Missouri Brown Recluse Spider: A Review and Update

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Almost every physician in Missouri knows of the medical connection between a distinctive painful focal necrosis of the skin and the bite of the local spider, *Loxosceles reclusa*. Most know that this connection was discovered in 1957 by Atkins and Flynn working at the state medical school in Columbia.[1,2] Twenty years later in 1978, again in Columbia, Campbell and Forrester discovered the chemical agent that causes the necrosis in skin, sphingomyelinase-D.[3,4,5] The enzyme affects platelets primarily.[6,7,8] Prior to these discoveries, local farmers had long recognized that some local spider had a terrible bite, but they didn't know which spider or why. A comparable experience with the bite of a similar spider, *Loxosceles lata* in Chile had preceded the medical discoveries in the United States, but no one knew of it, because it was reported in Spanish, only in their local journals, and in 1957, Medline searches didn't exist.[9]

After the initial description of cutaneous loxoscelism, other authors flocked to report cases and their own experiences.[10-20] Unfortunately, very few were able to prove that recluse spider bites actually were the cause of diseases they described. The entire loxoscelism literature is deficient in failing to produce the evidence that the bite of the *Loxosceles reclusa* was the cause of the illness reported. Especially in publishing new clinical findings, or exceptional cases or presumed deaths, credibility must be a premier concern. The spider must be recovered on the site promptly and identified expertly. Clinical impression alone, without other physical evidence, is not sufficiently convincing. At the minimum, all reports of entirely new clinical observations must be entirely persuasive. In this regard, the early clinical literature about loxoscelism is almost useless. For instance, several deaths from loxoscelism were reported in medical journals, but none of the reports is convincing.[21-25] We are not aware of any verifiable deaths caused by the bite of the North American brown recluse spider.

Thirty years of medical experience with loxoscelism only has added my opinion to those early assertions by Missouri farmers, that the disease is painful and frightening but it is not dire. This outlook is important in making any choice about therapy today. Almost all brown recluse spider bites heal nicely in two to three months without any medical treatment at all. Also the long-term medical outcome is excellent without any treatment. With some exceptions, it is unreasonable to advise major treatment for any properly diagnosed case. One must consider the risks, costs, time lost, fear, pain, wasted resources, and misdirection involved in such treatments. Current treatments include hyperbaric oxygen,[26,27] electric shock, vasodilator drugs, antibiotics, antihistamines, and, perhaps the best known, dapsone.[28] Anecdotally, various antivenins, anticoagulants, and antiseizure medications have been tried.

For awhile, in the 1960s, surgeons excised and closed the entire area of the bite as early as they could, just as they might do in debriding streptococcal necrotizing fasciitis.[29,30,31] Even apart from the huge costs, effort, and time lost, this treatment proved to be a medical failure. The wounds often failed to heal; grafts didn't take. As experienced therapists know, in almost all cases of cutaneous loxoscelism, time improves the situation impressively. The area of apparent necrosis will be greatly reduced naturally by 30-60%, or even more, in the first week of conservative therapy, and then the wound will heal with much less scar than is created by early excision. In my opinion, early debridement without closure or grafting also results in delayed healing, more scarring, and without relief of pain or reduction in risks. Excision of a necrotic skin site may be advisable, especially for the rare, large lesion, but only after 6-8 weeks of

wound care, by which time the adjacent tissues seem to recover and normal healing becomes possible. All in all, I advise that early surgery is counterindicated in the care of cutaneous loxoscelism.

Systemic loxoscelism is uncommon, especially in adults. By systemic loxoscelism, I refer to the hemolytic syndrome which defines this disease by our present knowledge.[32] There is a generalized inflammatory and immunologic systemic response, as shown in the toxic erythema, but these can be considered part of cutaneous loxoscelism. The hemolysis is Coombs negative exclusively in our series of patients, and occurs without measurable coagulopathy in most adults. The presence of a sustained coagulopathy with hemolysis indicates severe systemic loxoscelism. We estimate that we have seen or reviewed about 1,000 credible recluse spider bites, and we have seen about a dozen cases of impressive, sustained hemolysis. As a referral center, we gather unusual cases. It would be fair to estimate that systemic loxoscelism occurs in much less than 1% of cases of focal necrosis of the skin due to loxosotoxin.

Even when the patient does have free hemoglobin in their circulation and in their urine, this hemolytic episode usually is self-limited and needs no special treatment. In a very few cases (only four in 30 years) we recognized a coagulopathy that could pose some threat, but it always cleared up promptly with hydration alone. Again the more cautious approach to treatment seems best.

Much more of a concern to most patients is the itching and burning symptoms of the generalized toxic erythema caused by loxosotoxin.[33] This common cutaneous reaction mimics both a common papular drug reaction and a rubelliform viral infection, either of which could be easily misdiagnosed. This pruritic or painful eruption can occur within a few hours of the bite and persist for a week, ending with scaling and peeling of the hands that recalls pictures of scarlet fever rashes. At least 80% of our patients have some mild toxic erythema if one looks for it carefully on the skin. At the minimum, there may be only a persisting macular erythema (for two to three days) on the torso. Their skin feels hot and tender to the patient and this symptom may be reported erroneously as fever. Most have only the truncal papular rash but a few have involvement of arms and legs and, rarely, palms and soles. The pruritus may be much worse for the patient than the painful focal necrosis, in which case – in my opinion – short term treatment with oral steroids is a reliable remedy (for instance, Prednisone 60 mg in trial dose, taper-in only five days. Give once a day, a.m. dose). Patients with the toxic rash usually feel malaise, and even myalgia or arthialgia. We have seen one very ill patient with a toxic rash that resembled an erythroderma, and with a very long recovery time.

As to clinical presentation, and the early diagnosis or management, the prime credo for the physician is to consider necrotizing cutaneous infection as the first diagnosis whenever you recognize focal necrosis in skin. Consider loxoscelism only after excluding infection. All of our proven recluse spider bites have been under clothing, mostly on the thigh, upper arm or lateral torso. I have never seen a proven bite on the hand or foot, or face. Bites under the collar on the neck do happen, but are uncommon. Brown recluse spider bites cause clean infarctions in the skin. All medically significant recluse spider bites have central necrosis, that is, all of them are seen initially as central sinking blue-gray macules on the skin with a wide halo of mixed erythema and vasoconstriction (red-white-blue). If the central lesion is urticarial or nodular, another kind of injury is involved, not a recluse spider bite. Elderly people with diabetes, chronic liver disease, or alcoholism most often appear with spontaneous necrotizing fasciitis, while healthy children and young adults are the usual patients with loxoscelism.

How might we best anticipate necrotizing infection? Look for an inflammatory core lesion, rather than the clean infarction of a spider bite. Look for local tender adenopathy, exudation, steady-progression, multiple lesions, early severe systemic toxicity, high fever, hypotension, and a high white count with many immature PMNs as suggestions of deep infection. The patients seem very ill. Immediate biopsy and examination for bacteria is the diagnostic procedure of choice. Rapid response is essential in the care of necrotizing fasciitis. Surgery usually is required in the care of necrotizing fasciitis.

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In contrast, cutaneous loxoscelism is a focal, single necrotic lesion without adenopathy or lymphangitis early, not exudative, not progressive after about 18-24 hours, and associated with only mild fever or toxicity in almost all cases. The patients do not seem very ill. With experience, making this distinction is feasible, and with a few hours of close clinical attention to the rate of progression of the illness, the decision between infection and envenomation can be made reliably.

Most recluse bites referred to us arrive already on high-dose antibiotics. We have never encountered an infected bite, even in unmedicated patients. Antibiotics are not necessary, and may lend to a false sense of security or even induce errors in the proper diagnosis of cellulitis.

It is best not to use antibiotics except for the credible diagnosis of infection, as against loxoscelism.

We have had only two patients, both small children, who had proven loxoscelism, and also had kidney failure due to rapid hemolysis. One recovered spontaneously, and one was treated by peritoneal dialysis because a mild coagulopathy was present. Renal failure is an extremely rare complication of systemic loxoscelism, but a most important concern.

In typical systemic loxoscelism, about 1/4 of the blood mass (4 g/dL) is lysed, causing blood to appear in the urine within 24 hours, but to be cleared rapidly (48 hours), especially in young adults. Some may lose 7-8 g/dL of hemoglobin. Occasionally, the patients look very pale and jaundiced, but often no skin color change is noticed. Most are children and they feel faint, weak, and anxious. Some are somnolent and hypotensive. When encountering significant hemolysis with proven loxoscelism, record the decline in the hematocrit, and of increase of hemoglobin in the urine. We recommend these additional steps for full documentation: Order a STAT LDH and a prothrombin time. Both can be obtained quickly. The LDH is never normal in the presence of hemolysis and prothrombin time is quite specific for inappropriate coagulation. Follow the platelet count and level of fibrin-split products. Check for an increase of free hemoglobin in fresh urine, hourly. Maintain hydration and consider therapy with fresh frozen plasma. Resist the impulse to transfuse whole blood in this brief hemolytic episode. For the record or for publication, include a serum haptoglobin and Coomb's test, but these tests cannot be returned quickly. We have not yet cared for a patient who required treatment for the coagulopathy. Pleasantly, the natural disease is self-limited.

In a few adults, blood may appear transiently in the urine, indicating hemolysis, not renal injury, only to resolve in only a few hours. We have seen no cases of renal injury due to the venom except as caused by free hemoglobin. Similarly we have seen no pancreatitis or injury to the liver in any patients. Coagulopathy in adults from an ordinary spider bite is almost never seen.

Treatment

Conservative care without any drugs is entirely proper. With no physician's care at all, most recluse spider bites show an excellent outcome. In about a week, pain subsides and usually there is a striking reduction in the size of the necrosis. Medications for pain relief ought not be required beyond one week, at most. Healing may be slow, but all lesions heal, and mostly with a minimum of scarring. Surgery can offer little or nothing more. No medications are required to treat brown recluse spider bites.

I do treat the toxic erythema if the symptoms are severe. I am willing to revise bad scars, or debride very large lesions, but only after a long trial of natural healing. After reviewing many cases in which we used systemic steroids early or late or not at all, high dose and low dose, I could find no advantage in treating with systemic corticosteroids, as regards either the necrosis in the skin or the hemolysis.

Perhaps because of many reports in the surgical literature, dapsone therapy has been popular especially in emergency rooms. There are no prospective randomized blind studies in humans to indicate any benefit at all. In our one simple animal trial, pretreatment of rabbits (not humans) with dapsone did not lessen the necrosis due to small doses of loxosotoxin. Dosage may be critical. Also, venoms are "species specific," so only studies in humans would be decisive. Dapsone is not a trouble-free drug.[34,35,36] Dapsone is known to aggravate hemolysis, and

loxoscelism already entails hemolysis. Only early treatment is critical, and because one should have a test for glucose-6-PD deficiency prior to treatment, delay is usually imposed. Other adverse effects can follow on dapsone therapy.[37] But, in any event, can such treatment improve on the excellent natural outcome without dapsone? Nothing in any kind of therapy has been shown to be beneficial, as compared to the natural outcome.

As to the prevention of bites, decades of experience and studies have shown that pesticides will not rid the home of spiders, either immediately, or in the months after the fumigations. The spiders are well concealed and well protected. They also can simply return into the building later. They are resistant to residual insecticides because they lack absorbant foot pads. Do not promise the patient that they can be spider free by any extermination as long as they reside in the habitat.[38] Similarly, no public building within the habitat can be kept entirely free of loxosceles by any means.

In an overview, the value of studying venomous bites of any kind is to expose the mechanism of the disease. The amount of venom in one spider is minute, and yet can bring about a massive hemolysis. An enticing research problem is the mechanism by which this hemolysis comes about. We can look back 40 years with some regret at the disorganized approach to clinical research on loxoscelism, and we can resolve to do much better. We are closing the first half-century of the study of Missouri's most famous spider.[39,40] We can expect more marvelous results in the next 50 years. MoMed

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