

## JOINT TRAUMA SYSTEM CLINICAL PRACTICE GUIDELINE (JTS CPG)



### Bites, Stings and Envenomation (CPG ID: 60)

This CPG provides an overview of bites, stings and envenomation and presents a standardized approach to providers in the evaluation and treatment of patients with animal induced trauma and toxins.

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## BACKGROUND

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Bites, stings and envenomation can occur in almost all environments in which the military operates.<sup>1</sup> Depending on the species and location, these can be mild events to life threatening situations. The most notorious animals for envenomation are snakes which are responsible for the majority of morbidity and mortality. Worldwide, large vertebrates, spiders, scorpions, and a variety of marine species including sharks, crocodiles, jellyfish, fish, and sponges are also of medical importance.<sup>2</sup>

For snakes, the typical victims have extremity bites from either purposefully handling the snake (upper extremity) or stepping on or near a snake (lower extremity). In developing countries and/or when sleeping outdoors in austere environments, envenomation can occur while the victim is asleep. There are two snake families that are the greatest concern, Crotalinae (i.e. moccasins, rattlesnakes, pit vipers) and Elapidae (i.e. cobra, coral, mamba, marine snakes). The elapid snakes represent a huge variety of tropical and subtropical snakes and exist everywhere except Europe. The Crotalids are much more familiar to United States Medicine as they represent the overwhelming majority of snake envenomation in the United States, but remain a concern internationally as well.

Arthropods are a very diverse group of animals with numerous species producing a wide array of toxins. Most bites involve more danger from anaphylaxis, but several species of scorpions and spiders have significant neurotoxic bites. The most pronounced cytotoxic bites come from the genus *Loxosceles*. In the United States, the species most associated with the group is the Brown Recluse, but the genus inhabits North and South America, Europe and Africa.

Marine animals such as sharks and alligators lack venom, but their bites can produce significant tissue destruction and blood loss. In addition, other animals such as eels, rays, sponges, starfish, lion fish and stone fish can produce clinically significant venoms. Aside from local tissue injury directly related to the bite, these types of encounters can be associated with rapid decompression injuries, air embolism, anaphylaxis, and unique infections associated with the marine environment.

Bites from terrestrial animals, including humans, are extremely common and include human bites. These injuries are most commonly attributed to dogs in the United States, but in other parts of the world, large animals such as tigers, lions and some reptiles can make up a significant number of attacks. Envenomation is not a significant concern, but infection represents an underappreciated source of morbidity.

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## EVALUATION

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For all vertebrate bites and stings, plain radiographs of the area are crucial as barbs and teeth are frequently left in situ and will tend to cause infection or chronic wounds if left in place.

### SNAKE BITES

Snake venoms are pharmacologically complex and can be comprised of over 100 different proteins, peptides and enzymes. They are divided into two broad categories: local systemic toxicity. Locally toxic compounds include phospholipases and metalloproteases which are pro-inflammatory causing edema, blistering and tissue necrosis. Systemically toxic compounds have a variety of effects: pro and anti-coagulants leading to coagulopathy, neurotoxins which predominantly block acetylcholine (pre or post synaptically) but can also affect the autonomous nervous system, and cardiotoxins which can cause arrhythmia and vasospasm.<sup>2-4</sup>

Preventive measures can mitigate risks associated with traveling in terrain where venomous snakes are endemic. Personnel should not under any circumstances approach a snake. The striking distance of a snake is approximately ½ its body length. Closed toed footwear is critical, as are long pants. An in vitro study

demonstrated that common clothing served to increase the frequency of “dry” bites (strikes where no venom is delivered), as well as decrease the delivery of venom into a tissue model when compared to strikes against exposed skin.<sup>5</sup> Personnel should not attempt to capture or kill a snake for identification in the event of a bite, as this can lead to other individuals becoming envenomed and is of little clinical significance for the treating medical team. Even a dead snake if handled is capable of causing an envenomation.<sup>6</sup>

Initial trauma evaluation proceeds according to standard ATLS protocols. Neurotoxins can affect the muscles of respirations, and development of bulbar symptoms (difficulty swallowing, chewing, or speaking) is an ominous sign that ventilatory compromise is imminent.<sup>4</sup> After initial trauma evaluation and stabilization, an attempt at identification of clinical significance and species can be made. A significant number of bites are dry or from a nonvenomous snake, thus a period of monitoring can triage whether a true envenomation has taken place. Local symptoms usually occur within 30-60 minutes. Photographs of the snake can be helpful if obtained from a safe distance.<sup>6</sup> In the rare event that a living specimen is brought, contact your vector control office at any given base to handle the specimen.

Outside of the United States, in certain areas military facilities are required to have certain antivenins on hand as demonstrated in [Appendix A](#). Given how unreliable species identification is, polyvalent antivenins geared towards the predominant species in the area are typically used in treatment facilities. The locations of military activity will vary in the future, but the medical group pharmacist should have information on the various types and locations of antivenin for the area. Included in [Appendix A](#) is a list of locations within CENTCOM.

In the evaluation stage, marking the boundaries of erythema, edema and taking circumferential measurements of the limb can help monitor for progression. In addition, draw CBC, PT/INR, and fibrinogen to evaluate for coagulopathy. Thromboelastography (ROTEM/TEG) may be helpful to define degree of coagulopathy. An EKG should be obtained and the patient placed on cardiac monitoring. A complete metabolic panel should be drawn. Creatine kinase is useful to evaluate for rhabdomyolysis.<sup>2</sup> Additional labs to consider are urine protein, blood and myoglobin and in some cases when other coagulation studies are unavailable the whole blood clotting time (WBCT.) Given that approximately 20% are dry bites, there is a chance that no symptoms will develop. Clinical symptoms of true envenomation are as follows:

**Local Manifestations:** burning pain within minutes, edema, erythema, swelling, ecchymosis, hemorrhagic bullae, lymphangitis/lymphadenopathy, necrosis (late finding)

**Systemic Manifestations:** nausea and vomiting (earliest findings) weakness, headache, tachycardia, paresthesias, bulbar symptoms, diplopia, twitching, consumptive coagulopathy, rhabdomyolysis, muscle paralysis, renal failure, capillary leakage, pulmonary edema, hypotension, shock<sup>2-4,6</sup>

## MAMMAL & MARINE BITES

Large mammal and marine bites can generally be treated the same on the initial evaluation given that the most life threatening concerns represent a mixture of penetrating and blunt trauma. Radiographs of injuries are important to rule out foreign bodies such as teeth as well as fractures. A patient’s rabies (in mammalian bites) and tetanus status must be addressed as well.

Unique to marine bites, depending on depth, rapid ascent can result in air embolism and decompression sickness. Also given the aquatic environment, hypothermia and near-drowning can also be complicating factors. Finally, microbial contamination can be different, so identification of injury in either salt or fresh water is important.

## ARTHROPOD BITES/STINGS

Unlike other types of injuries, patients may not even recognize they were bitten by arthropods, as many injuries are painless or felt as a pinprick. Anaphylaxis is the most concerning initial effect and needs to be recognized and addressed immediately. For black widow and scorpion envenomation, the neurotoxic effects will be apparent, if present.

Loxoscelism will present as an ulcerative lesion, sometimes not until days after the initial envenomation. In general, within several hours after 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 will result in vasoconstriction and this can result in a pale border around the central ulcer/blister/darkening. Over the next several days the ulcer will enlarge and the borders demarcate until the 1-2 week mark. A bite that doesn't ulcerate after 72 hours will heal well without further intervention. In some cases a systemic loxoscelism can occur. If systemic complaints are present, a workup including a CBC, urinalysis for blood, metabolic panel, liver function and coagulation studies are appropriate.

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## TREATMENT

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For all bites, tetanus status must be considered and, if required, vaccine and/or immunoglobulin administered.

### SNAKE BITES

Initial treatment in the prehospital/field setting or areas where antivenin is not available is strictly supportive and includes removing all constricting clothing, immobilization of the extremity at heart level if possible and cleaning the wound.<sup>7</sup> If possible, mark the site of bite to demarcate initial erythema and swelling, which can help medical providers at the next level of care determine clinical progression. **Do not apply suction, tourniquets, cryotherapy, topical preparations, or local incision** as these are ineffective and harmful, as they may facilitate venom spread and have been associated with longer hospital stays and increased morbidity and mortality.<sup>8-10</sup> Controversy exists regarding the use of pressure dressings to reduce the spread of venom. Evidence concerning its utility is of poor quality, they are challenging to use correctly even in experienced hands, and there is potential to worsen local toxicity.<sup>11-13</sup> Unless there is significant experience with this modality, we recommend against attempting this treatment. If there is progression of disease, and the patient is unable to receive antivenin or transport to a facility with it, blood products and plasma expanders can be administered as necessary for any life threatening bleeding or hypovolemia that develops. Blood products, unlike antivenin, **DO NOT** reverse venom induced coagulopathy and in fact may worsen it. Exogenously administered Fresh Frozen Plasma (FFP), cryoprecipitate, and platelets provide further substrate for any un-neutralized venom, thereby exacerbating the consumptive coagulopathy.

Upon arrival to the emergency department, standard Advanced Trauma Life Support (ATLS) evaluation and treatments are initiated. If possible obtain a focused history to include the following:<sup>3</sup>

- General description of the snake and location of bite
- First aid measures used
- Patients medical conditions
- Drug and/or food allergies
- Allergy to horse or sheep products
- History of previous snake bite

After initial evaluation, a period of observation is acceptable if no clinical progression from initial markings, measurements, symptoms or significant changes in lab values. If 8 hours pass without any signs of toxicity,

discharge is acceptable for Crotinalae bites, 24 hours for Elapidae bites. In most circumstances outside the United States, given that the snake family can be considered unknown, **admission for 24 hours in all cases should be done**. If clinical progression is ongoing, it is our recommendation to place the patient in an ICU level setting and start antivenin. **If there is no clinical evidence of envenomation, do not give antivenin.**

Administration of antivenin is based on the severity of symptoms and not the weight of the patient. For children, if volume overload is a concern, use less saline when diluting (if in powder form). There are no absolute contraindications to antivenin. Pretreatment with low dose epinephrine for allergic reactions has been demonstrated to decrease incidence of anaphylaxis.<sup>14</sup> If the patient has had antivenin before, or has had anaphylaxis to antivenin, the treatment team should be prepared for this complication. In this group of patients, always pretreat with Diphenhydramine 50 mg IV and Epinephrine 0.25 mg IM and have epinephrine 1:1000 available.<sup>14</sup>

Patients requiring antivenin treatment should be in a critical care setting. Hourly monitoring of progression of disease, early recognition of impending airway compromise, and aggressive physiologic support are critical. Systemic reaction and cardiovascular and respiratory compromise are not uncommon with the administration of antivenin and must be addressed by the admitting teams. Serum sickness from antivenin administration can occur in up to 40% of cases. If clinical deterioration is ongoing, management of shock and rhabdomyolysis induced renal failure, and interventions including intubation and mechanical ventilation, continued resuscitation with crystalloids, dialysis, and other supportive measures may be required.

The deployed location antivenin dosing recommendations are not the same as Crotalidae Polyvalent Immune Fab (Ovine) (CroFab) in the United States, as the antivenins are not products of the United States. It is important to consult with pharmacy staff on proper preparation and dosing. It is common for all antivenins to be given in sets of vials. For example, the Razi and Saudi antivenins will be 5 vials per set, while CroFab is given in sets of six. Each polyvalent antivenin is designed to work against a different set of snakes. If no affect after 2 sets of the recommended amounts, one should suspect the antivenin does not cover the species the patient was bit by, and treatment should change to the second line antivenin.

Many snake venoms in Asia have a significant neurotoxic effect. To reverse or improve respiratory failure and neurotoxic symptoms, consider atropine 1 mg IV or IM every 3-5 minutes, doubling the dose if no symptom resolution. In addition, a test of edrophonium 0.25 mg/kg (max 10 mg) can be initiated. If symptoms improve, neostigmine 0.01 mg/kg (max 0.5 mg/dose) can be utilized. Not all snake venoms will respond to these medications as some block the release of acetylcholine pre-synaptically. However, if successful, intubation could potentially be avoided while antivenin administration proceeds. Monitor closely for anticholinergic symptoms such as ventricular fibrillation, dry mouth, ataxia, nausea or hallucinations.<sup>6,15</sup>

#### **Antivenin Algorithm (Razi 1st Line and Saudi 2nd Line for CENTCOM AOR)<sup>16</sup>**

**NOTE:** CENTCOM/CPG guidance differs from package inserts; consult with local pharmacist before applying to antivenins outside CENTCOM; see references for [CroFab Algorithm](#) for U.S. snakes

1. If conditions allow, splint and elevate affected extremity, minimize patient activity.
2. Transfer to facility where antivenin for local venomous snake population is present.
3. Accomplish ATLS protocols to include treatment of secondary hypovolemia as needed.
4. Evaluate for signs of envenomation. Mark boundaries of physically apparent manifestations with ink. Perform and/or check the following:
  - Physical exam
  - Complete Blood Count (CBC)
  - Prothrombin Time (PT), Partial Thromboplastin Time (PTT), and International Normalized Ratio (INR)

- Comprehensive Metabolic Panel (CMP)
  - Creatine Kinase (CK)
  - Fibrinogen
5. If clinical evidence present admit to ICU. If no initial clinical evidence, admit to ward for 24 hours of observation.
  6. Consider prophylaxis for anaphylaxis (Diphenhydramine 50 mg IV).
  7. Dilute 5 vials of antivenin in 500 mL of isotonic saline.
  8. Infuse saline/antivenin mixture at 100 mL/hr for 15 minutes.
  9. If the infusion is tolerated, increase rate to give entire 500 mL over 30-60 minutes.
  10. Provide supportive care including pain medications and transfuse for life threatening bleeding.
  11. Monitor for signs of progression over the next hour including repeat CBC, Fibrinogen, and PT/PTT/INR.
  12. If progression, repeat steps #7 through #11 until control. If after 10 vials, consider changing to 2<sup>nd</sup> line antivenin as species may not be covered.
  13. If coagulopathy, give a maintenance dose of 2 vials at 6, 12, and 18 hours after initial control.
  14. Continue to reassess patient hourly prior to discharge, and if evidence of recurrence of signs and symptoms, go back to step #4.
  15. Outpatient follow-up at 3 days and 7 days with repeat fibrinogen, PT/PTT/INR, and CBC, to monitor for serum sickness, return of symptoms or delayed symptoms.

#### Severe Anaphylaxis Algorithm<sup>17-19</sup>

1. Stop the infusion immediately.
2. Treat with 1:1000 epinephrine injection 0.5 mg IM, Diphenhydramine 50 mg IV, and Methylprednisolone 100 mg IV. Epinephrine can be repeated as needed and/or an infusion administered.

**NOTE:** Intubate for airway edema not rapidly responsive to epinephrine.

3. Reevaluate for antivenin need and resume if required at slower rate

Continuous monitoring for effectiveness must be done, as the half life of antivenin is less than the venom. Continuous clinical monitoring includes serial laboratory studies including, CBC, CMP, PT/PTT/INR, CK, and fibrinogen levels every 2 hours while signs of envenomation persist, in addition to urine output and vital signs hourly. After signs of clinical resolution, monitoring can decrease to every 6 hours. Fasciotomies or digital dermotomy may be required in any extremity if clinically suspicious for compartment syndrome after antivenin therapy. However, antivenin has significant effect and liberal use of Stryker needles for measuring compartment pressure (digital compartments cannot be reliably measured) is encouraged (unlike for blunt or penetrating trauma) as the venom can mimic compartment syndrome. Compartment pressures, even when elevated, may normalize after administration of antivenin.<sup>20,21</sup> If compartment pressures are greater than 35 mm Hg 4 hours after antivenin therapy or clinical concern persists with no capability to measure compartment pressures, only then should fasciotomy be performed.<sup>22</sup> **Compartment syndrome is rare in the setting of envenomation and fasciotomy should not be done before antivenin administration.**

## Digital Dermotomy

**Indications:** tense, pale insensate digit with poor capillary refill with lack of pulse on digital Doppler ultrasound

**Procedure:** longitudinal incision through the skin only from the web space to the mid distal phalanx

Acute and delayed (serum sickness) hypersensitivity reactions should be expected in all patients. Most cases consist of anaphylaxis, urticaria, and angioedema. If evidence of allergic symptoms appears, temporary cessation of antivenin infusion is done to facilitate treatment of hypersensitivity symptoms. However, it is very important that the antivenin be resumed following treatment.

Delayed symptoms related to venom toxicity days after initial bite have been reported as the duration of action of the venom exceeds that of most antivenins. It is recommended that bite victims that receive antivenin stay within close proximity of a facility that carries appropriate antivenin for their situation for at least seven days.

Rare and unique complications have been reported in the post envenomation period. Although they cannot be covered in the scope of this CPG, they should still be considered as being related to the venom. It is recommended that anything that can predispose a patient to bleeding like contact sports, elective surgical procedures, etc. should be avoided for 2 weeks.<sup>7</sup>

## MAMMALIAN BITES

Mammalian bites can present as a combination of penetrating and blunt injury. As they can be significant, they should be addressed similar to war wounds mentioned in other CPGs with aggressive washout and debridement if indicated. Rabies prophylaxis should be considered in all animal bites if outside of United States. If any doubt the default clinically should be to administer vaccine. For all bites, exploration and thorough washout is required as infection is of greatest concern. For puncture wounds caused by small cats, making a 1 cm incision and washout with delayed closure is recommended. Depending on location, primary closure can be considered for head and neck wounds if seen within 24 hours and for which aesthetic considerations are important. Large clean wounds are also considered low risk if on the trunk, arms or legs and seen within 12 hours. For all other bites, the recommendation is delayed primary closure or leaving it open to heal by secondary intention after washout. Close follow-up is required in 1 to 2 days to monitor for signs of infection. Routine antibiotic prophylaxis is not recommended. However, prophylactic antibiotics consisting of amoxicillin-clavulanate (clindamycin with trimethoprim-sulfamethoxazole or ciprofloxacin for penicillin allergic patients) for at least 3 days is recommended for high-risk wounds (associated significant crush injury, deep puncture wounds, cat bites, wounds requiring closure, or bites near joints, hands, face, or genitalia).

Of note are “fight bites” or human bites against a closed fist. Often these injuries can hide severe damage to tendons and joint capsules as well as be heavily contaminated with bacteria. Injuries over the dorsum of the metacarpophalangeal joints should all be treated with exploration, irrigation and debridement and left open. Orthopedic or hand specialty consultation is encouraged if available.

## MARINE BITES

Identical to mammal bites, initial trauma evaluation is done for penetrating and blunt injuries. These wounds can be significant, and therefore be treated similarly to war wounds mentioned in other CPGs. As mentioned in evaluation, knowledge of circumstances including depth and location can dictate care. Decompression sickness can occur if rapid ascent from depth was undertaken. While mostly consisting of joint symptoms, decompression sickness can have neurologic and cardiopulmonary effects. If the injury was known to occur at depths greater than 30 feet, transfer to a location with hyperbaric oxygen capability should be done as able. If symptoms of decompression were to occur, they are most likely to occur between 1 to 48 hours.

For all wounds caused in a marine environment, aggressive washout and debridement should be conducted and followed by either delayed primary closure or healing by secondary intention. *Aeromonas* infections should be considered if the injury occurred in fresh water, and *Vibrio* infections for salt water. Acceptable prophylactic antibiotics are trimethoprim-sulfamethoxazole, ciprofloxacin, or doxycycline for at least three days.

Marine animals such as catfish, lionfish, stingrays, etc. have barbs and are potentially venomous. Several species have antivenin available. Retained foreign body due to breaking of a barb or tooth within the tissue is very common. These foreign bodies will tend to fester or cause significant infection and need to be removed.

## ARTHROPOD BITES

While severe neurotoxic and anaphylaxis can occur from a host of venoms from various scorpions, spiders, and other insects, treatment is supportive and if the species is known to be a scorpion or a type of black widow, transport to a facility with appropriate antivenin is done if signs of systemic illness manifest in a manner identical to venomous snake bites.

Loxoschelism is the only bite that generally needs to be addressed surgically. Many of these bites present with ulceration after a course of antibiotics for the treatment of a bacterial infection or abscess. Unless clearly identified as a spider, we recommend a course of antibiotics for localized erythema and blistering, as cutaneous infections with *S. aureus* or *B. anthracis* will be more common. If clearly a spider bite, antibiotics are not indicated unless there is a subsequent infection. If unsure, administration of antibiotics covering gram positive skin flora is appropriate. Operating before demarcation will have minimal to no effect. If clinically identified as loxoschelism, debridement should be delayed until demarcation has completed at approximately 1-2 weeks. Skin grafting may be necessary for large wounds. Historically Dapsone and systemic steroids have been given for severe and systemic loxoschelism, but these treatments have not been shown to be particularly effective and can have significant side effects.<sup>23</sup> We recommend not administering anything other than antibiotics if evidence of infection. There are no antivenins available and supportive care for systemic signs are generally all that is indicated.

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## PERFORMANCE IMPROVEMENT (PI) MONITORING

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### POPULATION OF INTEREST

All patients injured by animals and arthropods.

### INTENT (EXPECTED OUTCOMES)

- All patients injured by envenomation are transferred to a site with antivenom capability.
- All patients injured by animal bites receive antibiotic, tetanus and rabies vaccines when indicated.

### PERFORMANCE/ADHERENCE METRICS

- Number and percentage of patient with envenomation (snake or arthropod bite) who receive antivenom or documentation that antivenom not needed.
- Number and percentage of patients with mammalian and marine bites who receive an antibiotic.
- Number and percentage of patients with mammalian bites who receive tetanus prophylaxis.
- Number and percentage of patients with mammalian bites who receive rabies prophylaxis or have documentation of rabies treatment not needed.

## 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 and the JTS PI Branch.

## RESPONSIBILITIES

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

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**APPENDIX A: MEDICAL FACILITIES AND STOCKED ANTIVENINS**

CENTCOM Medical facilities and their stocked antivenins. Current as of April 2017. If faced with a patient with an envenomation, discuss with pharmacist at location as to availability and type of antivenin before transport of patient.				
CENTOM FACILITIES	Razi Polyvalent Snake Antivenin	(Saudi) Polyvalent Snake Antivenin	Black Widow	Polyvalent Scorpion Antivenin
<b>Role 3</b>				
Camp Arifjan Kuwait	X	X		X
Navy MMU Kandahar	X	X		X
CJTH Bagram	X	X	X	X
379 EMDSS/SGSDAI UDID AB Qatar	X		X	X
28th CSH, Baghdad Iraq	X			X
<b>Role 2</b>				
FOB FENTY	X	X		X
386 EMDG/EMEDS Ali Al Salem	X	X		X
Erbil, Iraq	X	X		X
BDSC	X	X		
FOB DWYER	X			
332 EMDG, Al Jaber, KWT				X
HKIA Role II MTF, AFG				X
Camp Redleg, UAE	X	X		
USAMMC-SWA Qatar		X		X

**APPENDIX B: CROFAB TREATMENT ALGORITHM\*\*****Cottonmouth, Rattlesnake, Copperhead:**

1. If conditions allow, splint and elevate affected extremity, minimize patient activity.
2. Transfer to facility where antivenin for local venomous snake population present
3. Initially ATLS protocols are accomplished to include treatment of secondary hypovolemia as needed
4. Evaluate for signs of envenomation (Physical Exam, CBC, PT/PTT/INR, CMP, CK, Fibrinogen) and mark boundaries of physically apparent manifestations with ink
5. If clinical evidence present admit to ICU. If no initial clinical evidence, admit to ward for 24 hours of observation
6. If clinical evidence, administer 6 vials of CroFab and provide supportive care including pain medications and transfuse for life threatening bleeding
7. Monitor for signs of progression over the next hour including repeat CBC PT/INR, Fibrinogen, and PT/PTT/INR.
8. If progression, repeat steps #6 and #7 until control
9. Once arrest of progression, start maintenance infusion of 2 vials every 6 hours for a total of 6 vials
10. Continue to reassess prior to discharge, and if evidence of recurrence of signs and symptoms, go back to step #4
11. Outpatient follow-up at 3 days and 7 days with repeat Fibrinogen, PT/INR, and CBC, to monitor for serum sickness, return of symptoms or delayed symptoms

\*\*Kanaan NC, Ray J, Stewart M, et al. Wilderness Medical Society Practice Guidelines for the Treatment of Pitviper Envenomations in the United States and Canada. *Wilderness Environ Med.* 2015;26(4):472-487. doi:10.1016/j.wem.2015.05.007.

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**APPENDIX C: ADDITIONAL INFORMATION REGARDING OFF-LABEL USES IN CPGS**

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**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 in an appendix an appropriate information sheet for distribution to patients, 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.