Bee Stings
Immunology, Allergy, and Treatment

Part II of Two Parts

by BUDDY MARTERRE, MD

Although it's part of the business, few of us actually look forward to being stung. As beekeepers we need to know about the various reactions to bee stings and be responsible to ourselves, family, neighbors and friends in regard to bee stings. I hope this article will serve some of those purposes and be informative to both the beginner beekeeper and the most experienced. The first part of this article covered insects that sting, honey bee stings in particular, basic bee venom biochemistry, precautions and sting prevention, management of beekeeping emergencies, and basic immunology and allergy. This second part will cover sting reactions and types, sting treatments, allergy testing and desensitization results, and specific beekeeper recommendations.

Sting reaction types and treatments

The NORMAL reaction to a venomous insect sting is one of local pain and up to a few centimeters of edema (swelling) that resolves in a few hours to a few days (Figure 10). Any sting can become secondarily infected, but fortunately, this is fairly uncommon. Parenthetically, fire ant stings form a pseudopustule (Figure 11). These blisters may last for 10 days and should not be confused with a true infection (pustule). The pseudopustules from fire ant stings should be left intact (not unroofed or surgically drained).

The first 'treatment' of a normal reaction is to quickly remove the sting and smoke the area. Many local remedies have been suggested for the treatment of bee stings. These generally fall into 4 categories: 1) venom removal or suction devices, 2) bases such as urea, ammonia, and baking soda (to neutralize the acidity of the venom), 3) hygroscopic agents (to draw out the fluid) such as honey, mud, and various pastes, and 4) lotions to decrease the itch such as calamine lotion, Anusol, and Benadryl cream. All topical treatments require immediate application, so they are probably best used in non-beekeeping situations. And as far as local applications for sting prevention is concerned, DEET-containing bug sprays do nothing to deter vespid stings. Normal reactions *are not* an allergic response, and allergy testing and desensitization are *not* indicated after these.

A LARGE LOCAL reaction is confined to the general area of the sting, but over 24 – 48 hours it develops into a much larger area (sometimes the entire extremity) than a normal reaction (Figure 12). It starts as pain and a wheal (a several centimeter swollen itch). A few hours after the sting more redness, edema (swelling), and itching develop. Over 12 – 48 hours, the area can become quite swollen, painful, and may also have some associated ecchymosis (flecks of purple or red from a bruise within the skin itself). The swelling generally begins to resolve after two days, but the site may remain tender (and continue to itch) for a few more days. The total reaction lasts 4 – 7 days. Large locals around the face and mouth or on the hands may cause temporary disability. The large local is IgE-mediated, and therefore is an allergic response.

Treatment of a large local includes ice and elevation. Taking an anti-histamine or

Figure 10. Normal Sting Reaction of Face *Buddy Marterre, MD*

Figure 11. Pseudopustules of Arm from Fire Ant Stings *Courtesy of Murray S Blum*

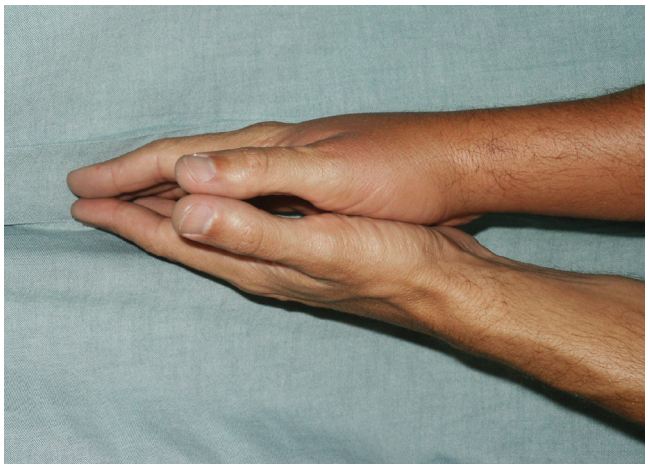

Figure 12. Large Local Reaction of Hand and Wrist
Buddy Marterre, MD

a leukotriene-receptor antagonist very soon after the sting may decrease the late phase reaction. Personally, this is what I do and it works for me! Oral steroids are useful in treating large locals to stings around the face and hands. Anti-Histamine choices are sedating drugs such as diphenhydramine (Benadryl), and non-sedating ones, such as fexofenadine (Allegra), loratidine (Claritin), and ceterizine (Zyrtec). Benadryl and loratidine may be obtained without a prescription (over the counter). Caution is advised with driving (or continued beekeeping) after taking a sedating anti-histamine (particularly if high doses are taken), however. Oral steroids in the form of prednisone short courses and dose packs require evaluation by a physician and prescription. As mentioned above, another class of prescription drugs that may help are the leukotriene-receptor antagonists montelukast (Singulair) and zafirlukast (Accolate). These drugs block the leukotriene receptors on mast cells and eosinophils and both have peak activity 3 – 4 hours after taking them. People who have (only) had a large local response, have little or no risk of a severe, life-threatening anaphylactic response in the future. Therefore, even though a large local reaction *is* an allergic response, allergy testing and desensitization *are not* indicated after these.

SYSTEMIC ALLERGIC responses involve two or more organ systems of the body and are called ANAPHYLAXIS. They can be mild and manifest as purely cutaneous (skin) responses, or may include symptoms of the gastrointestinal system or nervous system, or worse, the cardiorespiratory systems. A systemic cutaneous (or skin) response must be distant from the sting site (to differentiate it from a large local reaction) and typically involves the trunk or scalp. Generalized cutaneous responses include urticaria or hives (the familiar, itchy 5 – 40 millimeter red wheals and slightly raised flares – Figure 13) and/or angioedema (a rapidly-developing massive swelling of the face – Figure 14). Gastrointestinal symptoms include a metallic taste, nausea, vomiting, diarrhea, and abdominal cramps. Neurologic symptoms include light-headedness, dizziness, and tremor, but light-headedness and dizziness can also be due to a drop in blood pressure, which would be a cardiovascular effect.

Fortunately, cardiorespiratory system responses (severe ANAPHYLAXIS) occur in less than 1 % of people incurring a bee sting. Anaphylaxis may be preceded by generalized itching, hives, and edema, and the specific cardiovascular and respiratory system reactions can progress fairly rapidly (over 1 to 30 minutes). They include wheezing, stridor (airway compromise and inability to breathe), shock (very low blood pressure causing collapse), loss of consciousness, and death. Beekeepers, family members (or anyone) who has had a moderate or severe systemic allergy to bee stings *should* see an allergist for skin testing and immunotherapy.

Figure 13. Urticaria or Hives
courtesy of Dr. Raymond J. Mullins, allergycapital.com.au

Anaphylaxis to insect venom accounts for about 40 deaths per year in the US. About 40 % (or about 16) of those are attributable to honey bees, but this may be an underestimate (due to some un-witnessed venom-related deaths being falsely attributed to heart attacks). In comparison, lightning strikes account for about 85, animal bites 100, poisonings 3,600, smoking over 150,000, and cancer almost 500,000 deaths per year in the US!

The treatment mainstay of anaphylaxis is intramuscular epinephrine (Figure 15). Dose depends on size. Children that weigh less than 30 kilograms (66 pounds) need an EpiPen Jr (0.15 mg) and larger children and adults need a 'regular' EpiPen (0.30 mg). In either case the injection is given from the one-time-use pre-filled administration syringe into the anterolateral thigh and may (and sometimes should) be repeated every five minutes en route to an emergency room. There is also a new epinephrine injector called TwinJect, which can deliver two injections, but requires partial disassembly between injections. EpiPens and the TwinJect device require a prescription as there may be some risk to administering epinephrine to someone with severe heart disease. EpiPens come with 'practice' administration syringes and instructions. If you, anyone in your family, or the neighbors to your bee yard have a systemic allergy, have at least one epinephrine injector on hand and know how to use it! Other treatments for anaphylaxis include bronchodilator inhalers (prescription), and anti-histamines and steroids - as for large local reactions. Anyone experiencing anaphylaxis (epinephrine-treated or not) needs to be transported directly to an emergency room. Most of these patients will be admitted to the hospital overnight as sometimes the reactions recur (typically at 4 – 6 hours). Remember those secondary chemicals that the mast cells make that cause the late phase of allergy? Allergy testing and venom immunotherapy desensitization *is* indicated for anyone with a systemic allergic response to insect stings, including diffuse hives in anyone over 16 years of age. Allergy testing *is not* recom-

Figure 14. Facial Angioedema Same patient, before and after treatment
courtesy of siamhealth.com

Figure 15. EpiPen *Buddy Marterre, MD*

mended for urticaria / hives alone in a child (under 16).

MASSIVE ENVENOMATION (sometimes called a toxic reaction) occurs with greater than 500 honey bee stings. This is not an allergic response, but is related to the large amount of venom received by the victim. Very young children or chronically ill elderly people may be poisoned by 150 (or more) stings. The 'dose' of bee stings that has been calculated to kill half of the victims (LD50) is 19 stings per kilogram of body weight. Initial symptoms of bee venom toxicity include generalized edema (swelling), fatigue, nausea, vomiting, fever, and unconsciousness. The reaction is sometimes delayed by as much as 6 days and therefore requires immediate transportation to an emergency room and hospitalization. The problems are primarily the result of rhabdomyolysis (breakdown of muscle tissue) and myoglobinuria (the muscle breakdown products in the blood leading to kidney failure). Hemolysis (burst red blood cells), DIC or disseminated intravascular coagulation (abnormal clot formation inside the blood vessels with an overuse of clotting factors and subsequent bleeding) can also occur. Kidney failure and cardiac arrest cause most toxic bee sting deaths (which are considerably rarer than anaphylaxis deaths).

OCULAR (or eyeball) STINGS are fortunately quite rare (because of the extremely fast human blink response), but when they do occur they frequently lead to blindness. Immediate attention by an ophthalmologist is warranted. Specific ocular sting injuries include corneal edema, hyphema (blood in the anterior chamber of the eye), lens dislocation, cataract, and optic neuritis (inflammation of the optic nerve). Prevention is clearly the key to these injuries. Veils only cost a few dollars and can be donned in seconds! Table 6 summarizes venom reaction types and treatment.

Allergy testing and desensitization

Although large local reactions are allergic responses, allergy testing and desensitization immunotherapy are not indicated after these because the risk of a severe systemic reaction to re-sting is extremely low. People who have experienced a systemic allergic response (including urticaria or diffuse hives in someone over 16) certainly benefit from allergy testing and subsequent desensitization immunotherapy. Desensitization venom immunotherapy (allergy shots) is warranted in anyone who has had a systemic reaction and in whom the risk of a systemic reaction with re-sting is 20 % or greater and has also had a positive skin test to the venom. Skin testing is more sensitive than the RAST (which is a blood test checking for specific IgE antibodies to each venom). Skin testing begins with needle pricks to each individual species' venom and if negative, it proceeds to sequential intradermal injections of the venom at increasing doses. People with hypersensitivities to the venom from one Hymenoptera species may also have allergies to another. This is called cross-reactivity and is quite common within the subfamilies Vespinae (aerial and ground-nesting yellow jackets, hornets, and bald-faced hornets) and Apidae (sweat bees, honey bees, and bumble bees) since their venoms are so similar. It is less common between bee, 'vespid', and paper wasp venoms, but most people who have an allergic response to the venom of one Hymenoptera species also have an allergy to another.

Honey bee venom for testing and immunotherapy is currently collected by the use of an electrical micro-current grid that stimulates bees to deposit their venom on the underlying pad (with alarm pheromone greatly magnifying the colony's response). These bees do not die in the process of stinging the grid. Vespid venom is obtained by individual venom sac dissection. In the past, bee and vespid venom allergy desensitization was done with whole body extracts. Whole body extracts from bees and vespids were not an effective source of venom immunotherapy like pure venom is today. (Fire) ant immunotherapy is still done with whole body extracts, however, as different ant species do not cross react with one another. Good, controlled effectiveness studies have not been done for fire ant whole body extracts as they have for pure venoms of the other Hymenoptera species.

Desensitization venom immunotherapy (allergy shots) entails the administration of gradually larger doses of the venom(s) at regular intervals (usually twice a week) up to a target of 100 micrograms per dose over about 6 months. Maintenance shots are then typically continued (usually once a month) for at least 3 and usually 5 years. The decision to discontinue immunotherapy is complex and treatment may be extended for many years in high risk patients (those with several reactions and/or increased exposure – such as beekeepers).

The goal of desensitization immunotherapy is simple. Repeated exposure to the venom leads to a change in the way the regulatory T cells in the immune system react to the particular offending antigen. These T cells instruct the B cells to switch antibody production against venom proteins from allergic IgE to non-allergic IgG.

Table 6
Insect Venom Reactions and Treatments

Reaction	Treatments
Normal	**Ice, Topical**
Large Local	**Ice, +/- Anti-Histamine, +/- Prednisone, +/- Singulair or Accolate**
Systemic Allergy (Anaphylaxis)	
Cutaneous (Hives)	**If over 16, Epinephrine Desensitization Immunotherapy**
Other Systems (GI, Neuro)	**Epinephrine, Benadryl, Prednisone, Desensitization Immunotherapy**
Cardiorespiratory	**Epinephrine, Bronchodilators, Anti-Histamines, Steroids, Emergency Room/ Hospitalization, Desensitization Immunotherapy**
Massive Envenomation	**Emergency Room/ Hospitalization**
Ocular	**Emergency Room/ Ophthalmologist**

IgG antibodies cannot cause mast cell activation, and therefore mast cells do not degranulate and there is no subsequent anaphylaxis. As more B cells produce IgG against bee venom proteins, the IgG will block the antigen from being exposed to the IgE-laden mast cells. There is even evidence of IgE anti-idiotypic IgG production in patients undergoing desensitization (and beekeepers receiving regular stings). Anti-Idiotypic antibodies are IgG antibodies that are directed at the hypervariable region of the IgE antibody itself (an antibody to an antibody or kind of like another key to 'fool' the IgE lock).

Table 7
Approximate Risk of (Re-)Sting Reaction Type (Pooled Data)

Population	Normal Reaction	Large Local	Mild - Mod Anaphylaxis	Severe Anaphylaxis
General Public, NO VIT	85 %	10%	4 %	1 %
Beekeepers, NO VIT	70 %	20 %	7 %	3 %
History Large Local, NO VIT			7 %	0 %*
History Any Anaphylaxis, NO VIT			40 %	20 %
History Severe Anaphylaxis, NO VIT			20 %	55 %
History Any Anaphylaxis, 5 Years VIT			7 %	3.5 %

VIT = venom immunotherapy
* none reported

Venom allergy in the general population and in beekeepers

In the general population, about 85 % people have a normal reaction to bee stings, with about 10 % having large local reactions, 4 % mild (cutaneous) systemic reactions, and 1 % severe anaphylaxis. Re-Sting reactions are typically similar in severity to earlier reactions. Certainly, beekeepers (and their family members and neighbors to a lesser degree) have increased exposure to bee venom. About 25 % of beekeepers have high anti-bee venom IgE levels, and all beekeepers have increased anti-bee venom IgG. Despite 25 % of beekeepers having high anti-bee venom IgE, anaphylaxis to bee stings only occur in a minority of these individuals, for unknown reasons. Beekeeper's IgG levels increase and their IgE levels drop with both the number of stings they receive and their years of experience (thus regular stings have the same effect as allergy shot desensitization). Because of their increased exposure to bee venom, beekeepers have more allergic responses to stings than the general public. About 25 % of beekeepers have large locals and/or mild systemic (cutaneous) anaphylaxis to stings, and about 3 % experience severe cardiorespiratory anaphylaxis.

Skin testing is only indicated with a history of systemic hives and/or a more severe systemic reaction for patients over 16. For those less than 16, systemic hives alone is not an indication for skin testing. The history of the event and the reaction must always be taken into account prior to testing. Also, many people with large local reactions to venomous stings, have IgE antibodies to venom proteins and would therefore have a positive RAST and skin test. Because their risk of a subsequent severe systemic reaction to re-sting is extremely low, individuals with a history of large local reactions do not need immunotherapy (and should not be tested in the first place). Also, neither skin prick tests nor RAST results correlate well with allergic responses in beekeepers.

One Italian study showed that beekeepers with normal sting reactions incurred over 100 stings per year whereas those with large locals only incurred about 18. Another survey found that 90 % of allergic beekeepers wore gloves as compared to 69 % of non-allergic beekeepers. Apparently, allergic beekeepers take more precautions because of their heightened responses to stings.

Common allergic symptoms to inhaled allergens, such as pollen, insects and arthropods (like cockroaches and dust mites), animal dander, and fungi (molds) include runny nose, watery eyes, and an itchy face. People with these common symptoms are termed atopic. The risk of an allergic response to bee venom is higher in beekeepers who are atopic, have a history of a systemic reaction to a prior sting, and fewer years of beekeeping experience (less than 5 to 8 years). Atopic beekeepers can actually be allergic to beeswax, honey, propolis, and even bee parts.

In one very elegant study of 6 allergic beekeepers, the skin within their large local reaction and their blood and urine were analyzed 2 hours after a bee sting. Three of them had high histamine levels and the other three had high leukotriene levels, suggesting that allergic beekeepers *either* have high histamine release *or* increased leukotriene production, but not both. This implies that about half of beekeepers who have large local reactions might benefit from the immediate administration of a leukotriene inhibitor (Singulair or Accolate) (like me), whereas the other half would benefit from anti-histamines (Benadryl, Allegra, Claritan, Zyrtec) before or very soon after the sting.

Desensitization results (general population) and beekeeper recommendations

Table 7, "Approximate Risk of (Re-) Sting Reaction Type" summarizes this paragraph. It is data that I have pooled or compiled from many different (reliable) sources, as no single study has been undertaken to define all these risks. Less than 1 - 2 % of people, who have experienced a severe systemic reaction to Hymenoptera venom, experience another severe systemic reaction to re-sting during immunotherapy. Venom immunotherapy or allergy shots markedly reduce the risk of a systemic reaction to re-stings. After immunotherapy has been undertaken for five years, the risk of a systemic reaction is about 10 % (and only 3.5 % severe cardiorespiratory) to a re-sting. This is compared to a 50 – 60 % risk of re-experiencing a severe cardiorespiratory systemic reaction without any immunotherapy. If a systemic reaction does occur to a re-sting in someone despite 100 microgram per month maintenance venom immunotherapy, the dose is typically increased to 200 micrograms. The risk of systemic reaction in people who have had a large local reaction in the past is about 7 %, but none of those documented in large studies have been severe responses.

Beekeepers with large local reactions would be well advised to wear gloves. They may also consider a trial of taking either a leukotriene inhibitor and/or an anti-histamine immediately after being stung. They *do not* need to be evaluated or treated with immunotherapy by an allergist. With time (5 – 8 years) and occasional repeated sting exposure (just like with allergy shots), large local reactions will probably decrease in severity.

Anyone over 16 (beekeepers especially), who has experienced a generalized or systemic reaction (hives or anaphylaxis) to bee venom, should seek the advice of an allergist. Anaphylactic beekeepers who are insistent on continuing to manage bees might heed advice similar to that given by Eich-Wanger and Muller:

1. Give up beekeeping (temporarily).
2. Complete bee venom immunotherapy (with a higher than usual maintenance dose of 200 micrograms of venom).
3. Return to beekeeping only after a well-tolerated sting challenge in the allergist's office.
4. Always wear protective clothing while beekeeping and avoid more than two stings at a time.
5. Keep one or two EpiPens available when working hives or near bees and know how to use them.
6. Inform family members of your and your bee yard's whereabouts and carry a cellular phone.

Eich-Wanger and Muller reported on 69 beekeepers with an allergic reaction to bee stings, 42 of whom had had a severe reaction. Thirty-one of the 69 allergic beekeepers continued beekeeping. Twenty-two of the 31, who continued beekeeping, received venom immunotherapy and none of them developed a systemic reaction to re-stings, whereas 4 of the 9 who insisted on beekeeping without immunotherapy did. Interestingly, the 22 allergic beekeepers, who received allergy shots and successfully returned to beekeeping, then gave themselves one or two stings per week during the active season and one sting per month during the winter (as continued self-administered maintenance therapy).

About the author

I've had allergies all my life. I became very interested in bees while I was in college at Virginia Tech. But the beekeeping course I wanted to take interfered with biochemistry lab (my major), so instead I took graduate courses in immunology. After medical school and a general surgery residency, I did a fellowship in and then practiced transplant surgery. So while I learned and practiced more immunology (by transplanting 'foreign' organs), my personal experience with bee stings was still lacking. After my fellowship, I married an experienced intensive care nurse, who is now a certified pulmonary-allergy nurse. Then, I finally became a beekeeper and am now a Master Beekeeper in North Carolina. I have large local reactions to bee stings – and have experienced quite a few of those! Being concerned about my risk of more serious reactions, I went back to the immunology and allergy journals. Then, last year, I had an anaphylactic reaction (fortunately not to bee stings, but to salmon – which I had eaten many times before)! Thus, I am a doctor, a beekeeper, *and* a patient. In addition to all the photo credits, I'd also like to thank two excellent allergists for their review of this article: Aneysa Sane, MD from Wake Forest University Medical Center, and Larry Williams, MD from Duke University Medical Center.

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