

REVIEW ARTICLE

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Bites of Brown Recluse Spiders and Suspected Necrotic Arachnidism

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CUTANEOUS INJURY CAUSED BY SPIDER VENOM HAS BEEN RECOGNIZED by physicians in the United States only since the late 1950s, with recluse spiders (genus *loxosceles*) most frequently implicated. During the past five decades, the growing popular belief that spiders cause many cases of skin necrosis in the United States has resulted in the presumption that brown recluse spiders are to blame, even in geographic areas where they are extremely rare or nonexistent.

Among both physicians and the general public, the perceived threat of spider bites far exceeds the actual risk. The misdiagnosis of spider bites is given to a wide spectrum of dermatologic conditions, some of which are far more dangerous than a spider bite. Although much has been published about the pathophysiology and treatment of necrotic spider bites, therapeutic interventions continue without evidence-based justification.

Nearly 40,000 species of spiders have been described worldwide.¹ Almost all spider venom probably evolved for paralyzing prey — mostly insects, other arthropods, or small vertebrates. Although some spiders have defensive venom, it is usually not directed at humans and has little or no effect on mammalian tissue. A few spiders can cause deleterious envenomation, but most produce only minor injury; some are capable of causing skin necrosis in humans.

Although humans have always coexisted with spiders, the notion that spiders may cause necrotic skin ulcers is modern. Less than a century ago, Schmaus² first established the connection between spider bites and human skin injury (ulceration) in a case report documenting the bite of *Loxosceles reclusa* (reported as *L. rufescens*). In 1947, Macchiavello³ verified a suspected connection to *L. laeta* by producing necrosis in a guinea pig inoculated with spider venom. The first confirmed North American case of spider-bite ulceration was reported in 1957.⁴ In southern Brazil, loxoscelism is considered a serious public health problem, with 3000 annual reports of *loxosceles* bites.⁵ Spider bites are reported with increasing frequency, no doubt because of some overreporting.

During the past decade, some of the established scientific literature on spider toxicology from the latter part of the 20th century has been challenged. This article reviews evolving concepts of necrotic arachnidism.

EPIDEMIOLOGY OF ULCERATING SPIDER BITES

WHERE LOXOSCELES SPIDERS LIVE

In North America, ulcerating spider bites are caused by members of the genus *loxosceles*,⁶ which are found in the temperate and tropical regions of the Americas, Africa, and Europe.⁷ There are 11 species of native *loxosceles* spiders in North America.⁸ The brown recluse spider, *L. reclusa*, is responsible for most episodes of envenomation in its native range in central and southern states that include southeastern Nebraska, Kansas, Oklahoma, Texas, Louisiana, Arkansas, Missouri, Kentucky, Tennessee, Mississippi,

Alabama, northern Georgia, and southern portions of Ohio, Indiana, Illinois, and Iowa (Fig. 1).⁹ Five additional native loxosceles spiders occupy widespread areas in the southwestern United States. In Brazil, *L. intermedia*, *L. gaucho*, and *L. laeta* are medically important⁶; of these, *L. laeta* is the most toxic.⁷

Loxosceles spiders purportedly are transported beyond the areas where they are endemic in household goods and warehouse cargo.¹⁰ However, this logical but uncorroborated supposition has little effect on the actual epidemiology of loxoscelism, which essentially does not occur beyond the spiders' usual habitat.¹¹⁻¹⁴ Despite the fact that numerous medical articles have made the unsubstantiated claim that brown recluse spiders can be found throughout North America, these spiders are rarely verified in states where they are not endemic (one per state every several years, if at all).^{9,11,12} Diagnoses of bites of brown recluse spiders outside of areas where they are endemic are highly suspect.

LOXOSCELES SPIDER ACTIVITY

In areas where loxosceles spiders are endemic, buildings may support populations of these spiders,

which also thrive outdoors in much of their range.⁶ Indoors, they often hide in clothing, bedsheets, and blankets, particularly when such items are stored in a pile on a closet floor.¹⁵ The spiders have a large leg-to-body ratio, and their bodies are relatively flat, allowing them to escape into small crevices.¹⁶ Brown recluse spiders are nocturnal, and bites in humans (Fig. 2) usually occur at night⁶ in circumstances in which the spiders are threatened or trapped.¹⁵

IDENTIFICATION OF LOXOSCELES SPIDERS

The eye pattern is the easiest and most accurate way to identify loxosceles spiders (Fig. 3). Although most U.S. spiders have eight eyes, typically arranged in two rows of four, brown recluse spiders have six eyes arranged in pairs (dyads), with one anterior and two lateral dyads. This pattern is common to the 100 loxosceles species worldwide.

The pigmented, violin-shaped pattern on the cephalothorax is a distinguishing characteristic but is unreliable and commonly misinterpreted. The pattern is consistent in adult brown recluse spiders (although often faded in preserved specimens), but



Figure 1. U.S. Geographic Distribution of Verified Widespread Populations of Six Native Loxosceles Species.

The remaining native and nonnative species of loxosceles either are very rare or their distribution is highly circumscribed. The presence of recluse spiders is seldom verified outside the demarcated areas. More information is available at <http://spiders.ucr.edu/index.html>.



Figure 2. Verified Bite of *Loxosceles reclusa*.

Photograph courtesy of William V. Stoecker, M.D.



Figure 3. *Loxosceles reclusa*, Showing the Typical Violin Marking and Distinctive Six-Eye Pattern (Inset).

many *loxosceles* species in the western United States and some young brown recluse spiders have virtually no contrasting pigmentation in this area of the body. Other common eight-eyed spiders, such as cellar spiders (Pholcidae family), have similar patterns that result in their misidentification.⁸

Some North American spiders (e.g., spitting spiders, scytodes genus) have an eye pattern similar to that of *loxosceles*, but they are medically innocuous.¹⁷ Scytodes can be distinguished by their black stripes or by maculae on the dorsal surface of the cephalothorax and abdomen.

One of us (Mr. Vetter) is currently identifying any spider in the United States thought to be a brown recluse by the general public or members of the medical community. More than 1700 specimens from 36 spider families representing virtually every family of medium-sized, common brown spider in North America have been submitted. Spiders from the genus *kukulcania* (found in a southern distribution from California to Florida) are most frequently mistaken for brown recluse spiders (Fig. 4). One submission was a robust male *Kukulcania hibernalis* that had been mistakenly used in a medical school in Texas as a teaching example of the typical brown recluse spider. Of the specimens submitted thus far, 368 were native *loxosceles*, and only 1, collected in a home whose occupants had moved from Missouri, came from outside the known area of distribution (Fig. 1).

NONPATHOGENIC SPIDERS AND UNPROVEN SPIDER PATHOGENS

Other spiders that have been reported to cause necrosis include hobo spiders (*Tegenaria agrestis*) from the northwestern United States^{18,19}; yellow sac spi-

ders (*cheiracanthium* species)²⁰ and wolf spiders (Lycosidae family), found worldwide; crab spiders (*Sicarius testaceus* and *S. albospinosus*) from South Africa²¹; and white-tailed spiders (*Lampona cylindrata* and *L. murina*)²² and black house spiders (*badumna* species)²³ from Australia.

Recently, investigators have questioned whether many of these spider genera actually have a bite that can cause necrosis. For example, since the 1920s, *Lycosa raptoria* (a wolf spider) has been implicated as a major cause of necrotic arachnidism in Brazil.²⁴ The bite of at least one presumptive wolf spider (*L. antelucana*) has been documented with necrosis,²⁵ and high doses of wolf-spider venom injected into rabbit ears will induce necrosis.²⁶ However, a series of 515 documented bites of Brazilian wolf spiders (each with an identified spider) showed no evidence of local necrosis.²⁶ Likewise, no necrosis or even a clinically significant reaction was found in 130 confirmed cases of bites by *lampona* spiders²⁷ or in 25 cases of bites by *badumna* spiders.²⁸

In North America, *T. agrestis* (the hobo spider) was introduced from Europe in the 1920s or 1930s and spread into the Pacific Northwest by railroad.¹⁹ Its bite allegedly causes a necrotic wound similar to that of the brown recluse spider, along with a characteristic persistent headache.²⁹ Little documentation supports claims that hobo-spider bites actually induce necrosis.³⁰ In fact, in its native European habitat, the hobo spider is not considered poisonous to humans.³¹

DIAGNOSIS AND MISDIAGNOSIS

The diagnosis of spider bite is made by the collection and proper identification of the spider respon-



Figure 4. Kukulcania Species That Resembles *Loxosceles reclusa*.

This spider lacks a distinct violin pattern but is often envisioned as having one. It has eight eyes clumped together (inset).



Figure 5. Anthrax Misdiagnosed as Loxoscelism in an Area Where Loxosceles Spiders Are Not Endemic.

Reprinted from Roche et al.⁴⁴

sible for the cutaneous findings. Too often, the only available evidence is an oral report by the patient, which is often unreliable.³² Among 600 patients with suspected spider bites who sought medical care at either the University of Arizona Hospital or Los Angeles County Hospital, 80 percent of the bites were clearly caused by other arthropods (e.g., ticks, triatomid bugs, hymenoptera, bedbugs, fleas, flies, mites, blister beetles, blistering lepidoptera, solpugids [i.e., sun “spiders”], crickets, or even grasshoppers).³³ In 90 percent of suspected spider bites, the actual arachnid has been unavailable for identification.³⁴

Physicians should be especially wary of a history of presumptive loxosceles envenomation from a patient in an area in which loxosceles are not endemic. Medical diagnoses of bites by brown recluse spiders have outnumbered the historical verifications of the spiders in Florida,¹² Canada,¹³ the Pacific Coast,¹¹ and Colorado,¹¹ locations that invalidate most and possibly all of these diagnoses. One medical report from Colorado mistakenly identified loxoscelism as a locally common annual affliction,³⁵ despite the virtual absence of loxosceles spiders in the state.¹¹ Conversely, in areas with loxosceles populations, recluse spiders are found commonly and abundantly in homes in which no known incidents of envenomation have occurred.^{36,37} Alleged bite victims in areas where loxosceles spiders are endemic submit the spiders about 10 percent of the time.³⁸⁻⁴⁰

A wide array of infectious and noninfectious conditions are frequently misdiagnosed as the bites of brown recluse spiders, including 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,⁹ the Stevens–Johnson syndrome, toxic epidermal necrolysis, erythema nodosum, erythema multiforme, gonococemia, purpura fulminans,³³ factitious injury,⁴¹ sporotrichosis,⁴² and Lyme disease.⁴³ During the anthrax bioterrorism events in 2001, an anthrax victim on the East Coast (where brown recluse spiders are not endemic) received a diagnosis of loxosceles spider bite (Fig. 5).⁴⁴ A broad spectrum of dermatologic diagnoses should be reviewed when considering loxoscelism (Table 1).

Since numerous diseases mimic loxoscelism and since documented bites are rare, any diagnosis of loxoscelism should be considered highly suspect, even in households heavily infested with loxosceles, unless a spider is caught in the act and can be identified by an arachnologist. Diagnosis remains a clinical judgment dependent on proof of a loxosceles spider bite. Use of an enzyme-linked immunosorbent assay to detect venom has been tested in rabbits.³⁴ This assay detected venom up to seven days after injection. Venom was identified in plucked hair and skin aspirates, and especially in biopsy specimens. No commercially available assay exists for humans.

TREATMENT

Proper treatment of loxoscelism remains controversial. Initial care, at a minimum, should include rou-

Table 1. Conditions Potentially Misdiagnosed as Bites of a *Loxosceles* Spider.*

Infections
Atypical mycobacterial infection: <i>Mycobacterium ulcerans</i> , <i>M. tuberculosis</i>
Bacterial infection: staphylococcal, streptococcal, Lyme disease, cutaneous anthrax, syphilis, gonococemia, rickettsial disease, tularemia
Deep fungal infection: sporotrichosis (<i>Sporothrix schenckii</i>), aspergillosis, cryptococcosis
Ecthyma gangrenosum: <i>Pseudomonas aeruginosa</i>
Infection with environmental pathogens (e.g., <i>Chromobacterium violaceum</i>)
Parasitic infection: leishmaniasis
Viral infection: herpes simplex, herpes zoster
Vascular occlusive or venous disease
Antiphospholipid-antibody syndrome
Livedoid vasculopathy
Small-vessel occlusive arterial disease
Venous stasis ulcers
Necrotizing vasculitis
Leukocytoclastic vasculitis
Polyarteritis nodosa
Takayasu's arteritis
Wegener's granulomatosis
Neoplastic disease
Leukemia cutis
Lymphoma (e.g., mycosis fungoides)
Primary skin neoplasms: basal-cell carcinoma, malignant melanoma, squamous-cell carcinoma
Chemical, thermal, or traumatic injuries, including factitious injuries
Other conditions
Calcific uremic arteriolopathy
Cryoglobulinemia
Diabetic ulcer
Langerhans'-cell histiocytosis
Lymphomatoid papulosis
Other arthropod bites
Pemphigus vegetans
Poison ivy or poison oak
Pyoderma gangrenosum
Pressure ulcers
Radiotherapy
Septic embolism

* Data are adapted from Isbister and Whyte.⁴⁵

tine first aid: elevation and immobilization of the affected limb, application of ice, local wound care, and tetanus prophylaxis. Supportive care should follow. Reported specific therapies include hyperbaric oxygen, dapsone,³⁴ antihistamines (e.g., cyproheptadine),⁴⁶ antibiotics, dextran, glucocorticoids,⁴⁷ vasodilators,¹⁶ heparin, nitroglycerin, electric shock, curettage, surgical excision, and antivenom.³⁴

There is no consensus concerning the efficacy of any reported therapy; none have been subjected

to controlled, randomized trials. Many treatments are costly, painful, or potentially toxic. Because the injury from the bite of a brown recluse spider is usually self-limited and typically heals without medical intervention,⁴⁸ controlled trials would be essential to justify treatment before advocating any particular therapy.

DAPSONE

Dapsone, a sulfone antibiotic, has been recommended as a treatment for more than two decades because polymorphonuclear leukocytes are thought to play a prominent role in the pathophysiology of loxosceles-induced skin necrosis. Dapsone inhibits both chemotaxis and the polymorphonuclear myeloperoxidase–hydrogen peroxide–halide generation of oxygen free radicals.⁴⁹ King and Rees⁵⁰ observed that pretreatment with dapsone markedly reduced the size of skin lesions in guinea pigs injected with partially purified *L. reclusa* venom fraction. Dapsone also reduced lesion size in guinea pigs when administered up to 16 hours after envenomization.¹⁵ These observations notwithstanding, Phillips et al.⁵¹ found no benefit from dapsone in rabbits that had been inoculated with *L. deserta* venom as compared with controls. Despite the common use of dapsone, no prospective study in humans supports it as an effective treatment for loxosceles bites.⁵²

A major concern with using dapsone is that it causes some degree of hemolysis in all patients and may induce severe hemolysis with methemoglobinemia in patients who are deficient in glucose-6-phosphate dehydrogenase.⁵³ In most patients, hemoglobin levels are decreased by 1 to 2 g during therapy. Other side effects may include headache, gastrointestinal upset, hepatitis, exfoliative dermatitis, agranulocytosis (rarely), and lower motor neuron toxicity.⁵⁴ This last side effect is usually observed in patients receiving protracted therapy. Before dapsone is administered in patients with spider bites, a baseline assessment of glucose-6-phosphate dehydrogenase, a complete blood count, and a test of liver enzymes should be performed and be repeated weekly while the patient is receiving the drug.

GLUCOCORTICOIDS

Systemic or intralesional glucocorticoids are also commonly administered to patients with spider bites. Glucocorticoid therapy may not retard the formation of ulcers as much as it helps ameliorate the general systemic effects of the bite, including possible reactive erythema.¹⁰ In rabbits, the systemic

effects of loxosceles toxin can be blocked with systemic glucocorticoids up to eight hours after injection of the toxin.⁵⁵ Rabbits treated with 2 mg of methylprednisolone per kilogram of body weight, given intramuscularly or intralesionally within two hours after venom inoculation, followed by daily dosing for two days, had a shorter eschar duration than did rabbits that were treated four hours or more after the bite,⁵⁶ though no difference was found in the size of the eschar or the extent of the necrosis. In contrast, Fardon et al.¹⁶ reported no benefit from intralesional glucocorticoids in rabbits that were treated six hours after venom inoculation.

OTHER DRUG THERAPY

No benefit has been found for oral metronidazole,⁵⁶ local or intravenous diphenhydramine,¹⁶ or phenolamine as a treatment for loxosceles toxin in rabbits.¹⁶ Cyproheptadine has been used in humans because it blocks serotonin-induced platelet aggregation and ischemia, but Phillips et al.⁵¹ found that it had no additional benefit for the treatment of rabbits inoculated with *L. deserta* venom as compared with controls.

HYPERBARIC OXYGEN

Several authors have advocated the use of hyperbaric oxygen to inactivate the sulfhydryl-containing sphingomyelinase D in loxosceles venom by oxidizing sulfhydryl bonds. The treatment also increases oxygen tension in tissue and depletes polymorphonuclear leukocytes by pulmonary sequestration. In a study without controls, Maynor et al.⁵⁷ reported beneficial effects in 14 patients who were treated with hyperbaric oxygen. In another uncontrolled study, Svendsen⁵⁸ treated six outpatients who had clinically deteriorating lesions due to undocumented spider bites with oxygen administered at 2 atm for 90 minutes twice daily for one to three days. Two patients discontinued therapy because of claustrophobia; all six experienced uneventful healing. Hyperbaric oxygen has not been observed to be of benefit in experimental models using rabbits⁵¹ or piglets, even in conjunction with dapsone 24 to 72 hours after inoculation with *L. reclusa* venom.⁵⁹

ELECTRIC SHOCK

The rationale for treating loxosceles bites with electric shock arose after the reported success of electric stun guns for field therapy of insect stings and poisonous snakebites.⁶⁰ Osborn⁶¹ reported on 147 patients with confirmed and suspected spider bites

who were treated with high-voltage direct current. Among these, 16 patients had positive identification of *L. reclusa*. Treatment entailed energies of 40 to 50 kilovolt-seconds delivered for one to two seconds per shock pulse. Two pulses were delivered from a handheld stun gun through the center of the lesion and then four or more pulses were administered around the perimeter. Therapy was administered two hours to five weeks after the bites had occurred. In every case, improvement was reported by the patient or observed by the author. However, Barrett et al.¹⁵ reported no benefit to using two types of stun guns to shock anesthetized guinea pigs that had been exposed to *L. reclusa* venom; in this case, four 1-second shocks were administered 10 seconds apart.

EXCISION AND GRAFTING

Auer and Hershey⁴⁶ advocated excision and grafting of all necrotic spider bites with ulcers larger than 1 cm in diameter. They observed more rapid healing in a small cohort of patients who were treated with this regimen than in a group of patients hospitalized with possible loxosceles bites who were not treated surgically. Rees et al.⁶² compared early surgical excision, 12 hours to 3 days after a bite, with delayed excision, after 14 days of dapsone therapy. Among 31 patients with an unverified clinical diagnosis of loxoscelism, smaller excisions of ulcerated skin were required in the 17 patients pretreated with dapsone than in the 14 patients who were not pretreated.

ANTIVENOM

Commercial antivenom is not available in the United States. Therapeutic *L. laeta* rabbit antivenom is available in South America,⁶ and specific or polyvalent antivenom is used for presumed loxoscelism, especially in Brazil.⁶³ Equine-derived antivenom is effective in mice and rabbits and can be enhanced by treating the preparation with pepsin to obtain the F(ab')₂ fragment.⁶⁴ Other antivenom preparations have been used in animals. In 17 patients with documented spider bites, Rees et al.⁶⁵ found no difference in response in a comparison of dapsone alone, intralesional rabbit-derived *L. reclusa* antivenom alone, and dapsone plus antivenom. Gomez et al.⁶⁶ documented the effectiveness of intradermal antivenom administered in rabbits within four hours after inoculation with *L. deserta* venom; dermonecrosis did not attenuate if the antivenom was administered more than eight hours after inoculation.

In areas where *Loxosceles* spiders are endemic, vaccination might hold promise. Araujo et al.⁵ cloned a protein homologous to *Loxosceles* dermonecrotic toxin from a complementary DNA expression library made with *L. intermedia* venom glands and expressed in *Escherichia coli* cells as a fusion protein with β -galactosidase (called Li-rec protein). This protein functioned as an effective vaccine in mice.

SUMMARY

Loxosceles spider bites are the only proven medically important cause of necrotic arachnidism in North America, and loxoscelism occurs far less commonly than is perceived by patients or physicians. In patients with verified spider bites, an accurate diagnosis can be made only if the biting spider is identified by an experienced arachnologist. An offending spider that is found in an area where *Loxosceles* spiders are not endemic is most likely not *Loxosceles*, and necrosis is unlikely.

In rare instances, bites from brown recluse spiders can cause clinically important dermal necrosis and subsequent scarring, but even severe necrosis is rarely life-threatening. Because of the tendency for medical reports to highlight noteworthy extreme cases, physicians may be unaware that the bite of a brown recluse spider is typically self-limited and self-healing, without long-term consequences.⁴⁸

Patients often overemphasize spider involvement in idiopathic wounds, a tendency that can misdirect

physicians toward an erroneous diagnosis. Physicians should be skeptical of any undocumented history of a spider bite and should entertain a broad differential diagnosis before attributing a skin ulcer to a spider bite. Misdiagnosis of an ulcer as loxoscelism delays proper treatment, placing the patient at risk.

There is no therapy with proven efficacy for loxoscelism. Many questionable treatments have been tried in patients with an unverified diagnosis, and the medical literature on loxoscelism has been obfuscated by misdiagnosed conditions. Both situations have inflated the spectrum of symptomatology, which may partly explain the confusion about therapeutic efficacy.

Most practitioners would probably prescribe dapsone in patients with documented *Loxosceles* bites, but even with this therapy, there is marginal evidence to support its use. Dapsone has potentially serious toxicity and should be prescribed judiciously. Other therapies, such as glucocorticoids, hyperbaric oxygen, and early excision, are also of unproven value. In questionable cases, the best approach may be the conservative use of simple first aid and local wound care.

Recent advances in medical arachnology are resulting in a reassessment of how to approach patients with suspected necrotic spider bites. With refinement in the epidemiology of *Loxosceles* bites and a greater understanding of the pathophysiology of necrosis, physicians are acquiring the tools to diagnose and treat loxoscelism more effectively.

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