North American Scorpions

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Michael Levine and Anne-Michelle Ruha

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Introduction

Scorpions are arthropods with a hard exoskeleton and eight legs. Cephalad to the body are two large pinchers, which the scorpion uses to grasp prey. Caudal to the body is the tail, which terminates in the telson. This last segment contains both a venom gland and a stinger (Fig. 1).

While there are hundreds of different species of scorpions, only a few are capable of causing clinically significant envenomations in humans. Most of the dangerous scorpions worldwide belong to the Buthidae family, which includes the genera *Leiurus* (the Middle East), *Buthus* and *Androctonus* (North Africa), *Mesobuthus* (Asia, especially India), and *Tityus* (South America). The genus *Centruroides* is found in parts of North and Central America [1]. In the United States, the only native scorpion capable of producing a severe or life-threatening envenomation is the bark scorpion (*Centruroides sculpturatus*), which was previously referred to *as C. exilicauda*, although more recent data suggests these are, in fact, two different species [2]. *Centruroides sculpturatus* is found almost exclusively in the American southwest and parts of Mexico. In the United States, it is mostly concentrated in Arizona, although the bark scorpion is also found in New Mexico and parts of Nevada, Texas, and California [3, 4]. Rarely, such scorpions have "hitchhiked" on airplanes, resulting in envenomations outside of their normal geographical distribution [5].

M. Levine (✉)
Medical Toxicology, Banner Good Samaritan Medical Center, Phoenix, AZ, USA

Department of Emergency Medicine, Division of Medical Toxicology, University of Southern California, Los Angeles, CA, USA
e-mail: Michael.Levine@bannerhealth.com

A.-M. Ruha (✉)
Medical Toxicology, Banner – University Medical Center Phoenix, Phoenix, AZ, USA
e-mail: Michelle.Ruha@bannerhealth.com

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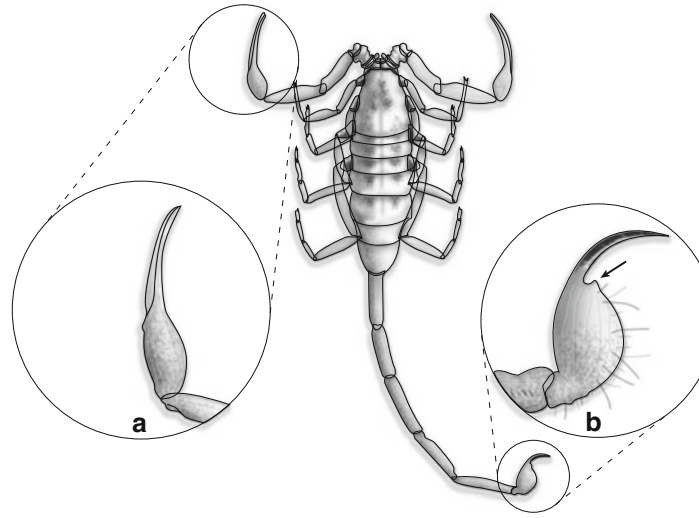

Fig. 1 Bark scorpion, *Centruroides sculpturatus (exilicauda)*. (**a**) Enlarged chela. (**b**) Enlarged vesicle showing a tubercle below the stinger. The body length including telson is 55 mm (From Ref. [37])

Fig. 2 Bark scorpion showing its long pedipalps and its unique tail

The bark scorpion is a small (mean length 6.5 cm with a range of 1–7 cm), tan/brown, nocturnal, non-burrowing animal which is capable of climbing vertically [3, 6, 7]. These animals reside both in rural and urban dwellings [7]. They prey on small lizards, insects, and arachnids. *Centruroides sculpturatus* can be distinguished from other scorpion species by its long pedipalps and its unique tail, whose terminal segment is rectangular, rather than square (Fig. 2).

While other species of *Centruroides* (e.g., *C. hentzi*, *C. gracilis*, *C. guanensis*, *C. vittatus*) and other genera (e.g., *Hadrurus* or *Vaejovis*) are present in the United States, stings by these scorpions are of little medical importance and rarely cause symptoms other than localized pain. Consequently, the rest of this chapter will focus exclusively on *C. sculpturatus*.

Historically, mortality following envenomations from *C. sculpturatus* was not uncommon.

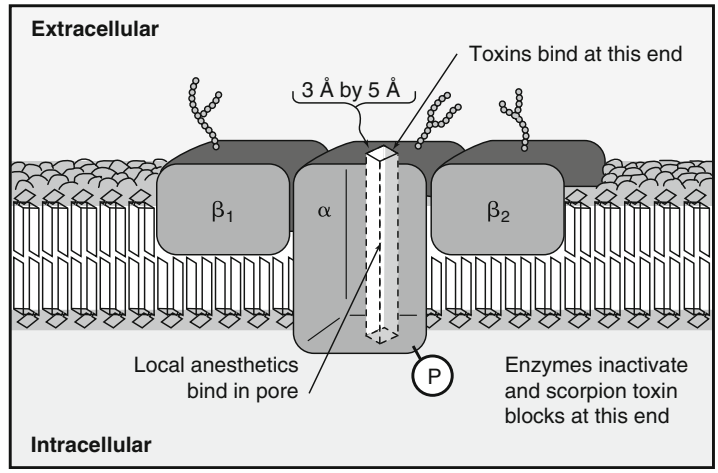

Fig. 3 Schematic representation of the voltage-gated channel in a neuron showing the site of scorpion toxin binding. The channel is roughly a 0.3 mm × 0.5 nm rectangular hole formed by four of the transmembrane helices within this subunit (From Ref. [38])

In the 1930s there were 40 deaths directly attributed to stings from the bark scorpion [8]. Deaths today, however, remain relatively rare. Despite accounting for more than 19,000 calls annually to US poison control centers, there were no reported fatalities in 2012 and only a single reported fatality in 2013. The declining mortality is largely attributed to both improved access to healthcare and improvements in supportive care [9].

The majority of envenomations occur in adults and require little intervention [4, 10]. Despite accounting for a smaller percentage of envenomated patients, pediatric patients are much more likely to become significantly ill and require critical care management [4].

Biochemistry and Clinical Pharmacology

Scorpion venom is a complex mixture of low molecular weight proteins, oligopeptidases, nucleotidases, lipids, mucoproteins, and amino acids [2, 11]. Among the various *Centruroides* species, there is a high degree of homology in the peptide sequence among the various toxins [12–14]. Mouse models demonstrate toxicity beginning at 1.12 mg/kg, with lethality consistently occurring at doses exceeding 3 mg/kg [2, 8]. Additional rodent studies have demonstrated reduced time intervals between envenomation and mortality with subsequent envenomations. However, this time difference was not associated with changes in serum levels of antivenom antibodies [15].

Toxicokinetic studies have been performed utilizing the venom from *C. limpidus*, a scorpion indigenous to Mexico. Following subcutaneous injections in a rabbit model, the venom is distributed in a two-compartment model. The volume of distribution was 850 ml/kg, with the maximal plasma concentration occurring approximately 1 h postinjection. The toxic fraction of the venom had an *alpha* elimination half-life of 0.35 h and a terminal elimination half-life of 1.9 h [16]. Despite the relatively short half-life in animals, limited human data with *C. sculpturatus* venom indicates patients may remain symptomatic with detectable levels for at least 20 h post envenomation [17]. The venom is primarily renally eliminated.

Pathophysiology of Toxic Effects

In general, scorpion venom targets voltage-gated sodium or potassium channels [11, 18] (Figs. 3 and 4). *Centruroides sculpturatus* venom has been shown to inhibit ERG potassium channels [12, 19] and prevent inactivation of the voltage-gated sodium channels [20–24] (Fig. 5).

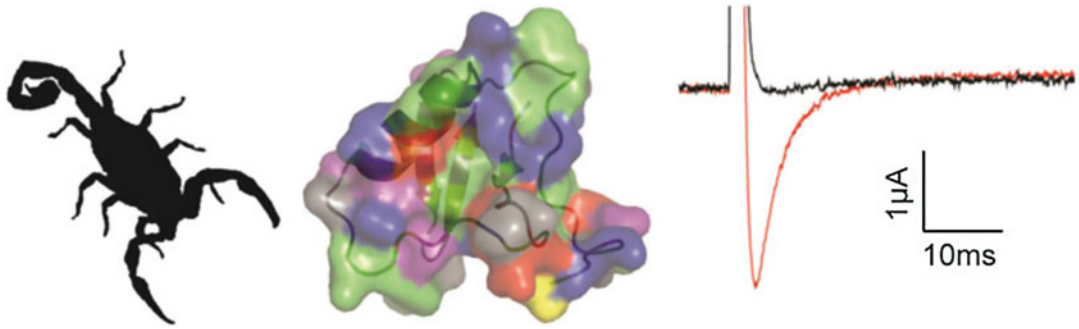

Fig. 4 β-scorpion toxins promote Nav channel opening. The β-scorpion toxin CssIV is found in the venom of the *Centruroides suffusus suffusus* scorpion (silhouette on the *left*), and amino acids important to toxin functionality have been identified in both the hydrophobic region and a ring of charged residues a (*middle* figure: protein backbone of the related β-scorpion toxin TsVII is shown together with the electrostatic surface of the protein). At 1 μM, CssIV opens rNav1.2a at voltages where the channel is normally closed. Current trace shown was evoked from a holding potential of −90 mV to a voltage of −40 mV when expressed in *Xenopus oocytes. Black* is control and red is after addition of 1 μM CssIV (*right*) (From Ref. [39])

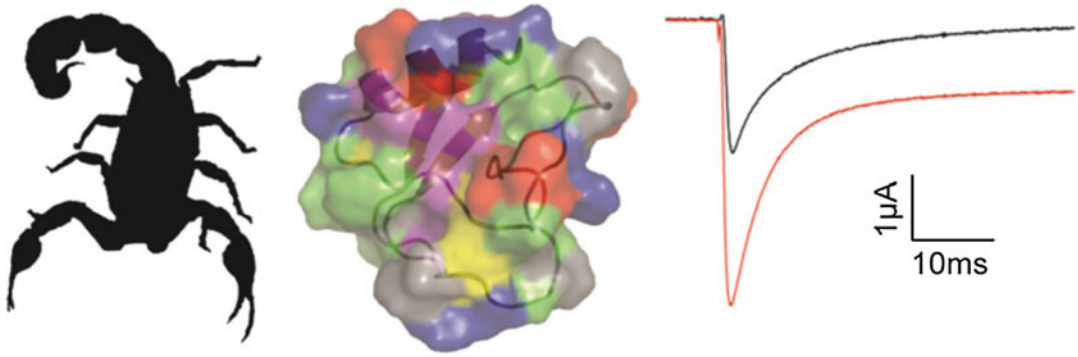

Fig. 5 α-scorpion toxins hamper Nav channel fast inactivation. The α-scorpion toxin AaHII is produced by the *Androctonus australis* Hector scorpion (silhouette on the *left*), and amino acids important to toxin functionality have been identified in both the hydrophobic patch as well as charged residues surrounding it (*middle* figure: protein backbone is shown together with the electrostatic surface of the protein). At 100 nM, AaHII inhibits fast inactivation of rNav1.2a currents evoked from a holding potential of −90 mV to a voltage of −20 mV when expressed in *Xenopus oocytes. Black* is control and *red* is after addition of 100 nM AaHII (*right*) (From Ref. [39])

Consequently, there is an increase in neuronal sodium influx, resulting in prolonged duration and amplitude of the action potential. A study examining the effects of the venom of various species of *Centruroides*, although not specifically *C. sculpturatus*, demonstrated reduced sodium conductance, left shift in the voltage-dependent activation and induction or resurgent currents at negative voltages [25].

Clinical Presentation and Life-Threatening Complications

The most severe envenomations occur in young children, although high-grade envenomations occur in all ages [4]. Following an envenomation, symptoms generally develop within minutes to an hour and may progress rapidly [9, 10]. The clinical effects of scorpion envenomation form the

Table 1 Grading system for envenomations by *C. sculpturatus* (Adapted from Ref. [4])

Grade	Symptom
I	Local pain or paresthesias
II	Pain or paresthesias distal to the bite site
III	Either isolated cranial nerve dysfunction or diffuse somatic skeletal neuromuscular dysfunction
IV	Both cranial nerve dysfunction and somatic skeletal neuromuscular dysfunction

basis for our current grading system, which is shown in Table 1.

Most patients develop only minimal symptoms and are thereby classified as having a grade I or II envenomation. These symptoms include pain or paresthesias either at the sting site (grade I) or more diffusely throughout the envenomated extremity and body (grade II).

Most children with high-grade envenomations experience autonomic hyperactivity, including tachycardia, hypertension, and/or fever [9, 26]. Vomiting is relatively common, especially at the onset of toxicity [9]. Respiratory distress, including hypoxemia or stridor, is also frequently observed. The respiratory findings may result from the combination of asynchrony of the respiratory musculature, loss of tongue control, and increased salivation. This may be compounded by the respiratory depressant effects of opioid analgesics, especially with concurrent administration of benzodiazepines. Respiratory findings occur in approximately one-third of patients with severe envenomation [9, 10].

The presence of cranial nerve or neuromuscular dysfunction defines a high-grade (grade ≥ 3) envenomation. Cranial nerve findings can include opsoclonus, disconjugate gaze, hypersalivation, tongue fasciculations, slurred speech, and occasionally stridor. The somatic skeletal neuromuscular findings can include myoclonic jerking movements of the extremities, arching and twisting of the torso, general restlessness, agitation, and tremor. While the myoclonic jerks may resemble seizure-like activity, they are typically asymmetric, the patient is awake and alert, and epileptic findings are not present on EEG.

Cutaneous findings are notably absent from stings by *C. sculpturatus*, although a positive tap test, performed by tapping the examiner's fingers over the sting site to elicit an increase in pain, may be noted. In addition, unlike other species of scorpions, direct cardiotoxicity is not expected following envenomation by *C. sculpturatus*.

Diagnosis

The diagnosis of bark scorpion envenomation is largely based on history and physical examination. Young children are often unable to provide the history of a sting, so details regarding the onset of effects (i.e., sudden inconsolable agitation in a previously well child) and recognition of characteristic clinical findings must be relied upon in diagnosing envenomation [27]. Because scorpions are nocturnal, patients may be awakened by the onset of symptoms. Cutaneous findings are usually absent. A positive tap test may help aid in the presumptive diagnosis; however in young children with severe agitation, it can be difficult to identify a positive response. While serum venom concentrations can be obtained [17], their use is limited to research settings and is not routinely available. Thus, the diagnosis remains clinical.

The differential diagnosis of scorpion envenomation includes both toxicologic (e.g., methamphetamine toxicity, black widow envenomation) [28, 29] and non-toxicologic etiologies (e.g., thyrotoxicosis, central nervous system infection).

Treatment

One of the primary reasons for the reduced mortality seen today is improved access to care, with supportive care being paramount [9].

Following envenomation, patients should be observed for progression of clinical effects. However, most patients with mild symptoms can be managed at home without referral to a medical facility [4, 10, 30, 31] (grade III recommendation).

Patients with a compromised airway, or those with ineffective ventilatory effort, should be intubated as per standard indications (grade III recommendation).

Patients with significant hypersalivation are sometimes treated with small doses of atropine; however, there is not sufficient evidence supporting this practice to recommend its routine use [9, 26, 32] (grade III evidence). Analgesics should be administered to those with significant pain (grade III recommendation). Most patients who have high-grade envenomations, and are thus unable to communicate verbally, should be assumed to have pain and can be treated with analgesics empirically. Due to its lack of significant histaminergic effects, fentanyl is the preferred analgesic [3] and should be administered with a starting dose of 1 mcg/kg intravenously (grade III recommendations). Additional doses can be titrated based on need. In addition to analgesics, benzodiazepines should be administered to assist in the control of neuromuscular excitation and agitation [9, 10] (grade III recommendation).

In August, 2011 the United States Food and Drug Administration approved *Centruroides* (scorpion) immune $F(ab')_2$ antivenom for the treatment of scorpion envenomation. While the approval is not based on grade of envenomation, because low-grade envenomations universally do well without therapy, and the expensive nature of the antivenom, its use is primarily reserved for those with grade III or IV envenomation. The use of this antivenom has been demonstrated to be highly safe and effective [33–35] (grade Ib evidence). The use of this antivenom in an emergency department may obviate the need for admission and/or transfer to a pediatric facility for admission [35]. The cost of such therapy can exceed $10,000, and some data suggests its use may not be a cost-effective option [36]. If antivenom is not an option for patients with high-grade envenomations, admission to an intensive care unit, and possible mechanical ventilation, is indicated. During the approximately 2-year period between September 2004 through July 2006 when antivenom was not available in Arizona, nearly 25% of all grade III or IV scorpion envenomations required intubation with ventilatory support [9].

While antivenom is an option for patients with high-grade envenomations, supportive care is paramount. Antivenom should be considered an adjunctive agent for severe envenomations, but its use is not necessarily the standard.

Indications for ICU Admission

Grade III or IV envenomations not treated with antivenom

Hypoxia that does not resolve after antivenom administration, especially if concern for significant aspiration

Mechanical ventilation

Key Points

- Most patients will develop only minor symptoms and not require admission.
- Antivenom may be administered for high-grade symptoms.
- Clinicians should prepare for possible respiratory compromise and treat any impending respiratory failure with endotracheal intubation.

Criteria for ICU Discharge

- Resolution of significant respiratory compromise
- Resolution of symptoms

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