Clinical Review

Insect Stings

Robert W. Clausen, MD
Detroit, Michigan

Recently, significant gains have been made in the care of the patient allergic to stinging insects. Though epinephrine continues to be the drug of choice for the management of the anaphylactic reaction, newer delivery systems allow self-administration of the drug immediately following a sting to abort or attenuate a subsequent reaction. Patients most at risk, those with a history of life-threatening episodes of anaphylaxis following a sting, can be diagnosed and treated with the recently released Hymenoptera venoms with the expectation of excellent results. This success, however, has been accompanied by the frustration of not knowing the natural course of the disease in sufficient detail to counsel in cases of less dramatic insect hypersensitivity.

During the warm summer months outdoor recreational activity increases, as do related emergency medical problems. Adverse reactions to insect stings are an instance of such problems. Recent advances in the understanding and treatment of patients experiencing allergic reactions to insect stings has led to some confusion as to which patients need further medical evaluation. The purpose of this article is to delineate the types of reactions possible following insect stings, to review their treatment, and to discuss recent advances in the subsequent management of sting-sensitive individuals.

From the Division of Allergy and Clinical Immunology, Henry Ford Hospital, Detroit, Michigan. Requests for reprints should be addressed to Dr. Robert W. Clausen, South Bend Clinic, 211 North Eddy at Colfax Avenue, South Bend, IN 46634.

Manifestations of Insect Sting Reactions

Nearly all insect stings are from members of the order Hymenoptera, which includes bumblebees, honeybees, yellow jackets, yellow hornets, white-faced hornets, wasps, and fire ants (Figure 1).[1]

Hymenoptera venom contains a number of toxic substances. These include various enzymes (phospholipase, hyaluronidase), biogenic amines (histamine, serotonin, acetylcholine) and peptides, and small proteins (kinin in vespid venoms, apamin, melittin, and mast-cell degranulating peptide in honeybee venom). These substances are used either to immobilize or capture the live prey upon which wasps, yellow jackets, hornets live, or as in the case of honeybees, as a defense tool.[2] Hymenoptera stings are to be distinguished from those bites (eg, of mosquitoes, deer flies, horse flies, spiders) that may also cause a person to seek emergency care.

The normal reaction that accompanies a Hymenoptera sting involves intense burning pain and redness at the site. A few minutes later, several

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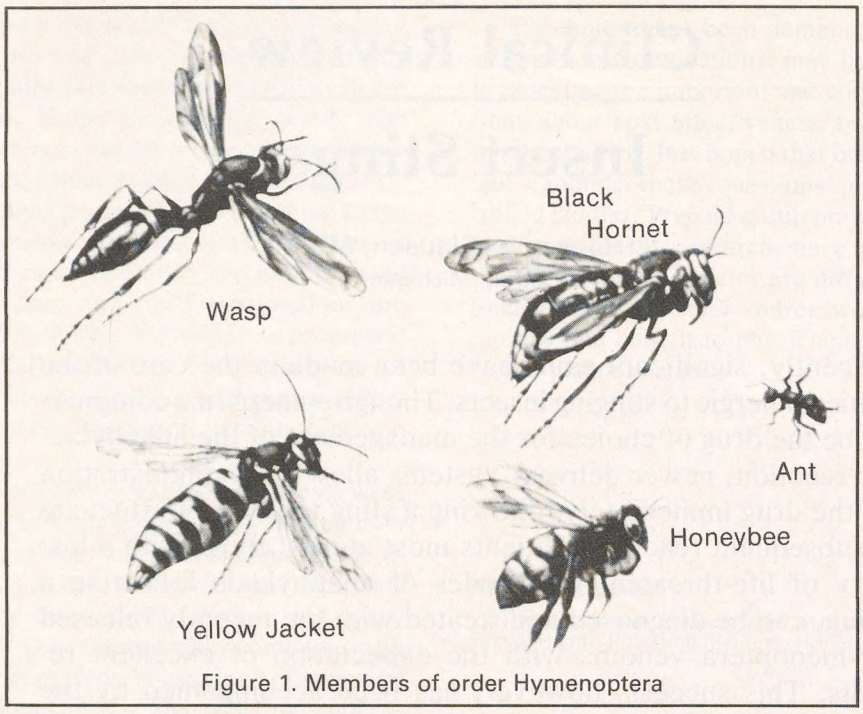

Figure 1. Members of order Hymenoptera

centimeters of skin may begin to itch and swell. The degree of swelling is dependent upon the looseness of the involved connective tissue. A sting on the ear or face may result in a significant degree of swelling and disfigurement, the normal sequela of a sting at that site, whereas only minimal changes may occur with a sting on the finger. The process is self-limited and will gradually resolve within 24 to 72 hours, with or without medication. Vespid stings, especially with scavenger insects such as yellow jackets, can result in a subsequent abscess formation of cellulitis, as stingers are often contaminated with bacteria from decaying fruit and garbage upon which the insects feed.

Clinical manifestations associated with an allergic reaction may be grouped by severity into (1) mild systemic reactions (generalized pruritis, erythema, urticaria, or angioedema), (2) severe systemic reactions (wheezing, abdominal cramping, nausea, and vomiting), or (3) life-threatening systemic reactions (laryngoedema, hypotension, and shock). Without treatment, allergic reactions may be self-limited or, at times, progress from mild systemic reactions to life-threatening symptoms and, occasionally, to death. Fatal reactions, conservatively estimated at 40 deaths per year,[3] may be the result of asphyxiation secondary to laryngoedema or severe bronchospasm, irreversible hypotension, or an associated cardiac arrhythmia.[4]

All of these allergic reactions appear to result from the IgE-mediated release of chemical substances from mast cells and circulating basophils (Figure 2).[5] These materials (eg, histamine and slow-reacting substance of anaphylaxis) produce increased vascular permeability, smooth muscle contraction, and vasodilation.

Large local reactions are defined as an area of swelling at the site greater than 10 cm or involvement extending across one large or two small joints without systemic manifestations. Though cell-mediated immunity has recently been reported as being partially responsible for some of the clinical manifestations,[6] not enough is known to classify these as clearly allergic or exaggerated toxic reactions. The natural history of this reaction pattern is unclear.[7]

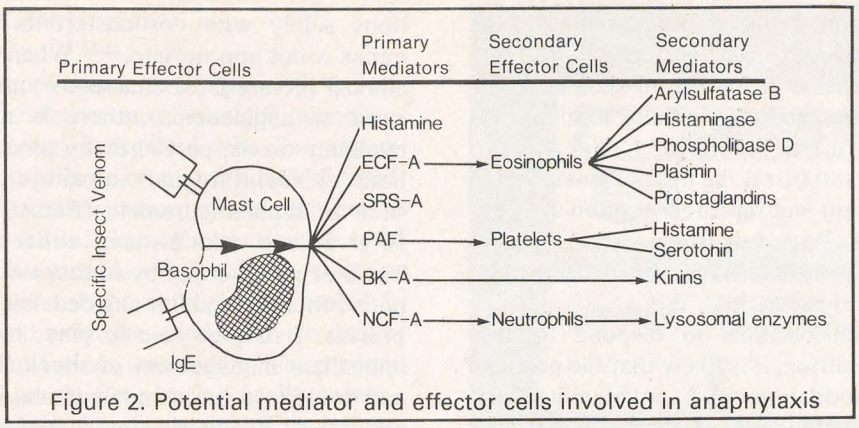

Figure 2. Potential mediator and effector cells involved in anaphylaxis

Delayed or late systemic reactions, though rare, have been reported.[8] They usually occur 2 to 10 days after a sting and are thought to be related to circulating immune complexes. The clinical picture is of serum sickness with fever, rash, arthralgia, hematuria, and severe headaches. Another rare delayed reaction, with uncertain etiology, is progressive central nervous system deterioration (Guillain-Barré syndrome).

Toxic reactions are thought to be the result of a large dose of pharmacologically active agents present in insect venom when a person sustains multiple stings. This occurs typically when a colony of insects or a swarm of bees is disturbed and threatened. In addition to evidence of multiple sting sites, the clinical picture may mimic that of a systemic allergic reaction.

Associated with many insect stings is a fear-panic reaction out of proportion with the clinical manifestations. The dizziness, abdominal upset, and occasional collapse are not infrequently the result of a vasovagal episode rather than a manifestation of an allergic or toxic reaction.

Diagnosis and Immediate Management of Sting Reactions

The diagnosis of an insect sting reaction is usually made by the clinical history. Although only a minority of patients can reliably identify the culprit insect,[9] an educated guess can be made circumstantially.[10] Honeybees or yellow jackets cause most of the sting reactions in the midwestern United States, while along the Gulf Coast, wasps and fire ants are the most common offenders. The honeybee stinger is barbed and is almost invariably evulsed from the insect and left imbedded in the patient. Honeybees are usually mild-mannered and will not sting unless stepped on or sat upon or unless their hive is disturbed. Yellow jackets, on the other hand, are ill-tempered and will sting without provocation. Yellow jackets are ground nesting insects that live below grass sod strips, in abandoned animal burrows, or around the roots of bushes. Certain species may nest between the walls of frame dwellings. They are scavenger insects, often feeding on fallen, rotten fruit in orchards or on discarded food in trash containers at picnic grounds. Wasps build nests in the eves of porches or barns, and frequently crawl inside attics to remain warm during the winter. Hornets may be aerial nesters or ground nesters; the hornets nests resemble Japanese lanterns. Bumblebees rarely are implicated in insect sting, although small children occasionally will be stung after catching a large, slow-flying bee while it is foraging on a flower.

The first drug in the treatment of any sting-related anaphylactic reaction is epinephrine. The alpha- and beta-adrenergic stimulating effects of epinephrine appear to be equally useful, resulting

in vasoconstriction, bronchial relaxation, and the reversal of enhanced vascular permeability secondary to the release of mediators such as histamine. Epinephrine should be initially administered subcutaneously (0.2 to 0.5 mL of 1:1000 aqueous solution in adults; 0.01 mL/kg up to a maximum of 0.3 mL in children) and repeated as often as every 10 to 15 minutes. With a decrease in tissue perfusion secondary to hypotension, the intramuscular route may be preferred.

When hypotension fails to respond to subcutaneous epinephrine, it is likely that the problem is peripheral vasodilation and hypovolemia. Vasoconstriction without replenishment of depleted intravascular volume may further aggravate impaired perfusion of vital organs, and volume replacement with saline or colloid is indicated. If the clinical condition remains critical or worsens, intravenous administration of epinephrine should be considered. This is given in a 1:10,000 aqueous concentration, 1 to 2 mL at a time. An ampule containing 50 mg of sodium bicarbonate may be administered prior to intravenous epinephrine to lessen the possibility of development of cardiac arrhythmias in the presence of an almost certain concomitant metabolic acidosis. Vasopressive agents rarely may be required to manage sustained hypotension and should be utilized cautiously because of their propensity to produce cardiac arrhythmias.

If the airway is clear, oxygen will help to reverse hypoxia and is the treatment of choice. The presence of bronchospasm not responsive to epinephrine dictates the use of aminophylline. This is administered as a bolus (5 to 6 mg/kg actual body weight up to a total dose of 500 mg) and run over 20 minutes. Respiratory therapy with aerosolized terbutaline or isoetharine (Bronkosol) may be efficacious in the reduction of bronchospasm. Assisted respiration is indicated if a more conservative regimen is unsuccessful.

The appropriate treatment for upper airway obstruction resulting from laryngoedema not responding to epinephrine is tracheostomy.[11] Because of the anatomic obstruction, endotracheal intubation is many times unsuccessful. Cardiac arrhythmia may also complicate management. Correction of hypoxia and acidosis is essential, and antiarrhythmic drugs may be needed to lessen myocardial irritability.

The management of acute anaphylactic reactions solely with corticosteroids and antihistamines is not appropriate.[12,13] When the presenting clinical picture is of cutaneous anaphylaxis (urticaria or angioedema), there is an unfortunate tendency on the part of many physicians to withhold epinephrine and substitute antihistamines such as diphenhydramine (Benadryl). Benadryl, 50 to 80 mg, administered either orally or as a liquid or parenterally by intramuscular or intravenous route may inhibit angioedema, urticaria, and pruritis. It has no role to play, however, in the immediate management of shock, laryngoedema, and bronchospasm. Antihistamines may be used *in addition to* epinephrine but should not be used as a substitute for epinephrine. Overgenerous parenteral doses of antihistamines have also resulted in the worsening of hypotension. Corticosteroids, because of their late onset of action, play no part in the acute management of anaphylaxis. Steroids, as well as oral antihistamines, may be considered in those instances in which amelioration is not complete and subacute bronchospasm or hypotension persists. In addition, they may lessen the chances of recurrence of symptoms in the hours following a sting.

Advice to Sting-Sensitive Patients

It is essential that any patient requiring emergency care have a clear idea concerning the care of future stings.

Local Measures

If stung, a person should slowly move away from the area, as rapid movement may provoke attack by more insects. When honeybee stings result in a retained stinger and attached venom sac, they should be flicked away, not pulled. How much venom remains in the avulsed sac is unknown,[14] but it is generally considered advisable to avoid squeezing it while the barbed stinger is removed. The area should be washed with soap and water and ice applied to minimize swelling and pain. Calamine lotion, oral antihistamines, and analgesics may also be used to reduce itching and pain.

Emergency Kits

If anything more than a local reaction is experienced, medical attention must be sought immediately. In addition, any individual who has experienced a systemic allergic reaction should be familiar in the self-administration of epinephrine to treat a subsequent anaphylactic reaction. A small emergency kit is available (Figure 3) that contains two doses of 0.3 mL of epinephrine, sealed in nitrogen to avoid oxidation, and ready to deliver from a preloaded syringe and needle. The medication should be administered at an easily accessible, fleshy site (deltoid muscle or thigh) and may be used again in 15 to 20 minutes if the clinical manifestations continue. An autoinjector (EpiPen) containing a premeasured dose of epinephrine is available to persons unable or unwilling to use the syringe and needle. Though packaged under nitrogen, exposure to ambient sunlight will hasten deterioration of epinephrine more rapidly than exposure to temperatures warmer than 4° C. Patients should periodically check the color of their epinephrine solution; the drug should be replaced when the solution acquires a pinkish brown tinge. The immunologic mechanism producing the large local reaction is still not completely known, and the use of epinephrine is, therefore, based on the clinical presentation and the judgment of the attending physician.

Epinephrine nebulizers for inhalation (ie, Primatene Mist, Bronkaid) are available without prescription and may mitigate some of the symptoms of upper airway edema; however, they are not absorbed in sufficient quantities to be useful in the management of systemic reactions, and their use as a self-administered source of epinephrine in emergency situations should not be encouraged.

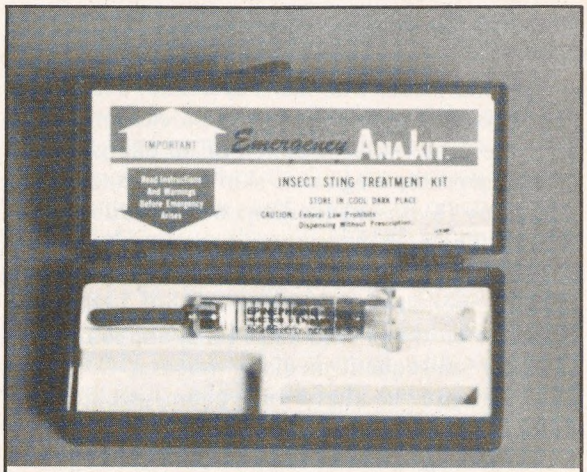

Figure 3. Emergency insect sting kit, showing premeasured 1:1000 epinephrine in a disposable syringe. The kit also includes chewable antihistamine tablets, a tourniquet, and alcohol pads. (Courtesy of Hollister-Stier)

Avoidance

Printed information should be available to patients delineating ways in which exposure to insects may be minimized. Individuals at risk should be cautious while engaging in outdoor activities. Food and odors attract insects. As a result, garbage should be wrapped and well covered, and caution exercised when walking in areas such as picnic grounds or orchards, where insects frequently feed on discarded food or fallen fruit. Sensitive individuals should avoid the use of strongly scented cosmetics or hair sprays as well as perfumes or colognes. Clothing should be neutral in color, vivid floral prints and bright shades should be avoided, and extremities as well as the head should be protected. Nests of insects near dwellings should be removed by willing friends or professionals.

Extra Precautions

Those who have allergic reactions to stinging insects should wear emergency medical identification such as a necklace or bracelet that will enable bystanders to render assistance if the person is incapacitated.*

*Tags may be obtained from the Medic Alert Foundation, Box 1009, Turlock, CA 95380.

Referral for Allergy Evaluation

Any individual who has a systemic, allergic reaction to an insect sting should be encouraged to seek the professional opinion of an allergist concerning possible diagnostic skin testing and immunotherapy (hyposensitization) with specific insect venom. The human immune response to an allergen (in this case, constituents of Hymenoptera venom) includes production of IgE, which is bound to basophils and mast cells, and is responsible for subsequent mediator release. Concomitant increase in titers of venom-specific IgG "blocking" antibodies also occurs.

In time, IgG titers fall, whereas in allergic individuals, titers of IgE remain for a variable period of time.[15] Though the exact mechanisms of immunotherapy have not been completely delineated, progressively greater amounts of antigen (venom) stimulate increasing titers of IgG. It is likely, but has not been proven, that the protection offered by immunotherapy is a function of IgG or blocking antibodies to venom protein.[15]

Historical Perspective

Since an early report in the 1930s by Benson and Semenov,[16] conventional allergy practice assumed the antigen responsible for sting reactions to be a constituent of both insect body protein and venom and therefore extract made from the entire insect body (whole body extract) was used in the diagnosis and treatment of those allergic to insect stings. Because of the impracticality of insect venom collection, the evaluation of Hymenoptera sensitivity was, for years, based almost solely on clinical history. Documented reports of treatment failures with whole body extract, however, called the efficacy of this sort of therapy into question.[17] In addition, large-scale studies demonstrated that the whole body extract used in skin tests was not effective in discriminating between sensitive and nonsensitive persons.[18,19]

More recent studies have shown that the antigen producing a human immune response is found only in the insect venom, not as a constituent of the body protein.[20,21] Investigators from Johns Hopkins University identified Hymenoptera-sensitive patients using venom-induced release of histamine from peripheral basophils.[5] These studies also correlated to positive wheal and flare skin tests with submicrogram quantities of insect venoms.[22]

Studies to ascertain the clinical efficacy of venom extracts for immunotherapy have been performed both at Mayo Clinic[23] and at Johns Hopkins University.[24] In a double-blind study, three groups of patients with histories of severe systemic reactions to insect stings were treated with venom preparations, whole body extracts, or a placebo. When a maintenance level of therapy was reached, patients in each group received an in-hospital sting with the offending insect. Among the venom-treated patients, only one had a mild systemic reaction to the challenge sting, whereas the incidence of severe systemic reactions was 64 percent in the group treated with whole body extract, and 58 percent in the group treated with placebo. The patients who reacted were then treated with the venom of the insects to which they were allergic, and after completion of hyposensitization, rechallenged. One of the 14 patients developed a single urticarial lesion 30 minutes after the sting. It was also shown that protection correlated with the venom-specific "blocking antibodies" of the IgG class.

This work has been further substantiated by the results of 280 patients undergoing venom immunotherapy who were either deliberately or accidentally stung by a positively identified insect.[25] Two hundred sixty-eight (96 percent) of the 280 patients were totally protected. The remaining 12 had reactions that were far less severe than those they had experienced prior to treatment.

The conclusions reached in these recent investigations are that anaphylactic reactions to insect stings are immunologically mediated by IgE (reaginic) antibody. Insect venoms were demonstrated to be superior to whole body extracts, both as diagnostic and as therapeutic agents. Moreover, sensitive patients who were treatment failures with whole body extract responded well to subsequent venom hyposensitization.

Diagnosis of Persistent Sting Sensitivity

With the advent of commercially available Hymenoptera venom to the medical community in

1979, a new era was initiated in the care of patients allergic to insect stings. Evaluation of the problem and administration of early stages of venom are both complex, and the initial history and skin testing are best carried out by allergists. Dilute solutions of Hymenoptera venoms (honeybee, yellow jacket, yellow hornet, white-faced hornet, and wasp) are utilized to assess the presence of venom-specific IgE attached to skin mast cells. It is the most sensitive test available to detect IgE antibodies to venom. Intradermal tests are done with tenfold increasing venom concentrations from 0.01 μg/mL up to 1 μg/mL, injecting enough material to produce a 5×5-mm wheal. Irritant or false-positive tests are produced in 30 percent of nonallergic persons at test concentrations above 1 μg/mL. The amount of venom injected by the average honeybee sting is about 50 μg[26]; consequently, the skin test, as performed, delivers a fraction of the amount of venom encountered with a sting.

The radioallergosorbent test (RAST) measures serum IgE antibody levels to venom and venom components. RAST determinations are most useful in patients who, for some reason, cannot be skin tested with insect venoms. Overall, RAST results are positive in about 80 percent of patients with positive skin tests.[27] The decision to initiate or withhold venom immunotherapy is made on the basis of the clinical history and the results of the venom skin testing, not solely on the basis of RAST results.

Treatment of Insect Sting Sensitivity

Venom immunotherapy is indicated for patients who have a history of systemic reactions to Hymenoptera stings and who have a significant positive intradermal skin test reaction to at least one venom at a concentration of 1 μg/mL or less. Children who have experienced potentially life-threatening sting reactions involving shock, laryngoedema, or severe bronchospasm, and who show significantly positive venom skin test deserve venom immunotherapy. Currently, the researchers at Johns Hopkins University are studying venom immunotherapy in children who experience non-life-threatening reactions (cutaneous reactions such as hives) following insect sting. Preliminary data[28] suggest that if left untreated, such children may not be at increased risk of life-threatening reactions with future stings. Because of the need for frequent reconstitution of lyophilized venom, the instability of venom at the low concentration used at the buildup phase, and the risk of reaction, this portion of immunotherapy should be under the care of an allergist. Maintenance immunotherapy every four to six weeks can be supervised by family physicians. Present recommendations are for monthly maintenance therapy with venom to be continued indefinitely.[11,29] Active research, however, is underway to find ways to modify such recommendations.

Unresolved Problems

Although a therapeutic method has been developed that appears to be highly efficacious in protecting against allergic reactions, many questions remain unanswered. Skin tests, while demonstrating the presence of venom-specific IgE, do not predict a future anaphylactic reaction or the severity of such a reaction if it were to occur.[11] At present, the only definitive test is a sting challenge.[30] The procedure is tedious, time-consuming, and dangerous and therefore limited to only a few medical centers.

The immunological mechanisms mediating large local reactions are only partially characterized and need to be further delineated for optimal therapeutic intervention. The natural history of some reactive patterns (ie, large local reactions and mild systemic anaphylactic patterns in children) is unknown and is only now being actively investigated in cooperative studies involving multiple centers.[7,31]

The safety of prolonged venom administration has been addressed only by retrospective evaluation of frequently stung beekeepers. Long- and short-term prospective studies relating to theoretical complications resulting from venom use in clinical practice are still ongoing.[32]

Another management problem with these patients continues to be the fear-panic reaction to an insect sting, which can result in a significant alteration in a person's lifestyle. The inability to be able to predict a person's reaction on subsequent

sting, coupled with the knowledge that IgE-mediated reactions to venom may decline spontaneously with time in untreated patients (similar to penicillin),[33,34] further frustrates both the allergist's and the family physician's attempts to reassure a patient or parents.

Finally, the economic factors involved in venom immunotherapy should be noted. The cost to the physician for the venom required for the first year of treatment for one patient ranges from $100 to $500, depending on the number of venoms needed for treatment. The cost to the patient is correspondingly higher. Although this cost may seem high at first glance, it should be remembered that the disease being treated is potentially life threatening, the cost of obtaining venom is appreciable, and the venoms are much better characterized and standardized than most extracts used to treat other allergic problems. In being pragmatic, the decision to begin a sting-sensitive patient on a venom immunotherapy program is often made not strictly on medical grounds but on economic grounds as well.

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