JOINT TRAUMA SYSTEM CLINICAL PRACTICE GUIDELINE (JTS CPG)

Global Spider and Scorpion Envenomation Management (CPG ID: 84)

This CPG provides an overview of spider and scorpion envenomation and presents a standardized approach to providers in the evaluation and treatment of patients with spider or scorpion induced poisoning.

Contributors

Lt Col Joseph K. Maddry, USAF MC
Maj Patrick C. Ng, USAF MC
Lt Col Andrew Hall, USAF MC
Capt William T. Davis, USAF MC
Col (Ret) Shawn M. Varney, USAF MC
Lt Col (Ret) Nurani M. Kester, USAF MC
Col Vikhyat S. Bebarta, USAF MC
Col Stacy A. Shackelford, USAF, MC

Publication Date: 09 Feb 2021

Supersedes: Bites, Stings and Envenomation, 30 Mar 2018

TABLE OF CONTENTS

BACKGROUND

Spider and scorpion envenomations can occur in many environments in which the military operates.[1] While most spider and scorpion envenomations result in mild symptoms, severe toxicity and death can occur.

Arthropods are a diverse group of animals with numerous species producing a wide array of toxins. Many arthropods possess a significant venom but lack a sufficient apparatus (fangs or talon) to inject it into humans. Most bites and stings involve more danger from anaphylaxis, but several species of spiders and scorpions have significant neurotoxic, cytotoxic, or hemotoxic venoms. Unfortunately, reliable data evaluating the impact of spider bites and scorpion stings on humans are lacking. Most knowledge is based on case reports and case series, frequently lacking expert review. Furthermore, the public frequently spreads inaccurate information (i.e. reporting a skin abscess resulting from *Staph. aureus* is a "spider bite").

Unlike other types of injuries, patients may not even recognize they were envenomated by arthropods, as many injuries are painless or felt as a pinprick. Anaphylaxis is the most concerning initial effect. Recognize and treat it immediately using standard acute allergic reaction therapies. Anaphylaxis from an arthropod envenomation is not an indication for antivenom. For all bites/stings, assess tetanus status and administer vaccine and/or immunoglobulin (for those not previously immunized against tetanus) if required. The following section describes the more clinically significant species of venomous arthropods, the toxicological syndrome they produce, and the treatment. Consider toxicology consultation using the ADvanced VIrtual Support for OpeRational Forces (AD.VI.S.O.R) line in any patient with systemic symptoms secondary to a spider or scorpion envenomation – Commercial: 1 (833)-ADVSRLN (238-7756) or DSN (312) 429-9089.

SPIDERS

While many spider species produce venom, the vast majority lack sufficiently large or strong enough fangs to penetrate human skin and cause clinically significant effects. However, spiders venomous to humans can be found throughout much of the world. Appendix A provides the geographical location of clinically significant venomous spider species.

WIDOW SPIDERS (*LATRODECTUS* SPECIES)

BACKGROUND

Multiple species of widow spiders (*Latrodectus spp.*) are found on various continents (North America, Asia, Europe, Africa, and Australia). They are generally black or brown with a red or yellow demarcation on their ventral and/or dorsal abdomen. A lack of a red or yellow demarcation on the spider does not exclude it from being a *Latrodectus spp*. They live in temperate and tropical latitudes and tend to inhabit shady enclosed spaces such as crevices, wood piles, and sheds. Humans are commonly bitten while in bed during the fall and early winter when the spiders are attempting to find warmth.

PATHOPHYSIOLOGY

Widow spider venom consists of multiple toxins which ultimately result in activation of the nervous system and muscle contraction.[2]

CLINICAL MANIFESTATION

Patients may or may not feel a pinprick upon the initial bite. A pair of small red spots at the envenomation site may be visible; however, the bite site is often not located.[3] Some patients do not develop systemic toxicity. In those patients who do, symptoms typically begin 15 to 60 minutes following the envenomation. The primary symptom is painful muscle cramping, starting at the bite site and progressing towards the center of the body. Patients may develop a painful, rigid abdomen secondary to abdominal muscle spasm which may be mistaken for peritonitis. The pain increases over time and may occur in waves. In some cases, the patient develops a temporary diaphoretic, grimaced, and contorted appearance of the face referred to as "*facies latrodectismica*."[4] Other symptoms include vomiting, diaphoresis, tachycardia, hypertension (often profound), and restlessness. Symptoms of *Latrodectus* envenomation last hours to days. Fatalities from *Latrodectus* envenomation are exceedingly rare and, when they do occur, are secondary to cardiac arrest (presumably from severe hypertension in patients with predisposing medical conditions) and wound infection.[5]

TREATMENT

Treatment consists primarily of supportive care, pain management, and wound care (to include tetanus prophylaxis). Given the low risk of infection, antibiotics are not routinely recommended.

Depending upon the severity of pain, acetaminophen, nonsteroidal anti-inflammatory agents, and opioids can be used for pain control. Benzodiazepines may improve muscle spasms.[6] Pain control and benzodiazepines are often sufficient to manage tachycardia and hypertension. In those patients with severe pain refractory to pain medications, antivenom (if available) may be indicated but may not be readily available.[7] Long term injury or death from *Latrodectus* is extremely unlikely. While rare, fatal allergic reactions to *Latrodectus* antivenom have occurred.[8] Fatal cases due to antivenom anaphylaxis have been reported in patients with asthma. Therefore, *Latrodectus* antivenom is not indicated in patients with otherwise manageable symptoms, particularly those that may be at higher risk (i.e. history of asthma). If administered, patients should be monitored for 4 hours, but prophylactic treatment for allergic reaction is not recommended. When patients do have significant symptoms meeting indications for antivenom, the antivenom is rapidly effective and curative. When necessary, expired vials of antivenom may be used.[9] The dose consists of one 2.5 milliliter vial of antivenom dissolved in one 2.5 milliliter vial of sterile water (provided in the antivenom kit) administered intravenously. While the package instructions permit intramuscular injection, this route is unlikely to provide sufficient absorption to manage symptoms.[10] While one dose is usually sufficient, a second dose may be administered if symptoms are not adequately controlled 15-30 minutes after the first dose.

In the event that medical personnel are unable to control the patient's symptoms with available pain medications and benzodiazepines, then medical evacuation is recommended.

VIOLIN SPIDERS (*LOXOSCELES* SPECIES)

BACKGROUND

Loxosceles reclusa in a venomous spider more commonly known as the brown recluse, violin spider, or fiddleback spider. As indicated by the common names, the spider has a brown shape/mark resembling a violin or fiddle on the dorsum of its cephalothorax. The *Loxosceles* genus has a worldwide distribution. The spiders prefer dark areas such as wood piles, crevices between rocks, and basements. While not aggressive, they will bite if antagonized.[11]

PATHOPHYSIOLOGY

Loxosceles venom is cytotoxic (toxic to living cells) and consists of two main constituents: sphingomyelinase-D and hyaluronidase. Hyaluronidase facilitates the spreading of the venom into tissue while sphingomyelinase-D causes necrosis and hemolysis. Sphingomyelinase also triggers an inflammatory reaction in red blood cells resulting in vessel thrombosis, tissue ischemia, and necrosis.[12]

CLINICAL MANIFESTATIONS

Loxoscelism will present as an ulcerative lesion, sometimes not until days after the initial envenomation. In general, within several hours after the initial bite there will be local ischemia resulting in pain, pruritus and swelling. A blister or a central area of purple discoloration will form. The venom causes vasoconstriction and can result in a pale border around the central ulcer/blister/discoloration. Over the next several days the ulcer enlarges and the borders demarcate until 1-2 weeks after the initial bite.[13]

In some cases, systemic loxoscelism can occur. The extent of the cutaneous reaction does not predict the development of systemic loxoscelism, which typically occurs 24 to 72 hours after the envenomation. Young pediatric patients are at greatest risk of reaction. Systemic loxoscelism manifestations include fever, weakness, vomiting, joint pain, petechiae, rhabdomyolysis, disseminated intravascular coagulation, and hemolysis. While rare, severe cases can result in hemoglobinemia, hemoglobinuria, kidney failure, and death.[14]

TREATMENT

Laboratory testing is not indicated for non-necrotizing local symptoms. Treatment of local symptoms includes wound care, tetanus prophylaxis, analgesics, and antipruritics as necessary. There is no antivenom available. Early excision, intralesional injection of corticosteroids, and dapsone are not indicated. The wound may be confused with a localized abscess, and diagnosis may be made following ineffective incision and drainage or antibiotic treatment. Corrective surgery can be performed after the wound has completed progression and has begun to heal, typically several weeks after the envenomation. Prophylactic antibiotics are not indicated, but should be used as appropriate if a secondary bacterial infection develops.[15]

Patients with an expanding necrotic lesion or symptoms of systemic loxoscelism should be admitted to a medical facility. A complete blood cell count, urinalysis for blood, metabolic panel, liver function and coagulation studies should be performed. In those patients who develop hemoglobinuria, increased IV fluid hydration can be used to attempt to prevent acute renal failure. Treat significant hemolysis with transfusions, including exchange transfusion in infants and young children with severe systemic loxoscelism.[16]

TARANTULAS

BACKGROUND/CLINICAL MANIFESTATIONS

There are more than 1500 species of tarantulas found throughout tropical and subtropical areas of the world. While tarantulas are often feared due to their large size and painful bite, their bite is not dangerous to humans. Some indigenous American tarantula species have barbed hairs with which they can strike their victims or they can generate a cloud of hairs (as a defense mechanism) by scratching their abdomen with their legs. These hairs can cause irritation and pruritus of the skin, eyes, and respiratory tract.[17]

TREATMENT

Tarantula bite treatment is supportive and includes cool compresses, analgesics, antipruritics, and tetanus prophylaxis as indicated. Adhesive tape can be used to remove barbed hairs from the skin. If hairs get in the eye, then irrigate copiously. If irrigation is ineffective, then removal by an ophthalmologic surgeon may be necessary. Skin irritation can be treated with topical and oral antihistamines and corticosteroids.[17]

FUNNEL WEB SPIDERS (*ATRAX*)

BACKGROUND

Australian funnel web spiders are capable of inducing a severe and potentially fatal neurotoxic envenomation syndrome. Unlike other species of the spiders, funnel web spiders can bite tenaciously and may have to be physically removed from the victim. They prefer to live on the ground in moist, temperate environments such as burrows, crevices between rocks, and near the foundations of homes. They are named for the tubular or funnel-shaped web they build.[18]

PATHOPHYSIOLOGY

The lethal component of funnel web spider venom is robustotoxin. It induces an autonomic storm by causing excessive release of acetylcholine, norepinephrine, and epinephrine.[19,20]

CLINICAL MANIFESTATIONS

Funnel web spider envenomation causes a biphasic envenomation syndrome. The first phase includes pain at the bite site, perioral tingling, piloerection, and regional fasciculations which may progress to muscle spasm. This muscle spasm may involve the face, tongue, and larynx leading to airway compromise. The increased stimulation of cholinergic and adrenergic systems causes nausea, vomiting, lacrimation, salivation, tachycardia, hypertension, cardiac dysrhythmias, and acute lung injury. Acute lung injury is the predominate cause of death during the first phase.[20]

In the second phase the symptoms of the first phase resolve and lead to the gradual onset of refractory hypotension, apnea, and cardiac arrest.[20]

TREATMENT

Prehospital management consists of pressure immobilization using an elastic crepe bandage applied tightly enough to limit lymphatic spread, but not to restrict blood flow. The venom of the funnel web spider is one of the few animal venoms to undergo local inactivation. The patient should be transported to the nearest medical facility with the bandage in place, and the bandage should not be removed until antivenom is readily available to be administered.[21]

An effective funnel web spider antivenom is available in Australia. An initial dose of 2 vials is indicated for patients with signs of envenomation, while a dose of 4 vials is indicated for pulmonary edema or decreased mental status. The initial dose is repeated every 15 minutes until the patient clinically improves. A dose of 8 vials is commonly reported in cases of severe envenomation.[21]

SCORPIONS

BACKGROUND

Scorpions envenomate humans by stinging them with the telson on their tail. The majority of medically significant envenomations occur in the Middle East, tropics (e.g., Southwest Asia, India, Central and South America), and North Africa. Scorpions are nocturnal, hibernate in the winter, and are active in the warm seasons. Humans are frequently envenomated by scorpions hiding in dark, hidden locations such as inside shoes and small crevices.

Given many scorpion envenomations occur in developing nations lacking significant medical infrastructure, data regarding scorpion envenomations and antivenoms are limited. Studies have estimated over 1.2 million scorpion envenomations per year globally with an overall fatality rate ranging from 0.27% to 0.52%.[22,23] The majority of severe and fatal envenomations occur in children under the age of ten due to their decreased body mass.

PATHOPHYSIOLOGY

Scorpion venoms are complex and can include phospholipase, acetylcholinesterase, hyaluronidase, serotonin, and neurotoxins. Scorpion venom increases neuronal release by blocking inactivation of the sodium channel, resulting in an increase in the amplitude and duration of neuron action potential. The overall result is excess stimulation of the central nervous system, the neuromuscular system, the sympathetic nervous system, and the parasympathetic nervous system.[24]

The components of scorpion venom are species specific and generally fall into the categories of neurotoxic and cardiotoxic; however, this terminology is misleading since the cardiotoxic effects are secondary to an excess release of catecholamines stimulated by the nervous system.[25]

The venom of one unique species of scorpion, *Hemicorpius lepturus*, found in Iraq and Iran is predominately cytotoxic, similar to the brown recluse spider.[26]

CLINICAL MANIFESTATIONS

Scorpion stings produce a painful local reaction often including the sensation of tingling or burning. Erythema at the injection site is common, and discoloration and necrosis sometimes occur.

Symptoms of excess sympathetic nervous system stimulation predominate over symptoms of parasympathetic nervous system stimulation. Sympathetic stimulation via excess catecholamine release produces hypertension, tachycardia, irritability, and agitation. In severe cases, patients may develop seizures and hyperthermia. Excess cardiovascular stimulation may result in myocardial ischemia, myocardial infarction, and cardiac dysrhythmia. In rare cases, severe outcomes occur like bradycardia and hypotension due to excess parasympathetic stimulation, or cardiovascular collapse resulting from catecholamine depletion.[27]

Clinical manifestations of the parasympathetic stimulation include salivation, nausea, vomiting, abdominal pain, pancreatitis, and priapism.[27]

Neuromuscular symptoms include tongue fasciculations, muscle spasms, dysphagia, and dysphonia. Roving eye movements is a classic finding of severe centruroides envenomation (the only clinically significant venomous scorpion indigenous to the United States). While infrequent, severe muscle spasm can result in airway compromise and respiratory arrest.[24]

Pulmonary edema commonly occurs in severe and fatal cases.[25] The pulmonary edema is both cardiogenic and non-cardiogenic in nature. The cardiogenic component is due to reduced cardiac output resulting from excessive sympathetic stimulation. The non-cardiogenic component is due to increased vascular permeability and release of vasoactive substances.

Hemiscorpius lepturus envenomations can cause local skin necrosis and in severe cases hemolysis, disseminated intravascular coagulation, and renal failure.[28]

TREATMENT

The diagnosis of scorpion envenomation is made clinically based on history, symptoms, and signs of envenomation. While older children and adults will almost universally report the initial painful sting, in nonverbal children the diagnosis may be more challenging. Laboratory analysis may reveal an elevated white blood cell count, serum glucose, lactate dehydrogenase, and amylase; however, these tests lack sufficient sensitivity or specificity to be clinically relevant. In those patients with moderate to severe symptoms, an electrocardiogram should be performed to evaluate for evidence of cardiac ischemia or dysrhythmias. A serum troponin may be measured to evaluate for cardiac ischemia.[29] If the envenomation occurred in Iraq or Iran and *Hemiscorpius lepturus* envenomation is suspected, a platelet count, prothrombin time, D-dimer, and fibrinogen level, blood urea nitrogen, and creatinine can be performed to evaluate for evidence of disseminated intravascular coagulation or renal failure.[30]

The majority of scorpion envenomations can be adequately managed with pain medications (ibuprofen, acetaminophen, and opioids) and routine wound management to include tetanus prophylaxis. Most patients, especially adults, will not develop significant symptoms. Patients should be observed for 4-6 hours after envenomation to ensure no delayed onset of symptoms. Prophylactic antibiotics are not indicated. Application of a tourniquet, cauterization, and incision and drainage are contraindicated in scorpion stings. Benzodiazepines may be used to treat significant agitation (which may cause hypertension) or seizures. Pharmacologic management of hypertension is generally not indicated. Intravenous vasopressors such as nitroprusside, nitroglycerin, labetalol, and phentolamine should be used in patients with severe or symptomatic hypertension refractory to benzodiazepines.[31]

For clinically significant envenomation, management is supportive and focused on the patient's symptoms. Benzodiazepines are the first line therapy for sympathomimetic toxicity.[31] Note that benzodiazepines under dosing for sympathomimetic toxicity and seizures is not uncommon. Administer Benzodiazepines aggressively to ensure symptom control. Intravenous propofol or phenobarbital in combination with endotracheal intubation may be used in severe cases. Other anticonvulsants such as phenytoin, levetiracetam, and valproic acid are generally not indicated since they do not treat the underlying sympathomimetic or anticholinergic toxidrome causing the seizures. Direct acting vasopressors (epinephrine and norepinephrine) are recommended to treat bradycardia and hypotension.

In patients with significant neuromuscular spasm, oral secretions, sedation, or other threats to the patent airway, perform endotracheal intubation to prevent aspiration and ensure adequate ventilation. Pulmonary edema should be managed with noninvasive or invasive ventilation in combination with optimization of cardiac output.[31]

The incidence of long-term sequelae resulting from scorpion envenomation is unknown; however, due to the potentially significant risk, priapism should be managed aggressively with antivenom (if available) and other standard treatments of priapism (aspiration and intracavernous injection of phenylephrine) with urology consultation.[32]

Antivenom is available for some species; data regarding the benefits and risks of many of these antivenoms are significantly limited. In patients with moderate to severe symptoms refractory to analgesics and

benzodiazepines, antivenom, if available, may be indicated. Due to the high risk of immediate or delayed allergic reactions to these antivenoms, intravenous histamine antagonists (i.e. diphenhydramine), steroids, and epinephrine should be immediately available at the patient's bedside prior to antivenom administration.

Appendix B provides scorpion sting clinical grading and treatment guidelines. Appendix C provides a list of scorpion antivenoms available by country and their dosing regimens. Several studies demonstrate improved efficacy of intravenous compared to intramuscular antivenom administration.[33] Antivenom dosing does not depend on patient weight or size and is the same for adult and pediatric patients.[34]

ADVERSE REACTIONS TO ANTIVENOM

Antivenoms have the potential to cause immediate and potentially life-threating, anaphylactoid reactions. Reactions can range from mild (pruritus, rash) to severe (wheezing, hypotension, respiratory distress, cardiovascular collapse, and death). Antivenoms may also cause serum sickness. Serum sickness is a type III hypersensitivity reaction which is characterized by flu-like symptoms with or without a rash that typically occurs between 2 days and 3 weeks after antivenom administration. Serum sickness is uncomfortable but not life threatening.[35]

ADVERSE REACTION MANAGEMENT

Unfortunately, data on the incidence of adverse reactions to antivenoms used outside of developed nations are lacking. Medical providers should anticipate a high likelihood for serious and potentially life-threatening anaphylactoid reactions to antivenoms not approved by the US Food and Drug Administration (FDA). For this reason, antivenom should only be used in patients with moderate to severe symptoms refractory to standard medical therapies (e.g., benzodiazepines and pain medications). Epinephrine should be immediately available at the patient's bedside prior to the administration of antivenom to ensure rapid administration if necessary.

For mild to moderate symptoms occurring during antivenom infusion (e.g., nausea, vomiting, urticaria, pruritus, chills, fever), stop the infusion immediately and treat symptoms with antiemetics, antihistamines (typically diphenhydramine), and steroids (i.e. methylprednisolone, prednisone, prednisolone). If the reaction is controlled after treatment and the patient's condition still requires antivenom, restart the antivenom at a slower infusion rate.

For severe reactions (i.e. respiratory distress, hypotension), immediately stop the antivenom infusion and treat using a standard anaphylaxis protocol (diphenhydramine 50 mg [1 mg/kg in pediatric patients] IV, methylprednisolone 125 mg [2 mg/kg in pediatric patients] IV, and 0.3 mg [0.15 mg in pediatric patients] of 1:1000 epinephrine intramuscularly).[36-39] Consider adding an H2 antihistamine such as famotidine. If necessary, intubate for airway edema not rapidly responsive to epinephrine. If antivenom is considered necessary to prevent death or disability, the antivenom may be reinitiated at a slower rate of infusion in conjunction with an epinephrine infusion.

In patients who develop serum sickness, management consists of symptomatic treatment with antihistamines and pain medications with or without a course of oral steroids.[35]

PERFORMANCE IMPROVEMENT (PI) MONITORING

INTENT (EXPECTED OUTCOMES)

- Rapid evaluation and transfer to site with antivenom capability for envenomation
- Tetanus prophylaxis when appropriate

PERFORMANCE/ADHERENCE MEASURES

- Transfer of patients with moderate to severe symptoms (grades 3 and 4) to antivenom if not available at site
- Aggressive use of benzodiazepines as indicated for agitation, neuromuscular stimulation, tachycardia, and hypertension
- Tetanus prophylaxis for all bites and stings

DATA SOURCE

- Patient record
- Department of Defense Trauma Registry (DoDTR)

SYSTEM REPORTING & FREQUENCY

The above constitutes the minimum criteria for PI monitoring of this CPG. System reporting will be performed annually. Additional PI monitoring and system reporting may be performed as needed.

The system review and data analysis will be performed by the JTS Chief, JTS Program Manager and the JTS PI Branch.

RESPONSIBILITIES

It is the clinical team leader's responsibility to ensure familiarity, appropriate compliance, and PI monitoring at the local level with this CPG.

REFERENCES

1. Warrell DA. Venomous bites, stings, and poisoning. Infectious Disease Clinic of North America. June 2012; Vol 26(2):207-223.
2. Garb JE, Hayashi CY. Molecular evolution of α-latrotoxin, the exceptionally potent vertebrate neurotoxin in black widow spider venom. Molecular Biology Evolution. May 2013; Issue 30(5):999-1014.
3. Maretić Z. Latrodectism: variations in clinical manifestations provoked by Latrodectus species of spiders. Toxicon. 1983; Vol 21, Issue (4):457-66.
4. Halmo LS, Hurst IA, Ng PC, Wang GS. Latrodectus Facies after Latrodectus Hesperus Envenomation in a Pediatric Patient. Journal of Emergency Medicine. Oct 2019; Vol 57, Issue (4):523-526.
5. Ramialiharisoa A, de Haro L, Jouglard J, Goyffon M. Le latrodectisme à Madagascar [Latrodectism in Madagascar]. Medecine Tropicale (Mars). Dec 1993; Vol 54, Issue (2):127-30.

6. Dart RC, Bush SP, Heard K, et al. The efficacy of antivenin latrodectus (black widow) equine immune $F(ab')_2$ versus placebo in the treatment of latrodectism: a randomized, double-blind, placebo-controlled, clinical trial. Annals of Emergency Medicine. Sep 2019; Vol 74, Issue (3):439-449.
7. Offerman SR, Daubert GP, Clark RF. The treatment of black widow spider envenomation with antivenin latrodectus mactans: a case series. The Permanente Journal. Summer 2011; Vol 15, Issue (3):76-81. doi: 10.7812/tpp/10-136.
8. Nordt SP, Clark RF, Lee A, Berk K, Lee Cantrell F. Examination of adverse events following black widow antivenom use in California. Clinical Toxicology (Phila). Jan 2012; Vol 50(1):70-73.
9. Sánchez EE, Migl C, Suntravat M, Rodriguez-Acosta A, Galan JA, Salazar E. The neutralization efficacy of expired polyvalent antivenoms: An alternative option. Toxicon. Oct 2019; Vol 168:32-39.
10. Isbister GK, O'Leary M, Miller M, Brown SG, Ramasamy S, James R, Schneider JS. A comparison of serum antivenom concentrations after intravenous and intramuscular administration of redback (widow) spider antivenom. British Journal of Clinical Pharmacology. Jan 2008; Vol 65(1):139-43.
11. Goddard J. Physician's guide to arthropods of medical importance. CRC press; 19 Apr 2016.
12. Chaim OM, Trevisan-Silva D, Chaves-Moreira D, et al. Brown spider (loxosceles genus) venom toxins: Tools for biological purposes. Toxins (Basel). Mar 2011; Vol 3(3):309-344.
13. Kurpiewski G, Forrester LJ, Barrett JT, Campbell BJ. Platelet aggregation and sphingomyelinase D activity of a purified toxin from the venom of Loxosceles reclusa. Biochimica et Biophysica Acta (BBA). 18 Dec 1981; Vol 678(3):467-476.
14. Robinson JR, Kennedy VE, Doss Y, Bastarache L, Denny J, Warner JL. Defining the complex phenotype of severe systemic loxoscelism using a large electronic health record cohort. PLoS One. 19 Apr 2017 ; Vol 12(4):e0174941.
15. Swanson DL, Vetter RS. Bites of brown recluse spiders and suspected necrotic arachnidism. New England Journal of Medicine. 17 Feb 2005; Vol 352 (7):700-707.
16. Said A, Hmiel P, Goldsmith M, Dietzen D, Hartman ME. Successful use of plasma exchange for profound hemolysis in a child with loxoscelism. Pediatrics. Nov 2014; Vol 134(5):e1464-7.
17. Kong EL, Hart KK. Tarantula Spider Toxicity. 31 May 2020. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing.
18. Nimorakiotakis B, Winkel KD. The funnel web and common spider bites. Australian Family Physicians. April 2004; Vol 33(4):244-251.
19. Hodgson WC. Pharmacological action of Australian animal venoms. Clinical and Experimental Pharmacology and Physiology. Jan 1997; Vol 24(1):10-17.
20. Isbister GK, Sellors KV, Beckmann U, Chiew AL, Downes MA, Berling I. Catecholamine-induced cardiomyopathy resulting from life-threatening funnel-web spider envenoming. The Medical Journal of Australia. 5 Oct 2015; Vol 203(7):302-304.
21. Braitberg G, Segal L. Spider bites - Assessment and management. Australian Family Physicians. Nov 2009; Vol 38(11):862-7.
22. Chippaux JP, Goyffon M. Epidemiology of scorpionism: a global appraisal. Acta Tropica. Aug 2008; Vol 107, Issue 2:71-79.
23. Goyffon M, Vachon M, Broglio N. Epidemiological and clinical characteristics of the scorpion envenomation in Tunisia, Toxicon. 1982; Vol 20:337-344.
24. O'Connor A, Ruha AM. Clinical course of bark scorpion envenomation managed without antivenom. Journal of Medical Toxicology. Sep 2012; Vol 8(3):258-262.

25. Bahloul M, Chaari A, Dammak H, et al. Pulmonary edema following scorpion envenomation: mechanisms, clinical manifestations, diagnosis and treatment. International Journal of Cardiology. 10 Jan 2013; Vol 162(2):86-91.

26. Dehghani R, Charkhloo E, Seyyedi-Bidgoli N, et al. A Review on Scorpionism in Iran. Journal of Arthropod-Borne Disease. 25 Dec 2018; Vol 12(4):325-333. eCollection 2018 Dec.

27. Cupo P. Clinical update on scorpion envenoming. Revista da Sociedade Brasileira Medicina Tropical. Nov-Dec 2015; Vol 48(6):642-649.

28. Dizaji R, Sharafi A, Pourahmad J, et al. The effects of Hemiscorpius lepturus induced-acute kidney injury on PGC-1α gene expression: From induction to suppression in mice. Toxicon. 30 Jan 2020; Vol 174:57-63.

29. Chakroun-Walha O, Karray R, Jerbi M, et al. Value of troponin levels in the diagnosis of cardiac dysfunction in moderate scorpion envenomation. Human and Experimental Toxicology. Jun 2018; Vol 37(6):580-586.

30. Sagheb MM, Sharifian M, Moini M, Sharifian AH. Scorpion bite prevalence and complications: report from a referral centre in southern Iran. Tropical Doctor. Apr 2012; Vol 42(2):90-91.

31. Rodrigo C, Gnanathasan A. Management of scorpion envenoming: a systematic review and meta-analysis of controlled clinical trials. Systematic Reviews. 8 Apr 2017; 6(1): Article 74.

32. Prasad R, Mishra OP, Pandey N, Singh TB. Scorpion sting envenomation in children: factors affecting the outcome. Indian Journal of Pediatrics. May 2011; Vol 78(5):544-548.

33. Abroug F, ElAtrous S, Nouira S, et al. Serotherapy in scorpion envenomation: a randomised controlled trial. Clinical Trial Lancet. 11 Sep 1999; Vol 354, Issue (9182):906-909. doi: 10.1016/s0140-6736(98)12083-4.

34. Boyer L, Degan J, Ruha A-M, et al. Safety of intravenous equine F(ab')2: Insights following clinical trials involving 1534 recipients of scorpion antivenom. Toxicon. Dec 2013; Vol 76:386-393.

35. León G, Herrera M, Segura Á, Villalta M, Vargas M, Gutiérrez JM. Pathogenic mechanisms underlying adverse reactions induced by intravenous administration of snake antivenoms. Toxicon. 15 Dec 2013; Vol 76:63-76.

36. Dhami S, Panesar SS, Roberts G, et al. Management of anaphylaxis: a systematic review. Allergy. Feb 2014; Vol 69(2):168-175. doi:10.1111/all.12318.

37. Simons FER, Ebisawa M, Sanchez-Borges M, et al. 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. World Allergy Organization Journal J. 2015; Vol 8(1):32. doi:10.1186/s40413-015-0080-1.

38. Simons FER, Ardusso LRF, Bilò MB, et al. 2012 Update: World Allergy Organization Guidelines for the assessment and management of anaphylaxis. Current Opinion Allergy Clinical Immunology. Aug 2012; Vol 12(4):389-399. doi:10.1097/ACI.0b013e328355b7e4.

39. Isbister GK, Bawaskar HS. Scorpion envenomation. New England Journal of Medicine. 31 July 2014; Vol 371(5):457-63.

APPENDIX A: LOCATION OF CLINICALLY SIGNIFICANT VENOMOUS SPIDER SPECIES

Geographical Location of Clinically Significant Venomous Spider Species			
Continent	**Latrodectus (i.e. Black Widow)**	**Loxosceles (i.e. Brown Recluse)**	**Funnel Web**
Africa	X	X	
Asia	X	X	
Australia	X	X	X
Europe	X		
North America	X	X	
South America	X	X	

APPENDIX B: CLINICAL GRADE AND TREATMENT OF SCORPION STINGS

Clinical Grade and Treatment of Scorpion Stings		
Grade	**Effects**	**Treatment**
1	Local effects only	Analgesia, tetanus prophylaxis
2	Mild/Moderate autonomic excitation (i.e. tachycardia, hypertension)	Benzodiazepines, cautious use of beta-antagonists and vasodilators
	Agitation and anxiety	Benzodiazepines
	Pain and paresthesias remote from the sting site	Analgesia
3	Pulmonary edema	Antivenom, noninvasive or mechanical ventilation
	Hypotension and cardiogenic shock	Antivenom, vasopressors (i.e., norepinephrine, epinephrine)
	Neuromuscular excitation, somatic neuromuscular dysfunction **or** cranial nerve dysfunction (associated with *Centruroides* species)	Antivenom, benzodiazepines
4	Multiorgan failure, coma, seizures, end-organ damage secondary to hypotension, somatic neuromuscular dysfunction **and** cranial nerve dysfunction (associated with *Centruroides* species)	Antivenom, vasopressors, sedation (benzodiazepine, propofol, phenobarbital), mechanical ventilation

Modified from Isbister and Bawaskar.[39]

APPENDIX C: SCORPION ANTIVENOMS AVAILABLE IN EACH COUNTRY

Antivenoms Available in Each Country			
Country	**Species the antivenom treats**	**Antivenom**	**Antivenom dosing regimen**
Morocco	*Androctonus australis garzonii, B. occitanus tunetanus, Tityus serrulatus*	Polyvalent scorpion antivenom	2-10 mL IV
Egypt	*Leiurus quinquestraitus, Androctonus amoreuxi, Androctonus crassicauda, Androctonus aeneas, Androctonus australis, Scorpio marus palmatus, Buthus occitanus*	Purified polyvalent anti-scorpion serum (equine)	5 1-mL ampules IV
Algeria	*Androctonus australis*	Scorpion antivenom (Pasteur Institute of Algeria)	10 mL IV Note: one study showed no benefit with this dose.
Mexico, United States	*Centruroides limpidus, C. noxius, C. suffuses, C. exilicauda*	Polyvalent scorpion antivenom	3 vials, each reconstituted in 5 mL of sterile normal saline (NS). Combine all 3 reconstituted vials in 50 mL NS infused IV over 10 minutes
Brazil	*Tityus serrulatus*	Soro antiescorpionico	20 mL IV
South Africa	*Parabuthus spp.*	Monovalent scorpion antivenom	5-10 mL IV
India	*Hottentotta/Mesobuthus tamulus*	Monovalent red scorpion antivenom	2-8 vials, each diluted into 10 mL of distilled water and administered IV over 5-7 minutes
Tunisia	*A. australis, B. occitanus*	Bivalent scorpion antivenom (Institut Pasteur, Tunis, Tunisia)	20 mL IV; however, one study showed no benefit
Saudi Arabia	*Leiurus quinquestriatus, Androctonus crassicauda, Buthus arenicola, Buthus mimax, Buthus occitanus, Leiurus quinquestriatus hebreus, A. amoreuxi*	Polyvalent scorpion antivenom	Manufacturer recommends 1 ampule, repeated until symptoms controlled. One study found a typical effective dose to be 5 to 20 1-mL ampules IV
Israel	*Leiurus quinquestriatus*	Monovalent scorpion antivenom	5 to 15 mL of antivenom diluted in 5% dextrose and 33% sodium chloride administered IV
Argentina	*Tityus trivittatus*	Scorpion antivenom	See package instructions.
Venezuela	*Tityus zulianus*	Scorpion antivenom	See package instructions.

Modified from Bahloul et al.[25]

APPENDIX D: ADDITIONAL INFORMATION REGARDING OFF-LABEL USES IN CPGS

PURPOSE

The purpose of this Appendix is to ensure an understanding of DoD policy and practice regarding inclusion in CPGs of "off-label" uses of U.S. Food and Drug Administration (FDA)–approved products. This applies to off-label uses with patients who are armed forces members.

BACKGROUND

Unapproved (i.e. "off-label") uses of FDA-approved products are extremely common in American medicine and are usually not subject to any special regulations. However, under Federal law, in some circumstances, unapproved uses of approved drugs are subject to FDA regulations governing "investigational new drugs." These circumstances include such uses as part of clinical trials, and in the military context, command required, unapproved uses. Some command requested unapproved uses may also be subject to special regulations.

ADDITIONAL INFORMATION REGARDING OFF-LABEL USES IN CPGS

The inclusion in CPGs of off-label uses is not a clinical trial, nor is it a command request or requirement. Further, it does not imply that the Military Health System requires that use by DoD health care practitioners or considers it to be the "standard of care." Rather, the inclusion in CPGs of off-label uses is to inform the clinical judgment of the responsible health care practitioner by providing information regarding potential risks and benefits of treatment alternatives. The decision is for the clinical judgment of the responsible health care practitioner within the practitioner-patient relationship.

ADDITIONAL PROCEDURES

Balanced Discussion

Consistent with this purpose, CPG discussions of off-label uses specifically state that they are uses not approved by the FDA. Further, such discussions are balanced in the presentation of appropriate clinical study data, including any such data that suggest caution in the use of the product and specifically including any FDA-issued warnings.

Quality Assurance Monitoring

With respect to such off-label uses, DoD procedure is to maintain a regular system of quality assurance monitoring of outcomes and known potential adverse events. For this reason, the importance of accurate clinical records is underscored.

Information to Patients

Good clinical practice includes the provision of appropriate information to patients. Each CPG discussing an unusual off-label use will address the issue of information to patients. When practicable, consideration will be given to including an appropriate information sheet for distribution to patients within an appendix, whether before or after use of the product. Information to patients should address in plain language: a) that the use is not approved by the FDA; b) the reasons why a DoD health care practitioner would decide to use the product for this purpose; and c) the potential risks associated with such use.