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Emergency Department Evaluation and Treatment for Children With Arthropod Envenomations: Immunologic and Toxicologic Considerations

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Arthropod envenomations are a significant cause of environmental injury in children. Bees, wasps, and spiders inflict injury via specialized venoms with a broad range of components, mechanisms, and potential treatments. Immunologic and toxicologic considerations in the evaluation and management of arthropod envenomations are important for the understanding of the progression of envenomations, prompt diagnosis of severe conditions including anaphylaxis, and the use of antivenom in selected cases.
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Arthropod bites and stings accounted for more than 75 000 reports to poison control centers in the United States in 2005 [1]. The phylum Arthropoda includes 2 clinically important classes: Insecta (order: Hymenoptera—bees, wasps, yellow jackets, and ants), and Arachnida (ticks, scorpions, and spiders). Virtually all arthropods possess some form of venom for immobilization and digestion of prey, yet only a select few species have developed venom delivery mechanisms capable of poisoning humans [2]. Pathophysiologic mechanisms of venom vary considerably among arthropods, and clinical immunologic considerations in the emergency department (ED) evaluation and treatment of these injuries are essential to patient management.

Hymenoptera: Bees and Wasps

Bee and wasp envenomations are the most widely documented arthropod exposures, with 4081 pediatric exposures and 1 death reported to poison control centers in 2005 [1]. Honeybees and bumblebees are part of the Apidae family. Yellow jackets, hornets, and wasps are part of the Vespidae family. Insect structure, behavior, and venom components differ between the 2 families; however, clinical symptoms of envenomation and treatment are similar. Bees are attracted to carbon dioxide (hence, the predilection for bees to fly around the facial area), bright colors (ie, clothing), and sweet odors (ie, perfumes, fragrances). Children commonly believe that bees are aggressive insects, but they are mostly docile creatures; indeed, the sometimes fearful behavior of children around a nearby bee may increase the risk of a sting. Mass envenomations may occur when a hive is physically disturbed by children throwing rocks or other objects at the hive [3].

Bees exist in intricate colonies of thousands, with specific duties designated to various colony members to protect the queen. Guard and soldier bees are tasked to defend the hive against trespassers (animals, humans, and

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other insects); however, less aggressive worker and foraging bees may also sting when disturbed [4]. Yellow jackets and hornets may inflict solitary stings more impulsively than the more docile honeybees, whereas Africanized bees are often involved in mass envenomations. The barbed surface of the honeybee stinger causes the insect to eviscerate itself as it attempts to fly away after stinging, often leaving a detached stinger imbedded at the site of injury. The venom sac may be visible at the proximal end of the stinger [5]. Bumblebees possess slightly smoother stingers and may be able to sting more than once [5]. Wasp (hornet and yellow jacket) colonies are composed of a few hundred insects. These insects deliver venom via nonbarbed stingers, possess more venom per sting than bees, and may attack singly or en masse [6]. Classically, a retained stinger in the wound indicates a bee sting, whereas the absence of a stinger on visual inspection suggests envenomation by a wasp. However, bee stingers may extrude after stinging and self-evisceration by honeybees, and bumblebees may escape without stinger detachment. Therefore, the absence of a stinger at the site of injury does not necessarily denote a wasp sting [6].

A limited subset of the US population (1-2 people per 1000) is allergic or hypersensitive to bee or wasp stings, culminating in up to 50 deaths per year. Fatal reactions may occur in some patients without previous histories of allergic sting reactions [7]. Evaluation and therapy depend upon the nature of the exposure (single vs mass envenomation) and clinical severity. Bee venom can cause injury via immune-mediated mechanisms, including local effects and anaphylaxis, or by systemic toxic effects of venom in mass envenomations. Bee venom contains an aqueous solution of 4 primary components: mellitin, phospholipase A_2, hyaluronidase, and mast-cell degranulation protein [8]. Mellitin is the most abundant component and mediates most of the local pain symptoms. Mellitin also causes the formation of pores in red blood cell membranes. Phospholipase A_2 subsequently cleaves fatty acids from the lipid side of the cell membranes, resulting in hemolysis. Clinically significant hemolysis occurs in few patients after bee stings. Hyaluronidase cleaves hyaluronic acid in connective tissue, allowing other venom components to travel easily to nearby tissues. Mast-cell degranulation protein induces histamine release from mast cells, resulting in inflammation and local or systemic vasodilation [8]. Local dermal reactions typically consist of local edema and spongiosis, endothelial cell hyperplasia, and necrosis. Lymphocytes, neutrophils, and eosinophils may infiltrate adjacent perivascular and reticular tissues [8]. Immunoglobulin (Ig) E–mediated type I anaphylaxis, usually in response to phospholipase A_2 or hyaluronidase, occurs independently of the number of stings, but may complicate either single stings or mass stingings. Cross-linking of IgE antibodies attached to basophils and mast cells results in the release of histamine, leukotrienes, and other cytokines, manifesting with urticaria, dyspnea, hypotension, bronchial constriction, and laryngeal edema [9]. The allergenic properties of bumblebee venom are similar to honeybee venom [10]. In mass envenomations, severe reactions or death may occur from anaphylaxis or directly from toxic systemic effects of venom.

Wasp venom contains a number of neurotransmitters, neuromodulators, and immunomodulators, including catecholamines, serotonin, tyramine, bradykinin, and mastoparans (histamine-releasing factors), all of which induce pain and inflammation [11]. Wasp venom also contains allergenic components, including phospholipase A, phospholipase B, hyaluronidase, and antigen 5, which mediate anaphylaxis and delayed hypersensitivity reactions [12].

Honeybees, bumblebees, Africanized bees, and wasps universally cause painful burning papules at the site of envenomation, with progression to erythematous wheal-and-flare reactions that begin to subside within 24 hours. Up to 50% of cases progress to larger edematous local reactions that may mimic cellulitis or become vesicular or bullous [13]. Up to 5% of patients experience systemic reactions, including anaphylaxis. Symptoms of systemic reactions may include nausea, vomiting, and dizziness in a dose-response fashion after multiple stings. Rarely do these systemic reactions occur after solitary stings in the absence of IgE-mediated anaphylaxis. Treatment of local reactions involves symptomatic local wound care with ice, cool compresses, and discretionary use of topical corticosteroids. Oral antihistamines may decrease itching. Efficacy and safety of systemic administration of corticosteroids have not been validated in controlled trials [13] but has been suggested in cases of severe swelling. Imbedded stingers should be removed as early as possible, mostly to alleviate pain but also to potentially prevent lingering envenomation. Despite anecdotal presuppositions about various methods of proper stinger removal in the ED setting, controlled trials demonstrate that the rapid removal of retained stingers may be performed via any available method including tweezing, scraping with a credit card, or by applying and removing adhesive tape [14].

Anaphylaxis must be treated promptly with epinephrine 0.01 mg/kg IM (1:1000 aqueous solution), repeated in 10 to 15 minutes if clinical improvement is not apparent [9]. Standard treatments of other symptoms of anaphylaxis, such as airway management, bronchodilators, fluids, and pressors, are indicated based on symptoms. Signs and symptoms of anaphylaxis in bee envenomation may be persistent or recrudescent. Therefore, clinical observation should take place for at least 6 hours after successful treatment. A short course of oral corticosteroids for 2 to 5 days is often used to prevent late-phase allergic reactions. Patients presenting with symptoms of systemic IgE-mediated envenomation reactions should be

prescribed an epinephrine autoinjector. All patients with a clinical history of anaphylaxis should be referred to an allergy specialist for review of epinephrine autoinjector use, insect avoidance counseling, allergy skin testing, and potential evaluation for immunotherapy. Venom immunotherapy has been shown to reduce the risk of systemic reactions in insect-sensitive patients with an efficacy of 95% to 97% [15].

Hymenoptera: "Africanized" Honeybees

In 1956, bee researchers brought African honeybees from Africa into Brazil for their presumed aptitude for honey production. Although African bees were well suited to live in the Brazilian tropics, it was later determined that these bees did not demonstrate superiority in honey production. African bees mated with the more docile European honeybees already present in North and South America, resulting in the aggressive hybrid "Africanized" honeybee. Still a poor honey maker, Africanized honeybee colonies have been increasingly migrating through North America every year [16]. Also referred to as "killer bees," Africanized honeybees attack in swarms, sting more readily, and have been described to chase fleeing victims [17]. Although they do not fly faster than European honeybees, Africanized honeybees fly longer distances, as much as 20 km [18]. Africanized honeybee specimens are almost identical to honeybees in appearance, and phenotypic distinction can only be made by trained entomologists. Mass envenomation with bee or wasp stings presents with nausea, vomiting, diarrhea, lightheadedness, lethargy, edema, and seizures secondary to histamine-mediated inflammation, hypotension, and direct toxic effects of venom components. These clinical signs are not immune-mediated [19]. Hemolysis, rhabdomyolysis, hemoglobinuria, and myoglobinuria may evolve over several hours to days after envenomation [20]. These laboratory parameters may be followed as crude indicators of systemic toxicity when they are noted to be abnormal; however, normal laboratory tests should not be relied upon solely to assess patient disposition. Acute tubular necrosis and oliguric renal failure can also develop and may necessitate dialysis [21,22]. Other serum laboratory abnormalities may include elevated liver transaminases, elevated lactate dehydrogenase, and decreased platelet counts [23]. Mass stingings may present with tens to thousands of stings (20-200 wasp stings, 500-1000+ bee stings in case reports). Early fatalities in mass Hymenoptera envenomations are likely secondary to anaphylaxis. On the other hand, dose-response fatalities in mass envenomations tend to occur several hours to days later, many with delayed onset of symptoms (up to 6-24 hours after the incident) [24]. Pediatric deaths have occurred with as few as 150 bee stings and 30 wasp stings. All children with more than 50 bee stings should be observed for at least 24 hours in a hospital setting [25-27]. Few data are available to recommend clinical observation guidelines in mass wasp stings; however, anecdotal evidence suggests careful observation in patients with more than 10 stings.

Hymenoptera: Fire Ant

Two species of imported fire ants, the black fire ant (*Solenopsis invicta*) and the red fire ant (*Solenopsis richteri*), are poisonous to humans, in part due to their aggressive nature and propensity to attack in swarms. Fire ants are presumed to have entered the United States through the Port of Mobile, Alabama, in the 1930s via cargo ships' soil ballast and are endemic to the southern states, eastern states, and in California [28]. One thousand ten pediatric exposures were reported to Poison Control Centers in 2005, 812 of which occurred in children younger than 6 years [1]. Fire ant colonies are found in small, dome-shaped dirt mounds that may be easily disturbed by children running, kicking, or jumping near the mounds. Several cases of swarming envenomations have occurred after children have disturbed the mound with sticks. Children are encouraged to routinely wear socks and long pants in endemic areas [29]. Hundreds of thousands of ants may inhabit a single colony, and mass stingings of several thousands of ants with little provocation are common. As a swarm of ants engulfs a child's extremity, chemical and vibrational signals transmitted throughout the colony apparently induce the ants to sting almost simultaneously. Each ant grasps the victim's skin with its mouthpiece and pivots on its jaw as it inflicts 6 to 10 painful stings, over a few seconds, in a circular pattern via an abdominal stinger [30]. Upon close examination the skin lesions appear as a ring of pinpoint pustules. This feature can help distinguish stings by solitary fire ants from injuries from other insects [31]. Stings progress to wheals that evolve into pustules within 24 hours.

In contrast to the venom of indigenous ants, fire ant venom does not contain formic acid. Instead, fire ant venom contains an oily mixture of cytotoxic alkaloids, resulting in painful, pruritic local skin lesions and systemic reactions such as edema [32]. A small fraction of fire ant venom contains aqueous alkaloids, including phospholipase, hyaluronidase, *N*-acetyl-β-glucosaminidase, and genus-specific antigens *Sol i I*, *Sol i II*, *Sol i III*, and *Sol i IV* [33]. These antigens are responsible for a 0.6% to 6% rate of IgE-mediated anaphylaxis to fire ant stings [34]. Standard treatment for anaphylaxis is recommended. Patients with mass envenomation should be observed for several hours to monitor for delayed symptoms or for recrudescence of systemic toxic effects of venom. Supportive care, including cool compresses, may relieve symptoms during the first 24 hours. Severe itching may respond to oral antihist-

amines and topical corticosteroids. Topical application of meat tenderizer has proved to have no therapeutic value [35]. Pain from large single lesions has been treated with local injections of lidocaine in case reports, but this practice is not recommended for mass envenomations [6].

Arachnida: Tarantulas

Tarantulas are found in the arid regions of the United States. Tarantulas bite when aggravated but pose more danger from the trauma of the bite itself than from envenomation in humans. Tarantula venom contains a number of polypeptides, including hyaluronidases, which cause local cytotoxicity and minor inflammation. Occasionally, a histamine-mediated reaction develops, but reports of anaphylaxis are extraordinarily rare. The hairs on the back of the tarantula present a greater risk to humans. When distressed, tarantulas rub their hind legs against the ventral surface of their abdomen to eject the hairs on their backs. These hairs promote localized epidermal histamine-mediated reactions, manifesting with pain and urticaria. These injuries are particularly prominent, however, when they occur in the eyes, mouth, nose, oropharynx, or trachea. Supportive treatment with cold compresses, analgesics, antihistamines, topical corticosteroids, and tetanus prophylaxis is recommended for most contact reactions with tarantula hairs. Imbedded hairs may be removed from skin surfaces by irrigation, tape removal, or tweezers. Ophthalmia nodosa, a granulomatous nodular reaction of the corneas, sclerae, and conjunctivae, may result from contact of tarantula hairs with the eye. This condition requires immediate evaluation and treatment by an ophthalmologist [36].

Arachnida: Brown Recluse Spider

Envenomation by the brown recluse spider (*Loxosceles reclusa*), with the characteristic violin-shaped markings on the dorsal aspect of its cephalothorax, is a subject of tremendous controversy. In 2005, 464 cases of pediatric brown recluse spider bites were reported to poison control centers [1]. Brown recluse spiders are endemic to only a handful of central southern states but are widely perceived to live in other areas of the United States. Because the bite itself is usually painless, and because a spider specimen is seldom seen or recovered around the time of presumed exposure, brown recluse spider bites have become a popular, although mostly inappropriate, diagnosis of presumption for severe, solitary skin lesions in many nonendemic states [37]. Although similar spiders, such as *Loxosceles deserta*, pervade parts of southern California, Nevada, and Arizona, these taxonomic relatives of the brown recluse spider do not cause the same characteristic necrotic skin lesions. Therefore, clinicians in nonendemic states must consider an extensive differential diagnosis before contemplating the diagnosis of a brown recluse spider bite [38].

Brown recluse spider venom contains both cytotoxic and allergenic components, including alkaline phosphatase, deoxyribonuclease, hyaluronidase, lipase, ribonuclease, and sphingomyelinase D [39]. Sphingomyelinase D is the most active component and is responsible for regional skin necrosis and hemolysis. Sphingomyelinase D is also responsible for a cascade of immune-inflammatory reactions, beginning with the hydrolysis of sphingomyelin into ceramide-1-phosphate. Ceramide-1-phosphate induces the release of arachidonic acid from endothelial cells and promotes the synthesis and release of thromboxane, leukotrienes, and prostaglandins [40]. Neutrophils and complement infiltrate the site of envenomation, leading to local ischemia, microvascular clotting and disintegration, destruction of skin tissue, and subsequent necrosis [41]. The wound margin takes several weeks to declare itself fully, and patients will require regular follow-up with a plastic surgeon for wound care and eventual wound closure [42]. Immunomodulatory therapy has not proved to be successful in the treatment of brown recluse spider envenomation. Early studies using dapsone to inhibit the infiltration of neutrophils into the injury site did not demonstrate an improvement in clinical outcome; indeed, recent studies on the use of dapsone, triamcinolone, and diphenhydramine in necrotic lesions from brown recluse spider envenomation have not demonstrated an improvement in clinical outcome [43]. Hyperbaric oxygen therapy is an unproven treatment modality [44]. Antivenom directed against sphingomyelinase D is not commercially available but is currently being investigated in experimental trials [45].

Arachnida: Black Widow Spider

In 2005, 551 pediatric cases of black widow spider envenomation were reported to poison control centers [1]. Widow spiders include the classic black widow spider (*Latrodectus mactans*) with a red hourglass pattern on the underside of its shiny black abdomen, the western black widow spider (*Latrodectus hesperus*), northern black widow (*Latrodectus variolus*), southern brown widow (*Latrodectus bishopi*), and brown button spider (*Latrodectus geometricus*). Australia is the home of the red back spider (*Latrodectus mactans hasselti*). Envenomation from these various *Latrodectus* species is similar, and cross-reactivity among venom and antivenom is well documented [46]. Widow spider venom does not contain allergenic components and clinical allergic reactions are extraordinarily rare. Instead, the chief pathogenic component of widow spider venom is α-latrotoxin, a neuro-

toxic polypeptide that binds to presynaptic nerve receptors at the neuromuscular junction and in the autonomic nervous system, promoting the release of acetylcholine into the synapse [47]. Although any muscle group may be involved, the abdominal musculature is characteristically affected with resultant severe pain and rigidity that may mimic an acute abdomen [48]. Other symptoms include nausea, vomiting, agitation, and diaphoresis. Severe hypertension occurs in 92% of cases, particularly in very young children [49]. Patients may experience some alleviation of pain and discomfort from opiates and benzodiazepines. Widow spider envenomations may require intravenous immunotherapy (ie, antivenom) for effective treatment. Antivenom is administered as an intravenous injection of equine-derived IgG antibodies to widow spider venom. One to two vials are generally sufficient to corral the nanomolar concentrations of circulating widow spider venom; however, additional dosing may be necessary in patients who do not demonstrate adequate recovery. Patients recover relatively quickly, sometimes as soon as 15 minutes after administration [50]. Antivenom should be considered in any patient who does not respond to supportive treatment. Potential for severe allergic reactions (ie, anaphylaxis) to antivenom should not preclude the use of antivenom in severe cases. Clark et al described a retrospective case series of 163 cases of black widow spider envenomations, 58 of whom were treated successfully with antivenom. Severe bronchospasm and death occurred in one patient [51]. As with any equine-derived globulin, a skin test must be performed before administration. Patients with either documented horse dander allergy or positive skin testing results have received black widow spider antivenom without complications. Conversely, patients without history of horse dander allergy and with negative skin testing results have experienced anaphylaxis from the globulin components of the antivenom [50]. Clinicians must weigh the risks and benefits of antivenom administration in patients with horse allergy and must monitor all patients undergoing antivenom therapy for allergic reactions. Consultation with a poison control expert may be warranted. Standard treatment is recommended for anaphylaxis.

Practical Considerations

Although immunologic considerations regarding insect envenomations are well documented, current practices suggest that many patients with potential immune-mediated hypersensitivity from insect exposures do not receive appropriate follow-up: only approximately 50% of patients with severe reactions receive a prescription for a rapid epinephrine autoinjector, fewer than 12% of patients received educational information regarding insect avoidance, and slightly more than one third of patients were referred to an allergy specialist [52]. Increased awareness of the nature and risk of immune-mediated manifestations of Hymenoptera envenomations and specialist referrals for appropriate patients may increase patient safety and prevent recurrent reactions. Awareness of the narrow prevalence of brown recluse spider exposures and the extensive differential diagnosis of necrotic skin lesions may save many patients from misdirected therapies [37]. Clinical familiarity with and suspicion of black widow envenomations may encourage early consideration of immunotherapy with black widow spider antivenom, and prevent severe outcomes, especially in young children in whom clinical history of black widow exposure may be difficult to determine [53].

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