

What's Eating You? Bees, Part 1: Characteristics, Reactions, and Management

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Bee stings are common in the United States. We review the characteristics of bumblebees, honeybees, and Africanized honeybees; the types and pathophysiology of sting reactions; and the medical management and prevention of bee stings. In part 2 of this series, we will discuss the use of venom immunotherapy, the diagnosis of systemic mastocytosis that initially presents as anaphylaxis, and the efficacy of immunotherapy in patients with mastocytosis.

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As members of the order Hymenoptera, bees deliver a venom-producing sting with which many people have had personal experience. With 0.5% to 3.0% of the US population considered allergic to venomous stings,^{1,2} and an average of 48 reported deaths annually in the United States (27.1% of all animal-related fatalities) attributed to insect stings,^{3,4} physicians should be familiar with the cutaneous and systemic reactions that can result from such stings. Furthermore, it is important to know how to manage and prevent these injuries and to educate patients on these matters. Although the focus of this article is on bees, much of the information also applies to other stinging insects, such as vespids (eg, social wasps that, like bees, live in colonies).

Classification and Characteristics of Bees

Insects in the order Hymenoptera, meaning "membrane wings," have 2 sets of front and hind wings that are connected by a series of little hooks called hamuli. A constriction in the abdomen distinguishes these insects from similar-looking insects, such as flies.⁵ The order is large and includes not only bees (family Apidae) but also wasps and hornets (family Vespidae) and ants (family Formicidae).^{2,6} Although there are many types of bees, only bumblebees (genus *Bombus*) and honeybees (including the Africanized honeybee, genus *Apis*) are considered of medical importance and will be the only ones addressed in this article. The female aculeate (Aculeata, a suborder of Hymenoptera, referring to the stinging capabilities of these insects) can inject its venom from a gland or sac (singularly or in pairs) through an ovipositor (a long tapered structure on the posterior portion of their body)(Figure 1). Venom is delivered by posterior stings, which generally are intended for defense only. The injection usually causes immediate pain with a nonfatal injury, which conditions the stung individual to avoid these insects.⁷

Bees are a familiar sight, with their distinctive black and yellow striped bodies. Bumblebees are approximately 20 mm long and have broad bodies, whereas honeybees are slightly smaller, at 15 to 20 mm long.⁸ It is impossible to distinguish Africanized honeybees from the European honeybees of the United States without administering behavioral or genetic tests.⁹ The bumblebee and honeybee species are distributed worldwide; the Africanized honeybee (a cross between several European honeybee species and the African species)⁷ was introduced to South America in 1956 and spread to Central America and Mexico before arriving in the south central United States in 1993.^{8,10-12} Most stings occur during temperate months (eg, spring, summer) and in areas of the United States where the insects' presence is high (eg, the South).^{11,13}

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Figure 1. A honeybee injecting venom through its stinger. Photograph © Scott Camazine (<http://www.scottcamazine.com/photos/BeeSting/>).

Because bees are social insects, they primarily sting when their nest is threatened. Bumblebees inhabit nests with up to 200 bees, whereas honeybees live in colonies of up to 100,000 members.⁷ Bumblebees build their nests in loose fibrous habitats that are close to the ground, such as grass clippings. Many honeybees live within man-made hives; however, in the wild, they build their nests in cavities of buildings or in hollow trees.⁵ The infamous reputation of the Africanized honeybee is well-deserved because of its readiness to attack in defense of its nest, respond in numbers, and swarm and pursue its victims.^{7,14} Because bees are used in crop pollination and food production, they are numerous. The large numbers and aggressive nature of bees (particularly Africanized honeybees) make humans especially vulnerable.⁷

The distinguishing feature of the domestic and Africanized honeybee sting is that the barbed ovipositor and venom sac are eviscerated from the body of the bee and remain embedded in the flesh of the victim.^{7,8} The honeybee itself dies after a single sting.^{8,15,16} The musculature between the venom glands will continue to pump venom through the stinger if not promptly removed. Thus, the stinger can embed itself deeper into the flesh, enabling the venom to reach more sensitive tissue.^{7,8,17} In honeybees, alarm pheromones produced by stingers evaporate and attract more bees to this vulnerable area.^{7,8} In contrast, bumblebee stingers do not detach, so a single bee may sting numerous times.^{8,16}

Local and Systemic Reactions

A bee sting is an instantly painful insult to the skin. The skin characteristically develops a raised red wheal with a central white punctum at the site of injury, with erythema and edema confined to the immediate surrounding skin and sometimes forming

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Figure 2. An immediate reaction to a bee sting. Photograph © Scott Camazine (<http://www.scottcamazine.com/photos/BeeSting/>).

an urticarial plaque (Figure 2).¹⁸ If a biopsy of the lesion is performed, histopathology may show a neutrophil and lymphocyte infiltrate in the papillary dermis, with plasma cells, eosinophils, and histiocytes appearing later⁸ and extending down to the reticular dermis.¹⁹ For nonallergic individuals, this reaction will disappear within hours and cause only minor discomfort.⁷ Individuals with an increased sensitivity to bee stings can develop local skin reactions greater than 5 cm in diameter^{7,8,13} up to 48 hours after the sting (Figure 3). At the site of the sting, the wheal may become papular, edematous, and indurated, and may take up to 7 to 10 days to resolve.^{8,15,20}

Allergic individuals can develop more generalized reactions that can be classified as mild, moderate, or severe,²¹ with symptoms usually presenting within 10 to 20 minutes after the sting.²² Mild systemic reactions may result in cutaneous symptoms, which differ from large local reactions only in that they are not contiguous with the sting site.²³ Moderate reactions involve organs other than the skin. The stereotypical symptoms of an allergy—sneezing, itchy watery eyes, generalized pruritus, and cough—all can occur. Other symptoms may include gastrointestinal tract distress, lightheadedness, headaches, fever, and muscle spasms, as well as difficulty breathing.^{8,16,24-26}

With a full immunologic response, severe symptoms of anaphylaxis can occur, including generalized

urticaria, bronchospasm, and bronchoconstriction resulting in angioedema, cardiovascular collapse, and loss of consciousness.^{4,19,24} Anaphylactic shock and death, with multiorgan failure, can occur within 30 minutes to 1 hour after even a single sting.²⁷ With increasing doses of venom, convulsions, myocardial infarction, acute renal failure,²⁸ and stroke may occur. At a median lethal dose of 19 stings per kilogram (approximately 500 bee stings), late death may result.^{29,30} Symptoms can mimic anaphylaxis because of the overwhelming amounts of venom or severe hypoxia of the cardiovascular and central nervous systems. Myoglobinuria, hemoglobinuria, or acute tubular necrosis also have been reported.^{9,28}

Pathophysiology of Reactions

Honeybee venom contains several components that are responsible for physiologic reactions in humans. About 50 µg of protein is injected with each sting.¹⁴ The enzymes phospholipase A₂ (PLA₂) and hyaluronidase are the main allergens in the venom. PLA₂ induces immunoglobulin E (IgE) production during the initial sensitization. Subsequent introduction of PLA₂ interacts with IgE that is affixed to mast cells and basophils, which results in the immediate release of mediators that can cause the symptoms of anaphylaxis. Hyaluronidase aggravates these initial injuries by causing changes in cell membranes that allow the other venom components (PLA₂ and IgE) to propagate their damage.

Melittin is a protein in the bee sting that decreases cell permeability. It is responsible for the immediate pain felt when stung. Both PLA₂ and melittin cause hemolysis. Peptide 401 causes mast cells to degranulate and release histamine. Apamin (a neurotoxin) and acid phosphatase also are components of bee venom.^{8,31-33} Of all these constituents, melittin is the most abundant substance in honeybee venom (50% by dry weight), followed by hyaluronidase.³² Other amines in the venom are histamine, dopamine, and norepinephrine.^{32,33} In the case of multiple stings, an excessive amount of amines, especially histamine, causes nonallergic toxic reactions, including flushing, headaches, and cardiovascular effects.⁹

The venoms of domestic and Africanized honeybees are similar. The more severe toxic reactions resulting from Africanized honeybee stings are not a function of more toxic venom but the cumulative effects of multiple bee stings.^{8,15} Although there naturally is some cross-reactivity between bumblebee and honeybee venom,⁸ there only is limited immunologic cross-reactivity between honeybee and vespid venom.^{23,34,35} The speed and degree of the bodily response to the venom form a spectrum of allergic manifestations.

Figure not available online

Figure 3. Large local reaction. Photograph courtesy of James Solomon, USDA Forest Service (<http://www.forestryimages.org>).

The IgE venom-specific antibodies formed from prior sensitization (type 1 hypersensitivity) are the impetus for the release of histamines, leukotrienes, and prostaglandins from mast cells and basophils. In a mild response, only cutaneous signs may occur. In more severe reactions, these mediators cause an increase in capillary permeability and peripheral vasodilation, leading to fluid sequestration, loss of vascular tone, and hypotension. Anaphylaxis and anaphylactoid shock, which are both forms of distributive shock, result from this vascular leakage and smooth muscle contraction. Disseminated intravascular coagulation can cause a generalized hemorrhage that contributes further to systemic collapse. Bronchoconstriction and the direct cardiotoxicity of the mediators can induce hypoxia and cause heart failure and arrhythmias.^{8,25,36} Anaphylactoid shock is an IgE-independent reaction that results from the excessive amount of vasoamines (especially histamine) present after multiple stings.^{8,37}

In an accelerated and exuberant response, hemodynamic collapse can occur without cutaneous or respiratory symptoms.²⁵ Autopsy reports have demonstrated laryngeal or bronchial edema and secretions resulting in obstruction and hyperinflation of the lungs, with similar effects (congestion and hemorrhage) in the cardiovascular and central nervous systems.^{25,36}

Biphasic or late protracted anaphylaxis can result from secondary mediators of inflammatory cells, such as eosinophils, neutrophils, or macrophages.^{8,38} Other delayed reactions or complications include serum sicknesslike syndrome, Guillain-Barré syndrome, glomerulonephritis, myocarditis, encephalitis, and Henoch-Schönlein purpura.^{1,14,39}

Preexisting pathology is likely to contribute to morbidity or mortality. For example, mast cells surrounding already diseased coronary arteries can release mediators that further attack the heart and

Strategies for Prevention of Insect Stings^{8,14,15,23,24,36}

Primary Prevention

- Avoid blooming flowers and overripe fallen fruit
- Have a qualified expert destroy insect nests near houses and other structures
- Wear long sleeves, pants, hat, and gloves while gardening
- Avoid using scented personal products before working outdoors
- Avoid loose-fitting light garments with black or brightly colored patterns
- Avoid drinking or eating sweets outside during the summer months
- Do not walk barefoot outside in grassy areas during summer months
- Drive with car windows up and air-conditioning on
- Carry an epinephrine self-injector at all times
- Notify someone if bees swarm in the neighborhood

Secondary Prevention

- If encountering a nest, retreat slowly and do not panic
 - If attacked, cover head, nose, and mouth with arms or with piece of clothing. Move away quickly, but without sudden movement, until safe
 - Allergic individuals should use their epinephrine kits immediately and seek emergency treatment as soon as possible
-

result in myocardial infarct. Arrhythmias and other cardiovascular events have been reported in association with anaphylaxis.^{4,40}

Immediate Management

The most important action to take at the moment of attack is to remove the victim from the immediate area of the nest to avoid further stings. It is necessary to remove the stinger (assuming there have been only a few stings) as soon as possible because the attached venom sac will continue to pump toxic venom. The method of removal is less important than the speed of elimination.¹⁷ The conventional method has been to use a hard plastic card, such as a credit card, to scrape or drag the offending stinger out of the skin without squeezing the venom sac. (Theoretically, squeezing the sac would forcibly instill more venom, aggravating the initial injury.) Drawbacks of the conventional method include the time lost in finding an object for scraping and the risk of breaking the stinger and leaving the tip in the skin. Plucking out the stinger with either the fingers or tweezers can be a quicker

method of removal.¹⁷ One study showed that venom sacs are emptied in one minute; thus, the objective should be to remove the stinger(s) as quickly as possible.⁴¹

The mainstays of treatment for acute reactions are symptomatic and depend on the extent of the sting injury. For self-limiting local cutaneous reactions, treatment may be limited to cool compresses; calamine lotion; topical hydrocortisone; and an oral pain medication, such as acetaminophen. For larger local reactions, the addition of an oral antihistamine or corticosteroid, such as prednisone, may be appropriate.²³ Elevation of the limb also can alleviate symptoms.⁸ Antibiotics are not necessary unless there is evidence of secondary infection.^{15,23}

If an epinephrine autoinjector is available, allergic individuals, especially those with respiratory manifestations, should have the medication immediately administered into the patient's thigh, with immediate transport to the nearest medical facility. At the hospital, aqueous epinephrine 1:1000 (1 mg/mL) administered

intramuscularly or subcutaneously (adults, 0.2–0.5 mL; children, 0.01 mg/kg, maximum 0.3 mg) may be further given, repeated at 5-minute intervals, as necessary. As a stimulant of adrenergic α -, β_1 -, and β_2 -receptors, epinephrine antagonizes the pathologic effects of the mediator release from the mast cells and basophils through vasoconstriction and bronchodilation while impeding further mediator release by increasing production of cyclic adenosine monophosphate.^{25,36} Intravenous epinephrine can stimulate arrhythmias and myocardial infarcts in patients with prior cardiac disease; therefore, this route only should be used in the event of cardiac arrest and severe shock. Additionally, electrocardiogram monitoring is required with intravenous administration.³⁶

The priority in this medical emergency is to ensure an airway in these patients and maintain their breathing and circulation. Thus, the supportive treatment of severe reactions also should include intubation (if necessary), oxygen, and intravenous fluids. Cardioversion may be necessary with new arrhythmias induced by stings.⁴²

Intravenous antihistamines and corticosteroids will decrease the body's reactivity to the venom. H1 blockers relieve pruritus, urticaria, and angioedema.³⁶ H2 blockers may counteract coronary vasodilation; when slowly administered intravenously, they may relieve persistent hypotension. Corticosteroids achieve their anti-inflammatory effects by inhibiting membrane phospholipases and the release of mediators,³⁶ and they may lessen the effects of a delayed anaphylactic attack.⁴²

Other β_2 -adrenergic stimulants and vasopressors, such as norepinephrine and dopamine, can be administered as adjunctive medications for systemic support. For a patient who is on beta-blockers, glucagon may be necessary to overcome the effects of this medication because it directly activates adenylyl cyclase without affecting β -adrenergic receptors.²⁵

Close monitoring of the patient's blood pressure and pulse are critical because a biphasic or late attack can occur in up to 20% of patients within 4 to 12 hours or more after a sting, even when the immediate reaction has been brought under control.^{8,38}

Prevention

In general, avoidance of bees and their habitats is the cornerstone of sting prevention; however, this is not always possible due to the wide dispersion of bees. The Table provides some strategies that can lessen the risk of insect stings.

Individuals with even mild systemic reactions should carry an epinephrine autoinjector with them at all times and use it if there is a possibility that a

systemic reaction is occurring. Autoinjectors should be inspected periodically for discoloration and protected from light and extreme temperatures; they also should be discarded and replaced before their labeled expiration date.⁴³ Use of epinephrine inhalers is discouraged, though they are widely prescribed in countries outside of the United States. Although bee sting victims may be more willing to use an inhaler than an autoinjector at the moment of attack, it has been shown that it is difficult to attain a therapeutic level of epinephrine with the inhaler in a short period of time.^{15,44} Moreover, the inhaler would be of little benefit if the patient became unconscious before having an opportunity to use it.⁴⁴ Any deployment of epinephrine outside of the physician's office warrants a trip to the emergency department as soon as possible to ensure that any systemic reaction is under control.⁸

Another important requirement for severely allergic persons is to wear a medical tag to identify their hypersensitivity and prevent misdiagnosis in the event of an attack.^{9,23,24,27} Insect repellents are not effective against stinging insects^{23,34}; however, bees that continue to attack can be killed by spraying them with soapy water.⁹

This article is the first of a 2-part series. The second part will appear in a future issue of Cutis®.

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