Loxoscelism

David L. Swanson, MD\textsuperscript{a,\ast}, Richard S. Vetter, MS\textsuperscript{b}

\textsuperscript{a}Department of Dermatology, Mayo Clinic, Scottsdale, AZ 85259, USA
\textsuperscript{b}Department of Entomology, University of California Riverside, Riverside, CA 92521, USA

Abstract Loxoscelism (bites by spiders of the genus \textit{Loxosceles}) is the only proven arachnological cause of dermonecrosis. Although \textit{Loxosceles} spiders can be found worldwide, their distribution is heavily concentrated in the Western Hemisphere, particularly the tropical urban regions of South America. Although \textit{Loxosceles} bites are usually mild, they may ulcerate or cause more severe, systemic reactions. These injuries mostly are due to sphingomyelinase D in the spider venom. There is no proven effective therapy for \textit{Loxosceles} bites, although many therapies are reported in the literature. © 2006 Elsevier Inc. All rights reserved.

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A small percentage of the spider species in the world are medically important with the majority causing systemic injury. Spiders of the genus \textit{Loxosceles} cause necrotic dermatologic injury through a unique enzyme, sphingomyelinase D, found only in one other spider genus and several bacteria.\textsuperscript{1} The first inklings of association of spiders in general with dermonecrosis were made in the late 19th century in the Western Hemisphere.\textsuperscript{2,3} In the early 20th century, suspected association specifically to \textit{Loxosceles} spiders was made by Schmaus\textsuperscript{4} in North America and by several authors in South America.\textsuperscript{3} Definitive verifications of \textit{Loxosceles} spiders as the etiology were finally determined in 1947 in South America\textsuperscript{3} and 1957 in North America.\textsuperscript{5} Although all \textit{Loxosceles} species tested so far have the dermonecrotic sphingomyelinase D enzyme, most \textit{Loxosceles} spider species have yet to be shown to be medically important.

\textit{Loxosceles} spiders are predominantly found in the temperate and tropical regions of the Americas, Africa, and Europe.\textsuperscript{6} There are approximately 100 species of \textit{Loxosceles} spiders; 80\% occurring in the Western Hemisphere. Many of these species are only known from a few specimens or have a highly restricted distribution, and, therefore, their significance is only of academic interest. Of the remaining species that have widespread distribution, several live in areas that are not heavily populated by humans or have had their range reduced from habitat destruction; hence, envenomations are a moot point. This therefore leaves just a few species that are common, widespread, find human domiciles acceptable for survival, and pose a realistic medical threat.

Distribution of \textit{Loxosceles}

There are 11 native and two nonnative species of \textit{Loxosceles} spiders in North America.\textsuperscript{6,7} The brown recluse spider, \textit{Loxosceles reclusa}, (Fig. 1) is the best known and is responsible for most American envenomations. In subtropical North America, the brown recluse can be found from Texas to northern Georgia. The anecdotal opinion of
seemingly American arachnologists, which was corroborated by a recent distribution study, is that as one gets closer to the Gulf of Mexico, *Loxosceles* specimens become scarce. Despite abundant reports of loxoscelism in Florida, *Loxosceles* spiders are only rarely found in the state and are not a rational source of loxoscelism.

There are 38 *Loxosceles* species in Central America, 30 endemic exclusively to Mexico. Eleven of these are only known by a few specimens from their original Mexican locality of discovery. Loxoscelism in Central America is not well represented in the medical literature. It is not known whether this is due to the lack of known envenomations or the lack of reliable reporting of loxoscelism.

Six *Loxosceles* species are endemic to the Caribbean islands of Cuba, Puerto Rico, the Dominican Republic, Haiti, Jamaica, the Bahamas, and both British and American Virgin Islands. In addition, the Euroafrican tramp species, *L. rufescens*, is established in Bermuda.

There are 34 *Loxosceles* species in South America, all endemic to the continent with only one extending north into Panama; at least 16 species are only known from one to a few specimens from the original locality of discovery. There are three widespread species routinely reported to cause dermonecrosis: *Loxosceles laeta* (throughout much of South America) (*Fig. 2*), *L. intermedia* (Brazil, Argentina), and *L. gaucho* (Brazil). *L. laeta* possibly being the most toxic. The greater medical significance of these species may be due to some South American species (ie, *L. laeta*) being larger and reportedly having more deleterious venom than their northern counterparts.

In the rest of the world, *Loxosceles* species are not as well represented. *Loxosceles rufescens* occurs around the entire Mediterranean region and is a tramp species found very sporadically around the world. Although it gets transported readily, established populations are severely circumscribed (ie, often found only in the one building that originally gets infested). There are 12 *Loxosceles* species in the remainder of Africa, with isolated populations scattered widely on the continent (eg, Ivory Coast, Ethiopia, Namibia, South Africa). China has two *Loxosceles* species. In Australia, there are very small populations of *L. rufescens* around Adelaide, but they pose little threat.

In general, *Loxosceles* spiders are nocturnal, preferring to hide during the day in crevices and other places of refuge. In natural environments, they are found under rocks or in burrows of other animals where they make a small retreat web of flocculent silk. In human habitats, they are often found behind furniture, in basements, in attics, in cupboards, and other places where they can squeeze into a small cavity. The folded flaps of cardboard boxes are favored places for retreat. In a Brazilian study, *L. intermedia* and *L. laeta* were absent from natural environments and found in urban settings, predominantly indoors, with a preference for substrates of paper, wood, and construction materials.

In South America, *Loxosceles* spiders are known as *araña de detrás de los cuadros* (the spider behind the picture) or *araña de los rincones* (spider of the corners). In North
America, they are known as recluse spiders because of their tendency to hide in areas away from humans.

Identification of *Loxosceles* spiders

Many medical publications definitively state that *Loxosceles* spiders can easily be identified by a violin or fiddle pattern on the dorsal surface of the cephalothorax. Although this is true in principle, lack of expertise causes nonarachnologists (including physicians) to mistake many varied darkened forms on spider bodies as violin patterns.\(^8\,17\) Although several *Loxosceles* species can indeed be readily identified by a violin, using this overly simplified diagnostic identifier will lead to mistakes because some *Loxosceles* species have almost no pigmentation in the violin area and other species have dark maculae on the dorsal body surfaces which will mask or complicate identification. A more useful diagnostic feature is that *Loxosceles* spiders have six eyes arranged in nontouching pairs in a U-shaped pattern (Fig. 3). Most spiders have eight eyes and can be excluded as this medically important group. One must be aware, however, that the eye pattern is not totally exclusive; there are additional closely related spiders (genera *Scytodes* and *Sicarius*) that share the same eye pattern. *Scytodes* spiders have benign bites\(^18\); *Sicarius* spiders can be medically important and are discussed below.

Other spiders purported to cause necrosis

Over several decades, many additional spiders from a diverse number of spider genera have been implicated in dermonecrosis including orbweavers, wolf spiders, funnel-weaving spiders, etc. Much of this has occurred by the simple implication of spiders by patients presenting with dermonecrosis, but while lacking the definitive proof of a spider caught in the act of biting and properly identified. Many of these events have been reported under the blanket term of *necrotic arachnidism*, and, unfortunately, most of the implicated spiders have been falsely elevated to a status of medical significance through circumstantial implication and repetitive citation in the medical literature. In the early 21st century, prospective studies with verified bites of spiders have the capability to give varied amounts of venom in defensive biting and, accordingly, vary the severity of the bite injury.\(^32\)

Venoms are a mixture of proteins with similar electrophoretic profiles in the region of low molecular mass proteins (20-40 kD).\(^33\) The toxins in both *L intermedia* and *L laeta* seem to be equivalent. One 30- to 35-kD protein, a nonproteolytic sphingomyelinase D, is endowed with all biological properties ascribed to whole *L laeta* venom and sphingomyelinasases from *L intermedia* including dermonecrotic and platelet aggregation and complement-dependent hemolytic activities.\(^33\,34\) Antibodies to this protein block dermonecrotic reaction.\(^34\) The protein has been cloned using a cDNA library constructed from the venom gland of *L intermedia*.\(^35\) It is a 31-kD protein with a pI of 7.37. The amino acid sequence has been deduced as having signal peptide, propeptide, and untranslated 3’ region with 218 nucleotides in the cDNA. Monoclonal antibodies against the protein neutralized 90% to 97% of the dermonecrotic activity of venom, even when administered intravenously up to 6 hours after envenomation.\(^36\)

Investigators have also described broad enzymatic activities in tissue from *Loxosceles* venom. These activities include hyaluronidase,\(^24\) alkaline phosphatase,\(^24\) and esterase.\(^37\)
ATPase, sphingomyelinase D, but not phosphodiesterase, phospholipase A or C, or collagenase. It is questionable whether or not *Loxosceles* venom has protease activity. Early reports suggested protease activity using a common means of extracting spider venom that involved electrostimulation, which also releases gastric contents. The reported venom proteases degraded fibrinogen, fibronectin, entactin, heparin sulfate, and basement membranes. Using venom from microdissected venom apparatus, Rekow et al were unable to demonstrate protease activity against hemoglobin or casein. It is possible that *Loxosceles* spider venom may have proteinase proenzyme activity. After treatment with trypsin, spider venom from extracted apparatus contains two serine proteases. In addition, there are two metalloproteinases recently characterized. Venom therefore may have intrinsic venom metalloproteinase activity in addition to that occurring through victim metalloproteinase activation. *Loxosceles intermedia* spider envenomation induces cleavage of an endogenous metalloproteinase, resulting in cleavage of glycoporphins from the erythrocyte surface and facilitating complement-mediated lysis. This activation is mediated by the alternative pathway.

*Loxosceles* spider gastric contents contain proteases capable of cleaving native collagen, gelatin, fibrinogen, fibronectin, fibrin, and elastin. These gastric contents are unable to induce necrosis in the rabbit model. Although not adequate to cause ulceration of the skin, it is possible that gastric contents act synergistically with sphingomyelinase activity from the venom.

An additional synergistic cofactor for tissue injury may be secondary infection. *Clostridium perfringens* can be isolated in the venom and fangs of *L intermedia*. The presence of *Clostridium* toxin can strikingly enhance dermonecrosis in a rabbit model of loxoscelism.

Bites occur when the spider is pressed against flesh, typically while dressing or by a sleeping human rolling over on the spider at night. In heavily infested areas therefore, clothing and shoes should be shaken before dressing, and worn items such as garden clothing or sports equipment in storage should be rigorously inspected or stored in spider-excluding containers. The risk of bites by *Loxosceles* spiders is, nonetheless, not as common as often purported as people can live with dozens to thousands of *Loxosceles* spiders without a medical incident.

**Pathophysiology**

In milder cases, *Loxosceles* bites may simply cause a very mild urticarial reaction. In the more severe cases, the initial bite is painless, but this is followed over 2 to 8 hours by sharp, penetrating pain that progressively changes into a burning sensation. There may be two small puncta at the bite site (Fig. 4). The bite area pales and the area immediately surrounding the bite becomes red and edematous, with mild to severe pain secondary to vasospasm and ischemia. A blister may form, and over the several days after the bite, there is typically a blue violet color, hard, stellate, sunken center. There is anesthesia of the center. Spread may occur gravitationally. Sloughing follows (Fig. 5). Healing by second intent takes 6 to 8 weeks. Most bites are medically insignificant; however, extremely rare ulcers may be as large as 40 cm across and extend into deep muscles. Thighs, abdomen, and buttocks give the worst lesions and scarring.

Early in the course of loxoscelism, a generalized toxic petechial or morbilliform erythema can occur, suggesting the presence of a protective immunity. It may be accompanied by malaise, nausea, headache, and myalgia. Purpura may also be seen. The rash is abated by systemic steroids, but steroids have no effect on ulcer.

Especially in children, there may be fever, malaise, weakness, nausea, vomiting, hemolytic anemia, thrombocytopenia, and disseminated intravascular coagulation; this

![Fig. 4 Early presumptive L reclusa bite. The lesion is approximately 2 cm in diameter. Two small puncta are seen in the center.](image-url)

![Fig. 5 Presumptive L reclusa bite. The lesion is displaying a central ulceration.](image-url)
may occur in as many as 16% of patients. Myonecrosis and rhabdomyolysis from loxoscelism may induce renal failure. Coma and death may occur, typically in small children who sustained *L. reclusa* bites in South America. In North America, although fatal *Loxosceles* bites have been reported, there are still no definitely proven deaths; one loxoscelism expert feels that none of the reported fatal cases are convincing.

The dermatohistopathology of *Loxosceles* bites includes dermal edema, thickening of blood vessel endothelium, leukocyte infiltration, intravascular coagulation, vasodilatation, destruction of blood vessel walls, and hemorrhage. This mirrors the experimental histopathology seen with intradermal injections of venom in rabbits. Initially, experimental injection of venom results in vessel instability, cytoplasmic endothelial cell vacuolization, and blebs. There is loss of adhesion of the endothelial cells to their extracellular substrate as well as each other. During the first 4 hours, there appear edema, hemorrhage, vessel wall degeneration, plasma exudation thrombosis, neutrophil accumulation in and around blood vessels with intensive diapedesis, dermal collection of polymorphonuclear (PMN) leukocytes, and subcutaneous and muscular edema. Over the next 5 days, there is massive neutrophilic infiltration into the dermis and subcutaneous muscle, with vessel destruction, thrombosis, hemorrhage, myonecrosis, and coagulative necrosis.

The necrosis of skin seems at least somewhat dependent on the presence of PMN leukocytes and complement. Smith and Micks depleted circulating PMN leukocytes in rabbits using nitrogen mustard and found marked inhibition of necrosis induced by injected *L. reclusa* venom. They also found a similar inhibition of necrosis in guinea pigs by depleting circulating complement, using either intravenous aggregated human gamma globulin or intraperitoneal zymosan. On the other hand, Tambourgi et al found that C6-deficient rabbits and rabbits with cobra venom–induced complement depletion still showed histological evidence of collagen and muscle cell damage. They found active tissue metalloproteinases derived from PMN leukocytes and fibroblasts, and speculated that these, at least in part, may play a role in the induction of necrosis and hemorrhage.

Venom sphingomyelinase degrades the sphingomyelin component of the red blood cell membranes causing hemolysis. The hemolysis as well as the accumulation of PMN leukocytes appears to be related to the activation of circulating complement. Venom sphingomyelinase can induce hemolysis in vitro without complement. *L. reclusa* sphingomyelinase D also stimulates serum amyloid, but not C-reactive protein, to activate platelets, leading to thrombocytopenia. The platelet activation is via an adenosine S'-diphosphate release mechanism and is inhibited by indomethacin. Tumor necrosis factor is induced. Spread of toxin to underlying tissues and the systemic loss of vessel and glomerular integrity may be due to the effect of extracellular matrix molecule degradation by serine and metalloproteinases in the spider bite, and also due to hyaluronidase activity. Defective wound healing may be conceivably secondary to fibrinectin and fibrinogen lysis, as these are involved in the mechanisms of hemostasis and tissue repair.

### Diagnosis

The standard for diagnosis of spider bites is collecting and properly identifying the biting spider responsible for the cutaneous findings. Other diseases are frequently misdiagnosed as loxoscelism. These include staphylococcal or streptococcal infection, herpes simplex, herpes zoster, diabetic ulcer, fungal infection, pyoderma gangrenosum, lymphomatoid papulosis, chemical burn, *Toxicodendron* dermatitis, squamous cell carcinoma, neoplasia, localized vasculitis, syphilis, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema nodosum, erythema multiforme, gonococccemia, purpura fulminans, sporotrichosis, Lyme disease, cowpox, and anthrax.

One emerging condition that is commonly misdiagnosed as loxoscelism in particular, and as generic spider bites in general, is methicillin-resistant *Staphylococcus aureus* infection. This misdiagnosis is made in both nosocomial and community-acquired settings. Greater awareness of the expression and epidemiology of this bacterial infection is reducing reliance on spiders as the etiology of dermonecrosis.

Because of the large number of diseases that mimic loxoscelism and the infrequency of documented bites even

### Table 1  Suggested reporting standards for loxoscelism

<table>
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<th>1. Proved envenomation</th>
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<tr>
<td>The spider must be recovered immediately and in close proximity to a clinical reaction on skin. The spider must be identified by an experienced entomologist and kept for later verification. The details of the case must be complete and the patient must be followed up properly with all appropriate expert review of the diagnostic problem.</td>
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<tr>
<td>2. Probable envenomation</td>
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<tr>
<td>Spiders must be found in the immediate vicinity and these must be confirmed by an entomologist to be <em>Loxosceles</em>. Typical proved loxoscelism must be medically well known in the region. The cutaneous lesion must be wholly typical of loxoscelism, as decided by clinically experienced experts.</td>
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<tr>
<td>3. Possible envenomation</td>
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<tr>
<td>The bite appears typical to experienced physicians; however, no spiders can be recovered in the immediate vicinity. <em>Loxosceles</em> spiders must have been found in the region and other probable or proved bites must have occurred recently.</td>
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<tr>
<td>4. Focal necrosis of the skin.</td>
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<td>Region has no or few <em>Loxosceles</em> spiders, as verified by an entomologist, proven recent loxoscelism is uncommon, and no <em>Loxosceles</em> spiders can be recovered in the immediate vicinity of the patient.</td>
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in endemic Loxosceles areas, any diagnosis of loxoscelism should be considered highly suspect unless a spider is caught in the act of biting and can be identified by an expert or, in cases without definitive spider involvement, only if the clinician has sufficient experience with verified Loxosceles bites. Multiple lesions contemporaneously or sequentially on one patient, or lesions presented by multiple patients living communally, should lead toward diagnosis of a contagious disease rather than accidental spider envenomations. Chronic lesions (>2 to 3 months’ duration) will also exclude loxoscelism, and chronic cutaneous ulcer etiologies should be considered. In nonendemic Loxosceles areas, the absence of a recluse spider as evidence should exclude the diagnosis of loxoscelism. For the purposes of reporting, Anderson53 has proposed a standard nomenclature (Table 1).

**Laboratory diagnosis**

The diagnosis of loxoscelism remains a clinical judgment dependent on proof of a Loxosceles spider bite. There is at least one potential venom test that has been developed and tested experimentally, using an ELISA. The authors detected venom from rabbit test subjects up to 7 days after injection. Venom was recoverable from plucked hair and skin aspirates, but the greatest yield was with biopsy specimens. There is currently no commercially available assay for humans.

**Therapy**

The proper treatment of loxoscelism remains controversial. Reported therapies include hyperbaric oxygen, dapsone,52 antihistamines including cyproheptadine,52 antibiotics, dextran, glucocorticosteroids,53 vasodilators,74 heparin, nitroglycerin, electric shock, curettage, surgical excision, and antivenin.52 It seems reasonable at minimum to provide routine first aid: elevation, immobilization, application of ice, local wound care, and tetanus prophylaxis.

Dapsone has been recommended for over two decades, based on the prominent role of PMN leukocytes in the pathophysiology of the injury. Dapsone inhibits the PMN myeloperoxidase-hydrogen peroxide-halide generation of oxygen intermediates, as well as inhibiting chemotaxis.75 King and Rees76 found that pretreatment with dapsone markedly reduced skin lesion size in guinea pigs injected intradermally with partially purified L reclusa venom fraction. Dapsone reduced lesion size when administered to guinea pigs up to 16 hours after venom inoculation.77 Notwithstanding, Phillips et al78 found no benefit in rabbits when dapsone was administered after Loxosceles deserta venom inoculation compared to control. This has been more recently confirmed using L reclusa venom.79 Despite the common usage of dapsone, no prospective human study supports dapsone as an effective treatment for Loxosceles envenomations in humans.80

Dapsone causes hemolysis in all patients and may induce severe hemolysis with methemoglobinemia in patients deficient in glucose-6-phosphate dehydrogenase. Most patients have a 1- to 2-g drop in hemoglobin during therapy. Other side effects include headache, gastrointestinal upset, hepatitis, exfoliative dermatitis, rarely agranulocytosis, and motor neuropathy.81 The latter is usually seen in protracted therapy. Patients should have a baseline glucose-6-phosphate dehydrogenase assessed, and initial complete blood count and liver enzymes measured before beginning therapy. They should be monitored weekly while receiving therapy with dapsone for spider bites.

Systemic or intraleisional glucocorticosteroids are also commonly given. These may have less benefit on ulcer formation than to ameliorate the general systemic effects, including the reactive erythema.53 The systemic effects of Loxosceles toxin can be blocked in rabbits with systemic steroids when given 8 hours after toxin injection but not if delayed for 24 hours.82 Rabbits treated with 2 mg/kg methylprednisolone intramuscularly or intraleisionally within 2 hours of inoculation, followed by daily dosing for 2 days, had shortening of their eschar duration, whereas rabbits treated at 4 hours or longer did not.83 There was no difference in the size of the eschar or necrosis. Fardon et al74 however, found no benefit from intraleisional glucocorticoi steroids.

No benefit has been found in rabbits with oral metronidazole,83 local or intravenous diphenhydramine, or phentolamine.74

The rationale for cyproheptadine is to block serotonin-induced platelet aggregation and ischemia. Phillips et al78 found no benefit from cyproheptadine for rabbit L deserta venom injection compared to control when given after inoculation.

Several authors have advocated hyperbaric oxygen for the treatment of Loxosceles bites. Maynor et al84 treated 14 patients with hyperbaric oxygen in an uncontrolled study and reported benefit. The rationale was that hyperbaric oxygen would inactivate the sulphydryl-containing sphingomyelinase D in Loxosceles venom by oxidizing sulphydryl bonds. Also, hyperbaric oxygen increases tissue oxygen tension and causes PMN sequestration in the lungs, removing them from circulation. Svendsen85 treated six outpatients with undocumented spider bites in an uncontrolled study with oxygen given at 2 atm for 90 minutes twice daily for 1 to 3 days. All six had clinically deteriorating lesions at the time of therapy. Only three completed therapy and showed healing. Phillips et al79 found no benefit from hyperbaric oxygen in their rabbit model compared to controls. Hobbs et al86 found no differences between hyperbaric oxygen, hyperbaric oxygen plus dapsone, or dapsone alone in piglets when treated 24 to 72 hours after inoculation with L reclusa venom.

The idea behind treating Loxosceles bites with electric shock arose after reported successes using electric stun guns.
for field therapy of insect stings and poisonous snakebites. Osborn reported 147 cases of confirmed and suspected spider bites treated with high-voltage direct current. Sixteen patients had positive identification of L. reclusa. Treatment involved 40 to 50 kV·s⁻¹ delivered for 1 to 2 seconds per shock pulse. Two pulses were delivered through the center of the lesion, then four or more around the perimeter using a handheld stun gun. Therapy was given from 2 hours to 5 weeks after the bites. Improvement was reported by the patient or seen by the author in every case. Barrett et al. however, reported no benefit in guinea pigs from shock using four 1-second shocks under anesthesia 10 seconds apart with Parali/Azer and Guardian stun guns.

Auer and Hershey advocated early excision and grafting of necrotic spider bites greater than 1 cm in diameter. They observed more rapid healing in a small cohort of patients than that observed in nonsurgical patients hospitalized with possible Loxosceles envenomations. Rees et al. compared early surgical excision, within 0.5 to 3 days from the time of the bite, to delayed surgery after 14 days of dapsone therapy. In 31 patients with the clinical, unverified diagnosis of spider bites, patients “needed” smaller excisions for their ulcerated skin after pretreatment with dapsone.

Therapeutic L. laeta rabbit antivenom is available in South America and is in common use. Equine-derived antivenom is effective in mice and rabbits, but can be enhanced by refining with pepsin to obtain F(ab‘)₂ fragments. Other antivenoms have been used in animal studies. Barbaro et al. found that specific antivenoms against the five major medically important Loxosceles venoms in North and South America (L. gaucho, L. laeta, L. intermedia, L. reclusa, and L. desertica) completely neutralized their respective venoms after a 1-hour preincubation. Rees et al. compared dapsone, intralesional rabbit-derived L. reclusa antivenin alone, and dapsone plus antivenin in 17 documented patients with spider bites and found no difference in response. All patients were also treated with erythromycin. Lesions healed in an average of 20 days.

In high-risk areas, vaccination might hold promise. Araujo et al. cloned a protein homologous to L. reclusa protein. This protein functioned as effective vaccine in mice.

**Conclusions**

Loxosceles spiders are the only important cause of skin necrosis from spider bites. Loxosceles spiders are common in much of the tropical and temperate world. Considering how prevalent they are, human bites from Loxosceles spiders are uncommon. When bites occur, they are usually mild, but they can occasionally cause ulceration and rarely systemic symptoms. Other more common diseases mimic spider bites, and, therefore, unless the culprit Loxosceles spider is caught in the act, practitioners must be willing to challenge the diagnosis of Loxosceles bite. There is no evidence-based effective therapy for loxoscelism at the present time.

**References**


