CHAPTER 115

Arthropods

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A 24-year-old man presented to the emergency department (ED) with a chief complaint of a "bite" on his right hand that occurred several hours earlier. He was unpacking a crate of vegetables in his grocery store when he initially felt the bite on his hand and noted several small brown spiders in the bottom of the empty crates. Within 2 hours, the bite became painful and blistered. His vital signs were: blood pressure, 130/80 mm Hg; pulse, 74 beats/min; respiratory rate, 12 breaths/min; temperature, 100°F (37.2°C). The only remarkable finding was a painful blister surrounded by erythema on the dorsal aspect of his right thumb. The lesion was cleansed with soap and water. Two hours later, the wound became slightly ulcerated and painful. Based on the history and physical findings, the presumptive diagnosis was a cutaneous reaction to a brown recluse spider bite. The patient was shown a picture of the suspected spider, and he identified the brown recluse as his presumed attacker. Dapsone and erythromycin were administered, and the patient was discharged for followup with a dermatologist. He was told to return if systemic symptoms developed.

The majority of arthropods are benign and environmentally beneficial. Some clinicians regard bites and stings as inconsequential and more of a nuisance than a threat to life. However, some spiders and ticks produce toxic venoms that can produce dangerous painful lesions or significant systemic effects. Important clinical syndromes are produced by bites or stings from the phylum Arthropoda, specifically the classes Arachnida (spiders, scorpions, and ticks) and Insecta (bees, wasps, hornets, and ants) (Table 115–1). Infectious diseases transmitted by arthropods, such as the various encephalitides, Rocky Mountain spotted fever, human ehrlichiosis, babesiosis, and Lyme disease, are not discussed in this chapter.

Arthropoda is the largest phylum in the animal kingdom. At least 1.5 million species are identified, and half a million are yet to be classified. It includes more species than all other phyla combined (Figure 115–1).[2] Arthropoda means "joint-footed" in Latin and describes their jointed bodies and legs connected to a chitinous exoskelelton.[2] Araneism or arachnidism results from the envenomation caused by a spider bite. "Bites" are different from "stings." Bites are defined as purposeful biting from the oral pole by species for either catching prey or blood feeding, and not inadvertent biting by plant-feeding species.[76,170] "Stings" occur from a modified ovipositor at the aboral pole that is no longer able to function in egg laying. Stinging behavior typically is used for defense. Most spiders are venomous, and the venom enables them to secure, neutralize, and digest their prey. They are not aggressive toward humans unless they are provoked. The chelicerae (jaws) of many species are too short to penetrate human skin.

Spiders can be divided into categories based upon whether they pursue their prey as hunters or trappers. Trappers snare their prey by spinning webs, feed, and enshrine excess victims in a cocoon for a later feast. Although capable of producing silk, hunters do not spin such intricate webs; rather, they forage or lie in wait for their insect prey.

The order of spiders (Araneae) differs from other members of the class because of various anatomic differences best assessed by an entomologist. Simplistically, the arachnids have 4 pairs of joined legs whereas insects have 3 pairs. The arachnid's body is divided into cephalothorax, pedicle, unsegmented abdomen, and 3 or 4 pairs of spinnerets from which silk is spun. Two pedipalps are attached anteriorly on the cephalothorax on either side of their chelicerae and are used for sensation. Spiders have 8 eyes but are quite myopic. Prey is localized by touch as they land in the spider's web. Most spiders are venomous (except for the family Uloboridae) and use their venom to kill or immobilize their prey. The remaining species of medical importance in the United States include the widow spiders (*Latrodectus* spp), the violin spiders (*Loxosceles* spp), and the hobo spider (*Tegenaria agrestis*). In Australia, the funnel web spider (*Atrax robustus*) can cause serious illness and death. In South America, the Brazilian Huntsmen (*Phoneutria fera*) and Arantia Armedeira (*Phoneutria nigriventer*) are threats to humans.

Most information on the clinical presentation of spider bites continues to be unreliable, based on case reports and case series. Frequently the cases do not have any expert confirmation of the actual spider involved, which can lead to propagation of misinformation about different spiders, particularly with necrotic arachnidism. For example, the white tail spider (*Lampona* spp) was suspected for more than 20 years to cause necrotic lesions. Only recently has a prospective study of confirmed spider bites refuted this myth by reporting more than 700 confirmed spider bites in Australia.[103,104] Because most arthropod-focused research involves characterizing the structure of spider toxins rather than verifying clinical presentations, it is important to focus on clinical studies that have definite bites confirmed by the actual presence of the spider and are defined by an expert to avoid spreading these myths. Definite spider bites or stings are defined as the following:[100] (1) evidence of a bite or sting soon after the incident or the creature

TABLE 115–1. Insects and Other Arthropods that Bite, Sting, or Nettle Humans

Arthropod	Description
Honeybee (*Apis mellifera*)	Hairy, yellowish brown with black markings
Bumblebee and carpenter bee (*Bombus* spp and *Xylocopa* spp)	Hair, but larger than honeybees and colored black and yellow
Vespids (yellow jackets, hornets, paper wasps)	Short-waisted, robust black and yellow or white combination
Schecoids (thread-waisted wasps)	Threadlike waist
Nettling caterpillars (browntail, Io, hag, and buck moths, saddleback and puss caterpillars)	Caterpillar shaped
Southern fire ant (*Solenopsis* spp)	Ant-shaped
Spiders (*Arachnida*) black widow, brown recluse	Body with 2 regions, cephalothorax, and abdomen; 8 legs
Scorpions (*Centruroides*)	Eight-legged, crablike, stinger at the tip of the abdomen; pedipalps (pincers) highly developed (not a true insect)
Centipedes (*Chilopoda*)	Elongated, wormlike, with many jointed segments and legs; 1 pair of poison fangs behind head

can be seen to bite or sting, (2) collection of the particular creature, either alive or dead, and (3) identification of the creature by an expert biologist/taxonomist in the field relating to the creature. Prospective studies using rigorous standards such as confirmed bites and stings, collection of the creature, complete data collection, recruitment of sufficient cases, and followup can only enhance the promotion of accurate information and expose the myths of necrotic arachnidism.

HISTORY AND EPIDEMIOLOGY

Since the time of Aristotle, spiders and their webs were used for medicinal purposes. Special preparations were concocted to cure a fantastic array of ailments, including earache, running of the eyes, "wounds in the joints," warts, gout, asthma, "spasmodic complaints of females," chronic hysteria, cough, rheumatic afflictions for the head, and stopping blood flow.[201]

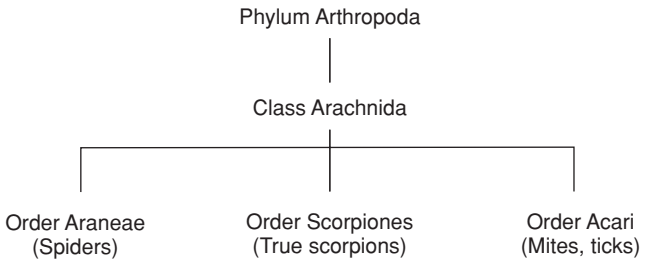

Figure 115–1. Taxonomy of the phylum Arthropoda.

The *Latrodectus* species has an infamous history of medical concern, hence the name *mactans,* which means "murderer" in Latin.[160] Hysteria regarding spider bites peaked during the 17th century in the Taranto region of Italy. The syndrome tarantism, which is characterized by lethargy, stupor, and a restless compulsion to walk or dance, was blamed on *Lycosa tarantula,* a spider that pounces on its prey like a wolf. Deaths were associated with these outbreaks. Dancing the rapid tarantella to music was the presumed remedy. The real culprit in this epidemic was *Latrodectus tredecimguttatus.*[160] Other epidemics of arachnidism occurred in Spain in 1833 and 1841.[133] In North America, there was a rise of spider exposures during the late 1920s, Rome reported large numbers in 1953, and Yugoslavia reported a large number of cases between 1948 and 1953.[28,133] These epidemics may be related to actual reporting biases as well as climactic variations.[160] Spider bites are more numerous in warmer months, presumably because both spiders and humans are more active during that season.

Approximately 200 species of spiders are associated with envenomations.[169,171] Eighteen genera of North America spiders produce poisonings that require clinical intervention (Table 115–2). In one series of 600 suspected spider bites, 80% were determined to result from arthropods other than spiders, such as ticks, bugs, mites, fleas, *Lepidoptera* insects, flies, beetles, water bugs, and *Hymenoptera*. Ten percent of the presumed bites actually were manifestations of other nonarthropod disorders.[169,171]

From 1995–2003, an annual average of 22,000 spider exposures and 50,000 insect exposures were reported to US poison centers. No more than 4 fatalities were reported per year. In 2003, deaths resulted from *Hymenoptera, Solenopsis,* and *Loxosceles* exposures and a tick exposure[214] (Chap. 130). Arachnophobia by the public and by physicians is a perceived danger that far exceeds the actual risk. Often the misdiagnosis of spider bites results from the wide presentation of dermatologic conditions. For example, cutaneous anthrax can be mistaken for a cutaneous necrotic spider bite. In most cases, mortality is rare if supportive care is available and the healthcare provider addresses

TABLE 115–2. North American Spiders of Medical Importance

Genus	Common Name
Araneus spp	Orb weaver
Argiope aurantia	Orange argiope
Bothriocyrtum spp	Trap door spider
Chiracanthium spp	Running spider
Drassodes spp	Gnaphosid spider
Heteropoda spp	Huntsman spider
Latrodectus spp	Widow spider
Liocranoides spp	Running spider
Loxosceles spp	Brown, violin, or recluse spider
Lycosa spp	Wolf spider
Misumenoides spp	Crab spider
Neoscona spp	Orb weaver
Peucetia viridans	Green lynx spider
Phiddipus spp	Jumping spider
Rheostica (*Aphonopelma*) spp	Tarantula
Steatoda grossa	False black widow spider
Tegenaria agrestis	Hobo spider
Ummidia spp	Trap door spider

the severe pain and associated catecholamine release that may affect the very young, the elderly, and those with underlying cardiopulmonary disease.

BLACK WIDOW SPIDER (*LATRODECTUS MACTANS;* HOURGLASS SPIDER)

Five species of widow spiders are found in the United States: *Latrodectus mactans* (black widow) (see ILLATRODECTUSMACTANS in the Image Library at goldfrankstoxicology.com), *Latrodectus hesperus* (Western black widow), *Latrodectus variolus* (found in New England, Canada, south to Florida and west to eastern Texas, Oklahoma, and Kansas), *Latrodectus bishopi* (brown widow of the South), and *Latrodectus geometricus* (brown widow or brown button spider) (see ILLACTRODECTUSGEOMETRICUS in the Image Library). Dangerous widow spiders in other parts of the world include *L. geometricus* and *L. mactans tredecimquttatus* (European widow spider found in southern Europe), *L. mactans hasselti* (red-back widow spider found in Australia, Japan, and India) (see ILLATRODECTUSHASSELTI in the Image Library), and *L. mactans cinctus* (found in South Africa). These spiders live in temperate and tropical latitudes in stone walls, crevices, wood piles, outhouses, barns, stables, and rubbish piles. They molt multiple times and as a result can change colors. The ventral markings on the abdomen are species specific, and the classic red hourglass-shaped marking is noted in only *L. mactans.* Other species may have variations on their ventral surface, such as triangles and spots. The female *L. mactans* typically is shiny, jet-black, and large (8–10 mm), with a rounded abdomen and a red hourglass mark on its ventral surface. Her larger size and ability to penetrate human skin with her fangs make her more venomous and toxic than the male spider, who is smaller, lighter in color, and has a more elongated abdomen and fangs that usually are too short to envenomate humans (Table 115–3). Black widow females are trappers and inhabit large untidy irregularly shaped webs. Webs are placed in or close to the ground and in secluded, dimly lit areas that can trap flying insects, such as outdoor privies, barns, sheds, and garages.[2]

Pathophysiology

The venom is more potent on a volume-per-volume basis than the venom of a pit viper and contains 6 active components with molecular weights of 5000–130,000 daltons.[2] The 6 components are α-latrotoxin (α-LTX), 5 latroinsectotoxins (α-, β-, γ-, δ-, ε-LITs) affecting insects, and latrocrustatoxin (α-LCT) active only for crustaceans.[84] α-Latrotoxin binds, with nanomolar affinity, to the specific presynaptic receptors neurexin I-α and Ca^{2+}-independent receptor for α-latrotoxin (CIRL), otherwise known as *latrophilin.*[25,90,99] The binding triggers a cascade of events: conformational change allowing pore formation by tethering the toxin to the plasma membrane, Ca^{2+} ionophore formation, and translocation of the N-terminal domain of α-LTX into the presynaptic intracellular space, and intracellular activation of exocytosis from dense and clear vesicles containing norepinephrine, dopamine, neuropeptides, and acetylcholine, glutamate, and γ-aminobutyric acid (GABA) respectively.[2,147,151] Neurexin I-α receptors, otherwise known as type I or calcium-dependent receptors, are from a family of neuron-specific cell membrane proteins with one transmembrane domain neuron-specific cell-adhesion molecule.[129,151] Neurexin I-α is not required for the excitotoxic action of α-LTX. Neurexin I-α–deficient mice were created and still were susceptible to α-LTX via stimulation of the CIRL receptor, or the type II receptor.[73] CIRL is a neuronal receptor that belongs to the family of 7-transmembrane domain G-protein–coupled receptors. Type II receptors bind to α-LTX independently of Ca^{2+} in the extracellular media. CIRL is thought to be coupled to phospholipase C, resulting in subsequent phosphoinositide metabolism that couples the function to secretion.[25,118] CIRL-1 and CIRL-3 are high-affinity neuronal receptors. CIRL-2 has 14 times less affinity to α-LTX than CIRL-1 but is expressed ubiquitously, specifically by placenta, kidney, spleen, ovary, heart, lung, and brain.[99] The nervous system is the primary target for α-LTX, but cells from other tissues also are susceptible to the α-LTX because of the presence of CIRL-2.[99]

Clinical Manifestations

Widow spiders are shy and nocturnal. They usually bite when their web is disturbed or upon inadvertent exposure in shoes and clothing, although one patient developed latrodectism following the intentional intravenous injection of a crushed whole black widow spider.[34] A sharp pain typically described as a pinprick occurs as the victim is bitten. A pair of red spots may evolve at the site, although the bite is commonly unnoticed.[39,132] The venom is primarily a neurotoxin and does not usually cause a significant local reaction. The bite mark itself tends to be limited to a small puncture wound or wheal and flare reaction that often is associated with a halo (Table 115–3). However, the bite from *L. mactans* may produce *latrodectism,* a constellation of signs and symptoms resulting from systemic toxicity. Some cases do not progress; others may show severe neuromuscular symptoms within 30–60 minutes. The effects from the bite spread contiguously. For example, if a person is bitten on the hand, the pain progresses up the arm to the elbow, shoulder, and then toward the trunk during systemic poisoning. Typically, a brief time to symptom onset denotes severe envenomation. Several signs and symptoms are described with the bite of the female black widow spider. Adult male black widow spiders are half the size of the female and are considered harmless.

Hypertoxic myopathic syndrome of latrodectism involves muscle cramps that typically present 15 minutes to 1 hour after the bite. The muscle cramps initially occur at the site of the bite but later may involve rigidity of other skeletal muscles, particularly muscles of the chest, abdomen, and face. The pain increases over time and occurs in waves that may cause the patient to writhe. Large muscle groups are affected first. Classically, severe abdominal wall spasm occurs and may be confused with a surgical abdomen, especially in children who cannot relate the history with the initial bite.[34] Muscle pain often subsides within a few hours but may recur for several days. Transient muscle weakness and spasms may persist for weeks to months.

Additional clinical findings include "*facies latrodectismica,*" which consists of sweating, contorted, grimaced face associated with blepharitis, conjunctivitis, rhinitis, cheilitis, and trismus of the masseters.[133] A fear of death, *pavor mortis,* is described.[133] The following symptoms also are reported: nausea, vomiting, sweating, tachycardia, hypertension, muscle cramping, restlessness, and rarely priapism and compartment syndrome at the site of the bite.[2,47,95,189] Extreme restlessness occurs. Recovery usually ensues

TABLE 115–3. Brown Recluse and Black Widow Spiders: Comparative Characteristics

	Brown Recluse (*Loxosceles*)	Black Widow (*Latrodectus*)
Description	Female brown, 6–20 mm, violin-shaped mark on dorsum of cephalothorax; female greater toxicity than male	Female jet black, 8–10 mm, red hourglass mark on ventral surface, female greater toxicity than male
Major venom component	Sphingomyelinase D	α-Latrotoxin
Pathophysiology of envenomation	Vascular injury, dermonecrosis, hemolysis	Lymphatic, hematogenous spread neurotoxicity
Epidemiology	Bites more common in warmer months North America (southern and western states): *L. reclusa* South America: *L. laeta, L. gaucho* Europe: *L. rufescens* Africa (southern): *L. parrami, L. spiniceps, L. pilosa, L. bergeri* Asia/Australia: Rare	Bites more common in warmer months in subtropical and temperate areas; perennial in topics North America: *L. mactans, L. Hesperus, L. geometricus* Europe: *L. tredecimguttatus* Africa (southern): *L. indistinctus* Australia: *L. hasselti* Asia/South America: Rare
Clinical effects	Cutaneous Initial (0–2 h after bite): painless, erythema, edema 2–8 h: Hemorrhagic, ulcerates, painful 1 week: Eschar Months: Healing	Cutaneous Initial (5 min–1 h after bite): local pain 1–2 h: Puncture marks hours: Regional lymph nodes swollen, central blanching at bite site with surrounding erythema CVS: Initial tachycardia followed by bradycardia, dysrhythmias, initial hypotension followed by hypertension GI: Nausea, vomiting, mimic acute abdomen
	Hematologic Methemoglobinemia, hemolysis, thrombocytopenia, DIC	Hematologic: Leukocytosis Metabolic Hyperglycemia (transient) Musculoskeletal: Hypertonia, abdominal rigidity, "facies latrodectismica" Neurologic CNS: Psychosis, hallucinations, visual disturbance, seizures PNS: Pain at the site ANS: Increase in all secretions; sweating, salivation, lacrimation, diarrhea, bronchorrhea, mydriasis, miosis, priapism, ejaculation
	Renal: Renal failure, secondary to hemolysis	Renal: Glomerulonephritis, oliguria, anuria Respiratory: Bronchoconstriction, acute lung injury
Treatment	Analgesia Wound care Dapsone (?) Hyperbaric oxygen (?) Antivenom (?) not available universally Corticosteroids	Analgesia Muscle relaxants Antivenom

within 24–48 hours, but symptoms may last several days with more severe envenomations.

Life-threatening complications include severe hypertension, respiratory distress, cardiovascular failure, and gangrene.[34,46,47,142,155,159] In the past 20 years, more than 40,000 presumed black widow spider bites have been reported to American Association of Poison Control Centers since its first publication in 1983. Death is rarely reported. There have been 2 fatalities in Madagascar from envenomation of the *Latrodectus geometricus,* one from cardiovascular failure and the other from gangrene of the foot.[159] The most recent fatality reported from Greece resulted from toxic myocarditis secondary to envenomation of *L. mactans tredecimguttatus,*[155] confirmed by a local veterinarian. The patient developed severe dyspnea, hypoxemia, cyanosis, cardiomyopathy, and global hypokinesis of the left ventricle confirmed by echocardiography followed by death 36 hours later; antivenom was not available; on autopsy, diffuse interstitial and alveolar edema, with mononuclear infiltrate of the myocardium and degenerative changes, were noted and on toxicologic analysis for xenobiotics, as well as all blood, urine, bronchial, and serologic viral cultures, were negative. The paucity of mortalities is presumed to result from the improvement in medical care, the availability of antivenom, or the limited toxicity of the spider.

Diagnostic Testing

Laboratory data generally are not helpful in management or predicting outcome. According to one study, the most common findings include leukocytosis and increased creatine phosphokinase and lactate dehydrogenase concentrations.[46] Currently no specific laboratory assay is capable of confirming latrodectism.

Management

Treatment involves establishing an airway and supporting respiration and circulation, if indicated. Wound evaluation and local wound care, including tetanus prophylaxis, are essential.[213] The routine use of antibiotics is not recommended.

Pain management is a substantial component of patient care and depends on the degree of symptomatology. One grading system divides the severity of the envenomation into 3 categories.[46] Grade 1 envenomations range from no symptoms to local pain at the envenomation site with normal vital signs. Grade 2 envenomations involve muscular pain at the site with migration of the pain to the trunk, diaphoresis at the bite site, and normal vital signs. Grade 3 envenomations include the grade 2 symptoms with abnormal vital signs, diaphoresis distant from the bite site, generalized myalgias to back, chest, and abdomen, nausea, vomiting, and headache. Using this grading system, grade 1 envenomations may require only cold packs and orally administered nonsteroidal anti-inflammatory agents. Grade 2 and 3 envenomations probably require intravenous opioids and benzodiazepines to control pain and muscle spasm. Traditionally, 10 mL 10% calcium gluconate solution was given intravenously (IV) to decrease cramping. It was infused over 10 minutes and repeated at 30 minutes. A retrospective chart review of 163 patients envenomated by the black widow concluded that calcium gluconate was ineffective for pain relief compared with a combination of IV opioids (morphine sulfate or meperidine) and benzodiazepines (diazepam or lorazepam).[46,114] Another study found greater neurotransmitter release when extracellular calcium concentrations were increased, suggesting that administration of calcium is irrational in patients suffering from latrodectism.[167] The mechanism of action of calcium remains unknown and its efficacy anecdotal; therefore we do not recommend calcium administration for pain management. Although often recommended, methocarbamol (a centrally acting muscle relaxant) and dantrolene also are ineffective for treatment of latrodectism.[114,172] A benzodiazepine, such as diazepam, is more effective for controlling muscle spasms and achieves sedation, anxiolysis, and amnesia. Management should primarily emphasize supportive care, with opioids and benzodiazepines for controlling pain and muscle spasms, because the use of antivenom risks anaphylaxis and serum sickness.

Latrodectus antivenom is rapidly effective and curative. In the United States, the antivenom formulation is effective for all species but is available as a crude hyperimmune horse serum that may cause anaphylaxis and serum sickness. The morbidity of latrodectism is high, with pain, cramping, and autonomic disturbances, but mortality is low. Hence controversy exists over when to administer the black widow antivenom. The antivenom can be administered for severe reactions (eg, hypertensive crisis or intractable pain), to high-risk patients (eg, pregnant women suffering from a threatened abortion), or for treatment of priapism.[95,160] Use of antivenom probably should not be considered for patients unless systemic symptoms otherwise designated as grade 3 are present because of the risk for anaphylaxis or anaphylactoid reactions.[46] The usual dose is 1–2 vials diluted in 50–100 mL 5% dextrose or 0.9% sodium chloride solution, with the combination infused over 1 hour (Antidotes in Depth: Scorpion and Spider Antivenoms). Skin testing may identify a highly allergic individual but does not eliminate the occurrence of hypersensitivity reactions; therefore we do not recommend skin testing. Pretreatment with histamine H_1- or H_2 -blockers and epinephrine may be beneficial in preventing histamine release and/or anaphylaxis, but their efficacy is unproven. Patients with allergies to horse serum products and those who have received antivenom or horse serum products are at risk for immunoglobulin IgE-mediated hypersensitivity reactions. Prevention consists of destroying the spider and taking precautions in areas inhabited by the spiders. When working in high-risk areas, gloves, heavy garments buttoned at the wrists and collars, and shoes should be worn.

In Australia, a purified equine-derived IgG-$F(ab)_2$ fragment antivenom for the red-back spider *Latrodectus hasselti* (RBS-AV) is available. A study showed that RBS-AV prevents latrodectism in mice envenomated with other widow spider venoms from the United States and Europe.[83] Inadvertent use of RBS-AV successfully treated envenomations from the comb-footed spider (*Steatoda* spp).[101] Hence RBS-AV may have a future role in treating black widow spider envenomations in the United States. The RBS-AV (CSL, Melbourne, Australia) is administered intramuscularly and given as first-line therapy to patients presenting with systemic signs or symptoms in Australia. Since its introduction in 1956, there have been no deaths, and the incidence of mild allergic reactions to RBS-AV is reported as 0.54% in 2144 uses.[198] However, a prospective cohort study of confirmed red-back spider bites failed to show that intramuscular antivenom was better than no treatment when all patients were followed up over one week.[102] This study lacked the power to definitely demonstrate no difference between intramuscular treatment and no treatment, but the study found that only 17% of patients were pain-free at 24 hours with treatment. Therefore, intramuscular antivenom appears to be less effective than previously thought, and the route of administration requires review.

BROWN RECLUSE SPIDER (*LOXOSCELES RECLUSA*; VIOLIN OR FIDDLEBACK SPIDER)

Loxosceles reclusa was confirmed to cause necrotic arachnidism in 1957, although reports of systemic symptoms following brown spider bites have appeared since 1872.[6] This spider has a brown violin-shaped mark on the dorsum of the cephalothorax, 3 pairs of eyes arranged in a semicircle on top of the head, and legs that are 5 times as long as the body. It is small (6–20 mm long), gray to orange or reddish brown (see ILLOXSCELESRECLUSA in the Image Library). *Loxosceles* spiders weave irregular white, flocculent adhesive webs that line their retreats.[71] Spiders in the genus *Loxosceles* have a worldwide distribution. In the United States, other species of this genus, which include *L. rufescens, L. deserta, L devia,* and *L. arizonica,* are prominent in the Southeast and Southwest.[4] They are hunter spiders that live in dark areas (wood piles, rocks, basements), and their foraging is nocturnal. They are not aggressive but will bite if antagonized (Table 115–3). These spiders live up to 2 years. They are resilient and can survive up to 6 months without water or food and tolerate temperatures from 46.4°F–109.4 °F (8°C–43°C).[76] Like the black widow spider, the female is more dangerous than the male and bites only when provoked. *Loxosceles* venom has variable toxicity, depending on the species, with *L. intermedia* venom causing more severe clinical effects in humans.[11]

Pathophysiology

The venom is cytotoxic. Purification techniques have identified 8 subcomponents, including various enzymes, such as hyaluronidase, deoxyribonuclease, ribonuclease, alkaline phosphatase, lipase, and sphingomyelinase-D.[122] The two main constituents of the venom are sphingomyelinase-D and hyaluronidase. Hyaluronidase is a spreading factor that facilitates the ability of the venom to penetrate tissue but does not induce lesion development.[122] Sphingomyelinase-D, with a molecular weight of 32,000 daltons, is the primary constituent of the venom that causes necrosis and hemolysis. Sphingomyelinase-D causes human platelets to release serotonin and red blood cells to release hemoglobin.[122] Sphingomyelinase also reacts with sphingomyelin in the red blood cell membrane to release choline and *N*-acylsphingosine phosphate, which triggers a chain reaction releasing inflammatory mediators, such as thromboxanes, leukotrienes, prostaglandins, and neutrophils, leading to vessel thrombosis, tissue ischemia, and skin loss.[122] The rest of the constituents in the venom contain alkaline phosphatase, proteases, collagenase, esterase, ribonuclease, and deoxyribonuclease.[54,207]

An early study in experimental animals describes the pathogenesis of the skin lesion requiring polymorphonuclear leukocytes and complement infiltration of blood vessels at the bite site with resultant blood vessel injury as the pathologic basis for skin loss.[181] They demonstrated early perivascular collections of polymorphonuclear leukocytes with hemorrhage and edema progressing to intravascular clotting. Coagulation and vascular occlusion of the microcirculation occur, ultimately leading to necrosis.

Clinical Manifestations

The peak time for envenomation is from spring to autumn. Most victims are bitten in the morning. The clinical spectrum of loxoscelism can be divided into 3 major categories. The first category includes bites in which very little, if any venom, injected. A small erythematous papule may be present that becomes firm before healing and is associated with a localized urticarial response. In the second category, the bite undergoes a cytotoxic reaction. The bite initially may be painless or have a stinging sensation but then blisters and bleeds, and ulcerates 2–8 hours later (Table 115–3). The lesion may increase in diameter, with demarcation of central hemorrhagic vesiculation, then ulcerate, and develop violaceous necrosis, surrounded by ischemic blanching of skin and outer erythema and induration over 1–3 days: This is also known as the "red, white, and blue" reaction (see ILLOXOSCELESEVENOMATION in the Image Library).[115,217] Necrosis of the central blister occurs in 3–4 days, with eschar formation between 5 and 7 days. After 7–14 days, the wound becomes indurated and the eschar falls off, leaving an ulceration that heals by secondary intention. Local necrosis is more extensive over fatty areas (thighs, buttocks, and abdomen).[121] The size of the ulcer determines the time for healing. Large lesions up to 30 cm may require 4 months or more to heal.

The third category consists of systemic loxoscelism, which is not predicted by the extent of cutaneous reaction, and occurs 24–72 hours after the bite. The young are particularly susceptible.[94,173] The clinical manifestations of loxoscelism include fever, chills, weakness, edema, nausea, vomiting, arthralgias, petechial eruptions, rhabdomyolysis, disseminated intravascular coagulation, hemolysis that can lead to hemoglobinemia, hemoglobinuria, renal failure, and death.[22,36,68,131,177,216] Another extremely unusual presentation of loxoscelism is upper airway obstruction. This life-threatening complication was reported in a child who was bitten on his neck and subsequently developed progressive cervical soft tissue edema with airway obstruction and dermonecrosis 40 hours later.[80] There has been one other report of stridor and respiratory distress following a brown recluse envenomation of the ear. Although the presentation is rare, respiratory compromise should be considered when an envenomation occurs near the airway.[75] In North American, the incidence of systemic illness is rare and mortality is low.[5]

Diagnostic Testing

Bites from other spiders, such as *Chiracanthium* (sac spider), *Phidippus* (jumping spider), *Argiope* (orb weaver), and *Tegenaria* (northwester brown spider), can become necrotic wounds. These spiders are often the actual culprits when the brown recluse is mistakenly blamed. Definitive diagnosis is achieved only when the biting spider is positively identified. No routine laboratory test for loxoscelism is available for clinical application, but several techniques are presently used for research purposes. The lymphocyte transformation test measures lymphocytes that have undergone blast transformation up to 1 month after exposure to *Loxosceles* venom. The lymphocytes incorporate thymidine into the nucleoprotein, providing a quantitative response.[3] A passive hemagglutination inhibition test (PHAI) has been developed in guinea pigs. The PHAI assay is based on the property of certain brown recluse spider venom components to spontaneously adsorb to formalin-treated erythrocyte membranes and the ability of the BRS venom to inhibit antiserum-induced agglutination of venom-coated red blood cells.[13] The test is 90% sensitive and 100% specific for 3 days postenvenomation and may prove useful for early diagnosis of brown recluse spider envenomation.[13] An enzyme-linked immunoassay (ELISA) specific for *Loxosceles* venom in biopsied tissue can confirm the presence of venom for 4 days postenvenomation.[13] The drawbacks of using a skin biopsy are the invasive nature of the procedure, which can result in further scarring with an increased potential for infection, and the lack of proof that skin biopsy can diagnose early envenomations prior to the development of dermatonecrosis. Another ELISA for detection of venom antigens has been developed that correctly discriminates the mice inoculated with antigens *Loxosceles intermidia* venom. The ELISA immunoassay, and antivenom may become useful early diagnostic tools if envenomation can be proved early, especially prior to the development of the purplish discoloration and blister formation that usually progresses to cutaneous gangrene.[44] A venom-specific enzyme immunoassay that uses hair, skin biopsies, or aspirated tissue near a suspected lesion to detect the presence of venom up to 7 days after injury is under investigation.[120,137] In Brazil, ELISA is used to detect the venom of *L. reclusa* in wounds and patient sera, but the technique is not in widespread clinical use.[40]

Laboratory data may be remarkable for hemolysis, hemoglobinuria, and hematuria. Coagulopathy may be present, with laboratory data significant for elevated fibrin split products, decreased fibrinogen levels, and a positive D-dimer assay. Other tests may show increased prothrombin time (PT) and partial thromboplastin time (PTT), leukocytosis (up to 20,000–30,000 cells/mm^3),

spherocytosis, Coombs-positive hemolytic anemia, thrombocytopenia, or abnormal renal and liver function tests.[2,7,71,169–171,213]

Treatment

Optimal local treatment of the lesion is controversial. The most prudent management of the dermatonecrotic lesion is wound care, immobilization, tetanus prophylaxis, analgesics, and antipruritics as warranted (Table 115–4).[2,71,208,213] Early excision or intralesional injection of corticosteroids appears unwarranted.[164] Corrective surgery can be performed several weeks after adequate tissue demarcation has occurred. One case series used curettage of the lesion to remove necrotic and indurated tissue from the lesion, thus eliminating any continuing action of the lytic enzymes on the surrounding tissue with positive results.[93] These patients had wound healing without further necrosis and minimal scarring. Electric shock delivered via stun guns was not found to be useful in a guinea pig envenomation model.[13] Cyproheptadine, a serotonin antagonist, was not beneficial in a rabbit model.[153] A randomized control study evaluating the efficacy of topical nitroglycerin for envenomated rabbits showed no difference in preventing skin necrosis and suggested the possibility of increased systemic toxicity.[127] Antibiotics should be used to treat cutaneous or systemic infection, but should not be used prophylactically.

Early use of dapsone in patients who develop a central purplish bleb or vesicle within the first 6–8 hours may inhibit local infiltration of the wound by polymorphonuclear leukocytes.[115] The dosage recommended is 100 mg twice daily for 2 weeks.[164] However, prospective trials with large numbers of patients are lacking. One study compared erythromycin and dapsone therapy, erythromycin and antivenom therapy, and erythromycin, dapsone, and antivenom therapy.[163] Although the treatment groups were very small, all groups showed wound healing at approximately 20 days. Use of dapsone in the management of a local lesion should be considered experimental until its use is validated by controlled randomized clinical trials. Hepatitis,[166] methemoglobinemia, and hemolysis (Chap. 122) are associated with dapsone use. If dapsone therapy is used, a baseline glucose-6-phosphate dehydrogenase and weekly complete blood counts should be performed.

TABLE 115–4. Management of Brown Recluse Spider Bite

General Wound Care
Clean
Tetanus prophylaxis as indicated
Immobilize and elevate bitten extremity
Apply cool compresses; avoid local heat
Local Wound Care
Serial observations
Natural healing by granulation
Delayed primary closure
Delayed secondary closure with skin graft
Gauze packing, if applicable
Systemic
Antipruritic/antianxiety and/or analgesic agents
Antibiotics for secondary bacterial infection
(?) Polymorphonuclear white blood cell inhibitors: dapsone, colchicine
Antivenom (experimental)
(?) Hyperbaric oxygen

An animal study evaluated the effects on the size of skin lesions induced by *Loxosceles* envenomation by treatment with hyperbaric oxygen therapy, dapsone, and combined hyperbaric oxygen therapy and dapsone.[91] However, the study design was limited and could find only a 100% difference in treatment groups. The study concluded that there was no clinically significant change in necrosis or induration by these treatment modalities. Further evaluation of these interventions remains appropriate. Another study using hyperbaric oxygen for treatment of *Loxosceles*-induced necrotic lesions in rabbits revealed no clinical improvement in the size of the lesion; however, the histology of the lesions improved. Whether this finding is of value in humans has not been determined.[191] Use of 1.2 mg colchicine, a leukocyte inhibitor, followed at 2-hour intervals with 0.6 mg for 2 days, then 0.6 mg every 4 hours for 2 additional days is sometimes recommended, but this treatment has substantial potential toxicity.[169,171]

Rabbit-derived intradermal anti-*Loxosceles* Fab (α-Loxd) fragments attenuated the dermatonecrotic inflammation of rabbits injected with *L. deserta* venom in a time-dependent fashion.[78] At time 0 after envenomation, lesion development was blocked. At 1 and 4 hours after envenomation, the α-Loxd Fab antivenom continued to suppress the lesion areas, although the longer the delay in treatment, the smaller the difference in treatment and control lesion areas. At 8 and 12 hours, there was no difference in lesion size. The typical 24-hour delay in lesion development makes the diagnosis difficult, and the antivenom would be useless if administered so late in the clinical course. Use of antivenom would be facilitated if the spider were caught and positively identified or another test could be used to positively identify *Loxosceles* envenomation. Currently this antivenom is not available for commercial use. Patients manifesting systemic loxoscelism or those with expanding necrotic lesions should be admitted to the hospital. All patients should be monitored for evidence of hemolysis, renal failure, or coagulopathy. If hemoglobinuria ensues, increased IV fluids and urinary alkalinization an be used in an attempt to prevent acute renal failure. Hemolysis, if significant, can be treated with transfusions. Patients with a coagulopathy should be monitored with serial complete blood cell count, platelet count, PT, PTT, fibrin split products, and fibrinogen. Disseminated intravascular coagulopathy may require treatment, based on severity.

HOBO SPIDER (TEGENARIA AGRESTIS, NORTHWESTERN BROWN SPIDER, WALCKENAER SPIDER)

The hobo spider is native to Europe and was introduced to the northwestern United States (Washington, Oregon, Idaho) in the 1920s or 1930s.[209] These spiders build funnel-shaped webs within wood piles, crawl spaces, basements, and moist areas close to the ground. They are brown with gray markings and 7–14 mm long. They are most abundant in the midsummer through the fall. They bite if provoked or threatened, but otherwise are reticent to bite and retreat quickly with disturbance.[18] The medical literature is sparse in reported hobo spider bites that are verified by a specialist. There is only one confirmed Hobo spider bite resulting in a necrotic lesion.[42] The case describes a 42-year-old woman with a history of phlebitis who felt

a burning sensation on her ankle, rolled her pants, and found a crushed brown spider, later confirmed to be *T. agrestis.* She complained of persistent pain, nausea, and dizziness, and a vesicular lesion developed within several hours. The vesicle ruptured and ulcerated the next day. The lesion initially was 2 mm, but over the next 10 weeks enlarged to 30 mm in diameter and was circumscribed with a black lesion, at which time she sought medical advice. She was given a course of antibiotics, which did not limit the progression of this ulcer. Subsequently, the patient was unable to walk, and she was found to have a deep venous thrombosis. The other cases implicating Hobo spiders as a cause for dermatonecrotic injuries are based on proximity of the Hobo spider or other large brown spiders that are unidentified and on a rabbit model bioassay.[209,210] The Hobo spider from Europe is considered benign. When analyzing the venom from the European Hobo spiders and US Hobo spiders using liquid chromatography, little variability was found to account for the necrotic effects, which suggests that the Hobo spider toxicity syndrome needs to be revisited. New evidence suggests that Hobo spiders may have been falsely accused.[23] More investigation using large prospective studies must include verification of the spider by an expert arachnologist or definitive identification of an envenomed patient. *Tegenaria* spp is difficult to identify reliably, unless the arachnid's genitalia is examined microscopically.[211] These standards will allow for a more evidence-based approach rather than encouraging anecdotal information as a substitution for fact.

Pathophysiology

The toxin has been fractionated, with 3 peptides identified as having potent insecticidal activity, and no discernible effects in mammalian in vivo assays.[108] The peptide toxins TaITX-1, TaITX-2, and TaITX-3 exhibit potent insecticidal properties by acting directly in the insect central nervous system, and not at the neuromuscular junction.[108] Insects envenomated with *T. agrestis* venom and the insecticidal toxins purified from the venom developed a slowly evolving spastic paralysis. Currently, little is known about the toxin and its mechanism of action in humans.

Clinical Manifestations

The toxicity of Hobo spider venom is questionable; however, it occasionally causes necrosis secondary to infection. Other causes of dermatonecrotic lesions should be considered. The most common symptom associated with the spider bite is a headache that may persist for 1 week.[42] Other symptoms, including nausea, vomiting, fatigue, memory loss, visual impairment, weakness, and lethargy, are reported.[42,210]

Diagnostic Testing

No specific laboratory assay confirms envenomation with *T. agrestis* spider.

Treatment

Treatment emphasizes local wound care and tetanus prophylaxis, although systemic corticosteroids for hematologic complications may be of value. Surgical graft repair for severe ulcerative lesions may be warranted when there is no additional progression of necrosis.[42,157]

TARANTULAS

Tarantulas, ancestors to the true spider, belong to the family Theraphosidae, a subgroup of Mygalomorphs (Greek word *mygale* for field mouse).[45,175] There are more than 1500 species, with approximately 40 species found in the deserts of western United States. Because of their great size and reputation, tarantulas are often feared. They are the largest and hairiest spiders, popular as pets, and can be found throughout the United States as well as tropical and subtropical areas (see ILAPHONOPELMASMITHI1 in the Image Library). The lifespan of the female can exceed 15–20 years. They have poor eyesight and detect their victims by vibrations. Their defense lies in either their painful bite with erect fangs or by spraying their victim with barbed urticating hairs that are released on provocation.[45]

Tarantulas bite when provoked or roughly handled. Based on the few case reports, their venom has relatively minor effects in humans but can be deadly for canines and other small animals, such as rats, mice, cats, and birds.[33,105] A study from Australia covering a 25-year span reported only nine confirmed bites by theraphosid spiders in humans and seven confirmed bites in canines and two of which the spider then bit the human.[105] Four genera of tarantulas (*Lasiodora, Grammostola, Acanthoscurria,* and *Brachypelma*) possess urticating hairs that are released in self-defense when the tarantulas rub their hind legs against their abdomen rapidly to create a small cloud (see ILAPHONOPELMASMITHI2 in the Image Library).[76] There are 4 different types of hairs. Type 1 hairs are found on tarantulas in the United States and are the only hairs that do not penetrate human skin. Type 2 hairs are incorporated into the silk web retreat but are not thrown off by the spider. Type 3 hairs can penetrate up to 2 mm into human skin. Type 4 hairs belong to the South American *Grammostola* spider and cause severe respiratory inflammation. Tarantula hairs cause intense inflammation that may remain pruritic for weeks.

Pathophysiology

Tarantula venom, specifically the venoms of *Dugesiella henzi* (Arkansas tarantula) and members of the genus *Aphonopelma* (Arizona tarantula), contains hyaluronidase, nucleotides (adenosine triphosphate [ATP], adenosine diphosphate, and adenosine monophosphate), and polyamines (spermine, spermidine, putrescine, and cadaverine) that are used for digesting their prey from the inside out.[35,113,175] The role of spermine is unclear, but hyaluronidase is a spreading factor that allows more rapid entrance of venom toxin by destruction of connective tissue and intercellular matrix. ATP potentiates death in mice exposed to the *D. hentzi* venom and lowers the LD_{50} in comparison to venom without ATP.[43] Both venoms cause skeletal muscle necrosis when injected intraperitoneally into mice.[150] The primary injury results in rupture of the plasma membrane, followed by the inability of mitochondria and sarcoplasmic reticulum to maintain normal levels of calcium in the cytoplasm leading to cell death. *Aphonopelma* venom is similar to scorpion venom in composition and clinical effects. Novel toxins have been discovered in the venom that can act on potassium channels, calcium channels, and the recently discovered

acid-sensing ion channels that may elucidate the molecular mechanism of voltage-dependent channel gating and their respective physiologic roles.[63,64]

Clinical Manifestations

Although relatively infrequent in occurrence, bites may or may not present with puncture or fang marks. They range from being painless to a deep throbbing pain that may last several hours without any inflammatory component.[105] Fever has been associated even in the absence of infection, suggesting a direct pyrexic action of the venom. Rarely, bites create a local histamine response with resultant itching, and hypersensitive individuals could have a more severe reaction and less commonly mild systemic effects such as nausea and vomiting.[76,105] Contact reactions from the hairs are more likely to be the health hazard than is the spider bite. The urticating hairs provoke local histamine reactions in humans and are especially irritating to the eyes, skin, and respiratory tract. Inflammation can occur at all levels from conjunctiva to retina. An allergic rhinitis can develop if the hairs are inhaled.[113] Tarantula hairs resemble sensory setae of caterpillars, both are type 3 that can migrate relentlessly and cause multiple foci of inflammation at all levels of the eye.[97] Ophthalmia nodosa, a granulomatous nodular reaction to vegetable or insect hairs, is reported with casual handling of tarantulas.[17,21] Other eye findings include spines in the corneal stroma, anterior chamber inflammation, migration into the retina, and secondary glaucoma and cataracts.[26]

Treatment

Treatment is largely supportive. Cool compresses and analgesics should be given as needed. All bites should receive local wound care, including tetanus prophylaxis if necessary. If the hairs are barbed, as in some species, they can be removed by using adhesive or cellophane tape followed by compresses or irrigation with 0.9% sodium chloride solution. If the hairs are located in the eye, then surgical removal may be required, followed by medical management of inflammation. Urticarial reactions should be treated with oral antihistamines and topical or systemic corticosteroids.

FUNNEL WEB SPIDERS

Australian funnel web spiders are a group of large mygalomorphs that can cause a severe neurotoxic envenomation syndrome in humans. The fang positions of funnel web spiders are vertical relative to their body, which requires the spider to rear back and lift the body to attack. The length of fangs can reach up to 5 mm. This spider can bite tenaciously and may require extraction from the victim.[139] The *Atrax* and *Hadronyche* species have been found along the eastern seaboard of Australia. *Atrax robustus,* also called the Sydney funnel web spider, is the best known and is located around the center of Sydney, Australia.[139] Funnel web spiders tend to prefer moist, temperate environments.[139] They are primarily ground dwellers and live in burrows, crevices in rocks, around foundations of houses. They build tubular or funnel-shaped webs.[76] At night, the spiders ascend the tubular web and wait for their prey. The Sydney funnel web spider is considered one of the most poisonous spiders. It was responsible for 14 deaths between 1927 and 1980, at which time the antivenom was introduced.[193]

Pathophysiology

Robustotoxin (atracotoxin or atraxin) is a protein with a molecular weight of 4854 daltons. It contains 42 amino acids and is the lethal component of *A. robustus* venom.[139] Robustotoxin produces an autonomic storm, releasing acetylcholine, noradrenaline, and adrenaline. A 5 μg/kg intravenous infusion dose of robustotoxin from male *A. robustus* spiders causes dyspnea, blood pressure fluctuations leading to severe hypotension, lacrimation, salivation, skeletal muscle fasciculation, and death within 3–4 hours when administered to monkeys.[145] Versutoxin, a toxin from the Blue Mountain funnel web spider, is closely related to robustotoxin and has demonstrated voltage-dependent slowing of sodium channel inactivation.[148]

Clinical Manifestations

A biphasic envenomation syndrome associated with *A. robustus* is described in humans and monkeys.[195,196] Phase 1 consists of localized pain at the bite site, perioral tingling, piloerection, and regional fasciculations (most prominent in the face, tongue, and intercostals). Fasciculations may progress to more overt muscle spasm; masseter and laryngeal involvement may threaten the airway.[196] Other features include tachycardia, hypertension, cardiac dysrhythmias, nausea, vomiting, abdominal pain, diaphoresis, lacrimation, salivation, and acute lung injury, which often is the cause of death in phase 1.[215] Phase 2 consists of resolution of the overt cholinergic and adrenergic crisis; secretions dry up, and fasciculations, spasms, and hypertension resolve. The apparent improvement can be followed by the gradual onset of refractory hypotension, apnea, and cardiac arrest.[196]

Treatment

Pressure immobilization using the crepe bandage to limit lymphatic flow and immobilization of the bitten extremity may inactivate the venom and should be applied if symptoms of envenomation are present. Funnel web venom is one of the few animal toxins known to undergo local inactivation.[193,194] The patient should be transferred to the nearest hospital with the bandage in place. Monkey studies and a human case report suggest the utility of pressure immobilization.[81,197] Pressure immobilization should be removed when the patient is located at a facility that can administer antivenom. A purified IgG antivenom protective against *Atrax* envenomations was developed in rabbits by Sutherland.[193] One ampule of the antivenom contains 100 mg purified rabbit IgG or 125 units of neutralizing capacity per ampule.[215] It has been effective for more than 40 humans bitten by the *Atrax* species.[194] The starting dose is 2 ampules if systemic signs of envenomations are present, and 4 ampules if the patient develops pulmonary edema or decreased mental status. Doses are repeated every 15 minutes until clinical improvement is seen.[215] Up to 8 ampules is common in a severe envenomation. Anaphylaxis has not been reported.[194] The manufacturer no longer recommends premedication. Even serum sickness seems to be rare after funnel web antivenom administration. There has been 1 case after the patient received 5 ampules of antivenom for an *A. robustus* envenomation.[138]

SCORPIONS

Scorpions are invertebrate arthropods that have existed for more than 400 million years.[48] Of the 650 known living species, most of the lethal species are in the *Buthidae* family (Table 115–7). The genera of the family *Buthidae* include *Centruroides, Tityus, Leuirus, Androctonus, Buthus,* and *Parabuthus*.[48] Unlike most spiders, scorpions envenomate humans by stinging rather than biting. Their 5-segmented tail contains a bulbous segment called the *telson* that contains the venom apparatus (see ILTITYUSSERRULATUS in the Image Library). More than 100,000 medically significant stings likely occur annually worldwide, predominantly in the tropics and North Africa.[1,20,56,85,106,119] According to American Association of Poison Control Centers data from 1995–2003, approximately 11,000–14,000 scorpion annual exposures occurred in the United States, mostly in the southwestern region, but no deaths have been reported. These members of the class *Arachnida* rarely cause mortality in victims older than 6 years.[165] The poisonous scorpions in the United States are *Centruroides gertschii.* The most important is *Centruroides exilicauda,* previously called *Centruroides sculpturatus Ewing* (bark scorpion; Table 115–5).

Pathophysiology

Components of scorpion venom are complex and species specific. Scorpions from the family Buthidae are the most harmful to humans.[88,158,165] The venom is thermostable and consists of phospholipase, acetylcholinesterase, hyaluronidase, serotonin, and neurotoxins. Components of *C. exilicauda* venoms are primarily neurotoxic. Four neurotoxins designated toxins I–IV have been isolated from *C. exilicauda*. Some of the toxins target excitable membranes, especially at the neuromuscular junction, by opening sodium channels. The results are repetitive depolarization of nerves in both sympathetic and parasympathetic nervous systems causing acetylcholine and catecholamine release, increased neurotransmitter release, catecholamine release from the adrenal gland, catecholamine-induced cardiac hypoxia, and action at the juxtaglomerular apparatus, causing increased renin secretion.[52,165] *Tityus* scorpion sting is related to elevated concentrations of interleukin (IL)-1β, IL-6, IL-8, IL-10, and tumor necrosis factor (TNF)-α, which correlate with the severity of envenomation and hyperamylasemia.[62,70] The kinin system seems to participate in the pathogenesis of human *Tityus* envenomation.[69]

TABLE 115–5. Scorpions of Toxicologic Importance[85,105]

USA: *Centroides exilicauda*
Brazil, South America: *Tityus serrulatus*
Mexico: *Centroides sufusus*
India: *Buthus tamulus*
Spain: *Buthus occitanus*
Saudi Arabia: *Leirus quinquestriatus, Androctonus crassicauda*
Middle East: *Leirus quinquestriatus, Buthus minax, Androctonus* spp
North Africa: *Androctonus Australis, Buthus occitanus, Leirus* spp
South Africa: *Androctonus crassicauda*
Persian Gulf: *Androctonus crassicauda*
Australia: *Lychas marmoreus, Lychas* spp, *Isometrus* spp, *Cercophonius squama, Urodacus* spp

Clinical Manifestations

Scorpion stings produce a local reaction consisting of intense local pain, erythema, tingling or burning, and occasionally discoloration and necrosis without tissue sloughing (Table 115–7). Depending on the scorpion species involved, systemic effects may occur, including autonomic storm consisting of cholinergic and adrenergic effects. Cardiotoxic effects include myocarditis, dysrhythmias, and myocardial infarction.[55,66,86,87,135,174] ECG abnormalities may persist for several days and include sinus tachycardia, sinus bradycardia, bizarre broad notched biphasic T-wave changes with additional ST elevation or depression in the limb and precordial leads, appearance of tiny Q waves in the limb leads consistent with an acute myocardial infarction pattern, occasional electrical alternans, and prolonged QTc interval.[87,89] Other reported effects include pancreatitis, coagulation disorders, acute lung injury (ALI), massive hemoptysis, cerebral infarctions in children, seizures, and a shock syndrome that may precede but usually follows the hypertensive phase.[19,59,66,86,87,174,184]

In the United States, *C. exilicauda* stings produce local paresthesias and pain that can be accentuated by tapping over the envenomated area (tap test) without local skin evidence of envenomation.[51,165] Symptoms begin immediately after envenomation, progress to maximum severity in 5 hours, and may persist for up to 30 hours.[48,165] Autonomic symptoms include hypertension, tachycardia, diaphoresis, emesis, and bronchoconstriction. The somatic motor symptoms reported include ataxia, muscular fasciculations, restlessness, thrashing, and opsoclonus; rarely, children require respiratory support[52,158] (Table 115–6).

Treatment

Because most envenomations do not produce severe effects, local wound care, including tetanus prophylaxis and pain management, usually is all that is warranted. In young children or patients who manifest severe toxicity, hospitalization may be required. Treatment

TABLE 115–6. Envenomation Gradation for *Centruroides Exilicauda* (Bark Scorpion)

Grade	Signs and Symptoms
I	Site of envenomation Pain and/or paresthesias Positive tap test (severe pain increase with touch or percussion)
II	Grade I plus Pain and paresthesias remote from sting site (eg, paresthesias moving up an extremity, perioral "numbness")
III	One of the following: Somatic skeletal neuromuscular dysfunction: jerking of extremity(s), restlessness, severe involuntary shaking and jerking, which may be mistaken for seizures Cranial nerve dysfunction: Blurred vision, wandering eye movements, hypersalivation, trouble swallowing, tongue fasciculation, upper airway dysfunction, slurred speech
IV	Both cranial nerve dysfunction and somatic skeletal neuromuscular dysfunction

Modified with permission from Curry SC, Vance MV, Ryan PJ, et al: Envenomation by the scorpion Centruroides sculpturatus. J Toxicol Clin Toxicol 1983–1984;21: 417–448; Allen C: Arachnid Envenomations. Emerg Med Clin North Am 1992;10:276.

emphasizes support of the airway, breathing, and circulation. Corticosteroids, antihistamines, and calcium have been administered without any known benefit.[51]

The severity of envenomation dictates the need to use antivenom. Continuous intravenous midazolam infusion has been used for *C. exilicauda* scorpion envenomation until resolution of the abnormal motor activity and agitation occurs.[74] Atropine has been used to reverse the excessive oral secretions in *C. exilicauda* scorpion envenomation, with some success in healthy children.[192] Routine use is not recommended and should be limited to species whose envenomations cause a prominent cholinergic crisis, such as *Parabuthus transvaalicus* in southern Africa.[192] The possibility of potentiating the adrenergic effects and causing cardiopulmonary toxicity is reported, so routine use of atropine is not recommended.[15] Atropine use to reverse the effects of stings from scorpions from India, South America, the Middle East, and Asia is contraindicated, because these scorpions cause an "autonomic storm" with transient cholinergic stimulation followed by sustained adrenergic hyperactivity.[14,192]

One grading system suggests using antivenom for severe grade III and grade IV envenomations, which include somatic and/or cranial nerve dysfunction (Table 115–6).[51] A goat serum-derived anti-*Centruroides* antivenom is no longer available in Arizona, but was used successfully in a limited number of severe cases.[29] This approach is not universally accepted. Proponents believe antivenom may resolve symptoms sooner, whereas opponents cite serum sickness as a substantial concern (Antidotes in Depth: Scorpion and Spider Antivenoms).[29] A retrospective chart review of children younger than 10 years who experienced severe *Centruroides* scorpion envenomation found that anti-*Centruroides* antivenom resulted in rapid resolution of all symptoms in all 12 patients treated.[29] Of the patients treated with antivenom, 3% developed immediate hypersensitivity reactions and 58% had a delayed rash or serum sickness.[126] An equine-derived $F(ab)_2$ product called Alacramyn, developed in Mexico against the *Centruroides limpidus* venom, can be used to treat *C. exilicauda* bites, but US use of this foreign pharmaceutical is controversial.[16,183]

Scorpion envenomation can be prevented by wearing shoes when walking, particularly at night, because of the nocturnal nature of scorpions. Shoes, sleeping bag, and tents should be shaken out prior to use. Cracks and crevices should be filled, wood piles and rubbish piles eliminated, and insecticides used in infested areas. The bark scorpion (*C. exilicauda*), which is fluorescent, can be demonstrated in the dark using a Woods lamp.

TICKS

In 1912, Todd[203] described a progressive ascending flaccid paralysis after bites from ticks. Three families of ticks are recognized: (1) *Ixodidae* (hard ticks), (2) *Argasidae* (soft ticks), and (3) *Nuttalliellidae* (a group that has characteristics of both hard and soft ticks). The terms *hard* and *soft* refer to a dorsal scutum or "plate" that is present in the *Ixodidae* but absent in the *Argasidae.* Both types are characteristically soft and leathery, and both have clinical importance. *Ixodidae* females are capable of enormous expansion up to 50 times their weight in fluid and blood.[72] Ticks have 4 stages in their life cycle: egg, larva, nymph, and adult. The paralytic syndrome can occur during the larva, nymph, and adult stages and is related to the tick obtaining a blood meal. The following discussion focuses only on tick paralysis or tick toxicosis, and not on any of the infectious diseases associated with tick bites.

Most of the major tick-borne diseases in North America are transmitted by Ixodid ticks, except for relapsing fever, which is spread by the soft tick of the genus *Ornithodorus* or the louse. In North America, *Dermacentor andersoni* (North American wood tick) and *Dermacentor variabilis* are the most commonly implicated causes of tick paralysis.[79,204] While in Australia, the *Ixodes holocyclus* or Australian marsupial tick is the most common offender.[79,204]

Pathophysiology

Venom secreted from the salivary glands during the blood meal is absorbed by the host and systemically distributed. Paralysis results from the neurotoxin "ixovotoxin,"[1] which inhibits the release of acetylcholine at the neuromuscular junction and autonomic ganglia, very similar to botulinum toxin.[82,144] Both demonstrate temperature dependence in rat models and shows increased muscular twitching activity as the temperature is reduced.[49,128]

Clinical Manifestations

Usually the tick must remain on the person for 5–6 days in order to cause systemic symptoms. Several days must pass before tick salivary glands begin to secrete significant quantities of toxin. Once secreted, the toxin does not act immediately and may undergo binding and internalization, in a similar sequence to botulinum toxin.[49,110] Ticks typically attach to the scalp but can be found on any part of the body, including the ear canals and anus. Children, particularly girls, and adult men in tick-infested areas are predominantly affected. One large series of 305 cases in Canada reported that 21% were adults older than 16 years.[178] Among the children, 67% were girls; in adults 83% were male. The distribution was attributed to the difficulty of detecting ticks in long hair and the possible greater exposure of adult men to tick-infested environments. Children may appear listless, weak, ataxic, and irritable for several days before they develop an ascending paralysis that begins in the lower limbs. Fever usually is absent. Other manifestations include sensory symptoms such as paresthesias, numbness, and mild diarrhea. These symptoms are followed by absent or decreased deep-tendon reflexes and an ascending generalized weakness that can progress to bulbar structures involving speech, swallowing, and facial expression within 24–48 hours, as well as fixed dilated pupils and disturbances of extraocular movements.[82,178] If the tick is not removed, respiratory weakness can lead to hypoventilation, lethargy, coma, and death. Unlike the *Dermacentor* spp of North America, removal of the *I. holocyclus* tick does not result in dramatic improvement for several days to weeks. The maximal weakness may not be reached until 48 hours after the tick has been removed or drops off.[82] It is imperative to closely observe patients for possible deterioration. The differential diagnosis includes Guillain-Barré syndrome (GBS), poliomyelitis, botulism, transverse myelitis, and spinal cord lesions. The cerebrospinal fluid remains normal and the rate of progression is rapid, unlike GBS and poliomyelitis.[65,176] The edrophonium test is negative. Nerve conduction studies in patients with tick paralysis may resemble those of patients with early stages of GBS: findings in both conditions include prolonged latency of the distal motor nerves, diminished nerve conduction velocity, and reduction in the amplitudes of muscle and sensory-nerve action potentials.[65]

Treatment

The most important aspect of treatment is considering tick paralysis in the differential diagnosis of any patient with ascending paralysis. Other than removal of the entire tick, which is curative, treatment is entirely supportive. The *I. holocyclus* of Australia is considerably more toxic and patients are more likely to deteriorate before they improve, so they must be closely observed for several days until improvement is certain.[82] Antitoxin, a hyperimmune serum prepared from dogs, is the usual treatment for paralyzed animals, and has been used sparingly in severely ill humans because of the risk of acute reactions and serum sickness.[82]

Prevention of tick bites includes wearing protective clothing and spraying clothes with insect repellant. Diethyltoluamide (DEET) repels ticks, but does not kill them. Permanone is a new tick aerosol spray repellant for use on clothing. It contains permethrin, which kills ticks on contact.[117] According to one study, permethrin in concentrations of 0.036–2.276 mg/m^2 induces 90–100% tick mortality, with100% effectiveness for 1 month, and a decrease in effectiveness to 52% after the first washing.[117] Close inspection of all body parts and especially the scalp is important. Proper removal of the tick is very important, otherwise infection or incomplete tick removal may occur. The tick should be grasped as close to the skin surface as possible with blunt curved forceps, tweezers, or gloved hands. Steady pressure without crushing the body should be used, otherwise expressed fluid may infect the patient. After tick removal, the site should be disinfected. Traditional methods of tick removal using petroleum jelly, topical lidocaine, fingernail polish, isopropyl alcohol, or a hot match head are ineffective and/or may induce the tick to salivate or regurgitate into the wound.[146]

HYMENOPTERA: BEES, WASPS, HORNETS, YELLOW JACKETS, AND ANTS

Within the order *Hymenoptera* are three families of clinical significance: *Apidae* (honeybees and bumblebees), *Vespidae* (yellow jackets, hornets, and wasps), and *Formicidae* (fire ants). Insects of this subclass (Figure 115–2) are of great medical importance because their stings are the most commonly reported and can cause acute toxic and fatal allergic reactions (Table 115–7). An estimated 40 deaths per year are attributed to anaphylaxis secondary to hymenoptera stings.[12,182]

Apis Mellifera and *Bombus* species (honeybees and bumblebees) build nests away from humans and are passive unless disturbed. Apids can only sting once because their stinger is a modified ovipositor that resides in the abdomen. The structure is barbed and has a venom sac attached. Once the stinger embeds into the skin, the stinger disembowels the bee. Vespids, on the other hand, are more aggressive and build nests in trees and under awnings; yellow jackets inhabit the ground. They have smaller barbs that can be extracted from human skin and are able to sting multiple times.[76] The introduction of the Africanized honeybee in Brazil (because originally they were thought to be a more efficient honey producer) has caused significant economic and health issues. The bees have migrated toward the southern border of the United States, are less productive as a honey producer, and pose a greater threat to humans. African bees are characterized by large

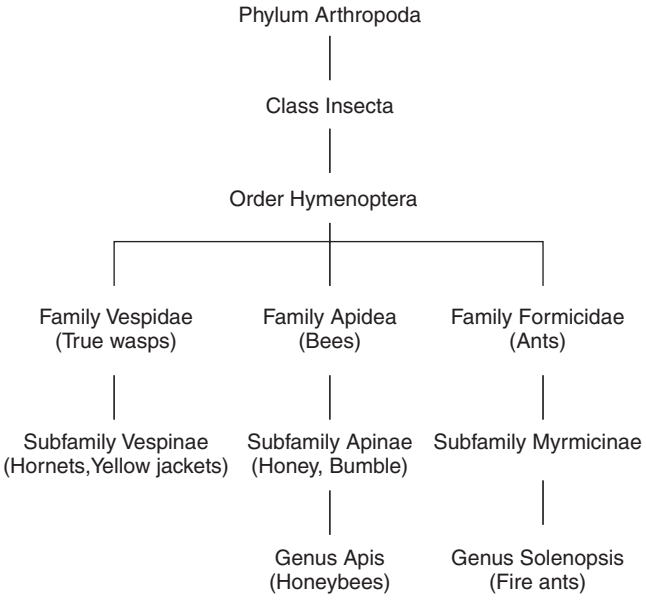

Figure 115–2. Taxonomy of the order Hymenoptera.

TABLE 115–7. Classification of Reactions to Hymenoptera Sting

Reaction	Clinical Presentation
Local	
Minimal	Localized pain, pruritus, swelling
	Lesion <5 cm
	Duration several hours
Large	Localized pain and pruritus
	Contiguous swelling and erythema
	Lesion >5 cm
	Duration 1–3 days
Systemic	
Minimal	Localized pain, pruritus, swelling
	Distant and diffuse urticaria, angioedema, pruritus and/or erythema, conjunctivitis
	Abdominal pain, nausea, diarrhea
Severe	Dermatologic
	Local: Pain, pruritus, and swelling
	Distant: Urticaria, angioedema, pruritus, and/or erythema
	Gastrointestinal
	Nausea, abdominal pain, diarrhea
	Respiratory
	Nasal congestion, rhinorrhea, hoarseness, bronchospasm, stridor, tachypnea, cough, wheezing
	Cardiovascular
	Tachycardia, hypotension, dysrhythmias, myocardial infarction
	Miscellaneous
	Seizures, feeling of impending doom, uterine contractions

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TABLE 115–8. Composition of Hymenoptera Venom

Vespid (wasps, hornets, yellow jackets)
Biogenic amines (diverse)
Phospholipase A, phospholipase B
Hyaluronidase
Antigen 5
Acid phosphatase
Mast cell degranulating peptide
Kinin
Apids (honeybees)
Biogenic amines (diverse)
Phospholipase A, phospholipase B (?)
Hyaluronidase
Acid phosphatase
Minimine
Mellitin
Apamin
Mast cell degranulating peptide
Formicids (fire ants)
Biogenic amines (diverse)
Phospholipase A
Hyaluronidase
Unidentified others
Piperidines

Modified with permission from Sinkinson CA, French RS, Graft DF, eds: Individualizing therapy for Hymenoptera stings. Emerg Med Rep 1990;11:134; King TP, Valentine MD: Allergens of hymenptera venoms. Clin Rev Allergy 1987;5:137 Stablein JJ, Lockey RF: Adverse reactions to ant stings. Clin Rev Allergy 1987;5:161.

populations, can make nonstop flights of at least 20 km, and have a tendency toward mass attack with little provocation.[140]

Pathophysiology

Several allergens (Table 115–8) and pharmacologically active compounds are found in honeybee venom. The three major venom proteins for the honeybee are melittin, phospholipase A_2, and hyaluronidase.[125] Other proteins include apamin, acid phosphatase, and other unidentified proteins. Phospholipase A_2 is the major antigen/allergen in bee venom.[27]

Melittin is the principal component of honeybee venom. It acts as a detergent to disrupt the cell membrane and liberate potassium and biogenic amines.[10] Histamine release by bee venom appears to be largely mediated by mast cell degranulation peptide. Apamin is a neurotoxin that acts on the spinal cord. Adolapin inhibits prostaglandin synthase and has antiinflammatory properties that may account for its use in arthritic therapy.[179] Phospholipase A_2 and hyaluronidase are the chief enzymes in bee venom.

Vespid venoms contain 3 major proteins that serve as allergens and a wide array of vasoactive peptides and amines.[125] The intense pain following by vespid stings is largely caused by serotonin, acetylcholine, and wasp kinins. Antigen 5 is the major allergen in vespid venom.[141] Its biologic function is unknown. Mastoparans have action similar to mast cell degranulation peptide, but weaker.[10] One study found that phospholipase A_2 may be responsible for inducing coagulation abnormalities.[152]

Clinical Manifestations

Normally, the honeybee sting is manifested as immediate pain, a wheal-and-flare reaction, and localized edema without a systemic reaction. Vomiting, diarrhea, and syncope can occur with a higher dose of venom resulting from multiple stings.[30] Rarely, a sting in the oropharynx produces airway compromise.[182] Toxic reactions occur with multiple stings (>500 stings are described as possibly fatal) [76] and include GI symptoms, headache, fever, syncope and, rarely, rhabdomyolysis, renal failure, and seizures.[30] Bronchospasm and urticaria are typically absent. This type of toxic reaction is different from the hypersensitivity reactions or anaphylactic reactions because it is not an IgE-mediated response, but rather a direct effect from the venom itself.

Hypersensitivity reactions, including anaphylaxis, occur to hymenoptera stings. These reactions are IgE mediated. The IgE antibodies attach to tissue mast cells and basophils in individuals who have been previously sensitized to the venom. These cells are activated, allowing for progression of the cascade reaction of increased vasoactive substances, such as leukotrienes, eosinophil chemotactic factor-A, and histamine. An anaphylactic reaction is not dependent on the number of stings. Patients who are allergic to hymenoptera venom develop a wheal-and-flare reaction at the site of the inoculum. The shorter the interval between the sting and symptom onset, the more likely the reaction will be severe. Fatalities can occur within several minutes; even initially mild symptoms may be followed by a fulminant course. Generalized urticaria, throat and chest tightness, stridor, fever, chills, and cardiovascular collapse can ensue.

Treatment

Application of ice at the site usually is sufficient to halt discomfort. The stinger should be removed by scraping with a credit card or scalpel, as opposed to pulling, which may release additional retained venom. Topical aspirin preparations or paste have not been proven to be effective in reducing swelling or pain with bee or wasp stings, and they significantly increased the duration of redness.[9] Therapy is aimed at supportive care.

Prevention, especially in the allergic person, includes avoiding bright clothing, flowers, scented deodorants and shampoos, perfumes, and barefoot walks outdoors. An emergency kit containing a prefilled spring-loaded epinephrine syringe (EpiPen delivers 0.3 mg, EpiPen Jr. delivers 0.15 mg) with careful instructions from a physician, an antihistamine (diphenhydramine), and an emergency alert card or tag should be carried or worn by the sensitized individual. Individuals with a clear history of anaphylaxis should followup with an allergist for skin testing and venom immunotherapy for positive results. Immunotherapy significantly reduces the potential risk of anaphylaxis with subsequent stings.[77,98] Commercial preparations of venom from the honeybee, yellow jacket, white-faced hornet, yellow hornet, and wasp can be used for diagnosis and immunotherapy for patients with life-threatening reactions to stings. Several authors have discussed the indications and safety of immunotherapy.[125,218]

FIRE ANTS

There are native fire ants in the United States, but the imported fire ants *Solenopsis invicta* and *Solenopsis richteri* are the significant pests and have no natural enemies. They are native to Brazil, Paraguay, Uruguay, and Argentina, but were introduced into Alabama in the 1930s. They have spread rapidly throughout the southern United States, damaging crops, reducing biologic diversity, and inflicting severe stings to humans.[199] *Solenopsis*

invicta, the most aggressive species, now infests 13 southern states and has been introduced into Australia.[185,187] Allergic reactions to ant stings were limited to the jumper ant (*Myrmecia pilosula,* other *Myrmecia* spp) and the greenhead ant (*Rhytidoponera metallica; Odontomachs, Cerapachys,* and *Brachyponera* spp) in Australia until February 2001, when the red imported fire ant was identified at two sites in Brisbane.[185] The mode of introduction is unknown but may have originated from the transport of infested sea cargo. The incursion is estimated to be 5 years old. Fire ants range from 2–6 mm in size and live in grassy areas and garden sites near still and flowing water. The nests are largely subterranean and have large, conspicuous, dome-shaped above ground mounds (up to 45 cm above the ground), with many openings for traffic. The mounds can contain 80,000–250,000 workers and one or more queens that live for 2–6 years and produce 1500 eggs daily.[212] Fire ants are named for the burning pain inflicted after exposure that can result in necrosis at the site. The imported fire ant attacks with little warning. By firmly grasping the skin with its mandibles, both the fire ant and the jumper ant can repeatedly inject venom from a retractile stinger at the end of the abdomen. Pivoting at the head, the fire ant injects an average of 7 or 8 stings in a circular pattern.[187] In the United States, residents of healthcare facilities who are immobile or cognitively impaired are at risk for fire ant attacks, especially when the facility lacks pest control techniques for fire ants.[58] Healthcare personnel often are unaware of the behavior of these insects, and the special measures required for their control.

Pathophysiology

The clinical sequelae from fire ant stings are related to the biologic activity of the venom. The venom inhibits sodium and potassium adenosine triphosphatases, reduces mitochondrial respiration, uncouples oxidative phosphorylation, adversely affects neutrophil and platelet function, inhibits nitric oxide synthetase, and perhaps activates coagulation.[107,109] Unlike the venoms of wasps, bees, and hornets that contain mostly aqueous containing proteins, the imported fire ant venom is 95% alkaloid, with a small aqueous fraction that contains soluble proteins.[130] Of the alkaloids, 99% is a 2,6-disubstituted piperidine that has hemolytic, antibacterial, insecticidal, and cytoxic properties.[57] These alkaloids do not cause allergic reactions, but produce a pustule and pain. The aqueous portion of the venom contains the allergenic activity of fire ant venom, *Sol i* I-IV.[92,187] The proteins identified in the venom include a phospholipase, a hyaluronidase, and the enzyme *N*-acetyl-β-glucosaminidase.[57,187]

Clinical Manifestations

Three categories are suggested based on the reactions to the imported fire ant: local, large local, and systemic.[188] *Local reactions* occur in nonallergenic individuals. *Large local reactions* are defined as painful, pruritic swelling at least 5 cm in diameter and contiguous with the sting site. *Systemic reactions* involve signs and symptoms remote from the sting site. The sting initially forms a wheal that is described as a burning itch at the site, followed by the development of sterile pustules. In 24 hours, the pustules umbilicate on an erythematous base. Pustules may last 1–2 weeks.[76] Late cutaneous allergic reactions can occur in some persons who experience indurated pruritic lumps at the site of subsequent stings.[57] Large reactions may lead to tissue edema sufficient to compromise blood flow to an extremity. Anaphylaxis occurs in 0.6–6% of persons who have been stung.[187] Often, healing occurs with scarring in 10–14 days.

Diagnosis

Clinical clues such as pustule development at the sting site after 24 hours, species identification, and history may help to identify fire ant exposure. No laboratory assays to determine exposure are available. Fire ant allergy can be determined by correlating the clinical manifestation of fire ant sting reactions with imported fire ant–specific IgE determined by skin testing or radioallergosorbent test.

Treatment

Local reactions require cold compresses and cleansing with soap and water. Some authors recommend topical or injected lidocaine with or without 1:100,000 epinephrine and topical vinegar and salt mixtures to decrease pain at the site of the bite and sting.[96,134] Topical application of aluminum sulfate and papain is not effective for reducing pain or pruritus.[32,168] Large local reactions can be treated with oral corticosteroids, antihistamines, and analgesics. Secondary infections should be treated with antibiotics. Systemic reactions should be treated with subcutaneous or intravenous epinephrine.

BUTTERFLIES, MOTHS, AND CATERPILLARS

Butterflies and moths are insects of the order *Lepidoptera.* Several moth and butterfly families have species whose caterpillars are clinically important, that is, they contain spines or urticating hairs that secrete a poison that is irritating to humans on contact. *Lepidopterism* is a general term that describes the adverse effects to humans when they are exposed to moths and butterflies.[143] Caterpillar, which means *hairy cat* in Latin, is the larval stage for moths and butterflies. In the United States, several significant stinging caterpillars are of note. The puss caterpillar (*Megalopyge opercularis*) often is considered one of the most important and toxic of the caterpillars in the United States because it has been reported to be such a nuisance, especially in Texas.[190] Other names for the puss caterpillar are woolly/hairy worm, wooly slug, opossum bug, tree asp, Italian asp, and little perrito in Spanish.[190] The caterpillars look furry and are covered in silky tan to brownish hairs that hide short spines containing an urticarial toxin. The spines are yellowish with black tips, and the hairs vary in colors ranging from pale yellow and gray to brown.[24] Other significant stinging caterpillars in the United States are the flannel moth caterpillar (*Megalopyge crispata*), the Io moth (*Automeris io*), the saddleback caterpillar (*Sibine stimulata*), and the hickory tussock caterpillar (*Lophocampa caryae*).[123] In South America, especially Brazil, *Lonomia obliqua* caterpillars are notorious for causing severe pain and a hemorrhagic syndrome.[38,53] In Australia several caterpillars are of medical importance: mistletoe brown tail moth (*Euproctis edwardsi*), processionary caterpillars (*Ochrogaster lunifer*), cup moths (*Doratifera* spp), and the white-stemmed gum moth (*Chelepteryx collesi*).[8] Pine processionary caterpillars (*Thaumetopoea pityocampa*) are the most important defoliator of pine forests in the Mediterranean and central European countries, with significant consequential economic and occupational repercussions for workers who frequent these pine forests.[205]

Pathophysiology

Little is known about the composition of the venom, which probably varies according to the different caterpillar species. Some toxins contain proteins that cause histamine release, such as thaumetopoien isolated from *Thaumetopoien pityocampa* or pine processionary caterpillar.[205,206] Another protein isolated from the *L. obliqua* caterpillar causes coagulopathy; its mechanism of action is not fully known but it somehow activates factors X and II.[61,112] The venom and hair structure of *Lagoa crispata,* which has often been confused with the southern Texas puss caterpillar, has been characterized.[124] The venom is stored at the base of the hollow setae (spines) where the poison sac and nervous tissue are located. Upon contact with these spines, the toxin is released. The toxin may be a protein or a substance that conjugates with proteins.[67] The varying differences of caterpillar venom and their clinical effects emphasize the importance of positive identification of caterpillars.

Clinical Manifestations

The clinical effects of caterpillar exposure can generally be separated into 2 types—stinging reaction and pruritic reaction—although overlap may occur. Stinging caterpillars, such as *Megalopyge opercularis,* envenomate by contact with their hollow spines containing venom. The reaction is characterized as a painful, burning sensation with local effects and, less commonly, systemic effects. The area may become erythematous and swollen, and papules and vesicles may appear. The classic gridlike pattern develops within 2–3 hours of contact. Reported symptoms include nausea, vomiting, fever, headache, restlessness, tachycardia, hypotension, urticaria, seizures, and even radiating lymphadenitis and regional adenopathy.[154] Another stinging caterpillar previously mentioned is the *L. obliqua* caterpillar, which causes the hemorrhagic syndrome that presents as a disseminating intravascular coagulopathy and as secondary fibrinolysis with skin, mucosal, and visceral bleeding, acute renal failure, and intracerebral hemorrhage.[38,112] Pruritic reactions occur upon exposure to the itchy caterpillars that have nonvenomous urticating hairs, which can produce a mechanical irritation, allergic reaction, or a granulomatous reaction from the chronic presence of the hairs. Several species that cause allergic reactions are the white-stemmed moth (*Chelepteryx collesi*), Douglas fir tussock moth (*Orgyria pseudotsugata*), and gypsy moth caterpillar (*Lymantria dispar*).[143] Caterpillar hairs can cause ocular trauma, otherwise known as *ophthalmia nodosa.*[186] The range of ocular pathology depends on the penetration factor and the effect of the released urticating toxins.[37] The ocular spectrum has been classified into 5 types by Cadera et al:[37]

Type 1: Brief exposure time of 15 minutes. Symptoms of chemosis, inflammation, epiphora, and foreign body sensation may last for weeks.

Type 2: Chronic mechanical keratoconjunctivitis (hairs in bulbar/palpebral conjunctivitis). Foreign body sensation is relieved by removal of hairs. Cornea abrasions may be present.

Type 3: Gray-yellow nodules or asymptomatic granulomas.

Type 4: Severe iritis with or without iritis nodules. Hairs in the anterior chamber and possible intralenticular foreign body.

Type 5: Vitreoretinal involvement. Hairs may enter through the anterior chamber or iris lens or by transscleral migration. May cause vitreitis, cystoid macular edema, papillitis, or endophthalmitis.

Treatment

Treatment of ocular lesions depends upon the exposure classification. Most patients can be classified as type 1 or 2. Irrigation with saline should be followed by meticulous removal of setae, followed by topical steroids and antibiotics. Type 3 requires surgical excision of the nodules. Type 4 requires topical steroids with or without iridectomy for nodules or operative removal of setae. Type 5 requires local treatment with or without systemic steroids. Resistant cases may require vitrectomy with removal of setae. Treatment for dermal contact should be immediate, with removal of the embedded spines using cellophane tape and application of ice. Opioids may be necessary, if minor analgesics do not provide relief. If muscle cramps develop, benzodiazepines should be administered. One study recommended use of 10 mL 10% calcium gluconate administered intravenously, which provided pain relief.[136] Topical corticosteroids can be used to decrease local inflammation. Antihistamines such as diphenhydramine (25–50 mg for adults and 1 mg/kg, maximum 50 mg, in children) can be used to relieve pruritus and urticaria.[136,154] Nebulized β-agonists and epinephrine administered subcutaneously may be required for more severe respiratory symptoms and anaphylactoid/anaphylactic-type reactions. For hemorrhagic syndrome resulting from exposure to *L. obliqua* caterpillar, an antidote called the antilonomic serum (SALon) is available and is used for treatment of the hemorrhagic syndrome in Brazil.[60]

BLISTER BEETLES

Blister beetles are plant-eating insects that exude a blistering agent for protection. They can be found in the eastern United States, southern Europe, Africa, and Asia. Most are from the order Coleoptera, family Meloidae. *Epicauta vittata* is the most common of more than 200 blister beetles identified in the United States.[111] When the beetles sense danger, they exude cantharidin by filling their breathing tubes with air, closing their breathing pores, and building up body fluid pressure until fluid is pushed out through one or more leg joints.[76] Cantharidin is a potent blistering agent found throughout all 10 stages of life of the blister beetle.[41] Cantharidin is produced only by the male blister beetle and is stored until mating. The female loses most of her reserves as she matures. In the wild, the female repeatedly acquires cantharidin as copulatory gifts from her mates.[41] Cantharidin, also known popularly as *Spanish fly,* takes its name from the Mediterranean beetle *Cantharis vesicatoria.* It has been used as a sexual stimulant for millennia. The aphrodisiac properties are related to the ability of cantharidin to cause vascular engorgement and inflammation of the genitourinary tract, hence the reports of priapism and pelvic organ engorgement.[202] Cantharidin has been used for treatment of bladder and kidney infections, stones, stranguria (bladder spasm), and various venereal diseases.[111] In the last century, cantharidin was commonly used for treatment of pleurisy, pneumonia, arthritis, neuralgias, and various dermatitides. A topical 1% commercial preparation can be used for removal of warts and molluscum contagiosum.[50,180] Cantharidin poisoning has been reported by cutaneous exposure,[31] unintentional inoculation,[156] and inadvertent ingestion of the beetle itself.[200] Fewer than 30 cases of Spanish fly poisoning have been reported since 1900.[111]

Pathophysiology

Cantharidin is a natural defensive toxicant produced by blister beetles and shares a structural similarity with the herbicide Endothall.

Although the mechanism of action has not been elucidated, one mechanism based on an in vitro study suggests that cantharidin inhibits the activity of protein phosphatases type 1 and 2A. This inhibition alters endothelial permeability by enhancing the phosphorylation state of endothelial regulatory proteins and results in elevated albumin flux and dysfunction of the barrier.[116] Enhanced permeability of albumin may be responsible for the systemic effects of cantharidin, which lead to diffuse injury of the vascular endothelium and resultant blistering, hemorrhage, and inflammation.

Clinical Manifestations

The clinical effects can mostly be attributed to the irritative effects on the exposed organ systems. The secretions cause an urticarial dermatitis that is manifested several hours later by burns, blisters, or vesiculobullae.[31] Symptoms may be immediate or delayed over several hours. In addition to the local effects, cantharidin can be absorbed through the lipid bilayer of the epidermis and cause systemic toxicity, with diaphoresis, tachycardia, hematuria, and oliguria from extensive dermal exposure.[202] If the periorbital region is contaminated, edema and blistering can evolve. Ocular findings from direct contact with the beetle or hand contamination include decreased vision, pain, lacrimation, corneal ulcerations, filamentary keratitis, and anterior uveitis.[156] When cantharidin is ingested, severe GI disturbances and hematuria can occur, described primarily as cantharidin toxicosis in horses.[161] Initial patient complaints may include burning of the oropharynx, dysphagia, abdominal cramping, vomiting, hematemesis followed by lower GI tract hematochezia, and tenesmus.[149]Although equids develop cantharidin toxicosis from their diet, there is one case of inadvertent blister beetle ingestion by a child who thought it was the edible *Eulepida mashona* or white grub; the child developed hematuria and abdominal cramping.[200] Genitourinary effects include dysuria, urinary frequency, hematuria, proteinuria, and renal impairment. Most symptoms resolved over several weeks. However, death from renal failure with acute tubular necrosis has been reported.[202] Most human exposures involve inadvertent contact with the beetle or its secretions, resulting in dermatitis, keratoconjunctivitis, and periorbital edema secondary to hand–eye involvement, also called the *Nairobi eye.*[156]

Diagnostic Testing

Cantharidin toxicosis has been identified for equine and ruminant exposures by screening urine and gastric contents with high-performance liquid chromatography and gas chromatography-mass spectrometry.[161,162] This method has not been used in clinical practice.

Treatment

Treatment is largely supportive. Wound care and tetanus status should be assessed. For keratoconjunctivitis, an ophthalmologist should be consulted early in the clinical course and the patient treated with topical corticosteroids (prednisolone 0.125%), mydriatics (cyclopentolate 1%), and antibiotics (ciprofloxacin 0.3%).

SUMMARY

Healthcare providers should have an extensive knowledge regarding bites and stings by arthropods and arachnids so that they can recognize the local and systemic reactions. Treatment of arthropod-borne disease rarely entails use of antivenoms. Proper hygiene to prevent secondary infections, avoiding contact with arthropods, decreasing the arthropod population mechanically and/or chemically, and use of repellents are important measures to decrease morbidity from arthropods. The patient should bring the arthropod to the hospital, if possible, to facilitate identification, and every attempt should be made to describe the evolution of the bite to assist in the differential diagnosis.

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