting and evidence by skin test or in vitro methods of venom-specific IgE antibodies. VIT can provide an up to 98% protection against future sting events. VIT consists of gradually increasing doses of venom, usually beginning at 0.1 to 1.0 mcg/ml. Using current guidelines, the venom for winged Hymenoptera is given subcutaneously until a total dose of 100 mcg is achieved for each of the venoms being treated (Bonifazi et al. 2005; Reisman and Livingston 1992; Golden et al. 1981). The usual venom exposure from most Hymenoptera stings is 20–50 mcg; therefore, a treatment dose of 100 mcg for each venom would represent a protective dose approximating two to five stings (Schumacher et al. 1994b). This maintenance dose was based upon published protocols and is the manufacturers' recommended dosing per the FDA-approved package inserts. A maintenance VIT dose of 100 mcg provides a protection from anaphylaxis in up to 98%, whereas a maintenance VIT dose of 50 mcg/ml, recommended by a single investigator, can provide protection in approximately 80–90% of stings (Bonifazi et al. 2005; Graft et al. 1998). In few cases, the patient experiences local and/or systemic reactions during treatment, resulting in difficulty achieving a full maintenance dose of 100 mcg. In such cases, a maintenance dose of 50 mcg, though suboptimal, may provide adequate protection. In most cases, local reactions should not prevent the achievement

of a full 100 mcg dose, and every effort should be made to achieve this dose. There have been no long-term safety or toxicity issues associated with VIT, including in young children and pregnancy.

The physician should monitor VIT patients at regular intervals of 6 to 12 months. During treatment with VIT, between 3% and 12% of patients will experience a systemic reaction, mostly during the early build-up phase (Golden et al. 2011). These reactions are usually mild. Honeybee-allergic patents and those patients with elevated baseline serum tryptase seem to be at a somewhat higher risk of a systemic reaction during VIT. In addition, patients on beta-blockers or ACE inhibitors have a somewhat higher risk (Rueff et al. 2009). Local reactions to VIT present an important, frequent but generally less serious problem than systemic reaction during VIT. Approximately one-third of venom-allergic patients on VIT will experience local reactions during treatment. Although troublesome to the patient, these local reactions for VIT do not predict an increased risk for future, systemic reactions to VIT. These reactions can be uncomfortable, and as a result, the physician may make adjustments in dosing. It is important to recognize that these adjustments in VIT are primarily made for comfort, not for safety.

30.6 Large Local Reactions and VIT

Large local reactions to Hymenoptera stings are often caused by an IgE-mediated late-phase response. These reactions are not considered life-threatening and are associated with no more than a 5–10% risk of a future sting, systemic allergic reaction. Venom allergy testing is generally not indicated (Bilò and Bonifazi 2008). However, there are data to suggest that in some patients where the reactions are debilitating, or progressively worsening, VIT may be a consideration to reduce the severity of the local reactions (Demain et al. 2010). An example would be severe facial swelling in a mailman following wasp stings. So, in special circumstances, venom testing and VIT are indicated in patients with large local sting reactions.

30.7 Duration of VIT

The duration of VIT for venom-allergic patients is unclear (Bonifazi et al. 2005; Graft et al. 1998; Golden et al. 1996, 2000; Muller et al. 1991). The majority of patients are sufficiently protected after completing a 5-year treatment plan; however some authors suggest that lifetime therapy may be warranted. Some experts suggest that repeat venom skin testing can be helpful for determining who may discontinue VIT (Forester et al. 2007; Muller et al. 1992). Although this information may be helpful, the loss of skin test reactivity is not a guarantee of an absence of risk to venom-induced anaphylaxis. Lifelong VIT should be considered in individuals who have experienced a previous life-threatening event; have honeybee allergy, mast cell disease, and comorbid conditions; or have had a systemic reaction during VIT (Georgitis and Reisman 1985; Golden et al. 1998, 2017; Lerch and Muller 1998). Those patients requiring a higher than usual venom dose, having severe anxiety concerning future stings, or having high risk for recurrent stings should also consider lifelong VIT.

30.8 Recent Developments in Insect Allergy

Advances in our understanding of the role of clonal mast cell disorders, basophil biology, and utility of serum tryptase have enhanced the evaluation of Hymenoptera sting allergy. Many of these advances will contribute to improved diagnosis and management of insect-allergic individuals. For example, the effective management of patients with a compelling history of insect-induced anaphylaxis, yet are skin and blood test negative for venom-specific IgE, has been a challenge. Occult mastocytosis or other mast cell disorders are now recognized as a potential explanation. A multicenter study of predictors of severe anaphylaxis reported elevated serum tryptase is one of the predictors (Bonadonna et al. 2010; Oude Elberink et al. 1997; Álvarez-Twose et al. 2010). Hymenoptera allergy is a frequent finding in individuals with mastocytosis. The effectiveness

of VIT is less in subjects with mastocytosis or clonal mast cell disorders (Rueff et al. 2010). The 2017 insect allergy practice parameter more thoroughly addresses the role for obtaining tryptase levels in the evaluation of insect allergy and supports the role of VIT in patients with clonal mast cell disease (Georgitis and Reisman 1985; Golden et al. 2017). Finally, several recent cases have reported the usefulness of the immunomodulatory effects of omalizumab, a monoclonal antibody specific for IgE antibody, in the management of difficult to treat insect anaphylaxis in subjects with indolent or occult mastocytosis (Galera et al. 2009; Kontou-Fill et al. 2010). Though not an FDA-approved indication, in special circumstances, omalizumab may be a consideration (Georgitis and Reisman 1985; Golden et al. 2017).

In addition to the evolving understanding of clonal mast cell disorders and Hymenoptera allergy, the role of basophils in the diagnosis and management of insect anaphylaxis is also expanding. Although not commonly used in the United States, the basophil activation test may be informative in managing individuals with a history of systemic reactions to insect stings without specific IgE (Kruse et al. 2009; Kosnik and Korosec 2011; Peternelj et al. 2009).

30.9 Conclusion

Insect allergy is one of the three most common triggers of life-threatening anaphylaxis and is by far the most treatable. It is crucial that physicians and the public understand proper diagnosis, treatment, and management of this potentially life-threatening allergy. While the other two causes, food and medication anaphylaxis, are managed primarily by avoidance, Hymenoptera allergy can be managed prospectively with VIT, which provides up to 98% protection from subsequent sting anaphylaxis. Effective management of the acute event, a thorough history of the sting circumstances, recognition of the likely culprit insect, appropriate venom testing, VIT, and optimal use of auto-injector epinephrine are necessary for ideal outcomes. Acute management includes establishing the presence of a Hymenoptera sting-related anaphylactic event, followed by appropriate use epinephrine. Occult mast cell disease may be playing an important role in Hymenoptera sting reactions, and a basal tryptase level may be very helpful. However, long-term management does not end with the dispensing of an epinephrine auto-injector but includes appropriate referral, determination of venom-specific IgE, and, if indicated, IT.

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