ANTIDOTES IN DEPTH

Antivenom (Scorpion and Spider)

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The terms *antivenom* and *antivenin* often are used interchangeably. Wyeth, the maker of Crotaline and *Micrurus* antivenom, and Merck and Co., the makers of *Latrodectus* antivenom, adopted *antivenin* in the brand names for their products. Brand name recognition has largely been responsible for the use of the term *antivenin* in place of *antivenom.* Except where it refers to a specific brand name, the term *antivenom* is used in this Antidotes in Depth and throughout this textbook.

Antivenom for spiders and scorpions is prepared by immunizing animals with venom and then collecting the immune serum for administration.[4,37] Monkeys, horses, goats, sheep, chicken, camels, and rabbits have been used as sources of antivenom.[41] The animals are placed on an immunization schedule to allow production of immunoglobulins, mostly specific immunoglobulin IgG. Optimal antibody production typically takes approximately 6 weeks. The choice of animal used to make an immune serum is more often dictated by the availability of a species, financial considerations, and tradition than by scientific modeling. Horses are used by the majority of antivenom producers. Horses are easy to maintain, and large volumes of serum can be obtained at one time without harming the animals. Although manufacturers may state that a specific animal gives a less immunogenic product, no studies have compared immune sera of different animals for human compatibility or tolerance. Varying efforts by the manufacturer are made to remove animal proteins such as albumin. The antidotal fraction of an antivenom exists as either whole IgG, or Fab, or $F(ab)_2$. Digestion of disulfide bonds of an IgG molecule with papain yields a mixture of Fab and Fc. The Fab component then can be isolated with affinity chromatography, and the highly antigenic Fc portion is discarded. Similarly, digestion of the IgG molecule with pepsin yields a mixture of $F(ab)_2$ and Fc. Although Fab and $F(ab)_2$ are more expensive to produce than their whole immunoglobin counterparts, they are generally regarded as less allergenic and therefore safer to use.

IgG is the easiest and most inexpensive to produce. It has a molecular weight of 150 kDa, the largest of the three antivenom types. Because of its size, it is less filterable at the glomerulus and has the smallest volume of distribution. IgG has a longer elimination half-life than either Fab or $F(ab)_2$.[27]

$F(ab)_2$ has an intermediate size (100 kDa) and elimination half-life. Because it lacks the Fc fragment of the IgG molecule, it has less potential to initiate anaphylaxis. The advantage of $F(ab)_2$ is that much of the allosteric configuration of the original IgG molecule is retained compared to Fab. This configuration theoretically allows for tighter binding to venom.

Fab is the smallest (50 kDa) in size and is eliminated renally. It has the largest volume of distribution and a greater ability to reach intracellular compartments. The pharmacokinetic properties of the venom have been suggested to define the development and characteristics of an antivenom.[27] Arachnid venoms with effects on the central nervous system tend to have low molecular weights and large volumes of distribution. Fab- and $F(ab)_2$-based antivenoms with their larger volumes of distribution may be more suitable for binding these low-molecular-weight, centrally acting components of arachnid venom.[27]

Immunoglobulin-based antivenoms can be given by the intramuscular, intravenous, or subcutaneous route. Intravenous antivenom therapy is preferred for its ability to achieve rapid peak serum concentrations and the ability to withdraw the offending antivenom in the event of an allergic reaction.[28] Intramuscular injection has been used in instances where intravenous access is unobtainable. In a rabbit model, the elimination half-life of *Buthus occitanus* venom is reduced faster when antivenom is given by the intravenous route than are comparable doses given intramuscularly. Pharmacokinetic comparisons of venom and antivenom suggest that the lower-molecular-weight components of scorpion venom are absorbed and distributed faster than antivenom, when administered intramuscularly or given subcutaneously. Therefore intravenous antivenom is the preferred route for neutralization of venom.[30,34,35]

The unavailability of specific antivenoms necessitates symptomatic treatment or use of a comparable foreign antivenom. In the United States, the specific goat-derived antivenom for *Centruroides* envenomation is no longer being produced. Clinical trials are underway for the use of Mexican equine $F(ab)_2$ for treatment of severe envenomation. In a study of 72 moderate scorpion stings in Para, Brazil, 32.7% who met criteria for antivenom administration did not receive treatment because of unavailability of the antivenom.[46] *Latrodectus* antivenom has been in short supply in the past, leading to the observation that *Latrodectus mactans* and *Latrodectus hesperus* could be neutralized by *Latrodectus hasseltii* antivenom.[18,19,39]

The exact identity of the species of arachnid is rarely known in the clinical setting. The spider or scorpion specimen usually is not available. The species usually is inferred more from the geographic region where the injury occurred than from the clinical presentation. For example, black widow envenomations that occur in southern Arizona are presumed to result from *L. hesperus* rather than *L. mactans*. Occasionally, stings or bites result from scorpions or spiders in imported foreign rugs and fruit. The clinician must also be aware that professional and amateur entomologists may be exposed to bites or stings from exotic species. However, in these instances, the exact genus and species, or at least the common name, usually are known.

CENTRUROIDES SPECIES

Centruroides exilicauda (formerly known as *Centruroides sculpturatus*) is the only scorpion of medical importance in the United States. It is indigenous to the deserts of Arizona but reportedly exists in Texas, New Mexico, California, and Nevada.[17] Occasionally, envenomations occur in nonindigenous areas of the country from "stowaway" scorpions in the luggage of travelers.[59]

The two poison centers in Arizona receive between 8000 and 10,000 calls annually for scorpion exposures (Chap. 130).[40] In the past, the mortality from scorpion envenomation in the

United States was twice as high as that of all other venomous animals combined.[48] Although the incidence of envenomation remains high, no deaths associated with the toxic effects of scorpion venom have occurred for more than 40 years. However, the recent death of a 62-year-old woman likely was secondary to an anaphylactic reaction to scorpion venom.[10] The low incidence of fatalities most likely is attributable to better methods of supportive care, the use of antivenom, and the development of pediatric intensive care units.[32]

Antivenom for the *Centruroides* spp was produced in horses in Mexico as early as the 1930s.[17] In 1947, antivenom was produced from rabbits and cats immunized with *C. sculpturatus* and *Centruroides gertschi*.[52] The Antivenom Production Laboratory at Arizona State University (APL-ASU) began producing antivenom to *C. sculpturatus* in goats in 1965. This antivenom was used for treatment of scorpion stings in Arizona until November 2004. Production of the APL-ASU antivenom has ceased. All stockpiles have expired; however, several hospitals retain vials of antivenom in their inventory.[40] No FDA approval was ever granted for this product; its use was restricted to the state of Arizona, where it was supplied free of charge to hospitals for compassionate use. Transport across state lines was prohibited.

In view of the limited mortality from envenomation and the risk of serious immediate hypersensitivity or serum sickness from administration of antivenom, there is rarely, if ever, an absolute indication for administration of *Centruroides* scorpion antivenom. Administration of antivenom, therefore, was reserved for patients with the most severe envenomations, typically in children younger than 6 years. A 4-level severity grading of scorpion envenomation is given in Table 115–7.[17] Administration of antivenom is recommended for patients with grade III or IV systemic toxicity. However, these same symptoms also can be successfully managed in an intensive care setting with aggressive airway management, monitoring, and benzodiazepine infusions.

In Mexico, two antivenoms are primarily directed toward neutralizing the venom of *Centruroides* spp. The Mexico-Pharma Polyvalent Scorpion Antivenom may also be effective against North American *Centruroides* stings; however, there is no known reliable repository of this antivenom in the United States.[3] Although antibody fragments (Fab) were developed from immune goat serum for treatment of *Centruroides* envenomation, they are not commercially available.[8] In June 2000, Silanes Laboratory received orphan drug status for Alacramyn, an equine-derived $F(ab)_2$ from *Centruroides limpidus*, *Centruroides noxius, Centruroides suffusus suffusus, and Centruroides meisei* (formerly known as *Centruroides elegans).* Currently, clinical trials of $F(ab)_2$ use in envenomed children are underway, stimulated by the absence of the ASU-APL product. One vial of Alacramyn contains sufficient $F(ab)_2$ to neutralize 150 mouse LD_{50} of *Centruroides* venom.[42] It is administered by slow IV infusion, 1 vial at a time with observation for 30 to 60 minutes before repeating. Dosing is similar in children and adults. It efficacy is documented in both animals and humans.[1,11,25] A prospective evaluation of serum venom concentrations in 14 clinically envenomed children was performed using enzyme-linked immunosorbent assay. After administration of antivenom, serum venom concentrations fell from 1000 to 4000 pg/mL to less than 200 pg/mL within 30 minutes and were unmeasurable within 2 hours.[25]

In a rabbit model, the total serum concentration of venom increased after administration of $F(ab)_2$, suggesting that $F(ab)_2$ is capable of pulling venom from its site of action into serum.[11]

Cross-neutralization of the venom of 8 different species of *Centruroides,* including *C. exilicauda,* has been documented in vitro.[22]

The incidence of allergic reactions to Alacramyn is reported to be 2.7%, similar to the 3.4% reported for the APL-ASU goat serum.[9,38] The average duration of symptoms in treated patients was 1.4 hours. In a study of 15 children, the 12 patients who receive APL-ASU antivenom had resolution of neurologic, respiratory, and cardiovascular symptoms within 3 hours of initiating therapy. In the 3 patients who did not receive antivenom therapy, symptoms lasted 15 to 24 hours.[9] If the current clinical trials of $F(ab)_2$ reveal the product to be safe and effective, the threshold to treat scorpion envenomation may be lowered by many clinicians. Alacramyn is tentatively set to be marketed under the name Anascorp in the United States.

LEIURUS SPECIES

The *Leiurus quinquestriatus* scorpion is indigenous to Africa, Asia, and the Middle East, including Egypt, Israel, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, Syria, and Turkey. Antivenom to *L. quinquestriatus* is made in France, Israel, and Turkey. The clinical effects of this scorpion are relatively resistant to treatment with antivenom. The manufacturer of Turkey antiscorpion antivenom recommends a dose of 1 mL antivenom for treatment of envenomation. The usual dose for control of symptoms is 5 to 20 mL antivenom given intravenously.

In observational studies, an intravenous infusion of 5 to 20 mL was needed to control venom effects, and only patients given antivenom within the first several hours demonstrated significant benefit.[2,31] The rate of allergic reactions for the Turkey antiscorpion antivenom is reported to be 1.6% to 6.6%.[31] The recommended dose of the Israeli *L. quinquestriatus* antivenom is 5 to 15 mL for intravenous use. Several authors report lack of clinical efficacy of this antivenom.[6,26,53]

Leiurus quinquestriatus antivenom was successfully used to treat a 2-year-old boy with envenomation by *Androctonus crassicauda*. Symptoms resolved 2 hours after antivenom administration.[47]

TITYUS SPECIES

Tityus species of scorpions are endemic to South America, particularly Brazil. An $F(ab)_2$ for *Tityus serrulatus* antivenom is available from Fundação Ezequiel Dias (FUNED), in Belo Horizonte, Brazil. The usual dose of the antivenom is 20 mL as an intravenous infusion.[20]

In a series of 18 patients with *T. serrulatus* envenomation treated with antivenom, vomiting and local pain decreased within 1 hour, and cardiorespiratory manifestations disappeared within 6 to 24 hours in all patients except the 2 who presented with acute lung injury.[20] Sixteen patients recovered completely by 24 hours. Additionally, the Instituto Buntantan in Brazil produces Soro antiarachnidico and Soro antiscorpionico for treatment of *Tityus* spp.[44]

ANDROCTONUS SPECIES

Scorpion antivenom in South Africa is an equine-derived antivenom available from the South African Vaccine Producers, formerly South African Institute for Medical Research (SAIMR), Johannesburg, South Africa.

Scorpifav, produced by Aventis Pasteur, is produced for treatment of *Androctonus* spp, *B. occitanus*, and *L. quinquestriatus*.

Buthus tamulus monovalent red scorpion antivenom serum produced by Central Research Institute of India is an equine-derived lyophilized antivenom for the venom of *Mesobuthus tamulus*. Although the manufacturer recommends a dosage of 1 vial, a dose of 5 vials reduced the mortality significantly in one study.[36,54]

In Pakistan, the treatment of scorpion stings was modified in 1991 to include the administration of 5 vials of antivenom. A retrospective case series of 950 patients treated with and without antivenom was compared to 968 cases after the 5-vial protocol was initiated. A statistically significant decrease in mortality occurred. The last recorded death resulting from a scorpion sting occurred in 1991 in a patient who did not receive antivenom.[54]

Parabuthus spp antivenom from South African Vaccine Producers is an equine-derived antivenom to *Parabuthus* spp. In one study antivenom became unavailable, allowing for a unique design of matched pairing of patients. Patients who received antivenom had a significant decrease in hospital stay after receiving 1 (5-mL) vial of antivenom. Pain, hypersalivation, fasciculation, tremor, and bladder distension responded best to serotherapy. Antivenom therapy did not significantly improve dysphagia, ptosis, or local swelling.[7]

LATRODECTUS SPECIES (*L. MACTANS, L. HESPERUS, LATRODECTUS BISHOPI, LATRODECTUS GEOMETRICUS, LATRODECTUS INDISTINCTUS*)

Administration of the black widow spider antivenom is controversial. Although black widow envenomation is associated with severe muscle pain, cramping, and autonomic disturbances,[12,13,33] mortality is low. Symptomatic treatment almost always can be accomplished with muscle relaxants and opioids individually or in combination. Some authors believe that antivenom has too high a risk-to-benefit ratio to justify its use.[50] In selected patients, however, use of antivenom may reduce pain and suffering, shorten the course of envenomation, and reduce or eliminate the need for hospitalization.[45,55] We believe that indications for antivenom administration include severe muscle cramping, hypertension, diaphoresis, nausea, vomiting, and respiratory difficulty that is unresponsive to other therapy (Chap. 115). Pregnancy is suggested as a possible indication for antivenom administration.[5,51]

Antivenoms for a number of *Latrodectus* spiders are available worldwide (Table A32–1). *Latrodectus mactans* antivenom is produced by Merck and Co. in North America. The Australian red-back spider *L. hasseltii* antivenom is manufactured in horses by CSL Ltd. South Africa (SAFR) produces antivenom for both the black widow *(Latrodectus indistinctus)* and the brown widow *Latrodectus geometricus*. Aracmyn, a polyvalent $F(ab)_2$, is an equine-derived antivenom created for *L. mactans* in both Argentina and Mexico and for *Loxosceles* spp.

In North America Antivenin (Merck and Co.) for black widow venom (*L. mactans*) is made by immunizing horses. Each vial of antivenin contains 6000 antivenin units standardized by biologic assay in mice. Because the venoms of Latrodectus species are virtually identical by immunologic and electrophoretic mechanisms, antivenom created for *L. mactans* is presumed to be effective in other species of Latrodectus as well.[39] A recent shortage of antivenin (Merck and Co.) prompted the discovery that antivenom against *L. hasseltii*, the Australian red-back spider, also neutralizes venom of *L. mactans* in a mouse model.[19] In a review of 163 cases of presumed *L. hesperus*, envenomations antivenom reduced the duration of symptoms from a mean of 22 hours to a mean of 9 hours. Symptoms usually subsided within 1-3 hours of administration of the antivenom. Hospital admission rate fell from 52% in those who were managed with opioids and muscle relaxants to 12% in those patients receiving antivenom.[12] Administration of antivenom was also effective, even when given as late as 90 hours after envenomation.[45,55]

Dosage of antivenin (Merck and Co.) is usually one vial (2.5 mL) diluted in 50 mL of saline for intravenous administration. Black widow spider antivenom can also be given IM; however, this route carries the disadvantage of slower, more erratic absorption, less control over the rate of administration, and the inability to stop administration of the drug should an allergic reaction occur. For these reasons, the intramuscular route is not recommended.

Despite the apparent efficacy of antivenom, the decision to give horse serum for a disease with limited mortality is of great concern. Death from bronchospasm and anaphylaxis is reported as a complication of antivenom administration, as is serum sickness.[13] Black widow antivenom is listed as a Pregnancy Category C agent.

In Australia, antivenom to the red-back spider (*L. hasseltii*, CSL Ltd.) is made by immunizing horses for production of $F(ab)_2$. Horse-derived $F(ab)_2$ has a lower reported incidence of allergic reactions, with early anaphylactoid reactions as low as 0.5% to 0.8%. The incidence of serum sickness is reported at less than 5%.[56,57]

In a report covering 1995 to 1996, only 20% of patients with *L. hasseltii* (red-back spider) bites required antivenom administration.[60] When treatment was given, 1 ampule was used in 76% of cases, 2 ampules were used in 18% of cases, and 3 ampules were administered in only 6% of cases.[60] Three patients who required 6 to 8 vials of antivenom after failing to respond to the usual 1 to 2 vials are reported.[29] No antihistamine or epinephrine pretreatment was given, and no allergic or serum sickness complications occurred.

European widow spider *(Latrodectus tredecimguttatus)* antivenom is no longer produced.[29]

Funnel-Web Spider (*Atrax* and *Hadronyche*) Envenomation

A rabbit IgG-based funnel-web spider antivenom is available in Australia. Since the introduction of the antivenom, no deaths have been reported.[29] The initial dose should be 2 ampules in patients with any signs of envenomation. Patients with evidence of acute lung injury or decreased consciousness should receive 4 ampules.[43] The dosage for children is the same as for adults.[16]

In severe envenomations, the following protocol should be used.[43] Two ampules (each 5 mL of 2.0% [100-mg]) rabbit IgG) antivenom should be administered very slowly intravenously (adult or child). The dose can be repeated in 15 minutes if no improvement is seen. The dose should be doubled for severe cases. A rapid response should occur. Administration of antivenom should be repeated until symptoms are completely reversed.[21] Not uncommonly, *Atrax robustus* envenomations require more than 3 ampules of antivenom.

TABLE A32–1. Worldwide Availability of Scorpion and Spider Antivenom[14,16,44,58]

Scorpions

Androctonus aenas
France: Antiscorpion Venom Serum, Pasteur Merieux
Androctonus amorexi
France: Antiscorpion Venom Serum, Pasteur Merieux
Androctonus australis
Algeria: Antiscorpion
France: Scorpifav, Aventis Pasteur
Germany: Scorpion Antivenom, Twyford
Androctonus crassicauda
Iran: Scorpion Antivenom
Turkey: Anti-Scorpion
Androctonus mauritanicus
France: Antiscorpion Venom Serum, Pasteur Merieux
Morocco: Serum antiscorpionique
Androctonus species
France: Antiscorpion Venom Serum, Pasteur Merieux
Buthotus saulcyi
Iran: Scorpion Antivenom
Buthus occitanus
France: Antiscorpion Venom Serum, Pasteur Merieux
France: Scorpifav, Aventis Pasteur
Germany: Scorpion Antivenom, Twyford
Buthus gibbosusbrulla
Turkey: Anti-Scorpion
Buthus tamulus
India: Anti-Scorpion Venom Serum (AScVS), Haffkine
Centruroides species (*elegans, gertschi, limpidus, suffuses, noxius, exilicauda*)
Mexico: Alacramyn, Bioclon
Mexico: GGBR Polivalent Scorpion Antivenom
Euscorpius carpathicus, italicus
Turkey: Anti-Scorpion
Leiurus quinquestriatus
France: Antiscorpion Venom Serum, Pasteur Merieux
France: Scorpifav, Aventis Pasteur
Germany: Scorpion Antivenom, Twyford
Israel: *Leiurus quinquestriatus*
Turkey: Anti-Scorpion
Mesobuthus eupeus
Iran: Scorpion Antivenom
Mesobuthus tamulus concanesis
India: Anti-Scorpion Venom Serum (AScVS), Haffkine
Odontobuthus doriae
Iran: Scorpion Antivenom
Palamnaeus species
India: Monovalent Red Scorpion Antivenom Serum
Parabuthus species
South Africa: Scorpion Antivenom, SAIMR
Scorpio maurus
France: Scorpion Antivenom Serum, Aventis Pasteur
Iran: Scorpion Antivenom
Turkey: Anti-Scorpion (subspecies fuscus)
Tityus bahiensis
Brazil: Soro Antiescorpionico, Instituto Butantan
Tityus serrulatus
Brazil: Anti Arachnidic Serum, Instituto Butantan
Brazil: Soro Antiescorpionico, Instituto Butantan

Spiders

Atrax species
Australia: Funnel-Web Spider Antivenom
Hadronyche species
Australia: Funnel Web Spider Antivenom, CSL Ltd.
Latrodectus mactans (Black widow spider)
Australia: Red-backed spider Antivenom
USA: Antivenin, Merck
Latrodectus hasselti
Redback Spider Antivenoms, CSL Ltd.
Latrodectus indistinctus
South Africa: Spider Antivenoms, SAIMR
Laitrodectus species
Mexico: Aracmyn, Bioclon
Loxosceles species
Mexico: Aracmyn, Bioclon
Loxosceles (*reclusa, rufescens*)
Brasil: Anti Arachnidic Serum
Loxosceles (*laeta, rufipes*)
Peru: Antiloxoscelico

LOXOSCELES SPECIES (*LOXOSCELES RECLUSA, LOXOSCELES LAETA, LOXOSCELES RUFESCENS, LOXOSCELES ARIZONICA, LOXOSCELES UNICOLOR*)

Envenomation by the brown recluse spider *Loxosceles reclusa,* is associated with low, but significant, morbidity, particularly in the southeast United States. Anti-*Loxosceles* Fab blocks dermonecrosis in a rabbit model, but only if it is given within 24 to 48 hours of envenomation in one study or as late as 48 hours in another study.[24,49] However, comparisons do not reveal significant differences between dapsone- and antivenom-treated animals and suggest that a combination may be the best therapy.[15,49] No commercially available antivenom exists in North America for treatment of *Loxosceles* envenomation. The late presentation of patients with necrotic lesions from a spider bite and the uncertainty of the genus of the arthropod vector make antivenom use for *Loxosceles* difficult to study. The Instituto Butantan in Brasil has produced an antivenom for *L. reclusa* and *L. rufescens.*

SUMMARY

The indications for antivenom administration in both spider and scorpion envenomations are controversial. The decision to use antivenom should be individualized to the patient, weighing the risk of giving a foreign immune serum, the level of available supportive care, the cost of supportive care, and the cost of obtaining or importing antivenom. The preferred route of administration is intravenous. One to two vials is the recommended dose for most antivenoms; higher doses may be needed to alleviate symptoms.

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