Spider bite

Geoffrey K Isbister, Hui Wen Fan

Spiders are a source of intrigue and fear, and several myths exist about their medical effects. Many people believe that bites from various spider species cause necrotic ulceration, despite evidence that most suspected cases of necrotic arachnidism are caused by something other than a spider bite. Latrodectism and loxoscelism are the most important clinical syndromes resulting from spider bite. Latrodectism results from bites by widow spiders (*Latrodectus* spp) and causes local, regional, or generalised pain associated with non-specific symptoms and autonomic effects. Loxoscelism is caused by *Loxosceles* spp, and the cutaneous form manifests as pain and erythema that can develop into a necrotic ulcer. Systemic loxoscelism is characterised by intravascular haemolysis and renal failure on occasion. Other important spiders include the Australian funnel-web spider (*Atrax* spp and *Hadronyche* spp) and the armed spider (*Phoneutria* spp) from Brazil. Antivenoms are an important treatment for spider envenomation but have been less successful than have those for snake envenomation, with concerns about their effectiveness for both latrodectism and loxoscelism.

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Introduction

Spiders have been a source of intrigue and fear by human beings for centuries, and numerous myths exist about the medical effects of spiders.[1] The predominant myth of the past few decades has been that bites from various species cause necrotic ulceration. Although this is partly true because bites by spiders from the genus *Loxosceles* can result in necrotic arachnidism and occasionally systemic illness, most suspected cases of necrotic arachnidism are not based on scientific evidence.

Despite there being more than 41 000 recorded species of spider in the order Araneae,[2] very few are medically important. In one study from Australia,[3] which described the clinical effects in 750 definite cases of spider bite covering 26 spider families, most spiders caused only minor effects. Worldwide there are two medically important clinical syndromes resulting from spider bite: latrodectism (caused by *Latrodectus* spp) and loxoscelism (caused by *Loxosceles* spp).[4,5] All other medically important spiders are confined to regions within single continents or countries, such as the Australian funnel-web spider (*Atrax* and *Hadronyche* spp)[6] and the armed or wandering spider (*Phoneutria* spp) from Brazil.[7,8] Spider venoms have become a source of interest in the past few decades. Several small peptides have been identified that interact with different ion channels, including sodium, potassium, and acid-sensing channels.[9–13]

Epidemiology, diagnosis, and prevention

The epidemiology of spider bite depends on the interaction between spider and human beings, spider ecology, and the environment. The distribution of medically important spiders is the most important factor in identification of where clinically important arachnidism occurs throughout the world and is discussed for each of the spider groups.

The diagnosis of spider bite is usually clinical, and definite bites should be based on a clear history of a spider biting the person and then being identified. Identification is best done by collection of the spider and expert identification. However, some spiders such as widow spiders can usually be identified by the general population, which is sufficient for the routine management of spider bite but not for research.[14] Laboratory diagnosis is rarely available in clinical settings, and identification of spider venom in human tissue has only been achieved in the research setting with *Loxosceles* spp[15,16] and *Phoneutria nigriventer*.[17]

The best prevention for spider bite is reduced contact between human beings and medically dangerous spiders. This can include chemical control of spiders in human habitations, and success varies for different spiders. Pyrethroid pesticides are toxic to *Loxosceles intermedia*.[18] Chemical repellents have been manufactured in some countries for loxoscelism prevention, but do not seem to be effective.[19]

Treatment

Antivenoms are a major therapeutic intervention for envenomation syndromes, and antivenoms exist for many spider groups.[20] However, antivenoms have been less successful in the treatment of arachnidism than have those for snake or scorpion envenomation. The use of antivenom is based on clinical experience, which has led to discrepancies in the proportion of patients treated. For example, in Brazil, antivenom is rarely used to treat *Phoneutria* envenomation despite substantial and distressing effects but is used widely to treat *Loxosceles* envenomation, although it is theoretically unlikely to be effective. Only two randomised controlled trials and a phase 2 study of *Latrodectus* antivenom have been done,

Search strategy and selection criteria

We searched Medline from January, 1966, to July, 2010; LILACS from January, 1982, to July, 2010; and Embase from January, 1980, to July, 2010, with the terms "arachnidism NOT scorpion", "latrodectism", "loxosceles", "phoneutria", and "spider envenoming". We included further articles from reference lists, review articles, and major textbook chapters on spider toxinology. Previous systematic reviews for randomised controlled trials of spider bite treatment were included and updated.

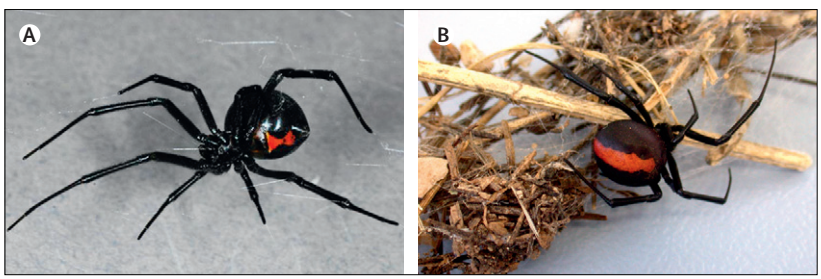

***Figure 1: Latrodectus* or widow spiders**
(A) Female *Latrodectus hesperus* or black widow spider from North America (photograph by Rick Vetter). (B) Female *Latrodectus hasselti* or redback spider from Australia (photograph by Geoff Isbister).

and the results provided contradictory evidence.[21–23] Although *Loxosceles* antivenom is used in South America and is efficacious in vitro,[24,25] the delay in clinical presentation and the irreversible nature of cutaneous necrosis means that this laboratory finding might not translate into effective treatment.[14,20,26] By contrast, antivenom for funnel-web spider envenomation is highly effective and potentially life-saving because it can be given early and reverse neurotoxic effects.[6,20]

Medically important spider bite and clinical syndromes

Latrodectus spp (widow spiders)

Latrodectism results from bites by widow spiders (*Latrodectus* spp), which have a worldwide distribution and continue to migrate between continents. There are 30 recognised species present throughout the Americas, Africa, Europe, Asia, and Australasia.[27] *Latrodectus* spp are medium-size spiders and generally shiny black in colour with ventral red hourglass markings (figure 1A). However, the body colour and markings vary greatly, such as the red back of *Latrodectus hasselti* (figure 1B), and the male spiders are much smaller than female spiders.[4,28] Most medically important bites are from the larger female spiders, but bites by male spiders have been reported in Australia.[29]

Much work has been done into toxins contained in widow spider venoms.[11–13] Alpha-latrotoxin is a 130 kDa neurotoxin that is thought to be responsible for the clinical effects in human beings. Although the effects of this toxin at the molecular and cellular level are well reported and result in neurotransmitter release, how this release causes the clinical effects seen in human beings is unclear.

The epidemiology of latrodectism differs throughout the world and is often poorly described. For example, in Australia most bites occur in and around the house in dry dark areas, including shoes, bike helmets, and garden equipment.[29] By contrast, in some South American countries bites occur in rural workers and mainly while outdoors. Although the clinical effects of latrodectism have been described as "so characteristic that any experienced physician would be able to make the diagnosis on first sight"[30] there seems to be substantial variation between species, ranging from predominantly a pain syndrome in Australasia[21,29] to a more systemic illness with the European widow spider, for which myocardial effects are reported.[31] Only one study[32] has compared different species in the same geographical region in South Africa and showed a difference between *Latrodectus indistinctus* and *Latrodectus geometricus*. The table provides a comparison of the clinical effects for six different *Latrodectus* spp for which sufficiently large case series have been published.[29,31–35]

Pain is an almost universal feature of latrodectism and can be local bite-site pain, regional or radiating pain, or back, chest, or abdominal pain. The onset of pain is usually gradual and can continue for hours to days. In Australia, local pain radiating up the bitten limb or from the bite site is typical,[21,29] whereas in North and South America back and abdominal pain predominate.[33,35] Diaphoresis is another characteristic feature of latrodectism and often occurs in unusual patterns that are almost pathognomonic of latrodectism—diaphoresis localised to the bite site, bilateral below-knee diaphoresis, and asymmetrical regional diaphoresis are some characteristic patterns.

Systemic envenomation occurs in about a third of cases, although the systemic features and the frequency vary for different species. Non-specific symptoms such as nausea, vomiting, headache, and fatigue are reported for most species. Muscle fasciculation and patchy localised paralysis can occur. Myocardial injury has been reported, but only from some species of widow spiders such as *Latrodectus tredecimguttatus*, and has resulted in fatalities.[31,36,37] Priapism is another unusual clinical effect reported for most *Latrodectus* species.[38–41]

The diagnosis of latrodectism is clinical and relies on a history of spider bite resulting in clinical effects that are consistent with latrodectism, which can vary for different *Latrodectus* species. Laboratory investigations are rarely needed, and no analytical assay exists to detect widow spider venoms in blood, urine, or at the bite site. Cardiac markers have been suggested if cardiac involvement is suspected. In some regions electrocardiograms are recommended, particularly for *Latrodectus tredecimguttatus*.

Several treatments have been used for latrodectism including antivenom,[20] analgesic agents,[21] benzodiazepines,[35,42] calcium,[43] and magnesium.[44] Evidence of the effectiveness of these treatments for latrodectism is scarce and consists only of case reports and case series. Although no evidence exists that analgesics are effective for latrodectism, non-opioid and opioid analgesics are well tolerated and deemed reasonable for symptomatic relief of pain in latrodectism. The dose given is similar to that for other acutely painful disorders, and should consist initially of a combination of non-opioid and opioid oral analgesia. Unrelieved pain should then be treated with parenteral opioids such as intravenous morphine. Benzodiazepines have been used for latrodectism because of muscle spasm and have had some anecdotal success.[35,42]

	Latrodectus hasselti	*Latrodectus mactans*	*Latrodectus curacaviensis*	*Latrodectus indistinctis*	*Latrodectus geometricus*	*Latrodectus mactans*	*Latrodectus tredecimguttatus*
Number of bites	68	163	77	30	15	89	56
Study design	Pr, PIC	R, ED	R	R	R	R	Pr, ED
Positive identification	100%	72%	75%	20%	67%	..	..
Pain							
Local pain*	100%	38%	56%	67%	93%	91%	90%
Radiating pain to limb	38%	18%	41%	57%	7%	..	..
Abdominal pain	9%	17%	17%	67%	27%	53%	35%
Chest pain, constriction	6%	4%	10%	30%	0%	..	14%
Back pain	..	56%	..	47%	7%	..	45%
Diaphoresis	34%	22%	28%	70%	..	70%	55%
Systemic effects							
Nausea	24%	11%	..	17%	0%	..	12%
Vomiting	4%	11%	5%	17%	0%	..	..
Headache	10%	9%	8%	21%	0%	..	12%
Abdominal rigidity	..	..	..	70%	7%	45%	..
Hypertension	1%	29%	4%	..	0%	17%	..
Agitation, irritation	..	..	14%	50%	13%	44%	..

Pr=prospective study. R=retrospective study. ED=emergency department study. PIC=Poison centre study. *In most studies, local pain seems to refer to persistent or severe pain only, rather than any discomfort of the bite (initial or persistent), which differs from the prospective study in Australia.[29]

Table: **Summary of clinical effects of widow spider bites from different regions of the world[29,31–35]**

The evidence for calcium and magnesium is scarce and therefore they cannot be recommended.

The effectiveness of antivenom is controversial. Historically the use of antivenom in some countries has depended on its availability,[20] reported success in retrospective series,[35,45,46] and the perceived risk of adverse reactions.[35] In Australia intramuscular antivenom has been used extensively for the treatment of severe local and systemic latrodectism for decades, despite little evidence.[45,46] By contrast, in the USA the perceived concern about early allergic reactions has restricted its use.[35] In the past decade several randomised controlled trials of widow spider antivenoms have been done that support the safety of the antivenom.[21–23] These controlled trials and a prospective case series suggest that acute reactions occur in about 5% of cases, including anaphylaxis in 1–2% and delayed reactions or serum sickness in up to 10% of cases.[21–23,47]

The controlled trials provide much less support for the effectiveness of antivenom than for its safety. However, two of the three trials are comparative studies between intravenous and intramuscular antivenom and the third is a small phase 2 pilot study.[21–23] Ellis and colleagues' trial[22] was underpowered and did not show a difference between intravenous and intramuscular antivenom at 1 h on the basis of a visual analogue score (VAS) of pain, the primary outcome. The RAVE study[21] was larger than that of Ellis and colleagues,[22] with 131 patients, but was unable to detect a clinically significant difference in pain 2 h after intravenous or intramuscular antivenom based on a VAS. A subgroup analysis of 19 patients in the RAVE study[21] detected antivenom in blood only after intravenous and not intramuscular administration of antivenom.[48] The inconsistent results between the clinical outcome in RAVE[21] and antivenom reaching the systemic circulation only after intravenous antivenom suggest that antivenom might not be effective by either route of administration and justifies a larger placebo-controlled randomised trial of intravenous antivenom. The phase 2 trial has been published only as an abstract.[23] In 24 patients randomly assigned to placebo or antivenom, no significant difference in pain scores was recorded between antivenom and placebo, but a benefit of antivenom was possible. Therefore, there is insufficient evidence to lend support to the effectiveness of widow spider antivenoms. However, the long history of safe use and anecdotal evidence means that antivenom continues to be recommended until further studies are completed.

Steatoda spp

Spiders of the *Steatoda* genus belong to the same family as *Latrodectus* spp (Theridiidae, comb-footed spiders) and have a very similar shape but are uniformly dark brown to black.[28,49] Phylogenic work has shown that they are closely related to *Latrodectus*, which is consistent with reported effects of bites from these spiders.[49–53] *Steatoda* spp exist in most parts of the world.

The clinical effects of bites by *Steatoda* spp are similar to but less severe than those by widow spiders, and are characterised by local and radiating pain that can be associated with systemic symptoms (nausea, vomiting, headache, and malaise).[49–52] In more severe cases, the clinical syndrome, sometimes referred to as steatodism,[52] is indistinguishable from latrodectism. Analgesics are appropriate for pain relief, as in latrodectism. Antivenom

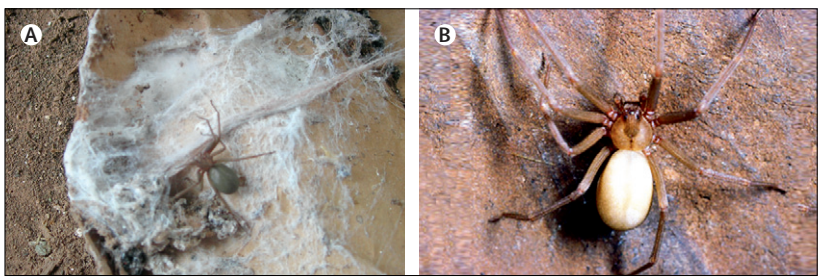

***Figure 2:* Loxosceles spiders**
(A) *Loxosceles amazonica* from South America (photograph Hui Wen Fan). (B) *Loxosceles reclusa* or recluse spider from southern USA. Photograph by Rick Vetter.

has been used to treat *Steatoda* bites with anecdotal reports of improvement.[49,50] In-vitro studies have shown that Australian redback spider (*Latrodectus hasselti*) antivenom will bind *Steatoda grossa* venom.[50] However, evidence is insufficient to recommend widow spider antivenoms for *Steatoda* bites, because most cases are minor and its use for widow spider envenomation is controversial.

Loxosceles spp

Loxoscelism results from bites by spiders from the genus *Loxosceles* (family Sicariidae), generally known as recluse, fiddle-back, or brown spiders. There are more than 100 species distributed worldwide,[4,54] but most live in South America where loxoscelism is a major health issue.[55,56] The first cases of loxoscelism in South America were described in the 1930s in Chile,[57,58] and then in Peru, Brazil, Argentina, and Uruguay.[26] Three species are most frequently reported to be responsible for bites in South America: *Loxosceles laeta*, distributed throughout most of South America; *Loxosceles intermedia*, found in Brazil and Argentina; and *Loxosceles gaucho* in Brazil.[26] Cases of loxoscelism in North America and Mexico are attributable to *Loxosceles reclusa* and *Loxosceles deserta*.[54,59] Outside of the Americas, *Loxosceles rufescens* rarely causes cases in Europe, South Africa,[60] and South Australia.[61]

Loxosceles are nocturnal spiders that are found in dry dark places outdoors, under rocks, wood, or tree bark (figure 2).[5] This species adapts well to the domestic environment where it hides in furniture, clothes, bed sheets, and in cupboards, facilitated by their flat body and large leg-to-body ratio. Most bites happen at night and occur when the spider is trapped against the person.[62]

Much research into *Loxosceles* venoms has been done.[5,63] The pathogenesis of loxoscelism and exact pathways of action for *Loxosceles* venom are not fully understood. The key components are a family of phospholipase D, which are involved in the development of dermonecrosis. Injection of venom triggers a complex inflammatory response, including the release of pro-inflammatory cytokines and lipid mediators.[64] Additionally, the venom has a direct haemolytic effect on red blood cells,[65,66] can cause complement activation and platelet aggregation,[67] and contains an hyaluronidase that increases the size of the tissue lesion, which is a hallmark of loxoscelism.[65]

Slightly more women than men are bitten because bites occur in the domestic environment,[55] and they happen more frequently in warm seasons.[56] Bite sites are mostly on the thigh, trunk, and proximal arms, reflecting the circumstances of the bite—ie, when the patient was dressing or sleeping.[68] Bite events are fairly painless and patients are often unaware of the spider bite, so the diagnosis of loxoscelism is seldom based on spider identification. Few patients capture and bring the spider for identification,[68–70] but the bite itself is identified by about 60% of patients. A few cases will probably result in no effect, and a further group will have self-limiting erythema and oedema.[4] However, the true extent of minor cases is impossible to determine because they will be underestimated by patients who might not feel the bite or disregard minor symptoms.

The cutaneous form of loxoscelism occurs in most cases and the systemic or viscerocutaneous form less frequently,[68,69] in up to 10% of cases dependent on the species of *Loxosceles* involved.[56,71] Cutaneous loxoscelism initially manifests as mild pain and erythema, which is frequently mistaken for cellulitis, and usually evolves into extensive skin necrosis and ulceration. The slowness of progression means that diagnosis is usually made 12– 24 h after the bite when there is painful oedema with induration, and an irregular area of ecchymosis and ischaemia, sometimes with haemorrhagic blisters (figure 3A). There is usually only evidence of necrosis after 72 h, with large and deep necrosis occurring in more than half of cases. From about day 5–7 the cutaneous lesion delimits and forms a dry necrotic eschar with well defined borders (figure 3B). The necrotic tissue detaches after about 2–3 weeks leaving an ulcer with tissue of granulation, which can take weeks or months to heal dependent on the depth and extent of the injury. Secondary infection is uncommon, even in the presence of extensive necrotic lesions. An oedematous variant of cutaneous loxoscelism occurs for bites on the face and is characterised by extensive oedema and erythema, but little necrosis. The cutaneous form is associated with non-specific systemic symptoms in up to 50% of cases in the first 24–48 h, such as generalised pruritus and rash, headache, nausea, vomiting, and low-grade fever.[71]

Systemic loxoscelism or viscerocutaneous loxoscelism is much less common than the cutaneous form but the frequency seems to vary in different species. 13–16% of cases are reported in series of loxoscelism with *Loxosceles laeta*,[56,71] whereas cases caused by *Loxosceles gaucho*[68] and *Loxosceles reclusa* are much rarer,[70,72–74] and none are reported for *Loxosceles intermedia*. The exact frequency and range of clinical manifestations is difficult to establish because most reports of systemic loxoscelism are of presumed rather than confirmed bites,[70,72–75] and clinical manifestations can differ between species.

Acute intravascular haemolytic anaemia is the hallmark feature of systemic loxoscelism.[71,73,74,76,77] Non-specific symptoms are common but can occur in

cutaneous loxoscelism. Although most cases of systemic loxoscelism are reported in children, large case series report it across all age groups with a possible predominance in younger people.[56,68,71] The typical presentation is with fever, malaise, vomiting, headache, and rash, with or without a history of spider bite. Jaundice will occur with late presentations. There is a progressive decrease in patients' haemoglobin concentration over 7–14 days,[71,78] and the lowest haemoglobin can be 5–8 g/L.[73] Haemolysis seems to be intravascular and is consistent with autoimmune haemolytic anaemia, testing positive on a direct antiglobulin test to complement C3 and IgG.[73,76,79–81] A positive direct antiglobulin test has not been reported in some cases, although testing is often not undertaken or is done too late.[78] Acute renal failure is less frequent and is associated with poor outcomes.[56,71,78] Schenone and colleagues[71] report eight fatal cases that were characterised by haemolysis, acute renal failure, and coma. Sezerino and co-workers[56] reported 17 of 35 cases with acute renal failure and four deaths.

Although disseminated intravascular coagulation[82] is usually listed as part of systemic loxoscelism, evidence to support this notion is scarce. In severe cases, mild thrombocytopenia occurs and a doubling of the clotting times,[71,78] which does not meet the criteria for disseminated intravascular coagulation.[83] In one fatal case, disseminated intravascular coagulation was probably secondary to a cardiac arrest and multiorgan failure.[81] Rhabdomyolysis is also reported for loxoscelism but in these cases there is only a small rise in creatine kinase to the low thousands U/L,[78] which is unlikely to be clinically significant or contribute to the acute renal injury.

The presence of a cutaneous lesion, non-specific systemic symptoms, and an epidemiological history compatible with *Loxosceles* bite is usually deemed sufficient to make the diagnosis of probable loxoscelism. Unfortunately in many cases the diagnosis of loxoscelism is often made late, once the skin lesions are well developed, and patients invariably receive multiple investigations before it is recognised. Conversely, necrotic lesions in general tend to be overdiagnosed as loxoscelism, but studies into the geographical distribution of this genus show that in most cases other causes are more likely.[84]

Several treatments have been suggested for loxoscelism, including antivenom, corticosteroids, dapsone, antihistamines, antibiotics, analgesics, hyperbaric oxygen therapy, electric shock, and surgical excision.[26,85] However, there is little evidence to lend support to any of these treatments,[86,87] including the role of antivenom and the timing of its use,[85] partly because of the lack of knowledge about loxoscelism's pathophysiology,[5] and the paucity of clinical trials to test these therapies.[85] A systematic review identified only three clinical studies,[85] which were small and poorly designed.[88,89] Our review did not identify any further studies. Several animal studies have been undertaken to test various therapies, but overall they do not indicate efficacy.[26,86,90]

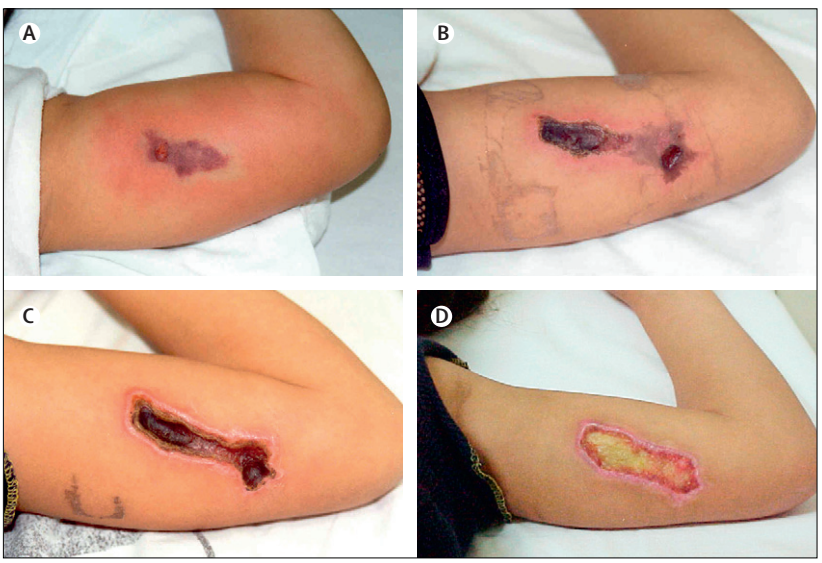

Figure 3: **Progression of cutaneous loxoscelism in a Brazilian patient who was bitten inside a house while putting on a shirt**
Ulceration and necrosis at day 1 (A), day 9 (B), day 16 (C), and day 25 (D). Photographs by Ceila M S Malaque.

Loxosceles antivenoms are available in Brazil, Argentina, Peru, and Mexico, and all are horse-derived $F(ab')_2$ antivenoms, apart from a whole IgG antivenom from Peru.[20] Antivenom was first developed in Brazil in 1954, and is used most extensively there.[26] Data about the benefit of antivenom are conflicting and no placebo-controlled trials in human beings have been undertaken.[85,20,26] Animal studies are inconsistent, with some indicating benefit only if given within 4 h,[24] whereas subsequent studies suggested benefit for up to 48 h in a rabbit model.[25] Antivenom is used in the belief that it will reduce the extent of the cutaneous lesion and possibly prevent systemic manifestations.

The indications for antivenom administration and timing of administration vary substantially but are usually based on the severity of envenomation. Unfortunately, the delayed recognition of loxoscelism means that antivenom is often given too late when patients have already developed substantial necrosis or systemic effects. Generally antivenom is not recommended more than 72 h after the bite. The Brazilian Ministry of Health recommends antivenom in cases with extensive cutaneous or systemic loxoscelism, usually with corticosteroids.[91]

Systemic corticosteroids are widely used, such as prednisone in high doses for short periods (40–80 mg per day for 5 days), particularly in Chile where antivenom is not available.[71] Results of a clinical study[85] that gave dapsone to 46 patients showed some effectiveness compared with antihistamines, but the combination with antivenom was not superior. Whatever specific treatment is chosen, appropriate wound care is essential for

Figure 4: **Northern tree funnel-web spider (*Hadronyche formidabilis*)**
Photograph by Geoff Isbister.

Figure 5: Phoneutria nigriventer, **the armed or wandering spider from Brazil**
Resting (A) and armed (B) position. Photographs by Hui Wen Fan and Denise M Candido.

cutaneous loxoscelism, and in cases of systemic loxoscelism patients are admitted to hospital and closely monitored. Treatment of intravascular haemolysis must include appropriate haematological investigation and red blood cell transfusions as needed.

Suspected necrotic arachnidism

The presentation of necrotic ulcers as suspected spider bites is common in primary care and emergency departments, despite scarcity of evidence for all but *Loxosceles* spp causing necrotic arachnidism. These patients present a difficult clinical dilemma because they need to be reassured that their condition is unlikely to be due to a spider bite; however, appropriate investigation needs to be undertaken to identify the cause. A good history will quickly establish whether a spider is the cause in most cases, and if there is no history of a definite spider bite then the focus should be on causes of ulceration. An approach to the investigation of these patients and possible causes is discussed elsewhere.[54,92] However, a diagnosis of *Loxosceles* should still be considered in endemic areas.

Atrax and *Hadronyche* spp (funnel-web spiders)

Funnel-web spiders are arguably the most deadly spiders worldwide. Fortunately they exist in a confined geographical region in eastern Australia and have little interaction with human beings. This containment, plus the fact that envenomation occurs only in a few cases, has meant that there are unlikely to be more than five cases of severe envenomation every year.[6] Only 13 fatalities from funnel-web spider envenomation have been reported, all of which occurred before 1981 when the antivenom was introduced.[6] Severe envenomation has been reported from six species, including the Sydney funnel-web spider (*Atrax robustus*), the southern tree funnel-web spider (*Hadronyche cerberea*), and northern tree funnel-web spider (*Hadronyche formidabilis*).

Funnel-web spiders are medium to large mygalomorph spiders that have prominent chelicerae with parallel fangs (figure 4). They are both ground-dwelling and tree-dwelling spiders, living in logs, rock crevices, or leaf litter. Most bites occur when the males leave their burrows in search of females. The venoms of several species of Australian funnel-web spiders contain small peptide neurotoxins.[11,93,94] The clinically important toxins are the δ-atracotoxins that slow tetrodotoxin-sensitive voltage-gated Na^+ current inactivation and reduce peak tetrodotoxin-sensitive currents.[95]

The bite of a funnel-web spider is painful because of the size of the fangs, and in most cases systemic envenomation does not occur. In cases of severe envenomation there is a rapid onset of life-threatening effects, which are similar for all species. Severe envenomation is characterised by both neuromuscular and autonomic excitation, and can be associated with pulmonary oedema. There is a mixture of catecholaminergic and cholinergic excess with bradycardia or tachycardia, hypertension, miosis or mydriasis, hypersalivation, lacrimation, diaphoresis, and piloerection. Neuromuscular excitation manifests as paraesthesia (local, oral, distal), fasciculations (local or generalised, and typically with tongue fasciculations), and muscle spasms. Non-specific symptoms such as vomiting, headache, and fatigue occur, and patients can be irritable or agitated. Before antivenom was introduced, late effects included hypotension, coma, and multiorgan failure. Mild systemic envenomation can occur with only local neuromuscular features and non-specific symptoms.

Patients with suspected funnel-web envenomation should have a pressure bandage with immobilisation applied, as for Australian snake bite. First aid should remain in place until the patient is in a hospital that has antivenom. Antivenom is the most important treatment in these cases and should be given urgently to any patient with severe envenomation. The effectiveness of funnel-web antivenom is supported by its use in more than 70 cases in which the length of hospital stay was reduced and there were no deaths.[6] A randomised controlled trial would be difficult to justify ethically because of the dramatic response seen when antivenom is administered

to patients. The antivenom seems to be effective for all species[94] and has a low rate of adverse reactions, with anaphylaxis and serum sickness occurring in less than 2% of cases.[6]

A frequent clinical problem is that patients are often bitten by big black spiders in eastern Australia, but they are not always funnel-web spiders. All such patients should be treated as having potential envenomation and observed for 2 h after the bite or after completion of first aid.[6] If the patient is still asymptomatic after 4 h they can be discharged. Mouse spiders (*Missulena* spp) and trapdoor spiders can look like funnel-web spiders but do not cause major effects.[96,97]

Phoneutria ssp

Spiders of the *Phoneutria* genus belong to the family of Ctenidae[2] and are reported throughout South America and Costa Rica. However, most reports of clinically important bites are from Brazil.[7,8,98] The South American wandering spider, *Phoneutria nigriventer,* is popularly known as the armed or banana spider, and is the most common *Phoneutria* species to cause bites in people (figure 5). It occurs in the central-western, southeastern, and southern parts of Brazil. *Phoneutria* are solitary, nocturnal spiders that construct no web and catch prey by active hunting and wandering large distances at night. They occasionally enter people's homes and when discovered assume a characteristic aggressive position (figure 5B). *Phoneutria nigriventer* venom contains a mixture of polypeptides and biologically active molecules that affect ion channels and cause neurotransmitter release.[99]

Phoneutria spiders cause thousands of bites in Brazil every year, most of which occur in March and April,[7] thought to be the spiders' mating season, when they are more often seen indoors. Bites occur when the spiders are encountered in shoes, piles of sticks or rubbish, and construction material, and patients are most commonly bitten on the arms and legs.[7]

Bites by *Phoneutria* spiders cause immediate local pain of variable severity that is associated with localised diaphoresis, piloerection, and erythema, often without evidence of fang marks. The pain radiates proximally up the bitten extremity. In most cases these symptoms are the extent of the envenomation but tachycardia and restlessness can occur. In a series of 422 confirmed bites almost 90% had mild envenomation.[7] Systemic effects include non-specific symptoms such as nausea, vomiting, and dizziness; and autonomic effects such as tachycardia, hypertension, profuse diaphoresis, salivation, visual disturbances, and priapism (especially in young boys). Moderate envenomation is characterised by diaphoresis, occasional vomiting, or both, in addition to bite-site manifestations. Severe envenomation is more frequent in children and occurs in less than 1% of cases. It is characterised by persistent vomiting and autonomic features that can progress to pulmonary oedema, shock, and death on rare occasions.[7,98]

In most cases with mild envenomation only symptomatic treatment is needed, which can include application of warm compresses, non-sedative analgesia, and local anaesthetic infiltration of the bite site. With more severe pain, opiates and sedatives might be necessary. Antivenom is reserved for moderate to severe envenomation; in one study antivenom was given to only ten (2%) of 422 patients.[7] Antivenom has been used to treat envenomation by *Phoneutria* spider bites in Brazil since 1925, and is a polyvalent $F(ab')_2$ antivenom used for *Phoneutria* and *Loxosceles* spider bites and *Tityus* scorpion stings. Treatment with antivenom within 3 h is associated with recovery within 24 h.

Future directions

The treatment of patients with suspected spider bite is not straightforward because of the overdiagnosis of skin necrosis as being attributable to spider bites while, at the same time, serious arachnidisms, such as loxoscelism, are not being recognised and treatment is delayed. Future research should focus on reporting of definite cases of spider bite to improve definition of the clinical syndromes and help clinicians to recognise envenomation. Well designed clinical trials to test antivenom therapy in both latrodectism and loxoscelism need to be undertaken urgently. Such studies are needed to prevent the unnecessary use of ineffective antivenom, which puts patients at risk of allergic reactions, and to better define the timing and dosing of antivenom when it is effective.

Contributors

GKI undertook the literature review, drafted the report except as below, wrote the final draft, and takes responsibility for the Seminar. HWF reviewed the Portuguese and Spanish literature, drafted the sections on loxoscelism and armed spiders, and reviewed the final draft.

Conflicts of interest

We declare that we have no conflicts of interest.

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References

1 Isbister GK. Necrotic arachnidism: the mythology of a modern plague. *Lancet* 2004; **364:** 549–53.

2 Platnick NI. The world spider catalog, version 11.0. American Museum of Natural History. 2010. http://research.amnh.org/entomology/spiders/catalog/index.html (accessed July 25, 2010).

3 Isbister GK, Gray MR. A prospective study of 750 definite spider bites, with expert spider identification. *Q JM* 2002; **95:** 723–31.

4 Vetter RS, Isbister GK. Medical aspects of spider bites. *Annu Rev Entomol* 2008; **53:** 409–29.

5 Tambourgi DV, Goncalves-de-Andrade RM, van den Berg CW. Loxoscelism: from basic research to the proposal of new therapies. *Toxicon* 2010; **56:** 1113–19.

6 Isbister GK, Gray MR, Balit CR, et al. Funnel-web spider bite: a systematic review of recorded clinical cases. *Med J Aust* 2005; **182:** 407–11.

7 Bucaretchi F, Deus RC, Hyslop S, Madureira PR, de Capitani EM, Vieira RJ. A clinico-epidemiological study of bites by spiders of the genus *Phoneutria*. *Rev Inst Med Trop Sao Paolo* 2000; **42:** 17–21.

8 Bucaretchi F, Mello SM, Vieira RJ, et al. Systemic envenomation caused by the wandering spider *Phoneutria nigriventer*, with quantification of circulating venom. *Clin Toxicol (Phila)* 2008; **46:** 885–89.

9 Diochot S, Salinas M, Baron A, Escoubas P, Lazdunski M. Peptides inhibitors of acid-sensing ion channels. *Toxicon* 2007; **49:** 271–84.

10 Corzo G, Escoubas P. Pharmacologically active spider peptide toxins. *Cell Mol Life Sci* 2003; **60:** 2409–26.

11 Nicholson GM, Graudins A. Spiders of medical importance in the Asia-Pacific: atracotoxin, latrotoxin and related spider neurotoxins. *Clin Exp Pharmacol Physiol* 2002; **29:** 785–94.

12 Rash LD, Hodgson WC. Pharmacology and biochemistry of spider venoms. *Toxicon* 2002; **40:** 225–54.

13 Grishin EV. Black widow spider toxins: the present and the future. *Toxicon* 1998; **36:** 1693–701.

14 Isbister GK. Data collection in clinical toxinology: debunking myths and developing diagnostic algorithms. *J Toxicol Clin Toxicol* 2002; **40:** 231–37.

15 Barbaro KC, Cardoso JL, Eickstedt VR, Mota I. IgG antibodies to *Loxosceles* sp. spider venom in human envenoming. *Toxicon* 1992; **30:** 1117–21.

16 Stoecker WV, Green JA, Gomez HF. Diagnosis of loxoscelism in a child confirmed with an enzyme-linked immunosorbent assay and noninvasive tissue sampling. *J Am Acad Dermatol* 2006; **55:** 888–90.

17 Chavez-Olortegui C, Bohorquez K, Alvarenga LM, et al. Sandwich-ELISA detection of venom antigens in envenoming by *Phoneutria nigriventer* spider. *Toxicon* 2001; **39:** 909–11.

18 Navarro-Silva MA, Duque JE, Ramires EN, et al. Chemical control of *Loxosceles intermedia* (Araneae: Sicariidae) with pyrethroids: field and laboratory evaluation. *J Econ Entomol* 2010; **103:** 166–71.

19 Catalan A, Araya JE, Varela H, Cortes W, Sagua H, Gonzalez CJ. Effectiveness of a repellent paint against the spider *Loxosceles laeta*. *Rev Med Chil* 2009; **137:** 240–45 (in Spanish).

20 Isbister GK, Graudins A, White J, Warrell D. Antivenom treatment in arachnidism. *J Toxicol Clin Toxicol* 2003; **41:** 291–300.

21 Isbister GK, Brown SG, Miller M, et al. A randomised controlled trial of intramuscular vs. intravenous antivenom for latrodectism—the RAVE study. *QJM* 2008; **101:** 557–65.

22 Ellis RM, Sprivulis PC, Jelinek GA, et al. A double-blind, randomized trial of intravenous versus intramuscular antivenom for Red-back spider envenoming. *Emerg Med Australas* 2005; **17:** 152–56.

23 Stanford CF, Bush SP, Clark RF, et al. A new Fab2 antivenom for widow spider envenomation (Latrodectism). *Clin Toxicol* 2007; **45:** 619.

24 Gomez HF, Miller MJ, Trachy JW, Marks RM, Warren JS. Intradermal anti-loxosceles Fab fragments attenuate dermonecrotic arachnidism. *Acad Emerg Med* 1999; **6:** 1195–202.

25 Pauli I, Minozzo JC, da Silva PH, Chaim OM, Veiga SS. Analysis of therapeutic benefits of antivenin at different time intervals after experimental envenomation in rabbits by venom of the brown spider (*Loxosceles intermedia*). *Toxicon* 2009; **53:** 660–71.

26 Pauli I, Puka J, Gubert IC, Minozzo JC. The efficacy of antivenom in loxoscelism treatment. *Toxicon* 2006; **48:** 123–37.

27 Garb JE, Gonzalez A, Gillespie RG. The black widow spider genus *Latrodectus* (Araneae: Theridiidae): phylogeny, biogeography, and invasion history. *Mol Phylogenet Evol* 2004; **31:** 1127–42.

28 Isbister GK, White J. Clinical consequences of spider bites: recent advances in our understanding. *Toxicon* 2004; **43:** 477–92.

29 Isbister GK, Gray MR. Latrodectism: a prospective cohort study of bites by formally identified redback spiders. *Med J Aust* 2003; **179:** 88–91.

30 Maretic Z. Latrodectism: variations in clinical manifestations provoked by *Latrodectus* species of spiders. *Toxicon* 1983; **21:** 457–66.

31 Afshari R, Khadem-Rezaiyan M, Balali-Mood M. Spider bite (latrodectism) in Mashhad, Iran. *Hum Exp Toxicol* 2009; **28:** 697–702.

32 Muller GJ. Black and brown widow spider bites in South Africa. A series of 45 cases. *S Afr Med J* 1993; **83:** 399–405.

33 Artaza O, Fuentes J, Schindler R. Latrodectism: clinico-therapeutical evaluation of 89 cases. *Rev Med Chil* 1982; **110:** 1101–05 (in Spanish).

34 Lira-da-Silva RM, Matos GB, Sampaio RO, Nunes TB. Retrospective study on *Latrodectus* stings in Bahia, Brazil. *Rev Soc Bras Med Trop* 1995; **28:** 205–10 (in Portuguese).

35 Clark RF, Wethern-Kestner S, Vance MV, Gerkin R. Clinical presentation and treatment of black widow spider envenomation: a review of 163 cases. *Ann Emerg Med* 1992; **21:** 782–87.

36 Sari I, Zengin S, Davutoglu V, Yildirim C, Gunay N. Myocarditis after black widow spider envenomation. *Am J Emerg Med* 2008; **26:** 630–33.

37 Pneumatikos IA, Galiatsou E, Goe D, Kitsakos A, Nakos G, Vougiouklakis TG. Acute fatal toxic myocarditis after black widow spider envenomation. *Ann Emerg Med* 2003; **41:** 158.

38 Trethewy CE, Bolisetty S, Wheaton G. Red-back spider envenomation in children in Central Australia. *Emerg Med* 2003; **15:** 170–75.

39 Hoover NG, Fortenberry JD. Use of antivenin to treat priapism after a black widow spider bite. *Pediatrics* 2004; **114:** e128–e129.

40 Stiles AD. Priapism following a black widow spider bite. *Clin Pediatr (Phila)* 1982; **21:** 174–75.

41 Quan D, Ruha AM. Priapism associated with *Latrodectus mactans* envenomation. *Am J Emerg Med* 2009; **27:** 759e1–2.

42 Russell FE. Muscle relaxants in black widow spider (*Latrodectus mactans*) poisoning. *Am J Med Sci* 1962; **243:** 159–61.

43 Key GF. A comparison of calcium gluconate and methocarbamol (Robaxin) in the treatment of latrodectism (black widow spider envenomation). *Am J Trop Med Hyg* 1981; **30:** 273–77.

44 Cesareo DA. "Red Back" spider bite and magnesium sulphate treatment. *Am J Trop Med* 1934; **14:** 33–44.

45 Wiener S. Redback spider bite in Australia: an analysis of 167 cases. *Med J Aust* 1961; **II:** 44–49.

46 Sutherland SK, Trinca JC. Survey of 2144 cases of red-back spider bites: Australia and New Zealand, 1963–1976. *Med J Aust* 1978; **2:** 620–23.

47 Isbister GK. Safety of i.v. administration of redback spider antivenom. *Intern Med J* 2007; **37:** 820–22.

48 Isbister GK, O'Leary M, Miller M, et al. A comparison of serum antivenom concentrations after intravenous and intramuscular administration of redback (widow) spider antivenom. *Br J Clin Pharmacol* 2008; **65:** 139–43.

49 Isbister GK, Gray MR. Effects of envenoming by comb-footed spiders of the genera *Steatoda* and *Achaearanea* (family Theridiidae: Araneae) in Australia. *J Toxicol Clin Toxicol* 2003; **41:** 809–19.

50 Graudins A, Gunja N, Broady KW, Nicholson GM. Clinical and in vitro evidence for the efficacy of Australian red-back spider (*Latrodectus hasselti*) antivenom in the treatment of envenomation by a Cupboard spider (*Steatoda grossa*). *Toxicon* 2002; **40:** 767–75.

51 Warrell DA, Shaheen J, Hillyard PD, Jones D. Neurotoxic envenoming by an immigrant spider (*Steatoda nobilis*) in southern England. *Toxicon* 1991; **29:** 1263–65.

52 Maretic Z, Levi HW, Levi LR. The theridiid spider *Steatoda paykullinana*, poisonous to mammals. *Toxicon* 1964; **2:** 149–54.

53 Pommier P, Rollard C, de Haro L. Steatoda spider envenomation in southern France. *Presse Med* 2006; **35:** 1825–27 (in French).

54 Swanson DL, Vetter RS. Loxoscelism. *Clin Dermatol* 2006; **24:** 213–21.

55 Schenone H, Rojas A, Reyes H, Villarroel F, Suarez G. Prevalence of *Loxosceles laeta* in houses in central Chile. *Am J Trop Med Hyg* 1970; **19:** 564–67.

56 Sezerino UM, Zannin M, Coelho LK, et al. A clinical and epidemiological study of *Loxosceles* spider envenoming in Santa Catarina, Brazil. *Trans R Soc Trop Med Hyg* 1998; **92:** 546–48.

57 Macchiavello A. La Loxosceles laeta causa del aracnoidismo cutâneo o mancha gangrenosa de Chile. *Rev Chil Hist Nat* 1937; **41:** 11–19.

58 Macchiavello A. Cutaneous arachnidism or gangrenous spot of Chile. *P R J Pub Heal Trop Med* 1947; **22:** 425–66.

59 Escalante-Galindo P, Montoya-Cabrera MA, Terroba-Larios VM, Nava-Juarez AR, Escalante-Flores I. Local dermonecrotic loxoscelism in children bitten by the spider *Loxosceles reclusa* (the "violin" spider). *Gac Méd Méx* 1999; **135:** 423–26 (in Spanish).

60 Newlands G, Atkinson P. Behavioural and epidemiological considerations pertaining to necrotic araneism in southern Africa. *S Afr Med J* 1990; **77:** 92–95.

61 Southcott RV. Spiders of the genus *Loxosceles* in Australia. *Med J Aust* 1976; **1:** 406–08.

62 Swanson DL, Vetter RS. Bites of brown recluse spiders and suspected necrotic arachnidism. *N Engl J Med* 2005; **352:** 700–07.

63 Tambourgi DV, Magnoli FC, van den Berg CW, et al. Sphingomyelinases in the venom of the spider *Loxosceles intermedia* are responsible for both dermonecrosis and complement-dependent hemolysis. *Biochem Biophys Res Commun* 1998; **251:** 366–73.

64 Barbaro KC, Lira MS, Araujo CA, et al. Inflammatory mediators generated at the site of inoculation of *Loxosceles gaucho* spider venom. *Toxicon* 2010; **56:** 972–79.

65 da Silva PH, da Silveira RB, Appel MH, Mangili OC, Gremski W, Veiga SS. Brown spiders and loxoscelism. *Toxicon* 2004; **44:** 693–709.

66 Chaves-Moreira D, Chaim OM, Sade YB, et al. Identification of a direct hemolytic effect dependent on the catalytic activity induced by phospholipase-D (dermonecrotic toxin) from brown spider venom. *J Cell Biochem* 2009; **107:** 655–66.

67 Tambourgi DV, Morgan BP, de Andrade RM, Magnoli FC, van den Berg CW. *Loxosceles intermedia* spider envenomation induces activation of an endogenous metalloproteinase, resulting in cleavage of glycophorins from the erythrocyte surface and facilitating complement-mediated lysis. *Blood* 2000; **95:** 683–91.

68 Malaque CM, Castro-Valencia JE, Cardoso JL, Francca FO, Barbaro KC, Fan HW. Clinical and epidemiological features of definitive and presumed loxoscelism in Sao Paulo, Brazil. *Rev Inst Med Trop Sao Paulo* 2002; **44:** 139–43.

69 Schenone H. Toxic pictures produced spiders bites in Chile: latrodectism and loxoscelism. *Rev Med Chil* 2003; **131:** 437–44 (in Spanish).

70 Wright SW, Wrenn KD, Murray L, Seger D. Clinical presentation and outcome of brown recluse spider bite. *Ann Emerg Med* 1997; **30:** 28–32.

71 Schenone H, Saavedra T, Rojas A, Villarroel F. Loxoscelism in Chile. Epidemiologic, clinical and experimental studies. *Rev Inst Med Trop Sao Paulo* 1989; **31:** 403–15 (in Spanish).

72 Anderson PC. Missouri brown recluse spider: a review and update. *Mo Med* 1998; **95:** 318–22.

73 McDade J, Aygun B, Ware RE. Brown recluse spider (*Loxosceles reclusa*) envenomation leading to acute hemolytic anemia in six adolescents. *J Pediatr* 2010; **156:** 155–57.

74 Elbahlawan LM, Stidham GL, Bugnitz MC, Storgion SA, Quasney MW. Severe systemic reaction to *Loxosceles reclusa* spider bites in a pediatric population. *Pediatr Emerg Care* 2005; **21:** 177–80.

75 Taylor EH, Denny WF. Hemolysis, renal failure and death, presumed secondary to bite of brown recluse spider. *South Med J* 1966; **59:** 1209–11.

76 Lane DR, Youse JS. Coombs-positive hemolytic anemia secondary to brown recluse spider bite: a review of the literature and discussion of treatment. *Cutis* 2004; **74:** 341–47.

77 Minton SA, Olson C. A case of spider bite with severe hemolytic reaction. *Pediatrics* 1964; **33:** 283–84.

78 de Souza AL, Malaque CM, Sztajnbok J, Romano CC, Duarte AJ, Seguro AC. *Loxosceles* venom-induced cytokine activation, hemolysis, and acute kidney injury. *Toxicon* 2008; **51:** 151–56.

79 Eichner ER. Spider bite hemolytic anemia: positive Coombs' test, erythrophagocytosis, and leukoerythroblastic smear. *Am J Clin Pathol* 1984; **81:** 683–87.

80 Nance WE. Hemolytic anemia of necrotic arachnidism. *Am J Med* 1961; **31:** 801–07.

81 Williams ST, Khare VK, Johnston GA, Blackall DP. Severe intravascular hemolysis associated with brown recluse spider envenomation. A report of two cases and review of the literature. *Am J Clin Pathol* 1995; **104:** 463–67.

82 Vorse H, Seccareccio P, Woodruff K, Humphrey GB. Disseminated intravascular coagulopathy following fatal brown spider bite (necrotic arachnidism). *J Pediatr* 1972; **80:** 1035–37.

83 Levi M. Disseminated intravascular coagulation. *Crit Care Med* 2007; **35:** 2191–95.

84 Vetter RS, Cushing PE, Crawford RL, Royce LA. Diagnoses of brown recluse spider bites (loxoscelism) greatly outnumber actual verifications of the spider in four western American states. *Toxicon* 2003; **42:** 413–18.

85 Manriquez JJ, Silva S. Cutaneous and visceral loxoscelism: a systematic review. *Rev Chilena Infectol* 2009; **26:** 420–32 (in Spanish).

86 Phillips S, Kohn M, Baker D, et al. Therapy of brown spider envenomation: a controlled trial of hyperbaric oxygen, dapsone, and cyproheptadine. *Ann Emerg Med* 1995; **25:** 363–68.

87 Barrett SM, Romine-Jenkins M, Fisher DE. Dapsone or electric shock therapy of brown recluse spider envenomation? *Ann Emerg Med* 1994; **24:** 21–25.

88 Rees RS, Altenbern DP, Lynch JB, King LE Jr. Brown recluse spider bites. A comparison of early surgical excision versus dapsone and delayed surgical excision. *Ann Surg* 1985; **202:** 659–63.

89 Rees R, Campbell D, Rieger E, King LE. The diagnosis and treatment of brown recluse spider bites. *Ann Emerg Med* 1987; **16:** 945–49.

90 Lowry BP, Bradfield JF, Carroll RG, Brewer K, Meggs WJ. A controlled trial of topical nitroglycerin in a New Zealand white rabbit model of brown recluse spider envenomation. *Ann Emerg Med* 2001; **37:** 161–65.

91 Brazilian Ministry of Health. Manual de diagnóstico e tratamento dos acidentes por animais peçonhentos. Brazil: Brazilian Ministry of Health, 1998: 181 (in Portuguese).

92 Isbister GK, Whyte IM. Suspected white-tail spider bite and necrotic ulcers. *Intern Med J* 2004; **34:** 38–44.

93 Nicholson GM, Walsh R, Little MJ, Tyler MI. Characterisation of the effects of robustoxin, the lethal neurotoxin from the Sydney funnel-web spider *Atrax robustus*, on sodium channel activation and inactivation. *Pflugers Arch* 1998; **436:** 117–26.

94 Graudins A, Wilson D, Alewood P, Broady K, Nicholson G. Cross-reactivity of Sydney funnel-web spider antivenom: neutralization of the in vitro toxicity of other Australian funnel-web (*Atrax* and *Hadronyche*) spider venoms. *Toxicon* 2002; **40:** 259–66.

95 Nicholson GM, Little MJ, Birinyi-Strachan LC. Structure and function of delta-atracotoxins: lethal neurotoxins targeting the voltage-gated sodium channel. *Toxicon* 2004; **43:** 587–99.

96 Isbister GK. Mouse spider bites (*Missulena* spp.) and their medical importance. A systematic review. *Med J Aust* 2004; **180:** 225–27.

97 Isbister GK, Gray MR. Bites by Australian mygalomorph spiders (Araneae, Mygalomorphae), including funnel-web spiders (Atracinae) and mouse spiders (Actinopodidae: *Missulena* spp). *Toxicon* 2004; **43:** 133–40.

98 Antunes E, Malaque CM. Mecanismo de ação do veneno de *Phoneutria* e aspectos clínicos do foneutrismo. In: Animais peçonhentos no Brasil. Biologia, clínica e terapêutica dos acidentes, 1st edn. São Paulo: Sarvier/FAPESP, 2003: 150–59.

99 Gomez MV, Kalapothakis E, Guatimosim C, Prado MA. *Phoneutria nigriventer* venom: a cocktail of toxins that affect ion channels. *Cell Mol Neurobiol* 2002; **22:** 579–88.