INTRODUCTION

The terms “antivenom” and “antivenin” often are used interchangeably. Although the origin of the term “antivenom” is obvious, “venin” is French for venom and “antivenin” is traditionally used in certain parts of the world. Wyeth Pharmaceuticals, the maker of Crotaline and *Micrurus* antivenom, and Merck & Co, Inc, the maker of *Latrodectus* antivenom, adopted “antivenin” in the brand names for their products. Brand name recognition was largely responsible for the use of the term “antivenin” in place of “antivenom.” In 1981, the World Health Organization determined the preferred terms for the English language to be “venom” and “antivenom.”

HISTORY

Two of the most notable genera of spiders of medical importance in the United States are *Latrodectus* (*L. mactans*, *L. geometricus*, *L. variolus*, *L. hesperus*, and *L. bishopi* are native, whereas *L. geometricus* was introduced) and *Loxosceles*. Commercially available antivenom does not exist in the United States for treatment of *Loxosceles* envenomation. Currently, there is one commercially available *Latrodectus* antivenom in the United States. Black Widow Spider Antivenin (Merck & Co, Inc) (Merck BW-AV) has been available in the United States since its US Food and Drug Administration (FDA) approval in 1936. The use of this antivenom in the treatment of *Latrodectus* envenomations remains controversial, as mortality from these bites is low in the United States, and complications including death following antivenom administration are rarely reported. Ongoing research and development of an F(ab′)_2 antivenom may ameliorate concerns and limitations related to potential adverse events resulting from administration of the Merck antivenom and production shortages limiting availability. As of June 2018, however, F(ab′)_2 black widow antivenom has not been approved for use by the US Food and Drug Administration (FDA) but is in clinical trials under the trade name Analatro.

PHARMACOLOGY

Chemistry, Preparation, and Mechanism of Action
Antivenom for spiders is prepared in a similar manner as other antivenom products by first immunizing animals with nontoxic amounts of venom. Monkeys, horses, goats, sheep, chicken, camels, and rabbits have been used historically to source antivenom. The animals are placed on an inoculation schedule to allow gradual production of immunoglobulins, most importantly IgG. Sufficient antibody production usually occurs within 6 weeks. The species availability, financial considerations, and tradition rather than scientific modeling is typically responsible for animal choice for immune serum production. The majority of antivenom producers use horses, since they are relatively easy to maintain, and large volumes of serum can be obtained at one time without harming the animal. During antivenom production varying efforts are made to remove animal proteins such as albumin. Antivenoms target, bind, neutralize, and promote elimination or redistribution of toxins from body tissues. To date, no studies have compared immune sera of different animals for human compatibility or tolerance.

The antidotal fraction of an antivenom exists as either whole IgG, Fab, or F(ab′)\(_2\). The IgG molecule is composed of 2 antigen-binding fragments (Fab fragments) that are fused together and attached to the larger complement binding fragment (Fc fragment). It is the larger Fc portion that is generally considered to be the most responsible for immune-mediated reactions. Digestion of the disulfide bonds of an IgG molecule by pepsin will cleave the Fc fragment, allowing isolation of pure F(ab′)\(_2\) fragments (2 fused Fab fragments with some intact hinge region). By contrast, digestion with papain cleaves the molecule more distally such that a larger Fc portion is removed from 2 separate Fab fragments. Both Fab and F(ab′)\(_2\) molecules are isolated with affinity chromatography, and the highly antigenic Fc portion discarded. Although Fab and F(ab′)\(_2\) are more expensive to produce than their whole immunoglobin counterparts, they are much less allergenic and therefore safer products.

Whole IgG antivenom is the easiest and least expensive to produce. It has a molecular weight of approximately 150 kDa, and is the largest of the 3 antivenom types. Because of its size, it is the least filterable at the glomerulus and has the smallest volume of distribution. Whole IgG has a longer elimination half-life than either Fab or F(ab′)\(_2\). F(ab′)\(_2\) antivenom has an intermediate size (~100 kDa) and elimination half-life. Although it lowers the risk of anaphylaxis compared to whole IgG, the F(ab′)\(_2\) portion retains much of the allosteric configuration of the original IgG molecule that is lost when Fab are formed. This configuration theoretically allows for tighter binding to venom. The Fab antivenom is the smallest (~50 kDa) molecule in size and is eliminated by the kidneys. It has the largest volume of distribution and a greater ability to reach extravascular compartments. Arachnid venoms that affect the central nervous system have low molecular weights and large volumes of distribution. Thus Fab and F(ab′)\(_2\) based antivenoms are theoretically best suited for this function.

Immunoglobulin-based antivenoms can be given by the intramuscular, intravenous, or subcutaneous route. Intravenous administration achieves rapid peak plasma concentrations, and the infusion can be stopped in
In the event of an allergic reaction. Intramuscular and intraosseous injection has been used when intravenous access is unobtainable.

**Pharmacokinetics and Pharmacodynamics**

Currently, there is no published pharmacokinetic or pharmacodynamic information available on Merck BW-AV in humans or animals. One study colleagues demonstrated Western blot binding of *L. hasseit* (redback spider) Antivenom (RBS-AV) to purified α-latrotoxin and similar protein bands derived from multiple widow spiders (*L. mactans, L. hesperus, L. lugubris, L. tredecimguttatus, and L. hasseit*). When co-mixed with the venoms from these species prior to administration, RBS-AV prevented the development of a reproducible and rapid muscle contracture of an in vitro chicken nerve-muscle preparation. A dose–response relationship was observed with varying doses of RBS-AV administration. This confirms a direct in vitro binding effect of RBS-AV against widow spider venoms.

Previous animal studies demonstrated that intramuscular administration of antivenom produced very low serum venom concentrations. In these rabbit studies of intramuscular administration, F(ab’)2 and IgG had poor bioavailability (36%–42%) and delayed time to peak concentrations of 48 to 96 hours.

Pharmacokinetic and pharmacodynamic characteristics of equine-derived antivenoms differ between species studied. Equine-derived antivenom maximum concentrations were greater in cows than in horses, and steady-state distribution volumes were higher in cows than in horses in one study. Similar results were observed in rabbit models. Pharmacokinetic and pharmacodynamic parameters observed in animal models should therefore be interpreted with caution with regard to behavior of antivenoms in humans.

Redback spider antivenom, available in Australia, has been administered intramuscularly to treat human envenomations, and clinical effectiveness equivalent to intravenous administration was reported. Subsequent studies, however, demonstrated the absence of RBS-AV in circulating serum up to 5 hours following intramuscular administration. Serum concentrations of RBS-AV were detected within 30 minutes of administration following intravenous administration. These results are consistent with animal studies demonstrating little if any effect on circulating venom when antivenoms are given intramuscularly.

Additional studies on the pharmacokinetic and pharmacodynamic properties of RBS-AV, Merck Black Widow Antivenom, and F(ab’)2 based black widow antivenoms are needed.

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

Although black widow bites are associated with severe muscle pain, cramping, and autonomic disturbances, mortality remains low. Symptomatic treatment with muscle relaxants and opioid analgesics is generally effective, although the duration of symptoms following severe envenomation may necessitate hospitalization for 1 to 2 days or more.
The use of Merck BW-AV appears to shorten the length of symptoms dramatically, allowing outpatient care in some cases. Studies of reported Latrodectus-envenomated patients in Australia, however, demonstrated little clinical difference between Latrodectus antivenom and placebo. In addition, anaphylaxis and other adverse events following the administration of Latrodectus antivenom are reported.

Because of low mortality and the potential for adverse events following administration, some authors question the use of BW-AV. We still believe Latrodectus antivenom is safe and effective when used appropriately, and recommended it in cases of severe envenomation where muscle cramping, hypertension, diaphoresis, nausea, vomiting, myocardial infarction, or respiratory difficulty are present and appropriate use of opioid analgesia and muscle relaxants are ineffective.

Latrodectus antivenom is also reported to successfully treat priapism complicating severe envenomation. Although the safety of antivenom is not clearly established in the developing fetus, pregnancy is a reasonable indication for Latrodectus antivenom administration, as the stress of severe pain and muscle cramps may have adverse fetal effects.

Antivenoms for a number of Latrodectus spiders are available worldwide (Table A37–1). A shortage of Merck BW-AV prompted the finding that antivenom against L. hasseltii (RBS-AV) also neutralizes the venom of L. mactans in a mouse model. Analatro, a polyvalent F(ab')2, is an equine-derived antivenom created for L. mactans in both Argentina and Mexico. A randomized placebo-controlled multicenter trial of Analatro in the United States demonstrated similar overall reduction of pain between antivenom- and placebo-treated patients. Clinically significant reduction in pain, however, was more rapid with Analatro (30 minutes vs 90 minutes).
TABLE A37–1
Worldwide Availability of Spider Antivenom

<table>
<thead>
<tr>
<th>Atrax Species, Hadronyche Species</th>
<th>Loxosceles Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Funnel Web Spider)</td>
<td>(Brown spiders)</td>
</tr>
<tr>
<td>Argentina: Anti Latrodectus Antivenom, Instituto Nacional de Produccion de Biologicos, Equine IgG</td>
<td>Brazil: Antiloxosceles Serum, Centro de Producao e Pesquisas de Immunobiologicos. Equine IgG</td>
</tr>
<tr>
<td>Australia: Funnel Web Spider Antivenom, CSL Ltd. Rabbit IgG</td>
<td>Brazil: Soro Antiarachnidico, Instituto Butantan (contains Loxosceles spp, Tityus spp and Phoneutria spp Antivenom), Equine IgG</td>
</tr>
<tr>
<td><strong>Latrodectus species</strong></td>
<td>Peru: Antiloxosceles Serum, Instituto Nacional de Salud, Centro Nacional de Production de Biologicos, Equine IgG</td>
</tr>
<tr>
<td>(Black Widow Spider, Redback Spider)</td>
<td></td>
</tr>
<tr>
<td>Australia: Red-backed spider Antivenom, CSL Ltd. Equine F(ab')&lt;sub&gt;2&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>Croatia: Antilatrodectus Mactans Tredecigmattatus Serum, Institute of Immunology, Equine IgG</td>
<td></td>
</tr>
<tr>
<td>Mexico: Aracmyn, Instituto Bioclon, Equine F(ab')&lt;sub&gt;2&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>South Africa: SAIMR Spider Antivenom, SAIMR, Equine IgG</td>
<td></td>
</tr>
<tr>
<td>USA: Antivenin Latrodectus mactans, Merck &amp; Company, Equine IgG</td>
<td></td>
</tr>
</tbody>
</table>

In a review of 163 cases of presumed *L. hesperus* and *L. mactans* envenomations, Merck *Latrodectus* antivenom reduced the mean duration of symptoms from 22 to 9 hours. Symptoms usually subsided within 1 to 3 hours of antivenom administration. The hospital admission rate fell from 52% in those who were managed with opioids and muscle relaxants to 12% in those patients receiving antivenom. A more recent review demonstrated immediate resolution of pain following BW-AV administration in suspected *L. mactans* envenomation. Following administration of RBS-AV in redback spider envenomation, however, only 34% of recipients reported significant pain relief at 2 hours.

**ROLE IN FUNNEL-WEB SPECIES (ATRAX AND HADRONYCHE)**

A rabbit IgG–based funnel-web spider (*Atrax robustus* and others) antivenom is available in Australia. Since the introduction of the antivenom, no deaths have been reported. Complete response following administration of antivenom was reported in 97% of envenomations in one series.
ROLE IN *LOXOSCELES* SPECIES (*L. RECLUSA, L. LAETA, L. RUFESCENS, L. ARIZONICA, L. UNICOLOR*)

Envenomation by the brown recluse spider *Loxosceles reclusa* is associated with low but significant morbidity, particularly in the midwest and southeast United States. Experimental anti-*Loxosceles* Fab blocked dermatonecrosis in a rabbit model, but only if provided within 24 to 48 hours of envenomation.\(^{16,37}\) Although no commercially available antivenom exists in North America for treatment of *Loxosceles* envenomation, antivenom produced against South American *Loxosceles* spiders has cross-reactivity with North American species like *L. reclusa*.\(^{13}\) The usual late presentation of patients with necrotic lesions from spider bites makes antivenom use for *Loxosceles* difficult to study. National laboratories in Brazil and Argentina produce antivenoms for *L. reclusa, L. boneti*, and *L. rufescens*.\(^{5,13}\)

ADVERSE EFFECTS AND SAFETY ISSUES

Despite the apparent efficacy of antivenom, the decision to give horse serum for a disease with limited mortality is serious. Death from bronchospasm and anaphylaxis is a rarely reported complication of whole IgG BW-AV (Merck) administration,\(^{8,23,34}\) as is serum sickness.\(^9\) Serum sickness is dose-dependent and is less likely when the typical dose of one to 2 vials are administered. A detailed review of one case of death following antivenom administration\(^7\) demonstrates that the antivenom was inappropriately prepared (not diluted) and inappropriately administered (intravenous push rather than slow infusion) to a patient with multiple drug allergies, atopy, and asthma. Resuscitation was further complicated by the development of a pneumothorax. A second death\(^34\) was reported in a 37-year-old man with history of asthma who received antivenom as an infusion and developed cardiac arrest as a complication of severe anaphylaxis. He died 40 hours after presentation.\(^34\)

In Australia, antivenom to the redback 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 allergic reactions as infrequent as 0.5% to 0.8%. The incidence of serum sickness is reported at less than 5%.\(^{23,43,44}\) Analatro, a similar F(ab’)\(_2\) product, is anticipated to be a safer antivenom than the currently available Merck whole IgG product. No serious adverse effects or deaths were observed in the previously described randomized controlled Analatro trial.\(^{12}\)

A review of the US National Poison Data System (NPDS) demonstrated a 3.4% rate of adverse drug reactions (ADRs) following administration of the BW-AV.\(^{33}\) This is consistent with previously reported rates of ADRs following BW-AV administration.\(^9\) Directly attributing complications to administration of antivenom is difficult as these patients received multiple therapies, including opioids, benzodiazepines, and calcium salts preceding antivenom administration, and NPDS does not attribute an ADE to a specific therapy. Similarly, the nature of these ADEs is not described in NPDS. However, it is noteworthy that no deaths occurred in 374
instances of use and only 5 patients received antihistamines, suggesting acute hypersensitivity reactions to the Merck BW-AV to be uncommon and that this antivenom is generally safe. Similarly, a review of 96 assessable instances of BW-AV administration over a 10-year period in a single state similarly demonstrated a low rate of adverse reactions. Four patients in the series had adverse effects ascribed to antivenom administration. These reactions were generally mild and included myalgias, fatigue, generalized paresthesias, flushing, and urticarial rash. There were no cases of dyspnea, angioedema, bronchospasm, hypotension, or death. This low rate of severe adverse reactions and lack of death suggests that Merck BW-AV is a safe product when prepared and administered correctly to patients without underlying atopy, asthma, or drug allergies.

PREGNANCY AND LACTATION

Black widow envenomations during pregnancy are relatively rare. In one study of 12,640 patients envenomated by a black widow spider, 97 (3%) were pregnant. When compared with nonpregnant women, no significant differences were observed in recommended or administered treatments including the use of antivenom. There are 6 reported cases of *Loxosceles* envenomations in pregnant women. All were managed with supportive therapy including analgesics, antihistamines, and a short course of low-dose steroids. Pregnancy outcomes were favorable in all reported cases. Merck BW-AV is Pregnancy Category C. It is not known whether antivenom is excreted in human milk.

DOSING AND ADMINISTRATION

The starting recommended dose of the Merck antivenom is one vial reconstituted with 2.5 mL sterile water for injection and then diluted in 50 mL of saline for intravenous administration over 15 min. Although BW-AV can also be given intramuscularly, this route carries the disadvantage of slower, more erratic absorption, less control over the rate of administration, and the inability to stop the administration should an allergic reaction occur. In addition, recent studies suggest intramuscular injection of antivenom may not yield significant serum concentrations. For these reasons, the intramuscular route is not routinely recommended.

The initial dose of antivenom in funnel-web spider envenomation is 2 vials in patients with any signs or symptoms of envenomation. Patients with acute respiratory distress syndrome or decreased consciousness should receive 4 vials. The following protocol is recommended for severe cases: 2 vials (each containing 100 mg of rabbit IgG) of antivenom are administered very slowly intravenously. The dose can be repeated in 15 minutes if no improvement occurs. The dose recommended for more severe cases. A rapid response is expected. Repeated administration of antivenom is recommended until symptoms are completely reversed. *Atrax robustus* envenomations are reported to require multiple infusions of antivenom. The recommended dosage for children is the same as for adults.

FORMULATION AND ACQUISITION
Each vial of the Merck BW-AV contains 6,000 antivenom units standardized by biologic mouse assay. Because *Latrodectus* venoms 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.\(^{30}\)

*Latrodectus* antivenin is supplied as a white to gray crystalline powder in vials containing not less than 6,000 antivenin units with thimerosal 1:10,000 added as a preservative, along with a 2.5-mL vial of sterile diluent for reconstitution. The antivenin must be stored and shipped at 2°C to 8°C (36°F–46°F), but never frozen. The reconstituted antivenin color ranges from light straw to very dark iced tea, although color has no effect on potency.\(^{2}\) A 1-mL vial of horse serum (1:10 dilution) for sensitivity testing is also included. We do not recommend utilization.

The Antivenom Index, maintained by the Association of Zoos and Aquariums (https://www.aza.org/antivenom-index/) and accessible by the nation’s Poison Control Centers, might also serve as a resource.

**SUMMARY**

The decision to use spider antivenom must be individualized to the patient’s clinical manifestations.

Because mortality following black widow envenomation is low, antivenom is reserved for cases in which symptoms are severe or do not respond to other therapies, and after a frank discussion with the patient of possible adverse effects.

Although a large body of literature suggests that Merck BW-AV is safe when properly prepared and administered to patients without asthma, adverse effects including severe anaphylaxis and death are reported.

A new, purified F(ab′)\(_2\) BW-AV is in clinical development, but is currently unavailable.

**REFERENCES**


