

# Bee Stings

## Immunology, Allergy, and Treatment

Part I 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 scientist. The first part will cover insects that sting, honey bee stings in particular, bee venom biochemistry, precautions and sting prevention, the management of beekeeping emergencies, and basic immunology and allergy. The second part will cover sting reaction types and treatments, allergy testing and desensitization results, and specific recommendations for beekeepers.

### Hymenoptera stings

The order Hymenoptera includes ants, bees, hornets, and wasps, many of which inflict stings (Table

1). Although solitary bees, such as sweat bees and carpenter bees, can inflict a sting, the risk of an allergic response to their venom is low because they are both unaggressive and the amount of venom they inject is low. More aggressive, primitively social paper wasps, yellow jackets, bald-faced hornets and European hornets from the Family Vespidae (Figures 1 – 4) – as opposed to eusocial honey bee workers from the Family Apidae – can sting more than once. If the flying stinging insect that inflicts a sting is unidentified, most often (unless the sting is still present



Figure 1. Wasp (*Polistes* sp.), Buddy Marterre, MD



Figure 2. Yellow Jacket (*Vespula vulgaris*), courtesy of Jarmo Holopainen

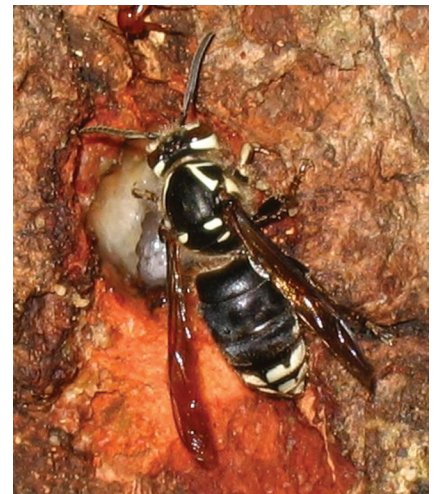


Figure 3. Bald Faced Hornet (*Dolichovespula maculata*), courtesy of Chris Wirth



Figure 4. European Hornet (*Vespa crabro*), Buddy Marterre, MD

Table 1

Hymenoptera Species with Venoms for Immunotherapy

Vespidae Wasps	
Vespinae	
Vespula	ground-nesting yellow jackets
Dolichovespula	aerial yellow jackets
Vespa	hornets
Polistinae	
Polistes	paper wasps
Formicidae Ants	
Myrmicinae	
Solinopsis	fire ants
Apidae Bees	
Apinae	
Apis	honey bees



**Figure 5. Imported Fire Ant (*Solenopsis invicta*), courtesy of Deyrup and Cover, antweb.org**

in the victim) the culprit was not a honey bee. Sting incidence in America varies with region. Yellow jackets are more populous than honey bees in the north, wasps are more prevalent in the southwest, and fire ants are more prevalent in the southeast. Imported fire ants - Family Formicidae, genus *Solenopsis* - also have a sting apparatus (Figure 5). And their venom is the most potent venom known in the animal kingdom! A general approximation of flying insect sting incidence throughout the US is yellow jackets (*Vespula* and *Dolichovespula*) 50 %, honey bee (*Apis*) 25 %, paper wasp (*Polistes*) 15 %, bumble bee (*Bombus*) 5 %, and European hornet (*Vespa*) 5 %.

### Honey bee stings

Bees sting defensively – when their hive, nest, or mound is thought to be under attack. For example, foraging bees will only sting if directly injured when they are away from the hive. Mature, adult, female worker bees in the hive deploy the sting from its sheath in response to alarm pheromone. This chemical messenger release is usually accompanied by a short ‘buzz’ and an astute beekeeper may even smell the banana oil-like



**Figure 6. Honey Bee Stinging an Arm, courtesy of Zachary Huang, PhD**

pheromone. Guard bees are attracted to dark colors, contrast (like hairlines), certain body odors (and perhaps the carbon dioxide you exhale), all drawing them toward your face and eyes. Certain perfumes, cosmetics, and banana oil may mimic alarm pheromone. Vibrations and fast movements further aggravate the situation.

Stinging bees flex their abdomens to jab the sting into their target. The honey bee sting (unlike the sting of other insects) has a barb which leaves it attached to its victim - complete with venom sac (Figure 6). The sting apparatus is also covered by muscles which continue to thrust the sting further into the victim. The venom then travels down through the hollow, hypodermic needle-type shaft (Figure 7). ninety % of the venom sac empties in the first 20 seconds. Alarm pheromone (highly volatile isopentyl acetate and other alcohols and esters) is released from the attached Koschevnikov gland, leaving the victim marked for further injury. In this way, many old guards can be recruited in an exponential defensive response when their hive is being threatened. And of course, the primary perceived threat is you – the beekeeper!

Honey bee queens have more poorly developed barbs than workers on their longer stings. The queen sting apparatus has a stronger attachment to their abdomen and queens do not produce alarm pheromone. They reserve their stings for other queens, but have larger venom sacs than workers, and can sting multiple times. Worker bees die in the process of stinging, as their sting and sometimes other abdominal contents are extruded.

### Bee (and other insect) venom biochemistry

Each European bee venom sac contains about 140 micrograms of venom (only about 100 micrograms per Africanized bee venom sac), but the average venom delivered is a dose of about 50 micrograms. Needless to say, there are a lot of very potent chemicals in bee venom that are bad for you (Table 2). Many of these chemicals are peptides (small protein chains) and enzymes (larger proteins



**Figure 7. Sting Apparatus, courtesy of Zachary Huang, PhD**

**Table 2  
Honey Bee Venom Biochemistry**

Melittin *
Phospholipase A2
Apamin *
Hyaluronidase
Acid and Alkaline Phosphatases
Mast Cell Degranulating Peptide *
Histamine, Dopamine, Norepinephrine
* unique to honey bees

that facilitate biochemical reactions). Together they cause the reaction that your body has to the sting (pain, swelling, itching, redness, etc). Some of these chemicals (or the body’s response to them) can also initiate very rapid reactions. An example would be the clotting cascade, which forms a clot within minutes of a cut. Many of these proteins are also recognized as foreign by the human immune system (antigens) and lead to allergic reactions in some individuals.

Forty – fifty percent of honey bee venom is mellitin. Mellitin is a chemical that is unique to bee venom and is a cytolytic, which means that it directly bursts cells. It contributes to itching and swelling, and is the primary cause of the sting’s pain. Mellitin can also dilate blood vessels, leading to low blood pressure. ten – twelve percent of honey bee venom is Phospholipase A2 (the most potent allergen). Phospholipases are enzymes that help mellitin destroy cell membranes (cell membranes have lots of phospholipids in them). Apamin is also unique to bee venom (3 %) and is a neurotoxin – it is toxic to nerve conduction. Hyaluronidase (2 %) is an enzyme that breaks down hyaluronic acid, which is one of the components of connective tissue or the tissue in between your cells that hold you together (like little microscopic tendons). Hyaluronidase contributes to the “spread” of the reaction. Phosphatases are enzymes that break off the phosphate portions of high-energy chemicals. Frequently these phosphate molecules begin cascades of other, very inflammatory biochemical reactions in your body (like the clotting cascade). Mast cell degranulating (MCD) peptides do just what they’re named for – they cause the mast cells in your body to release the many biochemicals (including histamine) in their granules. Mast cells will be covered more in the immunology section later. Histamine causes ‘leaky’ capillaries and contributes to the familiar wheal and flare reaction (slightly raised red area that itches) in allergic or atopic individuals.

Venoms from hornets (*Vespa*), aerial yellow jackets (*Dolichovespula*), ground-nesting yellow jackets (*Vespula*), and paper wasps (*Polistes*) lack mellitin, phospholipase A2, acid phosphatase, apamin, and MCD peptide. Their venom contains 10 - 25 % phospholipase A1 and

B as well as antigen 5, which honey bee venom does not contain, however. The proteins in the venoms of individual yellow jacket and hornet species (subfamily Vespinae) are quite similar. This leads to a lot of cross reactivity in the human immune response to them. Thus, venoms for testing hypersensitivity and immunotherapy desensitization are typically available separately for honey bees, wasps, and ‘mixed vespids’.

**Precautions and sting prevention**

Good technique can reduce the number of bee stings you receive (Table 3). Realize that the ‘mood’ of the hive can be affected by many things, such as season, weather, and many factors that may only be apparent to the bees. A long time ago I gave up trying to predict the mood of the five females I live with, much less the 50,000 females in a bee hive! Therefore, don’t assume that a given hive will be gentle just because it had a good temperament the last time you inspected it. Also, if you are a suburban beekeeper (like me), only keep very gentle bees near your house. And inquire as to your neighbor’s possible venom allergies.

Work hives on warm, sunny, calm days.

<b>Table 3 Precautions and Sting Prevention</b>
Wear white and ALWAYS WEAR YOUR VEIL
Avoid using perfumes and eating bananas
USE SMOKE judiciously
Work slowly and deliberately
Remove and smoke stings ASAP
Wash your bee suit and gloves frequently

Cold, windy conditions and impending thunderstorms make for irritable bees. Approach bee hives from the back. Do not stand in their flight paths. Wear white and ALWAYS WEAR YOUR VEIL. Avoid using perfumes and eating bananas before bee work. Use smoke judiciously, but use it almost every time you work in a hive’s brood nest (queen inspections very soon after introduction and quick, gentle feeding operations are exceptions). Work slowly and deliberately, avoiding quick movements and hive vibrations. Remove stings quickly without squeezing them and smoke the stings as soon as possible. And wash your bee suit (and gloves if you use them) frequently – particularly if you’ve received a bunch of stings!

**Management of emergencies**

It’s better to be prepared for a major battle and not have one than to only prepare for a minor skirmish and experience a major war. What do you do if you drop or knock over a hive and there are more angry, stinging bees than you ever thought possible coming at you? Table 4: Close the hive if you can (easily). Cover up. Get your smoker and smoke yourself (if it’s still lit). Calmly walk at least 20 yards

<b>Table 4 Management of Emergencies</b>
Close the hive if you can
Cover up
Kill any bees inside your veil
Get your smoker
Walk at least 20 yards away into brush (evergreens)
Return when calm (20 minutes)

away into some brush. Evergreens are particularly good at distracting bees. Walk. Do not run (unless you can run a 5 minute mile)! Don’t swat bees. Don’t return to the scene of the crime until you and the bees have calmed down (this takes about 10 or 20 minutes for the bees – I can’t say for you)!

If a bee gets inside your veil, kill it before it can sting your face. If you don’t have a veil on (heaven forbid) and bees are flying into your face, close your eyes and walk away (and get your veil). If you have a bunch of bees inside your veil (more than two or three), take it off, cover your face and let them sting your hands. And remember, every sting leaves you marked for more!

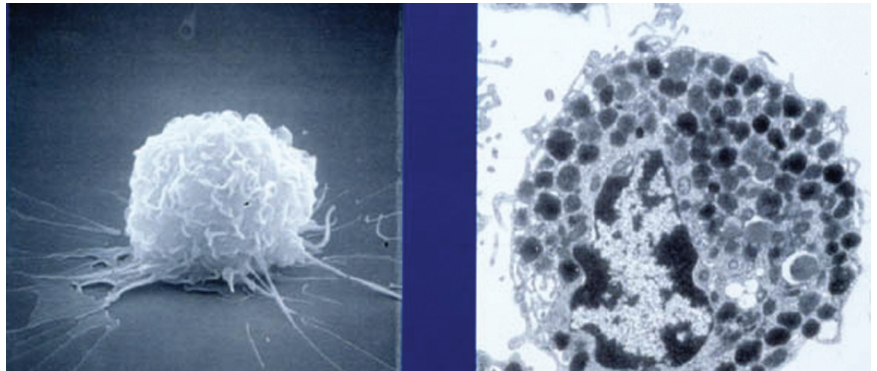
**Immunology and allergy**

The human immune system is highly complex. Its basic function is to recognize and destroy foreign tissue (like bacteria or viral-infected cells). In order to do this, it must not only recognize proteins that

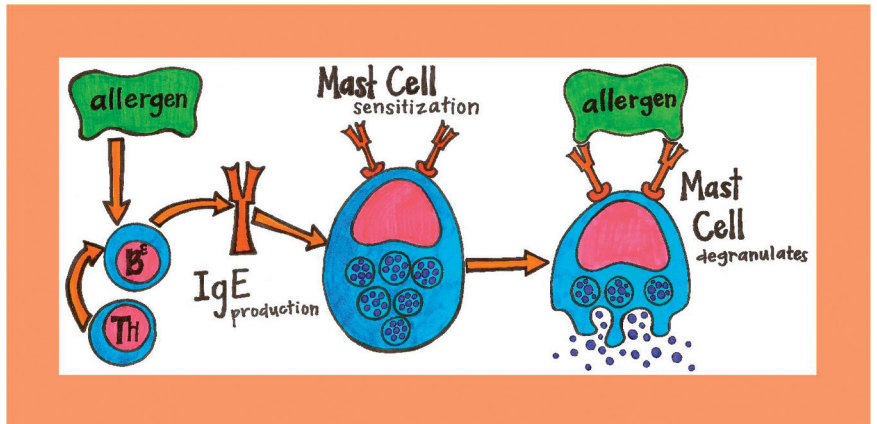
belong to the body (self), but distinguish these from proteins that don’t belong (non-self). The specialized white blood cells in the immune system that do this are called lymphocytes. Lymphocytes utilize complex protein receptors on their surface to recognize self and non-self and they generate two integrated responses to foreign proteins (such as those from bee venom). One effector arm of the immune response is the production of antibodies and the other is the production of other controlling and effector lymphocytes.

Antibodies are produced by B lymphocytes and are large complex proteins called immunoglobulins (Ig). Immunoglobulins or antibodies have a hypervariable region that fits around a small piece of a foreign protein (antigen) like a lock fits over a key. The fit is even more specific than a key and lock, however, because it is in three dimensions and also includes charge affinity (areas of negative charge on the antigen line up with areas of positive charge in the cleft of the antibody). There are many different classes of antibodies, but the primary class in the bloodstream that is involved with a ‘normal’ immune response is IgG and the class that is involved with an allergic or hypersensitivity response is IgE.

The controlling cells of the immune response are called T lymphocytes. They recognize the foreign antigen with receptors on their surface (very much like antibodies) and can induce B cells to make



**Figure 8. Electron Micrographs of Mast Cells with Granules** Left is scanning em, Right is transmission em (showing granules), courtesy of Soman N Abraham, Duke University Medical Center



**Figure 9. Diagram of Allergic Immune Response**, by Rachel Alexandra Marterre

specific antibodies to the antigen. Their response may include recruiting other cells to destroy it (using chemical messengers called cytokines – similar to pheromones in a bee hive) or by directly attacking the foreign antigen themselves. In both the case of antibody production by B cells and T lymphocyte generation, memory cells (both B and T) are generated that can then recognize the foreign antigen decades later. This is how immunity to a virus or bacteria or venomous sting can last a lifetime, even though exposure to it may have been years before or even in childhood.

The effector cells that are recruited by the T cells and the antibody classes that B cells make differ with different people, even in response to the same foreign antigen. The cytokine messenger profiles (that recruit other effector cells) also differ from individual to individual. Thus, some individuals may make allergic IgE antibodies to bee venom antigens even though most people make non-allergic IgG antibodies.

An allergic response to a venom antigen (now called an allergen) is also quite complex. It begins with IgE antibodies and mast cells. Mast cells are already present in the sting site (Figure 8). Mast cell surfaces are loaded with IgE antibodies that may react with many different types of antigens or allergens. After venom is injected into the skin, at least two IgE antibodies on the surface of a mast cell each react with the venom allergen, causing the immediate release of preformed substances in the granules of the mast cell, as well as the production of other new substances. Refer to the Figure 9 for a basic diagram of an allergic immune response. And recall, the mast cell degranulating peptide in bee venom can cause this reaction all by itself – even without a typical allergic response! With just a few stings, mast cell degranulating peptide's effects are only local, but with hundreds of stings the venom dose can cause toxic effects.

Once activated, mast cells release a lot of very potent preformed chemicals from their granules immediately, including histamine, proteases (enzymes that destroy

**Table 5**  
**Mast Cell Granule Contents and Products**

Histamine, Serotonin
Enzymes (that destroy proteins or initiate cascades)
Heparin (anticoagulant)
Eosinophil Chemotactic Factor of Anaphylaxis
Neutrophil Chemotactic Factor
Leukotrienes
Prostaglandins
Cytokines (which recruit other inflammatory cells)

proteins or initiate other cascades), heparin (an anticoagulant), and chemicals that attract eosinophils (another allergic effector cell) (Table 5). These primary mediators are released within minutes and their effects on the human body begin very quickly. Histamine dilates blood vessels, makes them leaky, and activates the endothelium (or lining of the capillaries). This leads to local edema (swelling), warmth, redness, and the attraction of other inflammatory cells to the site. In large amounts, it can drop blood pressure, and cause rapid swelling of the airway (leading to stridor or an inability to breathe) and constrict bronchial tubes (causing an asthmatic 'attack'). Histamine also irritates nerve endings (leading to itching or pain).

Upon activation, mast cells also begin to synthesize secondary chemicals which have more delayed effects including prostaglandins, leukotrienes, and cytokines. Some of these secondary chemicals (particularly the cytokines) are responsible for the late phase of allergy, which typically begins 2 – 4 hours after the insult. The prostaglandins and leukotrienes – like histamine – also cause bronchial constriction, dilation of blood vessels and leaky capillaries, but their onset is hours later and their effects more long-lasting. Aspirin can actually exacerbate these effects by causing more leukotrienes and fewer prostaglandins to be produced by the mast cells. The cytokines which are made

and released by the mast cells are primarily responsible for the late phase of anaphylaxis. They attract other effector cells of allergies, like eosinophils, basophils, and neutrophils (which significantly contribute to allergic responses). Once these processes get initiated, they can snow-ball in a hurry and cause a lot of problems very quickly. Again, if the allergic reaction becomes systemic (throughout the entire body), it is called anaphylaxis.

**That's enough science for one article. In part two, we'll discuss sting reaction types and treatments, allergy testing and desensitization results, and specific recommendations for beekeepers.**

#### 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.

# 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 cate-

gories: 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.

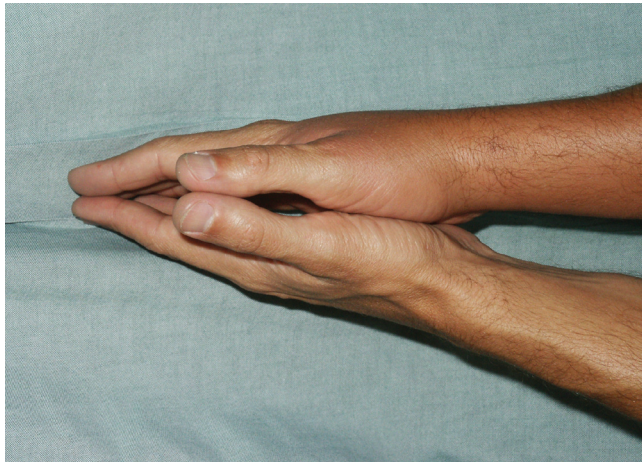
Treatment of a large local includes ice and elevation. Taking an anti-histamine or



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 cetirizine (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, diar-

rhea, 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



**Figure 13. Urticaria or Hives**  
courtesy of Dr. Raymond J. Mullins,  
[allergycapital.com.au](http://allergycapital.com.au)



**Figure 14. Facial Angioedema** Same patient, before and after treatment  
courtesy of [siamhealth.com](http://siamhealth.com)

bee stings *should* see an allergist for skin testing and immunotherapy.

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 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 sub-families 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**

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

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).

### 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

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

<u>Population</u>	<u>Normal Reaction</u>	<u>Large Local</u>	<u>Mild - Mod Anaphylaxis</u>	<u>Severe Anaphylaxis</u>
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				

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

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#### Selected Bibliography

- Annala IT, Annala PA, and P Morsky. 1997.** Risk assessment in determining systemic reactivity to honeybee stings in beekeepers. *Annals of Allergy, Asthma, and Immunology.* 78(5):473-477.
- Annala IT, Karjalainen ES, Annala PA, and PA Kuusisto. 1996.** Bee and wasp sting reactions in current beekeepers. *Annals of Allergy, Asthma, and Immunology.* 77(5):423-427.
- Annala I, Saarinen JV, Nieminen MM, Moilanen E, Hahtola P, and IT Harvim. 2000.** Bee venom induces high histamine or high leukotriene C4 release in skin of sensitized beekeepers. *Journal of Investigational Allergology and Clinical Immunology.* 10(4):223-228.
- Arcieri ES, Franca ET, de Oliveria HB, De Abreu Ferreira L, Ferreira MA, and FJ Rocha. 2002.** Ocular lesions arising after stings by hymenopteran insects. *Cornea.* 21(3):238-330.
- Bousquet J, Menardo J-L, Aznar R, Robinet-Levy M, and F-B Michel. 1984.** Clinical and immunologic survey in beekeepers in relation to their sensitization. *Journal of Allergy and Clinical Immunology.* 73(3):332-340.
- Davis CF. 2004.** *The Honey Bee Inside Out.* Bee Craft Limited, Stoneleigh, UK.
- Eich-Wanger C, and UR Muller. 1998.** Bee sting allergy in beekeepers. *Clinical and Experimental Allergy.* 28(10):1292-1298.
- Golden DBK, Kagey-Sobotka A, and LM Lichtenstein. 2000.** Survey of patients after discontinuing venom immunotherapy. *Journal of Allergy and Clinical Immunology.* 105(2 Pt 1):385-390.
- Golden DBK, Kagey-Sobotka A, Norman PS, Hamilton RG, and LM Lichtenstein. 2004.** Outcomes of aller-

gy to insect stings in children, with and without venom immunotherapy. *The New England Journal of Medicine.* 351(7):668-674.

- Golden DBK, Kwiterovich KA, Kagey-Sobotka A, Valentine MD, and LM Lichtenstein. 1996.** Discontinuing venom immunotherapy: Outcome after five years. *Journal of Allergy and Clinical Immunology.* 97(2):579-587.
- Goodman L. 2003.** *Form and Function in the Honey Bee.* International Bee Research Association, Cardiff, UK.
- Lerch E, and UR Muller. 1998.** Long-Term protection after stopping venom immunotherapy: Results of re-stings in 200 patients. *Journal of Allergy and Clinical Immunology.* 101(5):606-612.
- Levine MI, Lockey RF, eds. 2003.** *Monograph on Insect Allergy,* 4th ed, American Academy of Asthma, Allergy and Immunology, Pittsburgh, PA: David Lambert Associates.
- Reisman RE. 1992.** Natural history of insect sting allergy: Relation to severity of symptoms of initial sting anaphylaxis to re-sting reactions. *Journal of Allergy and Clinical Immunology.* 90(3 Pt 1):335-339.
- Schmidt, JO. 1992.** Allergy to Venomous Insects. In *The Hive and the Honey Bee.* JM Graham, ed. Dadant & Sons, Hamilton, IL, pp.1209-1269.
- van Halteren HK, van der Linden P-WG, Burgers SA, and AKM Bartelink. 1996.** Hymenoptera sting challenge of 348 patients: Relation to subsequent field stings. *Journal of Allergy and Clinical Immunology.* 97(5):1058-1063.
- Vetter RS, Visscher PK, and S Camazine. 1999.** Mass envenomations by honey bees and wasps. *Western Journal of Medicine.* 170(4):223-227.
- Winston ML. 1987.** *The Biology of the Honey Bee.* Harvard University Press, Cambridge, MA.