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Insect Sting Allergy

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The study of allergy to insect stings holds a unique position in the field of allergy, and because of the usually singular and notable times of exposure, it serves as a model for the development, natural history, and treatment of allergic phenomena. The death of King Menes of Egypt shortly after a wasp sting is often cited as one of the earliest historical examples of anaphylaxis [1]. Soon after the concepts of anaphylaxis were defined by Portier and Richert in 1902 [2], generalized reactions to insect stings were recognized as hypersensitivity phenomena [3]. Ten years later, Braun [4] described a typical patient with insect sting sensitivity and his use of insect venom for diagnosis and treatment. Although this initial treatment used the posterior one eighth inch of the insect to increase the yield of venom, that stipulation was later ignored and for decades, immunotherapy with whole-body extract was used for the treatment of patients with insect sting reaction [5]. In the 1950s and 1960s, events occurred that eventually led to the development of venom immunotherapy (VIT). Loveless and Fackler [6] reported the successful diagnostic and therapeutic use of extracts of venom sacs. Bernton and Brown [7] and Schwartz [8] independently found that whole-body extract skin tests did not discriminate insect allergic patients from subjects with no history of generalized reactions. Methods for collecting large quantities of honeybee venom were developed and the venom contents were characterized [9]. Vespid venom collection was more difficult requiring venom sac extirpation in a tedious one-insect-at-a-time process. In the 1970s, a few case reports of successful VIT appeared [10,11] and then, in 1978, Hunt and coworkers [12] from Johns Hopkins reported a challenge sting trial in which the superiority of VIT was demonstrated when compared with whole-body extract and placebo injections. The immunotherapy protocol with venom is the most effective treatment in the field of allergy. About 97% of venom-treated

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patients have no reaction when stung [13–15]. The few remaining patients are more appropriately considered partial successes rather than treatment failures because they tend to have reactions that are much less severe than those they have previously experienced.

Insect venoms for immunotherapy became commercially available in 1979. Since then, thousands of patients have received VIT. Venom injections greatly reduce the likelihood of serious allergic reactions and consequently improve the patient's quality of life by reducing anxiety and allowing patients to participate in the outdoor activities that they prefer. Guidelines have been published regarding the selection of patients and the method of VIT and for the discontinuation of VIT [16,17]. Venom injections have proved very safe, with a low occurrence of injection-induced systemic reactions and no reports of fatal reactions. Unfortunately, even after 25 years of use, many patients who should initiate VIT are not referred to allergists for evaluation despite data that demonstrate the lack of effectiveness of single or multiple doses of epinephrine [12,18]. It is hoped that this pattern of underutilization will diminish in the future.

Epidemiology

Systemic allergic reactions are reported by 0.4% to 3% of individuals [19–21]. There is a 2:1 male/female ratio that is probably a reflection of relative exposure. About one third of those experiencing allergic sting reactions are atopic [22]. Annually, about 45 deaths are attributed to insect stings in the United States (Table 1) [23]. Other data on fatal stings include the following: 20 in Ontario, Canada, from 1986 to 2000 [24]; four per year in the United Kingdom [25]; three per year in Switzerland [26]; and 11 per year in West Germany [27]. About one half of the fatal reactions occur in individuals with no prior history of allergic reactions to stings [28,29]. Many more men (about 3.5-fold) than women die from insect sting reactions, and greater than 80% of the deaths from insect stings occur in persons over 40 years of age [23]. The coexistence of coronary heart disease, atherosclerosis, or emphysema may determine a more severe outcome. The true number of deaths attributed to insect stings is undoubtedly higher because sudden deaths on a golf course or while working outside may be falsely labeled as heart attacks or strokes. In studies of postmortem sera from individuals dying from unknown causes, a significant number had clinically relevant levels of IgE antibodies to one or more Hymenoptera venom or elevated tryptase levels [30,31]. There are many more near-fatal episodes. In the initial controlled trial of VIT, 3 of the 14 patients in the placebo- and whole-body extract–treated groups who sustained challenge sting-induced systemic reactions had significant hypotension; in two of these patients the hypotension persisted despite multiple doses of epinephrine; one patient required intubation [18].

Table 1
Insect sting deaths in the United States

Year	No. of deaths								Total for the year	Sex (M/F)
	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70+		
1980	0	0	1	1	7	13	13	3	38	25/13
1981	0	1	2	7	6	12	6	5	39	35/4
1982	0	1	2	4	16	13	10	8	54	45/9
1983	2	0	3	8	9	9	10	8	49	43/6
1984	4	0	2	5	11	8	14	4	48	39/9
1985	1	1	4	4	8	10	9	4	41	32/9
1986	0	0	2	8	7	7	11	7	42	31/11
1987	1	0	0	5	9	15	12	11	53	42/11
1988	0	0	1	3	7	8	9	6	34	27/7
1989	0	0	2	6	9	13	15	8	53	40/13
1990	0	1	3	4	6	11	10	3	38	33/5
1991	1	1	4	11	11	13	14	9	64	48/16
1992	0	0	2	10	13	10	8	5	48	38/10
1993	0	2	1	6	8	5	11	6	39	31/8
1994	0	1	2	7	12	6	13	8	49	37/12
1995	0	1	0	7	12	13	11	15	59	46/13
1996	0	1	1	2	9	14	12	6	45	27/18
1997	0	1	5	5	10	10	10	2	43	40/3
1998	1	0	4	4	13	12	4	8	46	33/13
1999	0	0	0	5	13	15	5	5	43	31/12
Total	**10**	**11**	**41**	**112**	**196**	**217**	**207**	**131**	**925**	**723/202**

Data from Graft DF. Venom immunotherapy for stinging insect allergy. Clin Rev Allergy 1987;5:149–59.

The rate of venom sensitivity is higher than the rate of systemic reactions. In a stratified random sample of 320 adults in a light industrial setting, 3.3% had a history of systemic reaction to insect sting, but 17% had positive venom skin test (VST) and 26% had venom-specific IgE antibodies by radioallergosorbent testing (RAST) [21]. Evidence of venom sensitivity was more likely if the subject had been stung in the last 3 years. Interestingly, these history-negative positive VST subjects had a 17% risk of reaction to field sting [32]. Ludolph-Hauser and coworkers [33] reported a more frequent occurrence of elevated basal serum tryptase in patients with a history of severe systemic reactions to insect stings. Others have also reported severe reactions to insect stings in patients with systemic mastocytosis and often little evidence of venom sensitization is found [34].

The insects

The stinging insects belong to the order Hymenoptera. A sting is an injection of venom by the female of each species through a modified ovipositor. The most conspicuous members of the superfamily Apidae are the honeybee (*Apis mellifera*) and bumblebees (*Bombus* spp). Honeybees are small, fuzzy insects with alternating tan and black stripes. They are often

seen pollinating clover and flowering plants, are relatively nonaggressive, and generally sting only when caught underfoot. The barbs along the shaft of the honeybee stinger cause it to remain embedded at the sting site (autonomy). As it flies away, the honeybee dies through evisceration.

The honeybees in the United States were at one time only of European ancestry. Africanized honeybees were brought to Brazil in 1956 to improve honey production. One year later multiple colonies escaped and began interbreeding with the resident colonies. The Africanized honeybees have expanded northward and by 2002 were present in most of Texas and Arizona and southern areas of Nevada, California, and New Mexico. Africanized honeybees are often referred to as "killer bees" not because of increased venom potency or allergenicity but rather of their tendency to attack en masse; fortunately, even massive stinging incidents of 50 to 100 stings are not usually fatal. Nevertheless, there were at least 70 deaths attributed to Africanized honeybees in Venezuela from 1978 to 1981 [35] and 42 deaths in Mexico from 1987 to 1991 [36]. McKenna [36] recently accounted the 13 deaths in the United States until 2002.

Bumblebees are large, slow-moving, noisy bees with hairy bodies of alternating yellow and black stripes. They are also nonaggressive and account for only a small fraction of stings. Bumblebee stings have become more common, however, because they have been used in confined settings, such as greenhouses, to pollinate tomato plants [37].

The family Vespidae includes the yellow jackets, hornets, and wasps, which make papier-mâché–like nests of wood fiber. The more than 10 species of yellow jackets (*Vespula* spp) are identified by alternating yellow and black body stripes. They usually nest in the ground or in decaying logs near human dwellings and scavenge for food. Closely related are the yellow and white (bald-faced) hornets (also *Vespula* spp), which build teardrop-shaped nests that hang in trees or bushes. Both yellow jackets and hornets are extremely aggressive, especially in the late summer when crowded conditions develop in the nests.

Not quite as aggressive as the other vespids, the thin-bodied paper wasps (*Polistes* spp) build nests in the eaves of buildings in which the development cells are not enclosed by a paper envelope. Allergic reactions resulting from wasp stings account for less than 5% of the cases in the northeast; however, in the southern regions of the United States, they are much more prevalent. Vespids rarely leave a stinger at the sting site, a feature that can be a clue in culprit identification.

Interestingly, common names for these insects are different in the United States and Europe and this must be kept in mind when reviewing the literature [38]. The yellow jacket, yellow hornet, and paper wasp are all called wasps in Europe. The term "hornet" is reserved in Europe for the *Vespa crabro* (European hornet), a large insect that builds its nests in tree hollows and wall cavities. Fortunately, still relatively uncommon in the United States, they account only for a small fraction of stings.

The imported fire ant (*Solenopsis invicta*) is found in the southeastern and south central United States. Its range continues to increase and allergic reactions to fire ants are becoming more common [39]. The fire ant grasps the victim with its jaws, then pivots around, stinging repetitively in a semicircular pattern. The hallmark of their sting is the development of a sterile pustule at each sting site 24 hours later.

Venoms

The dried weight of the venom deposited by a honeybee, induced to sting a plastic film, is approximately 50 μg. A single sting from a yellow jacket is thought to deliver between 10 and 100 μg. Hymenoptera venoms contain a number of interesting constituents [40]. Most of the venoms contain histamine, dopamine, acetylcholine, and kinins, which cause the characteristic burning and pain and may allow for access to the systemic circulation. The allergens in the venoms are mostly proteins with enzyme activity. Although honeybees and have both phospholipase and hyaluronidase activities in their venom, the proteins bearing the same enzymatic functions in vespid venoms are immunochemically different. Antibody inhibition studies on sera from mice immunized with purified venom allergens show that extensive cross-reactivity exists between white-faced hornet, yellow hornet, and yellow jacket for hyaluronidase and antigen 5, but not phospholipase [41,42]. There is some cross-sensitization between *Polistes* wasp and yellow jacket for antigen 5 and there is limited cross-reactivity between honeybee, vespid, and fire ant venoms.

Spectrum of reactions

Following a Hymenoptera sting, most individuals experience a small urticarial area that is slightly raised with surrounding redness, pruritus, and pain that starts shortly after the sting and usually resolves in 2 to 3 hours. About 10% of the population develop large local reactions, which has been variably defined as swelling contiguous with the sting site larger than a 2-in diameter [43] or more than a 4-in diameter [44] lasting over 24 hours. Occasionally, these are large enough to involve an entire extremity and may last for as long as a week. Often, these are misdiagnosed as cellulitis and patients receive antibiotics, especially if there is a lymphatic streak toward the axilla or groin.

Systemic allergic reactions (anaphylaxis) may be mild with only cutaneous symptoms (pruritus; urticaria; angioedema of the eyes, lips, hands; and so forth) or severe with potentially life-threatening symptoms of laryngeal edema, bronchospasm, hypotension manifested by an uncomfortable feeling in the throat, gagging, difficulty swallowing, voice change, inspiratory stridor, chest tightness, wheezing, cough, dizziness, tunnel vision, or

loss of consciousness. Adults often describe a metallic taste in their mouth or an aura of impending doom, as if they are going to die. Nausea is common in large local and systemic reactions.

Systemic allergic reactions are, in general, less severe in children than adults. Of the approximately 45 deaths per year in the United States attributed to insect stings, only one or two occur in children [23]. Whereas 85% of adults with sting-induced systemic reactions report potentially life-threatening symptoms, such as laryngeal edema, bronchospasm, or hypotension, only 40% of children develop reactions of this level of severity [45]. Diagnosis of anaphylaxis is sometimes complicated by the absence of the more easily recognized cutaneous symptoms of an allergic reaction, such as urticaria. A patient may complain of light-headedness or a brief period of unconsciousness, be found to have hypotension, and the diagnosis of vasovagal reaction may be made. A vasovagal reaction is usually accompanied by bradycardia, however, whereas anaphylaxis often includes compensatory tachycardia in response to vasodilation and leakage of fluid from the blood vessels. An elevated serum tryptase, which signals mast cell degranulation, provides additional evidence for anaphylaxis [46].

Solley [47] recently reported his 17-year experience with insect stings and bites from Queensland, Australia. Of 1194 patients with anaphylaxis, 775 had urticaria with dyspnea, 425 had facial angioedema, and 457 had asthma. Additionally, 454 (38%) reported dizziness and 179 (15%) more patients manifested unconsciousness. Of particular note, 82 patients (7%) experienced dizziness, faintness, weakness, or coma as their sole expression of anaphylaxis; 48 (4%) had airways obstruction only; and an additional 79 (7%) had a combination of these two only.

A variety of atypical reactions have been described after insect stings [48,49]. When the syndrome of urticaria, fever, proteinuria, lymphadenopathy, and arthropathy has occurred, it has been termed ''serum sickness'' despite the imperfect analogy to classic serum sickness. Although one might worry that symptoms of serum sickness might recur when VIT is used, that has not been reported. Other uncommon outcomes after insect stings including renal disease and neurologic manifestations have been described, but they have not been shown to be IgE-mediated, and the mechanism of these events is unclear.

Treatment of acute sting reactions

Minor local swelling and pruritus are expected and can be treated with ice and antihistamines. If present, the imbedded stinger should be flicked off with a scraping motion. Some authorities believe that one should not grasp the fleshy venom sac to extract the stinger because more venom might then be injected through the stinger. Schumacher and colleagues [50], however, showed that essentially the entire honeybee venom load is injected in less than 20 seconds; one should quickly remove the stinger.

If a generalized reaction occurs, epinephrine is the keystone of management. Epinephrine halts the further release of mediators and reverses many of the effects of released mediators. An intramuscular (preferred) [51] or subcutaneous injection of epinephrine usually produces prompt resolution of symptoms. The dose of epinephrine is 0.3 to 0.5 mg (0.3 to 0.5 mL of a 1:1000 solution) for adults, and 0.01 mg/kg for children. This may be repeated in 10 to 15 minutes if necessary. An oral or parenteral antihistamine, such as diphenhydramine, 6.25 to 50 mg, is also usually given. It may lessen urticaria, but in more severe or progressive reactions, its use should not delay the administration of epinephrine.

Epinephrine may be ineffective in profound anaphylactic shock unless the functional hypovolemia of this state is corrected with intravenous fluids [18]. Severe reactions often require treatment with oxygen, H_2-antihistamines, and pressor agents. Corticosteroids are often used but they have a delayed onset of action. Intubation or tracheostomy is indicated for severe upper airway edema not responding to therapy. Close observation is essential. Overnight hospitalization is suggested for patients who have experienced severe reactions or who have complicated medical problems.

Decreasing future reactions

Preventing stings

Future stings can be avoided by taking common sense precautions to significantly reduce exposure. Shoes should always be worn outside. Hives and nests around the home should be exterminated. Good sanitation should be practiced because garbage and outdoor food, especially canned drinks, attract yellow jackets. Unfortunately, insect repellents have little or no effect. Avoidance of attractants, such as fragrances and brightly colored clothes, may be helpful.

Emergency epinephrine

To encourage prompt treatment, epinephrine is available in emergency kits for self-administration. These are used by insect sting–allergic individuals immediately after the sting to "buy time" to get to a medical facility. A practice self-injection with saline helps to allay such fears. The EpiPen (0.3 mg epinephrine) and EpiPen Jr. (0.15 mg epinephrine) offer a concealed needle and a pressure-sensitive spring-loaded injection device that make them suited for patients and families who are uncomfortable with the injection process. Epinephrine by inhalation may also be used to achieve a therapeutic plasma level and may be especially helpful for laryngeal edema and bronchospasm. Many patients in urgent care settings do not receive a prescription for self-administered epinephrine or referrals to allergists for consideration of VIT [52]. Patients who are receiving maintenance injections of

VIT are advised that emergency self-treatment will probably not be required; however, they should have the kit available if they are distant from medical facilities. A Medic-Alert bracelet is also advised.

How to initiate venom immunotherapy

Patient selection

VIT is a safe, highly effective method of preventing future sting reactions in insect-allergic patients. The selection of patients for VIT is determined by the likelihood that a future sting will cause an allergic reaction (Table 2), which is based on the clinical history and the results of venom skin tests (VSTs) (and occasionally RASTs). The risk of recurrence is higher for adults than for children, higher for those allergic to honeybee rather than vespid venom, and higher for patients whose previous reactions were more severe [53–55]. A careful history discloses the type, degree, and time course of symptoms, and often identifies the culprit insect. An individual who has experienced a sting-induced systemic reaction should be referred to an allergist who will perform skin tests with dilute solutions of honeybee, yellow jacket, yellow hornet, white-faced hornet, and *Polistes* wasp venoms and, if indicated, imported fire ant whole-body extract [56,57]. RAST cannot replace VST but may provide additional information [58]. The value of venom RAST is discussed in a subsequent section on the VST-negative patient. To date, fire ant venom has only been available in small research quantities; fortunately, the fire ant whole-body extract material contains a significant amount of venom and has been successfully used for skin testing and treatment. Table 3 lists the indications for VIT. At particularly low risk are children who have had reactions limited to the skin in which there is only a 10% rate of subsequent systemic reactions involving respiratory or cardiovascular symptoms [53]. Children who have had moderate or severe reactions should start VIT; those who do not start VIT have a significantly higher risk of

Table 2
Risk of systemic reaction in untreated patients with a history of sting anaphylaxis and positive venom skin tests

Original sting reaction		Risk of systemic reaction (%)	
Severity	Age	1–9 y	10–20 y
No reaction	Adult	17	—
Large local	All	10	10
Cutaneous	Child	10	5
Systemic	Adult	20	10
Anaphylaxis	Child	40	30
	Adult	60	40

From Golden DBK. Insect allergy. In: Adkinson NF, Middleton E, editors. Middleton's allergy: principles and practice. 6th edition. Philadelphia: Mosby; 2003. p. 1475–86.

Table 3
Selection of patients for immunotherapy

Reaction to sting	Result of skin test or RAST	Venom immunotherapy?
Child		
Systemic, non–life-threatening, immediate, generalized urticaria, angiodema, erythema, pruritus[a]	+ or −	No
Systemic, life-threatening, possible cutaneous symptoms, but also respiratory symptoms (laryngeal edema or bronchospasm) or cardiovascular symptoms (hypotension, shock)	+	Yes
Adult		
Systemic	+	Yes
Systemic	−	No
Child or adult		
Large local (>2 in diameter, >24-h duration)	+ or −	No
Normal (<2 in, <24-h duration)	+ or −	No

[a] It is unknown whether this rule applies to imported fire ant hypersensitivity in children.

reaction as adults, estimated to be 30% [59]. Some clinicians recommend VIT for an adult who experienced any degree of systemic reaction. Most individuals, however, have a stereotypic response to a sting with the symptoms on subsequent stings closely resembling the first episode [60]. When only a mild reaction has occurred, the physician and patient may jointly decide whether to embark on a course of VIT [61]; some experts advise treatment of adults with only cutaneous symptoms [62]. Individuals who have had severe allergic reactions should be advised not to depend only on avoidance and availability of epinephrine but also to receive venom injections. Patients with a history of systemic reactions have a reduced quality of life [63]; this is not improved by having self-administered epinephrine but is with VIT [64].

Individuals with large local reactions or negative skin tests are not candidates for venom therapy. The risk of anaphylaxis to future stings is about 5% to 10% in patients who have had large local reactions to insect stings; many, however, develop large local reactions again [43,44,65]. Many patients with large local reactions have evidence of a high level of venom sensitivity. Because it is also true that some patients with severe anaphylaxis have low levels of venom sensitivity, the level of skin test reactivity (and venom-specific IgE) is poorly correlated with the risk of systemic reactions [56]. A positive VST or RAST in the absence of a sting-induced systemic reaction is not an indication for therapy. Approximately 25% of the general population may have such evidence of sensitization to venom antigens, apparently resulting from past stings. This is usually transient, disappearing in 1 to 3 years [21].

Other factors may influence the decision concerning the need for VIT. Those with an increased risk of being stung, such as landscapers or other individuals who engage in outdoor activities, especially those that take them far away from available medical care, dispose the physician toward

initiating venom treatment. Part of the morbidity associated with stinging insect allergy includes psychologic effects of anxiety in the victim and family because of the threat of a sudden "unpreventable" systemic reaction. This high level of anxiety has frequently been exacerbated by a physician warning that "the next sting may be your last." Actually, most victims exhibit an individual pattern of anaphylaxis that varies only slightly in severity from one sting to another. Some investigators have proposed that a diagnostic sting challenge be used to select patients for VIT [60]. Patients who did not react would not be placed on VIT. Other reports, however, have described individuals who tolerated one sting challenge, but reacted later to a second challenge [66,67]. In the United States, the use of sting challenges to determine VIT candidates is impractical and most physicians believe that a challenge sting presents too great a risk [68], especially for patients with life-threatening reactions (ie, hypotension). Indeed, in one study life-threatening reaction recurred in 15% of subjects with histories of severe reactions [60].

The venom skin test–negative patient (never say never)

The patient with a history of a sting-induced systemic reaction and negative VSTs presents a unique challenge. It has been commonly assumed that negative VST responses indicate that there is no risk of systemic reaction to a sting. Golden and coworkers [69] recently reported, however, that of 307 subjects with a history of a sting-induced systemic reaction who underwent VST, 99 (32%) had negative VST. Of these, negative RAST was present in 56 patients; 36 had low (1–3 ng/mL) RAST; and 7 had high positive RAST (4–243 ng/mL). Sting challenges in 14 of 56 patients with negative VST and negative RAST resulted in two (14%) systemic reactions. Sting challenges in 37 of 43 patients with negative VST and positive RAST caused nine (24%) systemic reactions. Combined, the negative VST group had a systemic reaction rate of 22%, which was similar to the rate of 21% found in those with positive VST studied at the same time. It is now recommended that a patient with a convincing history of a sting-induced systemic reaction should have VST. If these are negative and the reaction was severe, venom-specific IgE should be measured and VIT initiated if positive. If negative RASTs are obtained, the VST should be repeated 3 to 6 months later [70,71]. Regardless of the VST and venom-specific IgE determinations, the patient should practice usual precautions of insect sting avoidance and should carry antihistamines and injectable epinephrine.

Venom selection

The venoms used for immunotherapy are the same as those used for skin testing (honeybee, yellow jacket, yellow hornet, white-faced hornet, wasp, and fire ant whole-body extract if applicable). The regimen begins with an injection of 0.01 μg and advances weekly to 100 μg (0.5 of 1:100 wt/vol for fire ant whole-body extract). The maintenance dose of 100 μg is given every 4 weeks for a year, after which the interval is lengthened to 6 to 8 weeks.

The choice of venoms is based primarily on VST results, and to a lesser extent on clinical history and patterns of venom cross-reactivity. It is currently recommended that immunotherapy include all venoms giving a positive skin test, the aim being to give the maximum security to the patient [62]. Even a patient who has reacted to only one type of insect should not be left with lingering doubts about future stings by other insects to which he or she shows skin test sensitivity. The most common culprit in North America is the yellow jacket, except for some areas of the south central and southwestern states, where wasps and honeybees, respectively, are predominant. In some cases, the skin tests are positive to only one or two venoms. Most yellow jacket–allergic patients also have positive skin tests to yellow hornet and white-faced hornet venoms, however, and consequently require treatment with mixed vespid venom containing the full dose of each venom (yellow jacket, yellow hornet, and white-faced hornet). Half of these patients are also positive to *Polistes* wasp venom and receive this in addition. RAST inhibition studies can disclose whether patients are sensitive to a cross-reacting allergen or multiple unique allergens. The allergenic cross-reactivity of the four vespid venoms has been demonstrated, as has the fact that most patients with multiple vespid venom sensitivity can be fully protected by immunotherapy with yellow jacket venom alone [72,73]. Honeybee venom is administered as indicated.

The 100-μg maintenance dose of venom was initially chosen because it represented approximately twice the venom content of a honeybee sting. One investigator has reported his 10-year experience with a maintenance venom dose of 50 μg [73]. The question of whether or not a lesser dose would suffice was examined in a group of patients who received a 50-μg maintenance dose. It was found that with the reduced venom dose, only 79% of subjects were protected from challenge sting-induced systemic reactions [74].

Yunginger and coworkers [75] reported on a very rapid 1-day rush regimen that had some success but caused many systemic reactions and had to be performed in a hospital. Bernstein and colleagues [76] described a 2- to 5-hour regimen of rush VIT in which 10 gradually increasing doses were administered every 10 to 15 minutes to achieve a total dose on day 1 of about 55 μg per venom followed by doses of 70, 80, 90, and 100 μg on days 3, 7, 14, and 21, respectively. Only 4 of 33 patients had reactions on day 1, and all were mild. These patients subsequently tolerated natural stings without incident.

How does venom immunotherapy work?

The mechanism of action of immunotherapy is only partially understood. The development of allergic sensitization to venom requires the sting-induced production of venom-specific IgE antibodies that are bound to tissue mast cells and circulating basophils. A subsequent sting may then result in the

binding of venom antigens to the IgE molecules followed by the release of mast cell and basophil mediators of anaphylaxis (histamine, leukotrienes, and so forth). It should be remembered that venom vaccines used to immunize patients with insect sting hypersensitivity are not clinically or immunologically identical to the venom injected by live stings. In the initial controlled trial of VIT, some patients tolerated injections of 100 μg of venom administered subcutaneously immediately before challenge stings that caused severe anaphylaxis to challenge stings [12,18]. Successful VIT is associated with many humoral and cellular immunologic changes that are summarized in a recent review [77].

VIT results in significant changes in venom-specific IgE and IgG antibody levels. IgE rises first, peaking at 8 to 12 weeks, before declining slowly over 3 to 5 years to pretreatment levels. The IgG level reaches its mean peak value of 15 μg/mL at 2 to 4 months, and then is fairly constant over 5 to 6 years of treatment in children. Adults have an average peak of 9 μg/mL and then decline to about 6 μg/mL. A few adult patients experience even more extreme declines for reasons that are presently unclear. The cause of the more vigorous IgG response in children is also not known. Analysis of venom-specific IgG levels in children and patient age, body weight, or surface area fails to show any correlation [78].

The production of antigen-specific IgG (blocking) antibodies has been considered the possible means of immunotherapeutic improvement. Lessof and coworkers [79] demonstrated that honeybee-allergic patients could tolerate challenge stings after passive immunization with the gamma globulin fraction of pooled beekeeper's serum that contained a high blocking antibody titer. The serum level of venom-specific IgG has been inversely correlated with the likelihood of challenge sting-induced systemic reactions in patients on VIT [80]. After 4 years of VIT, however, that correlation no longer held true. Other immunologic changes occur that could also influence the development of protection to insect stings. VIT seems to influence the T-cell phenotype away from the Th2-type, which produces interleukin-4 and interleukin-5, and toward the Th-1 type, which produces interferon-γ [81,82], or a regulatory type with expression of interleukin-10 and the production of IgG4 [83].

Management of venom immunotherapy

Safety of venom immunotherapy

VIT generally is well tolerated. Most patients receive their injections in an allergist's office until the maintenance dose is reached. Patients should remain for 30 minutes after each injection in a setting equipped to handle a systemic reaction. About 3% to 12% of patients have treatment-induced systemic reactions that generally are mild and occur in the early phases of VIT [15,84]. The reaction rate is no higher than that seen in conventional

pollen immunotherapy when effective immunizing doses are used [85]. If a systemic reaction occurs, the regimen is interrupted. One half of the dose that resulted in a systemic reaction is given the next week and, if tolerated, the schedule is resumed. Pretreatment with antihistamines reduces VIT reactions and may improve the efficacy of VIT [86,87]. A less serious, but more frequent, problem with VIT is the large local reactions that occur in 25% of children and 50% of adults, usually at doses about 20 to 30 μg. Although bothersome, they do not predict an increased risk of future systemic reactions to treatment and usually the best way to avoid them is to reach higher doses by proceeding with the injections regimen. Further advice in dealing with difficult cases can be found in the literature [88].

All new forms of treatment provoke concern of possible long-term complications. Yunginger and coworkers [89] provided some information regarding venom safety by studying beekeepers and their families who may experience as many as 50 or more stings per year. Although this population showed some minor urine or blood chemistry abnormalities, these did not show a correlation with sting frequency. Also, beekeepers do not have an increased risk of cancer. It should be noted, however, that parallel studies for vespid venoms are not available. No long-term toxicity or side effects have been associated with VIT thus far. Graft and coworkers [14] noted that 3 to 6 years of VIT in children was not associated with abnormalities in histories; physical examinations; or laboratory analyses (hematologic and chemical surveys, and urinalyses).

Few reports of VIT use during pregnancy have been published. Schwartz and coworkers [90] discussed 22 pregnancies in 15 women that resulted in 19 normal children, 1 first-trimester miscarriage, 1 miscarriage secondary to placenta previa, and 1 child with multiple congenital abnormalities of unknown cause. This rate of less than optimal outcome for pregnancy was not higher than expected with pregnancy in normal populations. In one closely studied case, VIT during pregnancy did not result in allergic sensitization to venom in the child [91].

Interval between venom injections

The maintenance dose of 100 μg is given every 4 weeks for a year; the interval is usually lengthened to 6 weeks during the second year and to 8 weeks during the third year of treatment [16]. Investigators from Israel described 160 individuals who had the maintenance interval lengthened to 3 months [92]. A subgroup of 47 reached the 3-month maintenance interval only 4.5 months after the maintenance dose was reached. Ninety-three stings in 80 patients on 3-month maintenance interval VIT resulted in four skin reactions (one occurred in one of the few patients on a 50-μg maintenance dose). After VIT was stopped in these patients, 65 stings in 46 patients resulted in four reactions (6.2% per sting, 8.7% per patient). Extending the interval between injections reduces the cost of VIT [93,94].

Monitoring of venom immunotherapy

Most patients begin therapy with IgG levels less than 1 μg/mL (usually undetectable), but occasionally they may be elevated because of the previous sting. IgG levels induced by the first 4 to 6 months of therapy are usually between 5 μg/mL and 20 μg/mL, with higher levels observed in children and when multiple venoms are administered [80]. Among immunized patients, those who continue to react to stings generally have exceptionally small increases in their venom-specific IgG antibodies. Patients who are not adequately protected by the 100 μg per venom dose are often protected with higher doses [95]. Because there are so few treatment failures with VIT, it may not be cost-effective to perform venom IgG antibody assays on all immunized patients [96].

At follow-up visits, usually annually, the patient's VIT schedule should be reviewed, noting dose and frequency of injections; local or systemic reactions to injections; and any stings (and their outcome) that may have occurred since the last visit. VSTs may be repeated every several years. Over time, VSTs tend to decline and become negative in a significant proportion of patients. In children, Graft and coworkers [97] found that 45% of those who had received 3 to 6 years of VIT developed negative VSTs to one or more venoms, whereas in adults, Golden and coworkers [98] reported that 20% had negative VSTs after 5 years and 50% to 60% after 7 to 10 years.

Honeybee allergy versus vespid allergy

Honeybee sensitivity is generally a more difficult problem than vespid venom sensitivity. Researchers in The Netherlands stung 324 patients and found that patients with history of honeybee sting reactions were twice as likely to react to challenge stings (52% versus 25%) [60]. Once VIT is commenced, Müller reported that honeybee-sensitive patients have more reactions to VIT (41% versus 25%) than those on vespid VIT [54]. Of concern, honeybee VIT is less effective in preventing future sting-induced systemic reactions (77% versus 91%) [54]. Finally, even after VIT is stopped, patients who received honeybee VIT are more than twice as likely to react to challenge stings (17% versus 4%–8%) delivered 1 to 2 years after VIT discontinuation [99].

Discontinuation of venom immunotherapy

In 1998, the American Academy of Allergy Asthma and Immunology published a position statement on the discontinuation of hymenoptera VIT [17]. This reviewed data that had been published on outcomes of patients who stopped VIT without a physician's recommendation; those who were able to stop VIT because they developed negative VSTs or significantly lower levels of venom-specific IgE; and those who had completed a specific duration of VIT, such as 3 or 5 years. Most have used challenge stings;

others have reported on the outcome of natural field stings. Importantly, the lack of certainty of identification of the insect clouds the interpretation of studies that used field stings.

When VIT was first used, many thought that it would need to be continued indefinitely. Early on, however, reports began to appear that chronicled the relatively good outcomes of patients who chose to stop their venom injections. Reisman and coworkers [13] reported from Buffalo on 88 patients, ages 10 to 76 years, who stopped VIT after 1 to 78 months without a physician's recommendation. Of these, 61 field stings in 41 patients occurred 1 to 72 months after VIT was terminated and there were 11 (18%) systemic reactions. In Baltimore, Golden and coworkers [100] noted a 22% reaction rate in patients who stopped treatment after 2 to 44 months of venom injections. These rates were much lower than the approximately 60% risk for untreated patients with histories of sting-induced systemic reactions and positive VST.

Next, studies were designed in which VIT was discontinued if the venom allergy had significantly diminished as measured by the fall in venom-specific IgE to low levels. Studies in which the VST became negative reported low numbers of entrants [33,97]. Urbanek and coworkers [101] studied the discontinuation of VIT in 31 honeybee-sensitive children and adolescents in whom venom-specific IgE had fallen to low or unmeasurable levels. One year after stopping VIT, a challenge honeybee sting resulted in a systemic reaction in only 1 (3%) of 29 patients; at 2 years after stopping VIT, 2 (14%) of 14 patients reacted. Randolph and Reisman [102] reported an 8% reaction rate to stings in patients who stopped VIT because of a two-log decline in venom-specific IgE levels. Studies using serum venom-specific IgE levels have been criticized because of potential for variance in assay methods and scoring systems between investigators. Reisman [103] retrospectively reviewed the outcome of 217 field re-stings in 113 patients after discontinuation of VIT and reported a relationship between the severity of the pre-VIT insect sting reaction and the likelihood and severity of sting reactions after a course of VIT was stopped. Systemic reactions occurred in 1 (4%) of 25 patients with initial mild reactions; 2 (5%) of 41 patients with initial moderate reactions; and 7 (15%) of 47 patients with initial severe reactions. In the latter group, five of the seven reactions were again of a severe nature. Furthermore, in Minneapolis a retrospective study found that 148 stings in 117 patients (most were intentional challenge stings) who had discontinued VIT resulted in only two reactions, both of which occurred in patients with initial severe sting reactions [104].

Most recently, studies have been designed in which VIT is administered for a specific duration of time. Haugaard and coworkers [105] of Denmark reported the outcome of sting challenges in 25 adults (mean age, 42.9 years) who had moderate to severe systemic reactions; were primarily yellow jacket sensitive; and had been on VIT for 36 to 83 months (mean, 42.8 months). Twenty-eight sting challenges with the relevant insects 12 to 36 months

(mean 25.2 months) after VIT was stopped resulted in no systemic reactions. In Switzerland, Müller and coworkers [99] studied 86 children and adults who had received honeybee venom for a mean period of 56.4 months (range, 32–119 months). All patients had tolerated a honeybee sting in the field or in a hospital challenge setting while receiving VIT. About 13 months (range, 10–24 months) after VIT was discontinued, patients returned for deliberate honeybee sting challenges, and 15 patients (17%) experienced mild systemic reactions.

Keating and coworkers [106] studied 51 patients in Minnesota after cessation of VIT for 2 to 10 years (mean, 5.2 years). Vespid VIT was administered to 46 patients, with 15 patients receiving honeybee venom injections. All patients tolerated stings by the relevant insects at the time VIT was discontinued. One year after stopping VIT, two patients reacted to intentional challenge stings; these patients resumed VIT. Further sting challenges ($N = 31$) resulted in no reactions. Two of 15 patients with initial severe reactions had reactions to challenge stings compared with none of the 36 patients with milder reactions. Also, the risk of reaction was higher in the 13 patients who received VIT for less than 5 years (2 of 20) than in the patients who received VIT for more than 5 years (0 of 31).

At Johns Hopkins in Baltimore, Golden and coworkers [98,107,108] performed the most comprehensive trial of discontinuation of VIT. They reported the results of challenge stings in 74 adults allergic to insect venom who had stopped treatment after 5 or more years of VIT. Eighty percent of these patients had a history of respiratory or vascular symptoms of anaphylaxis after a pre-VIT sting. VST responses were negative in 28% when VIT was discontinued (VIT duration: mean, 5.95 years; range, 5–9 years). One group of 29 patients was stung annually for 5 years; in year 4 they had two stings, 1 month apart. A second group of 25 patients had sting challenges every 2 years; in year 4 off VIT they received two sting challenges, 1 month apart. A third group of 20 patients had two stings 1 month apart after 2 years off VIT. Systemic reactions followed 8 (3%) of 270 stings in 7 (10%) of 74 patients [98]; only two reactions were clinically significant. By the end of the study, skin test responses were negative in 67% of the subjects.

Subsequently, Golden and coworkers [107] reported on their extended follow-up for these and other patients. Of the original 74 patients in their challenge sting study, 11 sustained field stings after 3 to 7 years off VIT and one developed a systemic reaction involving dyspnea. Of an additional 51 patients, 4 of 15 stings results in systemic reactions. In total, 12 (13.5%) of 89 patients had 14 (4.5%) reactions to 309 stings. Patients who had a systemic reaction to a venom injection or insect sting during VIT had a 46% rate of systemic reaction to stings after VIT was discontinued as compared with only 8% rate in those who had no reactions during VIT. Patients with more severe pre-VIT reactions did not have a higher frequency of reactions to stings but did tend to have more severe reactions. A follow-up paper noted that insect stings had caused systemic reactions in 16 (14%) of 113

patients who were stung after discontinuing 5 or more years of VIT [108]. It seems that patients with more severe reactions before VIT, patients who reacted to stings or venom injections while receiving VIT, and patients with honeybee-venom sensitivity tend to react to stings more frequently when VIT is stopped. No two situations are identical. For some patients, a decision to continue venom injections indefinitely, regardless of other factors, may be in order. Fortunately, most venom-treated patients can extend the interval between maintenance injections to 6 to 8 or even 12 weeks after 2 to 4 years of therapy.

The American Academy of Allergy Asthma and Immunology Position Statement [17] recommendations regarding discontinuation of VIT include the following: (1) the decision should be made on the basis of a thorough discussion of the issues by the physician and patient (individual patient variables, such as vocation or leisure activities, medications, and coexistent diseases, should be considered); (2) the conversion to a negative skin test is one criterion for stopping VIT; (3) patients with mild or moderate sting reactions before VIT was initiated may discontinue VIT after 3 to 5 years; and (4) in patients with severe (hypotension, laryngeal edema, or bronchospasm) sting reactions the physician may wish to continue venom injections for more than 5 years and perhaps indefinitely (because most of even these most-at-risk patients tolerate discontinuation of VIT after 5 years of treatment, stopping treatment is an option).

Summary

Insect sting allergy has served as an excellent model for the allergic process over the past century. In particular, during the last 30 years, a new form of diagnostic testing and treatment with venom has been one of the great success stories in the entire field of allergy. VIT reduces the risk of recurrent life-threatening reactions from about 60% to less than 2%. Progress and further questions continue with a search for a definitive diagnostic test that more accurately predicts which patients are at risk for future reactions, and defines which patients can stop VIT and which ones need to continue treatment.

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