LETTERS TO THE EDITOR

SPIDER BITES: ADDRESSING MYTHOLOGY AND POOR EVIDENCE

Dear Sir:

The August 2004 issue of the American Journal of Tropical Medicine and Hygiene contains a review of spider bites and spider envenoming that fails to do justice to this complex topic.\(^1\) It is based on a selective review of the literature which overemphasizes case reports of the severe effects of spider bites, many of them unconfirmed and merely suspected. Much of the information provided, particularly in relation to the problematic term “necrotic arachnidism,” is erroneous. Many of the references are incorrectly cited and in some cases misinterpreted, resulting in conflicting and confusing statements. We will address a number of major problems and errors in the review. Readers are directed to recent reviews on spider bites,\(^2,3\) antivenom therapy for spider bites,\(^4\) and the mythology of necrotic arachnidism,\(^5–7\) for current information on this topic.

Spider bites are common in most parts of the world, but the vast majority cause only minor effects. A more important problem in many areas is the exaggeration of spider involvement, which historically has been perpetuated by articles such as this one by Diaz, leading to overzealous diagnosis of bites, overaggressive treatment of idiopathic lesions, and improper treatment of conditions having nothing to do with spiders.\(^5–9\) Diaz exaggerates the importance of spider bites, suggesting that the majority cause clinically significant envenoming and that skin lesions are common. A large study in Australia\(^10\) demonstrated that most bites were trivial despite the presence of the redback spider (\textit{Latrodectus hasselti}, a widow spider) and, in a restricted area, the potentially lethal Australian funnel-web spiders (\textit{Atrax} and \textit{Hadronyche} spp.). In some other parts of the world, particularly where snake or scorpion envenoming are major health issues, spider bites are not a significant problem and patients rarely go to a hospital.

Diaz proposes six clinical syndromes associated with spider bites that are based neither on original research nor on systematic reviews of the literature. Although they include a number of previously defined syndromes (such as latrodectism and loxoscelism), Diaz introduces unhelpful terminology for the practicing clinician that is based on a flawed review of the literature. The division of the already misused term “necrotic arachnidism” into “loxoscelism” and other “non-Loxosceles necrotic araneism” is not based on any cited evidence and perpetuates mythology and poor science in spider toxicology. Recent evidence has demonstrated that the spiders reiterated by Diaz to cause necrosis do not in fact cause such an effect.\(^10–13\) The term loxoscelism is appropriate because it describes the effects of bites by a specific spider genus. The final syndrome created by Diaz is a mixture of allergic, traumatic, and chemically induced injuries not attributable to spider bites. Clinical effects of spider bite are best related to the particular species or genus of spiders responsible for the bite (e.g., latrodectism). Other classifications are best avoided.

The description of latrodectism is confusing and places too much emphasis on case reports and older reviews. There are few prospective studies of widow spider bites, but a recent review of the clinical effects for different \textit{Latrodectus} species based on the largest and most accurate studies available suggested that most species cause similar effects (excepting \textit{L. geometricus} which appear to cause much less severe effects).\(^2\) Apparent differences may be a result of dissimilar study designs (mainly retrospective without follow up), differing patient groups included (poison information center calls, hospital admission, or antivenom reports to the manufacturer), and widely differing definition of clinical effects and reporting biases. In addition, there were large differences in the reported effects for a single species, \textit{L. hasselti}, in three Australian studies of varying design,\(^14–16\) further supporting the dissimilarity in studies being the reason for the perceived differences in effects between species. Until prospective data exist for more species, it is reasonable to assume that latrodectism appears to present a similar clinical syndrome worldwide based on the best available evidence.

The description of many features of latrodectism in the review is very misleading. Diaz provides an enormous catalog of clinical effects culled from reviews and case reports, providing no indication of the frequency of each effect. In making such a list, each entry is given equal weight such that a pathognomonic sign cannot be differentiated from something that has only been reported once. This is clinically unhelpful and does not provide a representative picture of latrodectism. \textit{Latrodectus} bites are characterized by pain. The pain can be at the bite site, radiating proximally from distal limb bites, or abdomen, back, or chest pain. This is usually associated with non-specific systemic features (nausea, vomiting, headache, lethargy, and malaise), local and regional diaphoresis, and less commonly other autonomic and neurologic effects. In some geographic regions, muscles spasms are described, but manifestations such as fasciculations, local muscle spasms, weakness, respiratory arrest, rhabdomyolysis, and seizures appear to be relatively rare based on larger studies.\(^7\) Diaz also suggests that \textit{Latrodectus} bites are an outdoor phenomenon; this is misleading because these spiders frequent buildings, which is where many bites occur. The cause of latrodectism-associated deaths is not discussed and the rarity of such an outcome is not emphasized.

Widow spider antivenom is available in some areas where widow spider bites occur, including Australia, America, and South Africa. Antivenom is produced by immunizing horses with venom gland extract, usually combined with an adjuvant to enhance the immune response. The horses are not bitten by the spiders as stated by Diaz! \textit{Latrodectus} antivenoms are either F(ab\(^1\))\(_2\) (Australia) or IgG antivenoms, but there are currently no Fab \textit{Latrodectus} antivenins as Diaz states. The dose, route of administration, and infusion time differ for each \textit{Latrodectus} antivenom and the product information should be consulted before use. The risk of adverse reactions appears to be low for most \textit{Latrodectus} antivenoms, although this has only been investigated with large studies in Australia where administration was almost exclusively by the intramuscular route.\(^14\) The early reaction rate appears to be higher with the American black widow antivenin, a horse-derived unrefined IgG antibody, but few data are available for this
Approach to the investigation and diagnosis of necrotic skin ulcers of uncertain etiology presenting as suspected spider bites*

A Establish whether or not there is a history of spider bite
  Clear history of spider bite (better if spider is caught)
  Refer to information on definitive spider bites
No history of spider bite
  Investigation should focus on the clinical findings: ulcer or skin lesion
  Provisional diagnosis of a suspected spider bite is not helpful
B Clinical history and examination
  Important considerations
    Features suggestive of infection, malignant processes, or vasculitis
    Underlying disease processes: diabetes, vascular disease
    Environmental exposure: soil, chemical, infective
    Prescription medications
    History of minor trauma
    Specific historical information about the ulcer can assist in differentiating some conditions
    Painful or painless
    Duration and time of progression
    Preceding lesion
C Investigations
  Skin biopsy
    Microbiology: contact microbiology laboratory prior to collecting specimens so that appropriate material and transport conditions are used for fungi, *Mycoplasma* spp., and unusual bacteria
  Histopathology
    Laboratory Investigations: may be important for underlying conditions (autoimmune conditions, vasculitis), including, but not be limited to
    Biochemistry (including liver and renal function tests)
    Complete blood count and coagulation studies
    Autoimmune screening tests, cryoglobulins
    Imaging:
      Chest radiography
      Colonoscopy
      Vascular function studies of lower limbs
D Treatment
  Local wound management
    Treatment based on definite diagnosis or established pathology
    Investigation and treatment of underlying conditions may be important, (e.g., pyoderma gangrenosum or diabetes mellitus)
E Follow-up and monitoring
  The diagnosis may take weeks or months to be established so patients must have ongoing follow-up.
  Continuing management: coordinated with multiple specialties involved as necessary

* Modified from Isbister and Whyte.19

Diaz repeatedly implies that the dark brown violin pattern of the brown recluse is only present on the female. However, these spiders do not exhibit sexual dimorphism in regard to this feature; males also have a darkened violin.

The term “non-*Loxosceles* necrotic araneism” refers to a non-existent condition despite Diaz’s suggestion that many spiders have been implicated in causing necrotic lesions. Several recent prospective studies have demonstrated that many of these species cause only minor effects.10–13 In the case of ulcers attributed to Hobo spiders (*Tegenaria agrestis*) in the northwest United States, causation was largely presumptive, but claims were exaggerated by repetitive citation in the medical journals and textbooks. A recent critical review of the literature20 demonstrated that there was minimal definitive evidence that hobo spiders cause necrotic ulcers. The myth may have been based on a series of suspected bites,24 and cases reports and animal work.29 The unique published case of a definite hobo spider bite leading to necrosis occurred in a patient with pre-existing venous disease that alone can cause ulcerating lesions.29 Diaz provides a list of features purporting to differentiate *Loxosceles* and *Tegenaria* bites. This is highly dubious because there is no published series of definite *Tegenaria* bites. This information, based only on suspected bites and speculations by other investigators, will further propogate unsubstantiated information about these spiders.

Studies of proven wolf spider bites (Lycosidae: including *Lycosa*) in Australia13 and Brazil22 have showed no cases of ulceration. Prospective studies of black house spiders (*Badumna*)12 and white-tail spiders (*Lampona*)13 failed to demonstrate any cases of necrotic ulcers. Neither have *Cheiracanthium* spp. (sac or running spider) bites been definitely shown to cause necrotic lesions. Again, this group of spiders has been blamed based on suspected cases23 or unsubstantiated single case reports.24 In two recent series of bites (9 in 750 definite Australian spider bites and 8 American *Cheiracanthium* bites) (Vetter RS, Bush SP, unpublished data), there were no cases of necrosis.9 Diaz’s review includes much incorrect information about studies of spider venoms and their potential for causing necrosis. No work has been published on the venom of *Cheiracanthium* spiders, contrary to Diaz’s statement. Although Young and Pincus25 discovered hyaluronidases and proteases in midgut extracts of *Lampona* and *Badumna* spiders, this does not prove that they cause dermonecrosis. The comparison of venom gland extracts of *Loxosceles rufescens*, *Lampona clyndrata*, and *B. insignis* showed that *L. clyndrata* and *B. insignis* venom glands did not contain spingomyelinases, the dermonecrotic component of *L. rufescens* glands. The enzymes found in *L. clyndrata* and *B. insignis* midgut extracts are common to all spiders and do not therefore explain necrosis.

Diaz is incorrect in stating that collagenases and proteases are responsible for necrotic effects of spider bites.26,27 Atkinson and Wright28 showed that all spiders they tested contained collagenases, most likely from their stomachs. The amount of collagenase was proportional to the size of the spider. If collagenases were responsible for necrosis, bites of all spiders, including large web spiders (such as orb weavers), would cause necrosis, but this is clearly incorrect.10 Diaz is incorrect in stating that there is no antivenom available for

---

Antivenom,17 American physicians have been reluctant to use this antivenom for widow spider bites because of a perceived risk of anaphylaxis based on one fatal case.17,18 For more information on *Latrodectus* antivenom, the reader is referred to a recent review.4

Diaz’s discussion of necrotic skin lesions attributed to spider bites is confusing. In the case of loxoscelism, there is definitive evidence that bites cause necrotic ulcers, but the association of necrotic lesions or ulcers with other spider bites is highly speculative. The term “necrotic arachnidism” or the more specific term “necrotic araneism” should not be used where there is suspicion that spiders other than *Loxosceles* species are responsible. Investigation and treatment should focus on the clinical presentation and should not be diverted by the “alleged” spider bite.19 A clinical approach to skin lesions suspected to be associated with spider bites is provided in Table 1.
loxoscelism; antivenoms have been manufactured in Brazil, Peru, and Mexico for many years.\textsuperscript{4,29}

Australian funnel-web spiders are the most dangerous spiders in the world. The male is smaller, but appears to be more venomous for most species. Severe envenoming has been reported from bites by the Sydney funnel-web spider (\textit{Atrax robustus}) and five \textit{Hadronyche} species (Isbister GK and others, unpublished data). The clinical effects of severe funnel-web spider envenoming are characteristic, have been well described,\textsuperscript{3,30} but are misrepresented by Diaz. Most funnel-web spider bites cause local pain, puncture marks, and bite site bleeding, and severe envenoming develops in only 10–25% of the cases.\textsuperscript{31} Severe envenoming is characterized by autonomic effects (adrenergic and cholinergic), neuromuscular excitation, non-cardiogenic pulmonary edema (rarely myocardial injury), and central nervous system effects (usually agitation). It is not useful to describe the progress of envenoming in two phases. Neuromuscular paralysis, intractable hypotension, secondary coagulopathy, and multi-organ failure were reported in severe and fatal cases before the introduction of antivenoms.\textsuperscript{32} Coma (except occasionally in children) is rare, and apnea, diarrhea, and laryngospasm have not been reported in the literature as part of funnel-web spider envenoming.

To say that Australia funnel-web spider antivenom is the second most commonly used spider antivenom in Australia is misleading. Red back spider antivenom is used commonly, while funnel-web spider antivenom is used in only a few cases each year and is the least frequently used of all Australian antivenoms. The reader is referred to other reviews on spider bites\textsuperscript{2,3} for a reliable description of funnel-web spider envenoming and the appropriate treatment and use of antivenom.\textsuperscript{30}

Diaz makes the very confusing comment that many groups of spiders known not to cause medically significant effects, “can inflict severe bites . . . requiring treatment with cross-reacting antivenoms.” With the exception of \textit{Steatoda}, a genus clearly capable of causing moderate to severe effects treatable with widow spider antivenom, all other listed spiders cause minor effects and do not require antivenom treatment. According to a recent systematic review, mouse spiders (\textit{Missulena} spp.) very rarely cause severe envenoming.\textsuperscript{33} The bite by a grass spider \textit{Agelenopsis aperta} reported by Vetter did not cause severe effects, headache, pallor, and lethargy for 1–2 days.\textsuperscript{34} This exaggeration of “severe” effects in this review article is not uncommon in the literature on spider bite and continues to augment the mythology and fear about spiders that leads to inappropriate and excessive treatment and misdiagnosis.

The description of treatment of minor effects of spider bites is incorrect and follows a confusing generic approach to spider bite that Diaz has followed throughout this review. After any spider bite, the bite site should be cleaned and tetanus prophylaxis should be boosted if necessary. The use of analgesics for local symptoms is reasonable but rarely required. The application of ice is often recommended and if this relieves local symptoms is appropriate, although ice should not be applied directly on the skin to avoid cold injury. The reference to immobilization is unclear and is not required for most bites. However, a pressure immobilization bandage should be applied in any case of suspected Australian funnel-web spider envenoming, which includes any bite in eastern or southern Australia by a big black spider.\textsuperscript{35} It is not clear what will be achieved by elevating the bitten extremity.

Diaz’s concluding discussion of the differential diagnosis of spider bites sums up all the errors and misinformation in the review. If someone sees a spider biting them (or collects the spider), they have clearly been bitten by a spider and there is no differential diagnosis! Investigation and treatment is then based on the type of spider, the medical significance of the bite (usually none), and specific treatment (if available) in the uncommon case of bites by dangerous spiders. People with suspected spider bites who present with a variety of skin lesions should be investigated clinically (Table 1). In this situation, spider bite is a rare cause of necrotic lesions in those parts of the world inhabited by \textit{Loxosceles}. Other more common causes must first be investigated. The use of the term “necrotic araneism” or “necrotic arachnidism” should be avoided because it incorrectly suggests the etiology is a spider bite. Almost all spiders are venomous but the vast majority are not dangerous to humans. To avoid further perpetuation of misinformation and in the interests of advancing our clinical understanding of spider bites, it is important that future publications should focus on witnessed, definite bites with expert identification of the spider involved.

\section*{REFERENCES}


GEOFFREY K. ISBISTER, MD
Newcastle Mater Misericordiae Hospital
Newcastle, New South Wales 2298, Australia
University of Newcastle
Newcastle, Callaghan, New South Wales 2308, Australia
New South Wales Poisons Information Centre
The Children’s Hospital at Westmead
Sydney, New South Wales, 2145, Australia
E-mail: gsbite@ferntree.com

JULIAN WHITE, MD
Faculty of Health Sciences
University of Adelaide
Adelaide, South Australia 5005, Australia
Women’s and Children’s Hospital
North Adelaide, South Australia 5006, Australia

BART J. CURRIE, DTMH
Tropical Medicine and International Health Unit
Menzies School of Health Research
Darwin, Northern Territory 0811, Australia
Northern Territory Clinical School
Casuarina, Northern Territory 0811, Australia

SEAN P. BUSH, MD
Loma Linda University School of Medicine
Loma Linda, CA 92354

RICHARD S. VETTER
Department of Entomology
University of California
Riverside, CA 92521
Biology Division
San Bernardino County Museum
Redlands, CA 92374