JOINT TRAUMA SYSTEM CLINICAL PRACTICE GUIDELINE (JTS CPG)

Global Snake Envenomation Management (CPG ID: 81)

Guide providers in the evaluation and treatment of patients after snake bites.

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BACKGROUND

Snakebite, recently declared a neglected tropical disease and global health priority by the World Health Organization (WHO), results in an estimated 2.5 million envenomations, 138,000 deaths and over 500,000 cases of permanent disability worldwide every year.[1–10] Snake, spider, and scorpion envenomations are a common environmental and occupational hazard for military forces worldwide.[11–46] The consequences of an envenomation range from mild local effects to permanent disability or death, and the outcome is largely determined by the time to antivenom treatment and the level of training of the medical providers involved.

Once an envenomation has occurred, the provider and patient are racing against the clock to neutralize active venom components before extensive damage has occurred. Necrosis caused by cytotoxic venoms cannot be reversed, but it can be prevented by early antivenom administration or arrested before further damage can occur in cases of late antivenom treatment.[1,7,47,48] Hemotoxic venoms can induce coagulopathies within an hour of the envenomation which is quickly followed by a standard progression of worsening local and systemic external and internal bleeding. Neurotoxic venoms can act rapidly and be fatal. Africa is one of the few places in the world with snakes like the black mamba that are capable of killing a human within one hour due to direct effects of the venom, and most patients with mamba envenomation who are not rapidly treated with antivenom will die within 2 - 6 hours from respiratory arrest.[1,49] When a neurotoxic bite occurs, rapid antivenom administration prior to the onset of respiratory muscle weakness can arrest the progression of descending paralysis before serious systemic manifestations develop.[1,50,51] Every hour wasted between bite and antivenom administration is strongly associated with sharp increases in mortality and the development of chronic or permanent sequelae including amputation, disfigurement, PTSD, blindness, kidney injury, infections, and partial or complete loss of function of the bitten limb.[4,7,8,52–58]

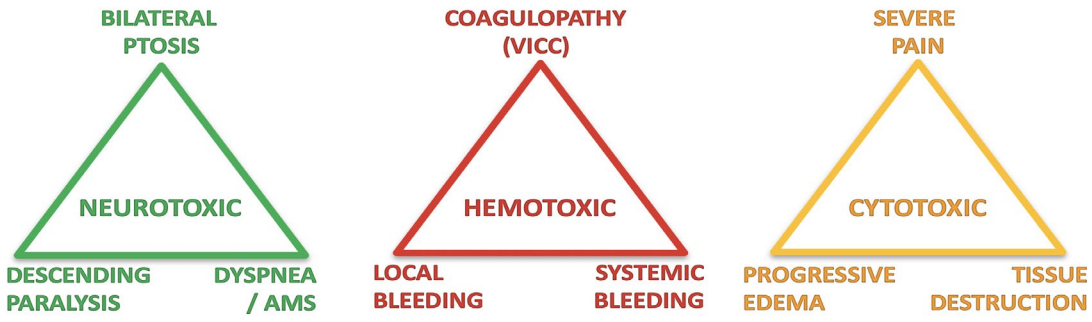
This CPG will cover the continuum of snakebite care for snake envenomations in all combatant commands.

GENERAL PRINCIPLES OF SNAKEBITE MANAGEMENT

Don't try to ID the snake. Snake identification is unreliable and should not be purposely attempted. DO NOT attempt to catch or kill the snake; treatment is clinical and the snake species does not need to be identified.

There are 3 major clinical syndromes of snakebite envenomation worldwide and 3 major signs and symptoms of each. All dangerous snakes capable of injuring or killing a human will produce at least one sign or symptom from at least one of the 3 major snakebite syndromes (neurotoxic, hemotoxic, and cytotoxic). Specific antivenoms required will vary regionally but the major triads are applicable globally.

Figure 1. Snakebite Clinical Triads



CLINICAL PEARLS ON SNAKEBITES AND ANTIVENOM TREATMENT

1. **Not all snakes are venomous and not all snake bites result in snake envenomations!**

   Most snake species pose no danger to humans, and only ~600 of the >3500 snake species worldwide are considered potentially dangerous to people. However, dangerous species are often drawn to human habitations in search of food, water, or shelter and envenomations are very common in the developing world.

2. **Roughly 25% of bites from dangerously venomous snakes are harmless "dry bites" where no venom is injected!**

   a. This means that even if you know that the snake which bit your patient is a dangerous species, it does not mean that they will require antivenom treatment. While the exact percentage varies by species, on average 25% of bites from venomous snakes are considered "dry bites" that are designed to scare away a potential threat that is too big to eat without wasting venom. Venom is metabolically expensive to produce and snakes will try to conserve their venom for potential prey items whenever possible.

   b. The dry bite phenomenon explains why many people believe that useless or potentially harmful interventions such as venom extractors or black stones are effective: these patients appear to have recovered miraculously thanks to the treatment they applied but in reality, they were never sick to begin with!

3. **Snakebite treatment should always be determined by the clinical presentation and evolution of signs and symptoms in the patient rather than the identity of the snake that bit them!**

   a. Remember that many snakebites are likely to have resulted from harmless snakes and that roughly 1/4 people bitten by a truly dangerous species are likely to be fine because of the dry bite phenomenon. Many dangerous species have harmless mimics and vice versa. Do not attempt to identify snake species if you are not a herpetologist. **Identifying the snake species will not change your patient care!**

   b. Do not treat patients simply based on the fact that they were bitten by a dangerous snake species.

   c. Always treat snakebite patients based on the signs and symptoms they develop. A patient who hands you a dead mamba and develops no signs or symptoms of envenomation does not require antivenom unless they develop progressive signs and symptoms of an envenomation. Conversely, a patient who has no recollection of a snakebite or believes that the species responsible was harmless will require treatment for an envenomation if they subsequently develop progressive swelling, systemic bleeding, or other signs of the three major snake envenomation triads.

4. **There are no absolute contraindications to antivenom for patients with symptomatic snake envenomations. The high risk of permanent damage posed by untreated venom in the body is far greater than the low risk of anaphylaxis associated with high-quality modern antivenoms.**

   a. Antivenom administration at the earliest possible opportunity is the gold standard of snakebite care and most effective way to reduce the risk of death or permanent disability in these patients.

   b. Early antivenom administration in the field at or near the point of injury may resolve the underlying envenomation before any serious systemic signs or symptoms develop.

   c. Ignore the packaging and manufacturer insert and treat according to the guidelines outlined in this CPG.

d. Dosing and administration of recommended antivenoms in this CPG can vary significantly between products; refer to the specific instructions included later in this CPG for whichever product you have on hand.

e. Antivenom may be given by IV or IO injection or infusion.[54,59] An IV is preferable but IO is an acceptable alternative and should not influence the efficacy of the medication.

f. DO NOT give antivenom by IM or SQ injection, even if packaging says you can. The serum concentrations of antivenom given by IM or SQ injection will never achieve more than a fraction of the serum concentrations rapidly achieved from the intravascular route.

g. DO NOT administer test doses of antivenom to check for hypersensitivity prior to giving the full dose. Test doses have no predictive value for identifying patients with hypersensitivity and waste both time and antivenom.[60–63]

h. **Antivenom dosage is not weight-based** and there is no difference in dosing between adults and children.

i. **The dose of antivenom needed is proportional to the dose of venom injected into the patient**. The quantity of venom injected into the patient corresponds to the severity of the envenomation syndrome(s).

j. Additional antivenom should be given as many times as needed until control of envenomation is achieved.

k. Overdosing antivenom is not a concern during the active treatment phase, and the worst-case scenario is an allergic reaction. If a patient develops a reaction to large doses, it will most likely manifest as a late reaction called serum sickness (fever, rash, arthralgia, etc.) 1 - 3 weeks later and can be managed with antihistamines or steroids if the patient is uncomfortable. Serum sickness may be uncomfortable but is not life-threatening.

5. **Establish a timeline and trend changes over time. Serial assessments and documentation are essential because the resolution of certain clinical findings will be used to determine when the right dose of antivenom has been given. At a minimum always document the following:**

   a. Time and date when bite occurred

   b. Time elapsed from bite to presentation under your care (record as minutes, hours, days, etc.)

   c. Time when the first dose of antivenom is given (defined as Hour 0, written as H0)

   d. Always repeat a complete snakebite assessment at hours 2, 4, 6, 12, and 24 (H2, H4, H6, H12, H24) since the first dose of antivenom was given in order to trend the clinical evolution of the syndrome over time.

6. **Snakebites are clinically dynamic emergencies and can change dramatically until control has been achieved.**

   Patients may present with one syndrome initially and develop signs and symptoms of another later on (for example, a patient who presents with local pain and mild swelling at H0 could develop local bleeding or ptosis at H4). Always look for signs and symptoms of all three triads when reassessing and redirect your treatments if needed according to the clinical evolution observed in your patient.

UNIVERSAL APPROACH TO THE SNAKEBITE PATIENT

INITIAL PRIORITIES

1. Airway, breathing, circulation, and rapid antivenom administration are the critical priorities during stabilization and treatment of a snakebite casualty.

    a. Assess ABCs; identify and address any immediate life threats before proceeding.

    b. Refer to the Sudden Collapse Syndrome Treatment Protocol for specific instructions on stabilization and management of patients who develop rapid onset shock ± angioedema, altered mental status, systemic bleeding, and/or diarrhea within the first 30 minutes after a snakebite

    c. Treat emergent secondary issues that may be present (such as anaphylaxis or hypovolemic shock) according to standard clinical protocols.

    d. Establish IV or IO access in a non-bitten limb before proceeding.

2. ***DO NOT apply constricting bandages or tourniquets*** as these may worsen local tissue injury and increase the risk of permanent disability.[64–66]

    If a tourniquet is already in place, do not remove it until you are ready to treat and resuscitate the patient as a rapid decompensation can occur.[67,68] When removing a tourniquet do so sequentially (loosen for several seconds - tighten - observe - repeat) over 20 - 30 mins; if symptoms develop at any time administer antivenom and wait at least 30 minutes before resuming tourniquet release. Ideally, this should not be done until antivenom is available but prolonged evacuation times without antivenom may necessitate the risk of earlier removal to prevent limb death. Refer to the Joint Trauma System Tactical Combat Casualty Care (TCCC) Guidelines for tourniquet conversion in these settings.

3. If and when conditions allow, minimize patient activity, and loosely immobilize bitten limb to reduce movement without constricting tissues.

    a. If antivenom is not available onsite, choose whichever evacuation option will safely get your patient to the antivenom in the shortest amount of time. This includes allowing the patient to walk to help when needed.

    b. If conditions allow during transport, maintain the bitten limb in a position of comfort that is elevated above the level of the heart.

    c. Once the patient has arrived at the clinic and can be placed in a bed, aggressively elevate the bitten limb (aim for a minimum 60º angle in a supine patient if possible and tolerated by patient) to reduce oncotic pressure on swollen tissues.

4. Evaluate for specific signs and symptoms of snake envenomation. See Table 1 and refer to specific criteria for initial antivenom treatment and repeat doses for additional information.

FOCUSED ASSESSMENT AND EXAMINATION

Perform a physical examination and history focused on identifying signs and symptoms of neurotoxic, hemotoxic, and cytotoxic envenomation syndromes.

1. Determine how long ago the bite occurred. Circle the site of the bite wound and write the specific time that it occurred with a permanent marker on the patient
2. Do not rely on fang marks to assess the possibility of a bite or envenomation. Snakebites can leave punctures, multiple lacerations, or even no obvious fang marks whatsoever.
3. Rapid examination for signs of **pain, swelling, or tissue destruction (cytotoxic syndrome).**
   Separately mark the leading edge of both pain (dashed line) and edema (solid line) with a permanent marker and record time of observation next to each line
4. Rapid examination for signs of **local or systemic bleeding (hemotoxic syndrome)**
   a. Inspect the bitten limb for persistent local bleeding > 30 mins from the bite wound (if visible) or other lesions.[1,70–72]
   b. Inspect the molar gingiva and other mucosa for signs of systemic bleeding.[1,69,70]
5. Rapid examination for signs of **neuromuscular weakness (neurotoxic syndrome)**
   a. Evaluate respiratory muscle weakness by single breath count testing[72] and repeat periodically to trend improvement or deterioration in respiratory function over time.
      - The single breath count (SBC) test requires no equipment to perform and is easily performed in austere settings:

        Ask the patient to take a deep breath and count as high as possible in their normal speaking voice without taking another breath. Demonstrate the test to the patient, then have them repeat it and record the highest number reached.
        - SBC correlates closely with spirometry.
        - Normal SBC is approximately 50 and SBC < 20 is associated with the need for mechanical ventilation.
      - If spirometry is available, this can be used in place of the single breath count test by evaluating the negative inspiratory force (NIF) and/or forced vital capacity (FVC).
        Conduct gross assessment and pay particular attention to the following:
        - Signs and symptoms of descending flaccid paralysis: Ptosis, diplopia, neck flexor muscle weakness, bulbar weakness, etc.[1,54,73]
        - Signs and symptoms of parasympathetic / cholinergic crisis: SLUDGE mnemonic - Salivation, Lacrimation, Urination, Defecation, GI distress, Emesis
   b. Perform and/or check the clinical laboratory tests listed below (if available).

UNSTABLE PATIENTS

Sudden Collapse Syndrome Treatment Protocol

Patient presents within 30 minutes of the bite with rapid onset shock ± angioedema, altered mental status, systemic bleeding, and diarrhea.[1]

1. Stabilize with IM or IV epinephrine and fluids as per anaphylaxis protocols
2. Intubate for airway edema not rapidly responsive to epinephrine
3. Follow epinephrine immediately with a high dose of the appropriate regional antivenom given by rapid IV or IO push during the resuscitation
4. Maintain blood pressure with IV or IO fluids and epinephrine until antivenom has taken effect to reverse the hypotension.

See Sudden Collapse Syndrome section for more information.

LAB TESTS

Advanced laboratory tests include:

- Complete Blood Count (CBC)
- Hemoglobin (Hb) or Hematocrit (HCT) if no CBC but separate testing for either Hb or HCT is available
- Prothrombin Time (PT), Partial Thromboplastin Time (PTT), and International Normalized Ratio (INR)
- Fibrinogen
- Comprehensive Metabolic Panel (CMP)
- Creatine Kinase (CK)

Simple coagulation test for austere environments: Use the Whole Blood Clotting Test (WBCT) as described in Appendix A to diagnose and monitor coagulopathy if advanced labs not available

TRANSPORT FACTORS

1. If the patient is being medically evacuated from the field or between roles of care, confirm that the receiving facility has an adequate supply of the appropriate regionally specific antivenoms listed in this CPG to ensure treatment coverage against local species of concern.

   NOTE: *Evacuation is not an alternative to antivenom administration. A patient whose snakebite warrants evacuation will require antivenom. The earlier it is given the greater the chance of full recovery without permanent disability. DO NOT delay administration of antivenom in the field to a patient with an envenomation.*

2. If clinical evidence of envenomation is present and treatment is occurring in a hospital setting, always admit to a bed with continuous vital sign monitoring if available. If no initial clinical evidence of envenomation, admit for 24 hours for observation. If treating in the field, continuously monitor patient trends for signs of progression, improvement, or deterioration.
3. Symptoms should be expected within 24 hours; if the patient is completely asymptomatic after 24 hours then they most likely received a dry bite and can be discharged. See Discharge Criteria.

INITIAL ANTIVENOM TREATMENT

Antivenom dosing, preparation, and administration recommendations vary by product. Coverage, initial dosing, preparation, and administration of antivenoms are included in this CPG. Refer to guidelines for the specific product prior to administering the antivenom.

Table 1. Simplified universal diagnosis and treatment criteria for snakebite worldwide

	Neurotoxic Syndrome	Hemotoxic Syndrome	Cytotoxic Syndrome
Mild	Local S/Sx (paresthesias; neuropathic pain; piloerection; muscle spasm, fasciculations)	Coagulopathy ± persistence of local bleeding from bite wound > 30 mins after bite	Severe pain; edema below elbow or knee; limited blistering within several inches of the bite wound
Moderate	Systemic S/Sx (bilateral ptosis GI symptoms; visual, auditory, or other sensory disturbances; widespread hyperesthesia)	Moderate systemic bleeding (old scabs, gingival bleeding, epistaxis, etc.); bruising distant from the bite wound	Edema above elbow or knee but not beyond shoulder or hip; moderate local blistering along bitten limb segment
Severe	Difficulty speaking; altered mental status; respiratory muscle weakness causing difficulty breathing; shock or otherwise unstable patient	Active GI bleed (usually hematemesis) or other internal bleeding; severe anemia; altered mental status; shock or otherwise unstable patient	Progressive edema beyond shoulder or hip; severe necrosis or widespread blistering; symptomatic bite to head, neck, or torso; altered mental status; shock or otherwise unstable patient
Criteria for additional AV doses at hours 2, 4, 6, 12, 24 (as needed)	*Additional doses if:* *persistence or worsening of systemic neurotoxic S/Sx. Continue to re-administer 2 vial boluses as needed at hours 2, 4, 6, 12, and 24 until indications of improvement begin to appear* (↑SBC, ↑LOC, ↑strength, etc.)	*Additional doses if:* *persistence, resumption, or new onset of any active external or internal bleeding* ***OR*** *S/Sx of active venom confirmed by secondary recurrence of abnormal WBCT*	*Additional doses if:* *significant increase in edema (such as beyond major joint)* ***OR*** *significant increase in pain (severity of pain and/or how far pain radiates up the bitten limb)*

S/Sx = Signs & Symptoms; SBC = Single Breath Count Test; LOC = Level of Consciousness; WBCT = Whole Blood Clotting Test

Table 2. All Combatant Commands – First Line Antivenoms

First Line Antivenoms for All Combatant Commands		
AFRICOM 1st Line Antivenoms	**First Line Antivenoms with Regional Coverage against All Three Major Syndromes (Neurotoxic/Hemotoxic/Cytotoxic)** **Sub-Saharan Africa:** Broad-spectrum coverage for all neurotoxic/hemotoxic/cytotoxic snakebite syndromes by known or unknown species - *POLYSERP-P: Initial dose = 6 vials / Additional doses = 2 vials as needed* **North Africa:** Broad-spectrum coverage for all neurotoxic/hemotoxic/cytotoxic snakebite syndromes by known or unknown species - *POLYSERP-M: Initial dose = 6 vials / Additional doses = 2 vials as needed*	
AFRICOM Abbreviations	**POLYSERP-P** = POLYSERP PAN-AFRICA **POLYSERP-M** = POLYSERP MENA	
CENTCOM 1st Line Antivenoms	**First Line Antivenoms with Regional Coverage against All Three Major Syndromes (Neurotoxic/Hemotoxic/Cytotoxic)** **CENTCOM**: Broad-spectrum coverage for all neurotoxic/hemotoxic/cytotoxic snakebite syndromes by known* or unknown species - *POLYSERP-M: Initial dose = 6 vials regardless of severity / Additional doses = 2 vials as needed* **CENTRAL ASIA**: *If patient has a confirmed *Gloydius halys* bite (rare!), use SIOBP-G as 1st line if available. If unavailable or unconfirmed ID give POLYSERP-M - SIOBP-G: *Initial dose = 2 vials / Additional doses = 2 vials as needed*	
CENTCOM Abbreviations	**POLYSERP-M** = POLYSERP MENA **SIOPB-G** = *Gloydius halys* monovalent	
EUCOM 1st Line Antivenoms	**First Line Antivenoms with Regional Coverage Against All Three Major Syndromes (Neurotoxic/Hemotoxic/Cytotoxic)** **UK or Scandinavia**: Broad-spectrum coverage all neurotoxic/hemotoxic/cytotoxic syndromes from European *Vipera* species - *VIPERATAB (1st line): Initial dose = 2 vials (one box), additional doses = 1 – 2 vials as needed* - *VIPERFAV (2nd line): Initial dose = 1 – 2 vials, additional doses = 1 vial as needed* **Outside UK/Scandinavia**: Broad-spectrum coverage all neurotoxic/hemotoxic/cytotoxic syndromes from European *Vipera* species - *VIPERFAV (1st line): Initial dose = 1 – 2 vials, additional doses = 1 vial as needed* - *VIPERATAB (2nd line): Initial dose = 2 vials (one box), additional doses = 1 – 2 vials as needed*	
EUCOM Abbreviations	**VIPERFAV** = VIPERFAV **VIPERATAB** = ViperaTAb	
INDOPACOM 1st Line Antivenoms	**First Line Antivenoms with Regional Coverage Against Neurotoxic Syndrome** **Southeast Asia**: Broad-spectrum for all neurotoxic - *TRC-NPAV: Initial dose 10 vials* *Additional doses = 5 vials as needed* - TRC-*NPAV* is the 1st line for all neurotoxic bites in SE Asia outside of the circumstances listed below: **Marine environments**: Sea snake envenomations - *CSL-SS: Initial dose = 3 vials* *Additional doses = 1 vial as needed* **Maluku/West Papua islands**: Neurotoxic - *CSL-P: Initial dose = 3 vials* *Additional doses = 1 vial as needed*	**First Line Antivenoms with Regional Coverage against Hemotoxic and/or Cytotoxic Syndromes** **Southeast Asia**: Broad-spectrum for all hemotoxic/cytotoxic (1st line in SE Asia) - *TRC-HPAV: Initial dose = 10 vials, additional doses = 2 vials as needed.* TRC-HPAV is the 1st line for all hemotoxic/cytotoxic bites in SE Asia outside of circumstances listed below: **Korean Peninsula/Eastern China**: Viper envenomations (Cytotoxic +/- Hemotoxic) Korean Mamushi species (*Gloydius brevicaudus, G. ussuriensis, G. intermedius*) - KOVAX-AKA*: Initial dose = 1 - 2 vials, additional doses = 1 vial as needed* **Taiwan / Se China / N Vietnam / Laos:** Sharp-nosed viper (*Deinagkistrodon acutus*) - NIPB-SNV*: Initial dose = 2 vials, additional doses = 1 vial as needed* **Japan**: Viper envenomations (Cytotoxic +/- Hemotoxic) If Japanese HABU (*Protobothrops spp.)* envenomation: - CSTRI-HABU*: Initial dose = 1 -2 vials, additional doses = 1 vial as needed* If Japanese Mamushi (*Gloydius blomhoffi*) envenomation:

First Line Antivenoms for All Combatant Commands		
	Eastern China/Taiwan: Neurotoxic - *NIPM-NBB: Initial dose = 5 vials* *Additional doses = 5 vials as needed*	- CSTRI-MAMU*: Initial dose = 1 -2 vials, additional doses = 1 vial as needed* **Japan/China/ N & S Korea/Vietnam/E Russia**: Rhabdophis spp. - Hemotoxic without Cytotoxic Spontaneous bleeding develops within several days of bite without cytotoxicity. - *JSI-AYA: Initial dose = 1 -2 vials, additional doses = 1 vial as needed*
INDOPACOM Abbreviations	**TRC-NPAV** = Neuro Polyvalent Antivenom **CSL-P** = CSL Polyvalent **CSL-SS** = CSL Sea Snake **NIPM-NBB** = Naja atra - Bungarus multicinctus Bivalent	**TRC-HPAV** = Hemato Polyvalent Antivenom **KOVAX-AKA** = Agkistrodon Mamushi Antivenom **JSI-AYA** = Anti-Yamakagashi Antivenom **CSTRI-HABU** = Kaketsuken Habu Antivenom **CSTRI-MAMU** = Kaketsuken Mamushi Antivenom **NIPM-SNV** = Sharp-nosed Viper Monovalent
NORTHCOM 1st Line Antivenoms	**First Line Antivenoms with Regional Coverage Against Neurotoxic Syndrome** **United States**: Coral snake envenomations *- Initial 3-5 vials NACSA, additional doses not needed if 5 vial initial dose given* **United States/Canada**: Pit viper envenomations* *- CROFAB: Initial dose = 4-6 vials, Additional doses = 4-6 vial as needed* *- ANAVIP (rattlesnakes only): Initial dose = 10 vials, Additional doses = 10 vials as needed* *Follow unified treatment algorithm (Lavonas 2011)	**First Line Antivenoms with Regional Coverage against Hemotoxic and/or Cytotoxic Syndromes** **United States/Canada**: Broad spectrum coverage all hemotoxic/cytotoxic syndromes* Any pit viper envenomation (rattlesnake, copperhead, cottonmouth): - *CROFAB: Initial dose = 4-6 vials, additional doses = 4-6 vials as needed* Rattlesnake envenomations only: - *ANAVIP: Initial dose = 10 vials, additional doses = 10 vials as needed* NOTE: Anavip is only indicated by FDA for rattlesnake envenomations; not for copperheads or cottonmouths at this time; however, it is likely effective against all North American pit vipers. Follow *Unified treatment algorithm for the management of crotaline snakebite in the United States* (Lavonas et al. 2011) for specific dosing and management guidelines on pit viper bites.
NORTHCOM Abbreviations	**CROFAB** = CroFab **ANAVIP** = ANAVIP **NACSA** = North American Coral Snake Antivenin	
SOUTHCOM 1st Line Antivenoms	**First Line Antivenoms with Regional Coverage Against Neurotoxic Syndrome** **Central America:** Neurotoxic polyvalent - *BIOCL-COR: Any severity = initial 10 vials Additional 5 vials as needed* **South America**: Neurotoxic polyvalent - *INS-AAP: Any Severity = 10 vials Additional 5 vials as needed*	**First Line Antivenoms with Regional Coverage Against Hemotoxic and/or Cytotoxic Syndromes** **Central and South America**: Broad-spectrum all hemotoxic/cytotoxic syndromes - *BIOCL-AVT: Initial dosing of this antivenom is based on severity* *- Mild – moderate: Initial dose = 10 vials BIOCL-AVT Additional doses = 5 vials as needed* *- Severe: Initial dose = 15 vials BIOCL-AVT Additional doses = 5 vials as needed*
SOUTHCOM Abbreviations	**BIOCL-COR** = CORALMYN **INS-AAP** = Antiveneno Anticoral Polivalente **BIOCL-AVT** = Antivipmyn Tri	

1. The presence of one or more of the criteria for each category in Table 1 (universal treatment) is generally sufficient to diagnose the syndrome, determine severity, and initiate treatment. Patients who present with "mixed syndromes" (signs and symptoms of > 1 syndrome present) receive the same initial doses of antivenom as those presenting with a single syndrome.

   To identify the appropriate antivenom and initial dosing for your patient, refer to the regionally specific snakebite treatment for each combatant command section later in this document. Each COCOM section includes instructions on preparation, dosing, and administration of each antivenom.

2. In certain instances, pretreatment with a low dose of SQ epinephrine prior to antivenom administration may be recommended to reduce the risk of an adverse reaction to antivenom therapy. Refer to pretreatment with epinephrine to prevent early adverse reactions for specific guidelines on pretreatment.

3. The majority of severe early reactions to antivenom occur within the first 5 - 60 minutes after antivenom administration. ***Observe and monitor the patient closely at the bedside for a minimum of one hour after each dose of antivenom has been given***.

   Refer to management of mild, moderate, and severe antivenom reactions for specific guidelines on how to manage mild, moderate, or severe reactions to antivenom therapy

ADJUNCT TREATMENTS & SUPPORTIVE CARE

SUPPORTIVE CARE & ONGOING MANAGEMENT

Provide supportive care and address secondary issues related to the envenomation as follows:

1. Anticipate the need for aggressive airway management with intubation and prolonged ventilation in all patients presenting with neurotoxic envenomation, particularly those who present late with impending respiratory failure or fail to respond to antivenom.

   - For any neurotoxic snakebite producing a cholinergic crisis, consider atropine 0.5 mg IV/IO titrated by auscultation to dry up bronchial and oral hypersecretions posing a risk to airway or breathing.

     Repeat original dose every 5 minutes until resolution of crackles, rales, bronchospasm has been achieved. Pediatric atropine doses should be weight based at a dose of 0.01 mg/kg, up to 0.25 mg.

   - For neurotoxic snakebites in the Middle East, North Africa, and Central Asia without cholinergic crisis, but causing ptosis and respiratory muscle weakness, consider administering trial dose of 0.5 mg atropine followed by 1.0 mg neostigmine IV/IO to temporarily reverse neuromuscular weakness and delay the need for intubation. Pediatric doses should be weight based at a dose of 0.01 mg/kg, up to a maximum of 0.25 mg atropine with 0.5 mg neostigmine.[54,74–77]

     Not all patients will respond, but those who do will show temporary improvement (reversal of ptosis, increased respiratory muscle strength, etc). If no response to neostigmine, do not reattempt. If positive response is achieved, repeat every 1 - 4 hours as needed (maximum dose in 24 hours = 10 mg adults / 5 mg pediatric) until antivenom has definitively reversed the paralysis.

2. For hemotoxic envenomations, all internal and external active bleeding should cease within 30 – 60 minutes of antivenom administration once the appropriate dose has been given. Packed red blood cell or whole blood transfusion can be considered if the patient is in hemorrhagic shock.[17,69,70, 78-82] Platelets, fresh frozen plasma, cryoprecipitate, TXA, and ***other agents are not effective in these cases*** due to the mechanism of the venoms.

3. Ketamine and fentanyl are preferable for analgesia. Histamine release from morphine may mask signs of an allergic reaction or worsen hypotension.
4. It is important to keep the limb significantly elevated (> 60º is ideal) whenever possible to limit dependent edema and swelling.
5. DO NOT routinely de-roof or aspirate blisters, bullae, or blebs unless they are causing significant discomfort or uncontrolled rupture appears imminent. If abscess is suspected, treat according to existing protocols for abscess management.
6. DO NOT perform fasciotomy for snakebites. Compartment syndrome is rare in snakebites. Even in cases of confirmed elevated intracompartmental pressure, patients who received antivenom without fasciotomy experienced better outcomes (shorter recovery time and less long term morbidity) than those who received fasciotomy.[83–86] Appropriate use of antivenom should resolve the underlying issue that is producing the elevated intracompartmental pressures.
7. DO NOT routinely administer antibiotics unless signs and symptoms of an infection are present. Direct infections are rare from most snakebites when prompt, appropriate treatment is given.[54]

ONGOING MONITORING & NEED FOR ADDITIONAL ANTIVENOM

1. Monitor the patient closely for signs of progression in the initial hours of treatment until control of symptoms has been achieved.

   Serial assessments for signs and symptoms of the neurotoxic, hemotoxic, and cytotoxic syndromes should be repeated at hours 2, 4, 6, 12, 24 (H2, H4, H6, H12, H24).

2. Within the first 24 hours, antivenom may be given at hours 0, 2, 4, 6, 12, and 24 according to the specific criteria for antivenom treatment listed under Criteria for Initial Antivenom Treatment and Repeat Doses.
   a. If the treatment criteria have not been resolved at any of these intervals, give an additional dose of antivenom at hours 2, 4, 6, 12, and 24 until control is achieved. Refer to specific dosage instructions for each product listed by COCOM.
   b. If symptoms reappear or persist for more than 24 hours after the first dose of antivenom was given, additional treatment intervals should be discussed with a physician expert.
   c. If 10 or more vials of a single antivenom have been given without any indications of improvement, consider changing to 2nd line antivenom if possible as species may not be covered. If any indications of improvement have been observed, continue with the antivenom you are using.
3. If the patient is asymptomatic but coagulopathy persists 24 hours after the first dose of antivenom was given, administer a dose of antivenom and repeat laboratory tests every 24 hours until resolution.
4. Continuous monitoring for effectiveness of antivenom dose must be done. Occasionally, pockets of venom can be trapped in swollen tissue compartments and escape into the bloodstream once circulation has improved. This is called recurrent envenomation and is most common within the first 24 - 48 hours after a severe bite with extensive swelling and blistering.[78,87–93]
   a. Continuous clinical monitoring includes hourly checks of vital signs, urine output, and detailed assessment for new or worsening signs of neurotoxic, hemotoxic, or cytotoxic envenomation.
   b. Serial laboratory studies including CBC, CMP, PT/PTT/INR, CK, fibrinogen levels (or WBCT if no advanced testing available) may be repeated every 2 hours while signs of envenomation persist.
   c. After signs of clinical resolution, monitoring can decrease to every 6 hours.

5. If indications of recurrent envenomation are detected more than 24 hours after the first dose of antivenom was given, treat as follows:
    a. Asymptomatic patient with coagulopathy and no other findings:
    Administer a dose of antivenom and repeat laboratory tests every 24 hours until resolution.
    b. Symptomatic patient with new or worsening pain, swelling, bleeding, neurotoxicity, or other indications of active envenomation:
    Administer an additional dose of antivenom every 2 hours until acute symptoms have resolved completely.

Discharge Recommendations

1. Patients should be held for at least 24 hours after resolution of all signs and symptoms, and the following steps should be completed prior to discharge:
    a. Repeat blood tests before releasing the patient to ensure resolution of coagulopathy.
    b. Administer a booster dose of tetanus toxoid if needed.
    c. Patients should be instructed to return if any new or worrying signs or symptoms develop.
2. Serum sickness is characterized by flu-like symptoms ± rash that typically develops between 1 - 3 weeks after antivenom administration. It is rare with highly purified modern antivenoms but may occur more frequently with some of the second and third line antivenoms listed in this CPG.[94–97]

    Serum sickness may be uncomfortable but is not dangerous. Management is either symptomatic or with a course of oral steroids.[94,95,97–99]

Criteria for Initial Antivenom Treatment & Repeat Doses

Cytotoxicity

The presence of significant local pain OR progressive edema OR signs of tissue destruction (bruising, blistering, necrosis) is an indication for initial administration of antivenom.[1,47,48,79,100–105] If any of these criteria (or other systemic signs and symptoms) are present, treat immediately and do not wait for irreversible damage to occur before deciding to give antivenom. Note that the progression of edema at any treatment interval is an indication to administer additional antivenom; however, edema may not begin to noticeably decrease for several days and severe edema may take 1 - 2 weeks or longer to completely resolve. WORSENING edema is therefore a treatment criteria, persistence of edema without any progression IS NOT a treatment criteria. Worsening pain that increases significantly in severity or moves proximally up the limb is another indicator for antivenom treatment.

Neurotoxicity

The onset, persistence, or resumption of systemic neurotoxic signs of envenomation (dyspnea, neck flexor muscle weakness, bulbar muscle weakness, reduced level of consciousness, ↓ respiratory muscle function, etc.) at any of the antivenom treatment intervals is always an indication to administer or re-administer antivenom.[1,50,107–109] Monitor respiratory function using negative inspiratory force (NIF) or forced vital capacity (FVC), single breath count test (SBC), capnography, spirometry, peak flow meters, etc.[1,54,72] In patients who have not reached the late stages of respiratory distress/arrest, the first indications that paralysis is improving may be apparent within 30 - 60 minutes once the right dose of antivenom has been achieved. In patients who are

already intubated, it may take hours for reversal to occur after antivenom. This typically occurs within 1 - 3 hours, but may take 6 - 12 hours or longer in some patients. There are numerous documented cases of patients who did not receive antivenom and required prolonged mechanical ventilation ranging from several days up to 13 weeks before recovery. Antivenom typically either reverses the syndrome before it progresses or dramatically shortens the duration of paralysis.

BLEEDING

The onset, persistence, or resumption of any active local or systemic bleeding at any of the standard assessment intervals (0, 2, 4, 6, 12, 24 hours) is always an indication to administer or re-administer antivenom regardless of the WBCT result at the time.[1,70,78,106,109–111] All external and internal bleeding will cease when the appropriate dose of antivenom has been given and actively circulating venom has been neutralized.

WBCT/COAGULATION TESTS

Tests of coagulation usually normalize within 2 - 6 hours after the effective dose of antivenom has been achieved but in some cases it may take longer for these labs to fully normalize after antivenom therapy.[78,112–120] WBCT procedure and interpretation is covered in Appendix A: Whole Blood Clotting Test (WBCT) for Venom-Induced Consumptive Coagulopathies (VICC).

There are three situations where an abnormal WBCT or other abnormal laboratory tests of coagulation (e.g. fibrinogen, PT/PTT/INR, etc) should be treated with antivenom:

1. Initial assessment at H0: Coagulopathy after a snakebite is an indication to give antivenom. If the coagulation test is abnormal but the patient is otherwise asymptomatic, repeat the test using a new glass tube to confirm the result prior to antivenom administration.[78,111,113,114,121]
2. H2, H4, H6, H12, H24: a previously normal coagulation test that changes to abnormal in the presence of any new symptoms meets criteria to administer an additional dose of antivenom. This also applies to a WBCT that was abnormal, normalized several hours after antivenom, but then changes to abnormal again later (recurrent envenomation).[78]
3. Coagulopathy remains abnormal at H24: If WBCT or other tests of coagulation remain abnormal at H24, administer an additional dose of antivenom and repeat every 24 hours until resolution of coagulopathy has occurred.

SUDDEN COLLAPSE SYNDROME

In rare cases, a patient may rapidly deteriorate in the first 5 - 30 minutes after the bite and present with profound hypotension, tachycardia, angioedema, altered level of consciousness, etc.[1,122–130] These patients should be aggressively treated for severe anaphylaxis and severe envenomation simultaneously. Treat anaphylaxis aggressively according to anaphylaxis protocols. Treat the envenomation with an initial high dose (at least 6 vials) of antivenom by rapid IV push, and support the patient with airway management, fluids, and other interventions as appropriate.[122,123,125,131,132] Most patients presenting with hypotension or angioedema are responsive to epinephrine, but may require IV epinephrine infusions to achieve this effect if they are unresponsive to IM epinephrine.[122]

How to Prevent Early Adverse Reactions to Antivenom

Epinephrine is the only prophylactic treatment (pretreatment) that has been shown to effectively reduce the incidence of early adverse reactions (EARs) such as anaphylaxis.[60,98,133–136]

1. ***DO NOT pretreat with steroids or antihistamines.***
2. ***DO NOT administer test doses of antivenom to check for hypersensitivity.***[60–63]

Relative contraindications to epinephrine pretreatment include age > 70, hypertension, ischemic heart disease, history of stroke, suspected or confirmed intracranial hemorrhage. No absolute contraindications.

1. Pretreatment with epinephrine prior to antivenom administration is not indicated by default for all antivenoms, and is recommended only under the following circumstances:
    a. Unstable snakebite patients with signs of shock.
    b. Known history of atopy (asthma, eczema, etc.), equine hypersensitivity, or severe reactions to antivenom in the past.
    c. Use of certain second or third line antivenom due to the high rate of serious EARs associated with these products.
2. Standard epinephrine pretreatment protocol:
    a. Adult dose is 0.25 mg of 1:1000 epinephrine given by SQ injection several minutes prior to antivenom administration.
    b. Pediatric doses should be weight based at a dose of 0.01 mg/kg, up to 0.25 mg.[60,134,135,137,138]
    c. Patients with signs of shock should be given epinephrine by IM injection in the lateral thigh

How to Manage Mild, Moderate & Severe Antivenom Reactions

Mild or Moderate Reaction during Infusion

1. Stop the infusion and manage mild or moderate reactions (e.g. nausea, vomiting, urticaria, pruritus, chills, fever, etc.) symptomatically as needed with antiemetics, antihistamines, steroids, etc.
2. Reassess the patient once the reaction has been controlled; if the antivenom treatment criteria for cytotoxic, hemotoxic, or neurotoxic syndromes have not resolved completely then resume the infusion at a slower rate over 30 minutes.
3. If giving via push, dilute the remaining dose of antivenom in a 100 - 500 mL bag of normal saline and give as 30-minute infusion.

Severe Reaction (Anaphylaxis) during Infusion

1. Stop the infusion and treat according to the anaphylaxis treatment protocol.
   Reassess the patient once the reaction has been controlled; if the antivenom treatment criteria for cytotoxic, hemotoxic, or neurotoxic syndromes have not resolved completely then resume the infusion at a slower rate over 30 minutes.

2. If giving via push, dilute the remaining dose of antivenom in a 100-250 mL bag of normal saline and give as 30-minute infusion.
3. If the reaction occurs, stop the infusion, and consult a physician expert via telemedicine to discuss next steps for management.

Anaphylaxis Treatment Protocol

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

If anaphylaxis occurs after antivenom administration, treat according to the following protocol:

1. First line treatment of anaphylaxis is rapid administration of 1:1000 epinephrine (initial adult dose = 0.5 mg IM in the lateral thigh for rapid absorption). Epinephrine can be repeated as needed until the patient has stabilized and/or an intravenous or intraosseous infusion administered as per standard protocols if the patient fails to respond to IM doses.

   Epinephrine should always be given prior to antihistamines or steroids to counter the immediate life-threats of bronchospasm and vasodilation.
2. After epinephrine has been given:
   a. Give methylprednisolone 125 mg IV
   b. Give diphenhydramine or promethazine 50 mg IV.
   c. Consider adding an H2 antihistamine such as ranitidine.

If anaphylaxis occurs during administration of antivenom, stop the antivenom administration to treat the reaction, then resume the antivenom administration as described below. [15,61,95,99,128,129,140–146]

Late Reactions to Antivenom (Serum Sickness)

1. Serum sickness is characterized by flu-like symptoms ± rash that typically develops between 1 - 3 weeks after antivenom administration. Serum sickness may be uncomfortable, but it is not dangerous.
2. Serum sickness may be uncomfortable, but it is not dangerous.
3. Management is either symptomatic with antihistamines, acetaminophen, or with a course of oral steroids for patients who are in significant discomfort.[94,95,97–99]

Special Situations

If Antivenom is Unavailable

1. Antivenom is the gold standard of care for symptomatic snake envenomations. Early treatment is the best strategy to prevent death, amputation, or other serious disability. Management of snake envenomations when antivenom is not available should be directed at getting the patient to the antivenom (or vice versa) as quickly as possible to prevent irreversible damage to organs and tissues.
2. Mission planning before deployment should include research and procurement of the appropriate regionally specific antivenom(s) recommended in this CPG for your area of operation. If currently deployed without antivenom, efforts to acquire the appropriate antivenom(s) recommended in this CPG for your area of operations should be initiated through proper channels as fake or low-quality antivenoms are frequently found in local pharmacies throughout Africa and elsewhere in the developing world.

3. For specific management until antivenom can be obtained, follow the checklist and skip the steps related to antivenom administration until it has been obtained.

   Refer to Supportive Care measures for specific recommendations.

Military Working Dogs/Multipurpose Canines

All antivenoms can be administered to military working dogs (MWD) and multipurpose canines according to the treatment criteria and initial doses listed in this CPG; other management should be based on the MWD CPG.

Late Presentations and Treatment Delays

There is no defined time limit to antivenom therapy for a symptomatic snakebite. Early antivenom within the first minutes or hours after a bite is the best means of preventing morbidity or mortality, but antivenom remains effective at resolving reversible issues like coagulopathy and preventing further irreversible tissue damage even in patients who present many hours or days after the snakebite.[56,69,78,146,147]

Outdated Interventions That Should Not Be Performed

1. DO NOT cut, suck, electrocute, burn, or use chemicals on the envenomation site.
2. **DO NOT apply constricting bandages, tourniquets, or other circulation-reducing intervention!**
3. DO NOT use venom extractors or other commercial snakebite first aid kits. [148–152]
4. DO NOT administer test doses of antivenom to check for hypersensitivity as these are ineffective and waste both time and antivenom.[60–63]
5. DO NOT administer antihistamines or steroids as prophylactic pretreatment for prevention of anaphylaxis or other early adverse reactions (EARs) to antivenom as neither is effective as a premedication.[133,134]

OCULAR ENVENOMATION BY SPITTING COBRAS (VENOM OPTHALMIA)

Spitting cobras have modified fangs that allow them to spray venom into the eyes of a predator or perceived threat.[153–155] The venom spray widens like buckshot as it travels and the snakes aim at the glint of sunlight reflecting off of the target's eyes. The venom is harmless unless it enters the eyes (causing instantaneous burning, lacrimation, blurred vision, etc.) or the bloodstream by injection (such as a bite), through open wounds on the skin or inside of the mouth, or by ingestion (such as drinking a glass of venom with an ulcer). If a significant amount of venom enters the bloodstream through an open wound and produces typical symptoms of a snakebite, it is treated with antivenom like any other envenomation. For ocular exposure alone without signs of systemic envenomation, antivenom is not indicated and the management is like any ocular chemical exposure with copious irrigation. Spitting cobras can also deliver a venomous bite, so it is important to rule out an actual snakebite in patients who have encountered one of these snakes.

Signs and Symptoms

Immediate signs and symptoms of venom ophthalmia include intense local pain, swelling and/or spasms of the eyelid, lacrimation, and leukorrhea.[156] The primary concern is corneal epithelial injury which can lead to blindness by secondary infection or scarring if not treated correctly.[7,25,54,156–158] Treatment of venom ophthalmia is relatively simple and similar to managing a patient who has been splashed in the eyes with a harmful chemical solution.

First Aid

Confirm that the patient did not experience a snakebite in addition to the ophthalmia. Immediately irrigate the eye with copious quantities of water, normal saline, or a bland fluid such as milk if nothing else is available. Remove clothing and decontaminate the patient from head to toe with soap and water to prevent second re-exposure to dried venom.[54]

Clinical Management

Apply topical anesthetic eye drops (tetracaine) to facilitate thorough irrigation and examination of the affected eyes. Irrigate the eyes thoroughly using water or normal saline for ≥ 15 minutes.[156]

Fluorescein stain and examination using a slit lamp or ophthalmoscope for corneal injury. If present, treat with antimicrobial eye drops (such as tetracycline and chloramphenicol) or ointments and mydriatics. Reassess daily with slit lamp examination. If absent, consider benefits vs risks of antimicrobial eye drops.

Additional Treatments to Consider

Topical eye drops containing either epinephrine (1:1000) or phenylephrine (10%) are reported to immediately relieve the burning sensation produced by the venom.[54,156]

Contraindicated Treatments

Antivenom (topical or systemic) is not indicated for patients with ocular exposure to snake venom.[54,156,159] Topical steroids are contraindicated for these patients.

REGIONALLY SPECIFIC SNAKEBITE TREATMENT

There are a number of different antivenoms included in this CPG for snakebite treatment in AFRICOM, CENTCOM, INDOPACOM, EUCOM, NORTHCOM, and SOUTHCOM. The coverage, initial dosing, preparation, and administration vary between products and details for each of them are included. Simplified algorithms for selecting and dosing each antivenom are also included in each regional section below.

Whenever possible, broad-spectrum, field-stable antivenoms are recommended to enable syndromic diagnosis and treatment at the point of injury without the need to identify the species responsible for the bite. Citations of the relevant literature on safety, efficacy, and dosing for each product are provided in the references section.

Determine the appropriate first line antivenom for your area of operations prior to deployment using this section, then refer back to the Universal Approach to Snakebite Assessment, Diagnosis, and Treatment earlier in the document for detailed instructions and a stepwise approach to snakebite management throughout the course of care. Abbreviated antivenom guidelines for each regional combatant command are included below.

Categorization of Medically Significant Snake Species

The World Health Organization (WHO) classifies the risk posed by various venomous snakes by designating each species as either Category 1 or Category 2 as described below. WHO guidelines state that the “species listed in Category 1 within a country, territory or area should be considered as being of highest priority for antivenom production on the basis that available knowledge implicates them as being responsible for the greater burden in that particular setting.” [160]

WHO Category 1: Venomous Snakes of Highest Medical Importance

Defined as “highly venomous snakes which are common or widespread and cause numerous snakebites, resulting in high levels of morbidity, disability or mortality.”

WHO Category 2: Venomous Snakes of Secondary Medical Importance

Defined as “highly venomous snakes capable of causing morbidity, disability or death, for which exact epidemiological or clinical data may be lacking; and/or which are less frequently implicated (due to their activity cycles, behavior, habitat preferences or occurrence in areas remote to large human populations).”

NOTE: Antivenom Infusion versus Direct Push:
For most first line antivenoms in this CPG, administration using either a) 100, 250, or 500 mL IV bag of isotonic fluids with 10-minute IV/IO infusion or b) direct IV push is recommended in order to get a full dose of antivenom onboard as quickly as possible and neutralize venom before further damage has occurred. However, if this is not possible it is acceptable to dilute antivenom in any size bag of isotonic solution you have available and give over 10 – 30 minutes.

CONTACT

For emergency consultations, call the ADVISOR telemedicine hotline (866-972-9966) and select toxicology from the phone menu.

For additional information about snake bite management or this CPG, email jordan@snakebitefoundation.org or call 415-218-2211.

AFRICOM

TREATMENT GUIDELINES

Safe and effective broad-spectrum, field-stable antivenoms are available for all three syndromes of snake envenomation in this AOR and treatment does not require identification of the species responsible. Snakebite treatment at the point of injury is recommended for AFRICOM due to prolonged evacuation times, high incidence of snakebites, and the high risk of death or permanent disability from many venomous snakes in the AOR if early antivenom treatment is not available.

ADVERSE REACTION MANAGEMENT

- If a mild or moderate reaction occurs, slow the infusion and treat symptomatically with antihistamines, steroids, and/or antiemetics as needed. Refer to management of adverse reactions for specific instructions.
- If a severe reaction such as anaphylaxis occurs, stop the infusion and treat according to the anaphylaxis protocol listed elsewhere in the CPG. Reassess the patient once the reaction has been controlled and resume the infusion at a slower rate if any of the specific criteria for antivenom treatment listed elsewhere in the CPG have not completely resolved.

Sudden Collapse Syndrome Treatment Protocol

Patient presents within 30 minutes of the bite with rapid onset shock ± angioedema, altered mental status, systemic bleeding, and diarrhea.[1]

1. Stabilize with IM or IV epinephrine and fluids as per anaphylaxis protocols.
2. Intubate for airway edema not rapidly responsive to epinephrine.
3. Follow epinephrine immediately with a high dose of the appropriate regional antivenom given by rapid IV or IO push during the resuscitation.
4. Maintain blood pressure with IV or IO fluids and epinephrine until antivenom takes effect to reverse hypotension.

See Sudden Collapse Syndrome section for more information.

CONTACT

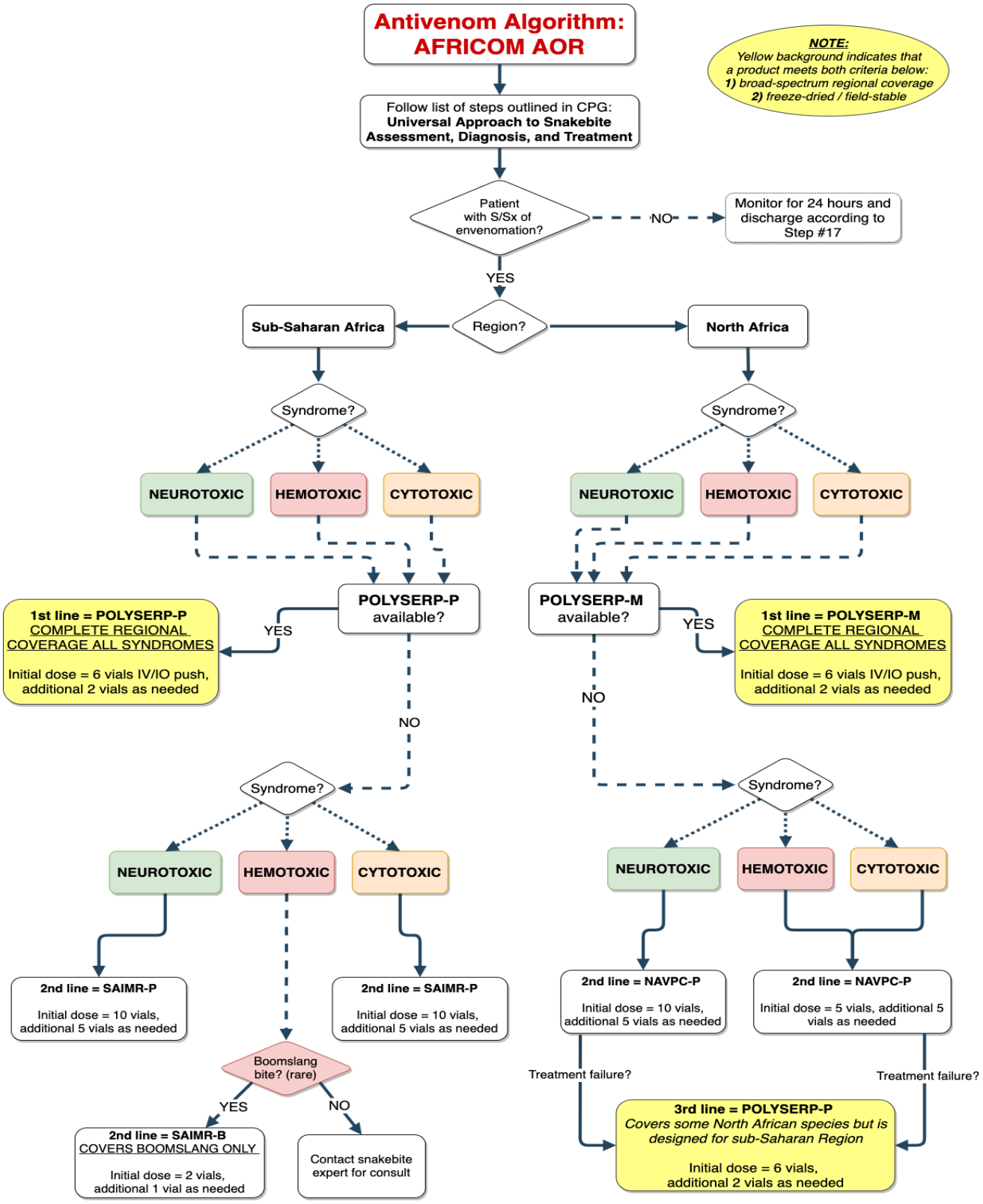
For emergency consultations, call the ADVISOR telemedicine hotline (866-972-9966) and select toxicology from the phone menu.

For additional information about snake bite management or this CPG, email jordan@snakebitefoundation.org or call 415-218-2211.

Table 3. AFRICOM: First Line Antivenoms

	Neurotoxic Syndrome	Hemotoxic Syndrome	Cytotoxic Syndrome
Mild	Local S/Sx (paresthesias; neuropathic pain; piloerection; muscle spasm, fasciculations)	Coagulopathy ± persistence of local bleeding from bite wound > 30 mins after bite	Severe pain; edema below elbow or knee; limited blistering within several inches of the bite wound
Moderate	Systemic S/Sx (bilateral ptosis GI symptoms; visual, auditory, or other sensory disturbances; widespread hyperesthesia)	Moderate systemic bleeding (old scabs, gingival bleeding, epistaxis, etc.); bruising distant from the bite wound	Edema above elbow or knee but not beyond shoulder or hip; moderate local blistering along bitten limb segment
Severe	Difficulty speaking; altered mental status; respiratory muscle weakness causing difficulty breathing; shock or otherwise unstable patient	Active GI bleed (usually hematemesis) or other internal bleeding; severe anemia; altered mental status; shock or otherwise unstable patient	Progressive edema beyond shoulder or hip; severe necrosis or widespread blistering; symptomatic bite to head, neck, or torso; altered mental status; shock or otherwise unstable patient
Criteria for additional AV doses at hours 2, 4, 6, 12, 24 (as needed)	Additional doses if: persistence or worsening of systemic neurotoxic S/Sx. Continue to re-administer 2 vial boluses as needed at hours 2, 4, 6, 12, and 24 until signs of improvement begin to appear (↑SBC, ↑LOC, ↑strength, etc.)	Additional doses if: persistence, resumption, or new onset of any active external or internal bleeding **OR** S/Sx of active venom confirmed by secondary recurrence of abnormal WBCT	Additional doses if: significant increase in edema (such as beyond major joint) **OR** significant increase in pain (severity of pain and/or how far pain radiates up the bitten limb)
AFRICOM 1st Line Antivenoms	Sub-Saharan Africa: Broad-spectrum coverage for all neurotoxic/hemotoxic/cytotoxic snakebite syndromes by known or unknown species - POLYSERP-P: Initial dose = 6 vials / Additional doses = 2 vials as needed North Africa: Broad-spectrum coverage for all neurotoxic/hemotoxic/cytotoxic snakebite syndromes by known or unknown species - POLYSERP-M: Initial dose = 6 vials / Additional doses = 2 vials as needed		
Antivenom Abbreviations	**POLYSERP-P** = POLYSERP PAN-AFRICA **POLYSERP-M** = POLYSERP MENA		

Figure 2. Antivenom Algorithm: AFRICOM AOR



FIRST LINE (AFRICOM - SUB-SAHARAN): POLYSERP-P

POLYSERP/Inosan, Spain - POLYSERP PAN-AFRICA Polyvalent (POLYSERP-P)
(Freeze dried/Unrefrigerated) [1,106,161–164]:

1. Field-stable. Broad-spectrum coverage for 24+ species Cyto/Hemo/Neuro.
2. Single-source treatment option for all neurotoxic, hemotoxic, and cytotoxic snake envenomations in sub-Saharan Africa when the causative species is either unknown or among the 24 snakes for which this product is directly indicated. Only polyvalent to include boomslangs and only antivenom for mole viper envenomations. Directly or indirectly covers all of the WHO category 1 and category 2 snakes in this region for which an antivenom currently exists.
3. Initial dose = 6 vials all syndromes, additional doses = 2 vials as needed.

THIRD LINE (AFRICOM - NORTH AFRICA): POLYSERP-P

POLYSERP/Inosan, Spain - POLYSERP PAN-AFRICA Polyvalent (POLYSERP-P)
(Freeze dried/Unrefrigerated) [1,106,161–164]:

Indicated for all neurotoxic, hemotoxic, or cytotoxic envenomations in North Africa with no signs of improvement after 10 vials of POLYSERP-M and/or NAVPC-P. Directly or indirectly covers some of the WHO category 1 and category 2 snakes in North Africa.

Feasibility of use in austere environments: Recommended for use in operational settings and specifically designed to fill the capability gap for ground medics operating in these areas. Updated version of Inoserp Pan-Africa made specifically for the austere and operational medicine environment. Freeze-dried, unrefrigerated, stable at temperatures >100º F for at least 180 days without loss of efficacy. Broad coverage and simple dosing enable administration in the field for any symptomatic snakebite by unknown species in this region. Special operations and conventional units deploying to austere operational environments and areas with critical threat venomous species should carry 8 vials per medic. It is recommended that a reserve quantity is stocked in all role 2 and role 3 facilities in AFRICOM in case additional antivenom is needed upon arrival, and also to restock field medics that have used their supply.

Adverse reactions: High efficacy against all major syndromes and very low 0.2% incidence of serious adverse reactions based on current publications.

Indications: Broad spectrum polyvalent directly indicated for the treatment of neurotoxic, hemotoxic, and cytotoxic envenomation syndromes caused by 24 different species of African snakes from the families Elapidae, Viperidae, Colubridae, and Atractaspididae.

- NEUROTOXIC: *Dendroaspis angusticeps, D. jamesoni, D. polylepis, D. viridis; Naja anchieta, N. annulifera, N. haje, N. senegalensis; Naja melanoleuca*
- CYTOTOXIC and/or HEMOTOXIC: *Atractaspis irregularis; Bitis arietans, B. gabonica, B. nasicornis, B. rhinoceros; Cerastes cerastes; Dispholidus typus; Echis leucogaster, E. ocellatus, E. pyramidum; Naja katiensis, N. mossambica, N. nigricollis, N. nubiae, N. pallida*

Pretreatment: Not routinely indicated unless patient is unstable, asthmatic/atopic, known hypersensitivity or other pretreatment criteria met. Low risk of severe allergic reactions and other EARs.

Initial dosing by syndrome:

- NEUROTOXIC initial dose = 6 vials
- HEMOTOXIC initial dose = 6 vials

- CYTOTOXIC initial dose = 6 vials

Additional dosing: Additional doses of 2 vials POLYSERP-P may be given at hours 2, 4, 6, 12, and 24 if needed.

Preparation and administration: Reconstitute every 2 vials of POLYSERP-P in the same 10 mL syringe by mixing the first vial, drawing it back up into syringe, and injecting it into the second vial to yield 2 vials/1 syringe (6 vial dose = 3 syringes total). Administer sequentially via slow, continuous direct IV or IO push over approximately 2 minutes each. If a reaction occurs stop the push, treat the reaction, reassess response to treatment criteria. Dilute remaining dose in a 100 mL bag of isotonic fluids and administer via slow IV or IO infusion over 30 mins if needed.

Direct push is recommended for convenience, but POLYSERP-P may also be administered via IV or IO infusion. Mix in a 50 mL or 100 mL bag of isotonic fluids and administer the entire bag over 5 – 10 mins.

FIRST LINE (AFRICOM - NORTH AFRICA): POLYSERP-M

POLYSERP/Inosan, Spain - POLYSERP MENA Polyvalent (POLYSERP-M) (Freeze dried/unrefrigerated) [156–172]:

1. Field-stable. Broad-spectrum coverage for 27+ species Cyto/Hemo/Neuro.
2. Single-source treatment option for all neurotoxic, hemotoxic, and cytotoxic snake envenomations in North Africa (Algeria, Egypt, Libya, Morocco, Tunisia, Western Sahara) when the causative species is either unknown or among the 27 snakes for which this product is directly indicated. Directly or indirectly covers all of the WHO category 1 and category 2 snakes in this region for which an antivenom currently exists.
3. Initial dose = 6 vials all syndromes, additional doses = 2 vials as needed.

Feasibility of use in austere environments: Recommended for use in operational settings and specifically designed to fill the capability gap for ground medics operating in these areas. Updated version of Inoserp MENA made specifically for the austere and operational medicine environment. Freeze-dried, unrefrigerated, stable at temperatures >100º F for at least 180 days without loss of efficacy. Broad coverage and simple dosing enable administration in the field for any symptomatic snakebite by unknown species in this region. Special operations and conventional units deploying to austere operational environments and areas with critical threat venomous species should carry 8 vials per medic. It is recommended that a reserve quantity is stocked in all role 2 and role 3 facilities in AFRICOM in case additional antivenom is needed upon arrival, and also to restock field medics that have used their supply.

Adverse reactions: High efficacy against all major syndromes and low incidence of serious adverse reactions of approximately 1% based on current publications.

Indications: Broad spectrum polyvalent directly indicated for the treatment of neurotoxic, hemotoxic, and cytotoxic envenomation syndromes caused by 27 different species of Middle Eastern, North African, and Central Asian snakes from the families *Elapidae* and *Viperidae*. First line for snake envenomations in this region when the causative species is unknown or among those for which the product is directly indicated.

- **NEUROTOXIC**: Naja haje, N. oxiana; Walterinnesia aegyptia
- **CYTOTOXIC** and/or **HEMOTOXIC**: *Bitis arietans; Cerastes cerastes, C. vipera, C. gasperettii; Daboia palestinae, D. mauritanica, D. deserti; Echis. carinatus sochureki, E. coloratus, E. khosatskii, E. leucogaster, E. megalocephalus, E. omanensis, E. pyramidum; Macrovipera lebetina obtusa, M. l. transmediterranea, M. l. turanica; Montivipera bornmuelleri, M. raddei kurdistanica; Naja nubiae, N. pallida; Pseudocerastes persicus persicus, P. fieldi; Vipera latastei*

Pretreatment: ***Not routinely indicated*** unless patient is unstable, asthmatic/atopic, known hypersensitivity or other pretreatment criteria met. Low risk of severe allergic reactions and other EARs.

Initial dosing by syndrome:

- NEUROTOXIC initial dose = 6 vials
- HEMOTOXIC initial dose = 6 vials
- CYTOTOXIC initial dose = 6 vials

Additional dosing: Additional doses of 2 vials POLYSERP-M may be given at hours 2, 4, 6, 12, and 24 if needed.

Preparation and administration: Reconstitute every 2 vials of POLYSERP-M in the same 10 mL syringe by mixing the first vial, drawing it back up into syringe, and injecting it into the second vial to yield 2 vials/1 syringe (6 vial dose = 3 syringes total). Administer sequentially via slow, continuous direct IV or IO push over approximately 2 minutes each. If a reaction occurs stop the push, treat the reaction, reassess response to treatment criteria. Dilute remaining dose in a 100 mL bag of isotonic fluids and administer via slow IV or IO infusion over 30 mins if needed.

Direct push is recommended for convenience, but POLYSERP-M may also be administered via IV or IO infusion. Mix in a 50 mL or 100 mL bag of isotonic fluids and administer the entire bag over 5 – 10 mins.

SECOND LINE (AFRICOM - SUB-SAHARAN AFRICA): SAIMR-P

South African Vaccine Producers, South Africa - SAVP SAIMR Polyvalent Snake Antivenom (SAIMR-P) (Liquid/refrigerated) [50,173–181] :

1. Not field stable. Broad-spectrum against 10+ species neurotoxic and cytotoxic only.
2. Unknown neurotoxic and/or cytotoxic envenomation in sub-Saharan Africa or with no indications of improvement after 10 vials of POLYSERP-P. Will not treat hemotoxic envenomations. Southern Africa: Directly or indirectly covers all WHO category 1 and category 2 species for which an antivenom currently exists. East/Central/West Africa: Covers many cytotoxic and neurotoxic snakes in West, Central, and East Africa but has major coverage gaps with no efficacy against all WHO category 1 or category 2 hemotoxic snake species.
3. Initial dose = 10 vials neurotoxic/cytotoxic only, additional doses = 5 vials

Feasibility of use in austere environments: Not recommended for operational settings. Requires cold chain refrigeration. Recommend storing small quantities at strategically located Role 2 & 3 facilities in AFRICOM AOR.

Adverse reactions: High efficacy but very high rates of anaphylaxis ranging from 25% - 75% have been documented in multiple publications.

Indications: This polyvalent can be used to treat neurotoxic and cytotoxic envenomations by 10 different species of African snakes. The product has been used successfully to treat additional species of African snakes through paraspecific neutralization, but research in this area is limited and most experiences are anecdotal. The 10 species listed below are the official treatment indications recommended by the manufacturer:

- NEUROTOXIC SNAKES: *Dendroaspis polylepis, D. angusticeps, D. jamesoni, Naja melanoleuca, N. nivea, N. annulifera*
- CYTOTOXIC SNAKES: *Bitis arietans, B. gabonica, Naja mossambica, Hemachatus haemachatus*

Initial dosing by syndrome:

- NEUROTOXIC initial dose = 10 vials
- Not indicated for hemotoxic

- CYTOTOXIC initial dose = 10 vials

Additional dosing: Additional doses of 5 vials SAIMR-P may be given at hours 2, 4, 6, 12, and 24 if needed.

Pretreatment: Recommended for this antivenom. Administer 0.25 mg epinephrine injected SQ prior to beginning antivenom infusion to reduce the risk of a serious reaction. Pediatric epinephrine dose is weight based (0.01 mg/kg).

Preparation and administration: Dilute the entire dose of antivenom in a single 250 - 500 mL bag of isotonic solution and administer by intravenous infusion over 10 - 30 minutes.

SECOND LINE, Boomslang (AFRICOM - SUB-SAHARAN AFRICA): SAIMR-B

South African Vaccine Producers, South Africa - SAVP SAIMR Boomslang Monovalent (SAIMR-B) (Liquid/Refrigerated) [173–181]:

1. Not field stable. Not broad-spectrum. Single species coverage.
2. Confirmed or suspected boomslang bite with no indications of improvement after 10 vials of POLYSERP-P. Monovalent that can only be used to treat the WHO category 2 boomslang. Does not provide coverage against any other WHO category 1 or category 2 species.
3. Initial dose = 2 vials boomslang only, additional doses = 1 vial as needed

Feasibility of use in austere environments: Not recommended for operational settings. Requires cold chain refrigeration. Recommend storing several vials at a small number of strategically located Role 2 & 3 facilities in sub-Saharan Africa.

Adverse reactions: No clinical trials but effective anecdotally and in case reports. Moderate to high rates of anaphylaxis are anticipated based on limited case reports of patients treated with SAIMR-B.

Indications: This monovalent is only effective for the boomslang.

- Hemotoxic: *Dispholidus typus*

Initial dosing by syndrome:

- Not indicated for neurotoxic
- Hemotoxic with confirmed or suspected boomslang bite (typical onset coagulopathy and bleeding 1 – 3 days after the bite; no significant pain, swelling, or tissue destruction)
  - Initial dose = 2 vials SAIMR-B
  - POLYSERP-P should be the first line treatment for this species if available due to lower risk of allergic reactions.
- Not indicated for hemotoxic envenomation by snakes other than the boomslang
- Not indicated for cytotoxic

Additional dosing: Additional doses of 1 vial SAIMR-B may be repeated, if needed, at hours 2, 4, 6, 12, and 24 until cessation of all active bleeding or at 6, 12, and 24 for coagulopathy without bleeding.

Pretreatment: RECOMMENDED for this antivenom. Administer 0.25 mg epinephrine injected SQ prior to beginning antivenom infusion to reduce the risk of a serious reaction. Pediatric doses should be weight based at a dose of 0.01 mg/kg, up to 0.25 mg.

Preparation and administration: Dilute the entire dose of antivenom in a single 250 - 500 mL bag of isotonic solution and administer by intravenous infusion over 10 - 30 minutes.

SECOND LINE (AFRICOM - NORTH AFRICA): NAVPC-C

National Antivenom & Vaccine Production Center, Saudi Arabia - Polyvalent Snake Antivenom (NAVPC-P) (Liquid/Refrigerated)[182-186]:

Unknown neurotoxic, hemotoxic, or cytotoxic envenomation with no indications of improvement after 10 vials of POLYSERP-M. Directly or indirectly covers some of the WHO category 1 and category 2 snakes in this region for which an antivenom currently exists.

1. Not field stable. Broad-spectrum coverage 6+ species of Neuro/Hemo/Cyto.
2. Unknown neurotoxic, hemotoxic, or cytotoxic envenomation with no indications of improvement after 10 vials of POLYSERP-M. Directly or indirectly covers some of the WHO category 1 and category 2 snakes in this region for which an antivenom currently exists.
3. Initial dose neuro = 10 vials. Initial dose hemo/cyto = 5 vials. All additional doses = 5 vials.

Feasibility of use in austere environments: NOT RECOMMENDED for operational settings. Requires refrigeration, moderate to high rates of adverse reactions are anticipated. Better alternatives exist. If purchased, it should be kept at Role 2 & 3 facilities in the Arabian Peninsula.

Adverse reactions: Insufficient evidence to determine risk of adverse reactions at this time.

Indications: This polyvalent can be used to treat neurotoxic and cytotoxic envenomations by 6 different species of Middle Eastern, North African, and Central Asian snakes. It may be able to neutralize venom from additional species through paraspecific neutralization but this has not been researched.[187–192] The six species listed below are the official treatment indications recommended by the manufacturer:

- NEUROTOXIC: *Walterinnesia aegyptia, Naja haje*
- HEMOTOXIC and/or CYTOTOXIC: *Bitis arietans, Echis coloratus, Echis carinatus, Cerastes cerastes*

Initial dosing by syndrome:

- NEUROTOXIC initial dose = 10 vials
- HEMOTOXIC initial dose = 5 vials
- CYTOTOXIC initial dose = 5 vials

Additional dosing: Additional doses of 5 vials NAVPC-C may be given at hours 2, 4, 6, 12, and 24 if needed.

Pretreatment: Recommended for this antivenom due to insufficient evidence for determining risk of EARs. Administer 0.25 mg epinephrine injected SQ prior to beginning antivenom infusion to reduce the risk of a serious reaction. Pediatric doses should be weight based at a dose of 0.01 mg/kg, up to 0.25 mg.

Preparation and administration: Dilute the entire dose of antivenom in a single 250 - 500 mL bag of isotonic solution and administer by intravenous infusion over 10 - 30 minutes.

AFRICOM ANTIVENOM FORMULATION COMPARISON

Formulation, storage, stability, safety, and efficacy for six antivenoms available in the AFRICOM area of responsibility. EchiTAb-Plus is included for reference but is not recommended due to limited species coverage, low availability, and high rates of anaphylaxis.
Note: Specific indications according to the package insert.

Table 4a. AFRICOM Antivenom Formulation Comparison

PRODUCT PROFILE	**[NAVPC-P]** NORTH AFRICA	**[POLYSERP-M]** NORTH AFRICA	**[POLYSERP-P]** SUB-SAHARAN	**[SAIMR-P]** SUB-SAHARAN	**[SAIMR-B]** SUB-SAHARAN	**[EchiTAb-Plus]** SUB-SAHARAN
Type of Immunoglobulin	$F(ab')_2$ fragment; Equine	$F(ab')_2$ fragment; Equine	$F(ab')_2$ fragment; Equine	$F(ab')_2$ fragment; Equine	$F(ab')_2$ fragment; Equine	Intact IgG; Equine
Coverage	6 species polyvalent	27 species polyvalent	24 species polyvalent	10 species polyvalent	1 species monovalent	3 species polyvalent
Elapids	• **Desert black snake: 1 species** (*Walterinnesia aegyptia*) • **Neurotoxic cobras: 1 species** *(Naja haje)*	• **Desert black snake: 1 species** (*Walterinnesia aegyptia*) • **Spitting cobras: 2 species** (*Naja nubiae, N. pallida*) • **Neurotoxic cobras: 2 species** *(Naja haje, N. oxiana)*	• **Mambas: 4 species** (*Dendroaspis polylepis, D. viridis, D. angusticeps, D. jamesoni*); • **Spitting cobras: 5 species** (*Naja nigricollis, N. pallida, N. nubiae, N. katiensis, Naja mossambica*) • **Neurotoxic cobras: 5 species** *(Naja haje, N. senegalensis, N. anchieta, N. annulifera, N. melanoleuca*)	• **Mambas: 3 species** (*Dendroaspis polylepis, D. angusticeps, D. jamesoni*); • **Spitting cobras: 2 species** (*Naja mossambica, Hemachatus haemachatus*); • **Neurotoxic cobras: 3 species** (*Naja melanoleuca, N. nivea, N. annulifera*)	----------	• **Spitting cobras: 1 species** *(Naja nigricollis)*
Viperids	• **Saw-scaled vipers: 2 species** (*Echis coloratus, E. carinatus*) • **Large African adders: 1 species** (*Bitis arietans)* • **Desert horned vipers: 1 species** *(Cerastes cerastes)*	• **Saw-scaled vipers: 7 species** (*Echis leucogaster, E. pyramidum, E. coloratus, E. khosatskii, E. megalocephalus, E. omanensis, E. carinatus sochureki*) • **Large African adders: 1 species** (*Bitis arietans)* • **Desert horned vipers: 3 species** *(Cerastes cerastes, C. vipera, C. gasperettii)* • **Old world vipers: 2 species** (*Daboia palestinae, D. mauritanica*)	• **Saw-scaled vipers: 3 species** (*Echis ocellatus, E. leucogaster, E. pyramidum*); • **Large African adders: 4 species** (*Bitis arietans, B. rhinoceros, B. nasicornis, B. gabonica*) • **Desert horned vipers: 1 species** *(Cerastes cerastes)*	• **Large African adders: 2 species** (*Bitis arietans, B. gabonica*)	----------	• **Saw-scaled vipers: 1 species** (*Echis ocellatus)* • **Large African adders: 2 species** (*Bitis arietans*)

		• **Large palearctic vipers: 4 species** *(Macrovipera deserti, M. lebetina obtusa, M. l. transmediterranea, M. l. turanica)* • **False horned vipers: 2 species** (*Pseudocerastes persicus, P. fieldi*) • **Eurasian vipers: 3 species** *(Vipera bornmuelleri, V. latastei, V. raddei kurdistanica)*				
Colubrids & Atractaspids	----------	----------	• **Burrowing asps: 1 species** *Atractaspis irregularis* • **Boomslang (1 species exists)** *Dispholidus typus*	----------	•**Boomslang** (*Dispholidus typus)*	----------

Table 4b. Antivenom Formulation Comparison

PRODUCT PROFILE	**[NAVPC-P]** NORTH AFRICA	**[POLYSERP-M]** NORTH AFRICA	**[POLYSERP-P]** SUB-SAHARAN	**[SAIMR-P]** SUB-SAHARAN	**[SAIMR-B]** SUB-SAHARAN	**[EchiTAb-Plus]** SUB-SAHARAN
Protein (mg/ml)	Unknown	≤ 100 mg/mL	≤ 100 mg/mL	111.7 ± 27.2	Unknown	40 ± ?
Preservatives	Unknown, likely cresol	None	None	≤0.35% cresol w/v	≤0.35% cresol w/v	Phenol (w/v?)
Formulation	Liquid; 10 ml vial	Lyophilized; 10 ml vial	Lyophilized; 10 ml vial	Liquid; 10 ml vial	Liquid; 10 ml vial	Liquid; 10 ml vial
Reconstitution	Liquid formulation	Less than 20 seconds	Less than 20 seconds	Liquid formulation	Liquid formulation	Liquid formulation
Cold chain required?	Yes, must be refrigerated	No, store unrefrigerated. Can be carried in pack.	No, store unrefrigerated. Can be carried in pack.	Yes, must be refrigerated	Yes, must be refrigerated	Yes, must be refrigerated
Maximum temp allowed?	"Store between 2 – 8 ºC (35.6 – 46.4 ºF)"	"Excursions permitted to 40 ºC (104 ºF) for up to 6 months"	"Excursions permitted to 40 ºC (104 ºF) for up to 6 months"	"Store between 2 – 8 ºC (35.6 – 46.4 ºF)"	"Store between 2 – 8 ºC (35.6 – 46.4 ºF)"	"Store between 2 – 8 ºC (35.6 – 46.4 ºF)"
N of published cases	**n = 252** cases in retrospective studies that examined safety and efficacy; quality limited.	**n = 315** cases reported in prospective observational studies evaluating safety and efficacy under austere conditions.	**n = 426** cases reported in prospective observational studies evaluating safety and efficacy under austere conditions.	**n = 144** cases in retrospective / prospective studies (anecdotal and observational) that reported safety and efficacy data.	**n = 5** case reports but that included safety and efficacy data but no studies to date.	**n = 206 cases in RCT**

Efficacy in clinical studies	- Appears effective against most snakebites in North Africa / Arabian Peninsula; coverage is poor outside of this area due to differences in local species. May be less effective for DIC. - The **combined CFR all was 3.57%** (9/252); deaths were a mix of ICH, DIC, cardiac arrest, respiratory arrest. Most fatalities presented early.	- Effectively treated cytotoxic, hemotoxic, neurotoxic syndromes of SBE at hospitals throughout Morocco since the country switched to using it in 2015. - The **combined CFR all was 3.17%** (10/316); mostly of organ failure, hemorrhagic shock, sepsis after long treatment delays before presentation to the hospital.	- Effectively treated cytotoxic, hemotoxic, neurotoxic syndromes of SBE at poorly equipped rural health centers in Mali, Senegal, Benin, and Guinea. - The **combined CFR all was 1.6%** (7/426); mostly hemorrhagic shock from carpet viper bites in patients with long treatment delays before presentation to the hospital.	- Effectively treated cytotoxic, hemotoxic, neurotoxic syndromes of SBE at health centers in South Africa (5 studies) and Tanzania (1 study). - The **combined CFR was 3% (**5/144); two were neurotoxic envenomations and 3 were pediatric cases with unspecified syndromes.	- No clinical studies but very effective for resolving hemotoxic effects from boomslang envenomations in case reports.	- 3 vial dose effectively treated hemotoxic syndrome of SBE due to *Echis ocellatus* in Nigeria. Hemotoxic saw-scaled viper bites only; no evidence of efficacy for other snakes / syndromes. - There were no fatalities reported; however, patients with severe envenomations, late-presenting patients, and those complex cases were excluded from the study.
Safety *(incidence of anaphylaxis)*	Very limited data and all studies acknowledge likely underreporting of reactions. Most reliable study showed **moderate incidence of anaphylaxis 5.5% (2/36);** small sample.	**Very low incidence of anaphylaxis (1%; 3/290)** in 290 cases reported and evaluated by the poison center of Morocco. No cases of serum sickness.	**Very low incidence of anaphylaxis (0.2%; 1/426))** in prospective clinical studies. Only one case of possible anaphylaxis that is more consistent with shock from the snakebite. No cases of serum sickness.	**Very high incidence of anaphylaxis (average 26%; rate is as high as 76% in some studies).** Serum sickness not reported. Underreporting likely.	**Very high incidence of anaphylaxis (60%)** in the only study that evaluated at adverse reactions to SAIMR-B. One case of serum sickness.	**High incidence anaphylaxis (10.8%, n = 21/194)** and 5 cases of serum sickness reported.

CENTCOM

Treatment Guidelines

Safe and effective broad-spectrum, field-stable antivenoms are available for all three syndromes of snake envenomation in this AOR and treatment does not require identification of the species responsible. Snakebite treatment at the point of injury is recommended for CENTCOM due to potential for prolonged evacuation times, high incidence of snakebites, and the high risk of death or permanent disability from many venomous snakes in the AOR if early antivenom treatment is not available.

Adverse Reaction Management

- If a mild or moderate reaction occurs, slow the infusion and treat symptomatically with antihistamines, steroids, and/or antiemetics as needed.
- If a severe reaction such as anaphylaxis occurs, stop the infusion and treat according to the anaphylaxis protocol listed elsewhere in the CPG. Reassess the patient once the reaction has been controlled and resume the infusion at a slower rate if any of the specific criteria for antivenom treatment listed elsewhere in the CPG have not completely resolved.

Sudden Collapse Syndrome Treatment Protocol

Patient presents within 30 minutes of the bite with rapid onset shock ± angioedema, altered mental status, systemic bleeding, and diarrhea.[1]

1. Stabilize with IM or IV epinephrine and fluids as per anaphylaxis protocols
2. Intubate for airway edema not rapidly responsive to epinephrine
3. Follow epinephrine immediately with a high dose of the appropriate regional antivenom given by rapid IV or IO push during the resuscitation
4. Maintain blood pressure with IV or IO fluids and epinephrine until antivenom has taken effect to reverse the hypotension.

See Sudden Collapse Syndrome section for more information.

CONTACT

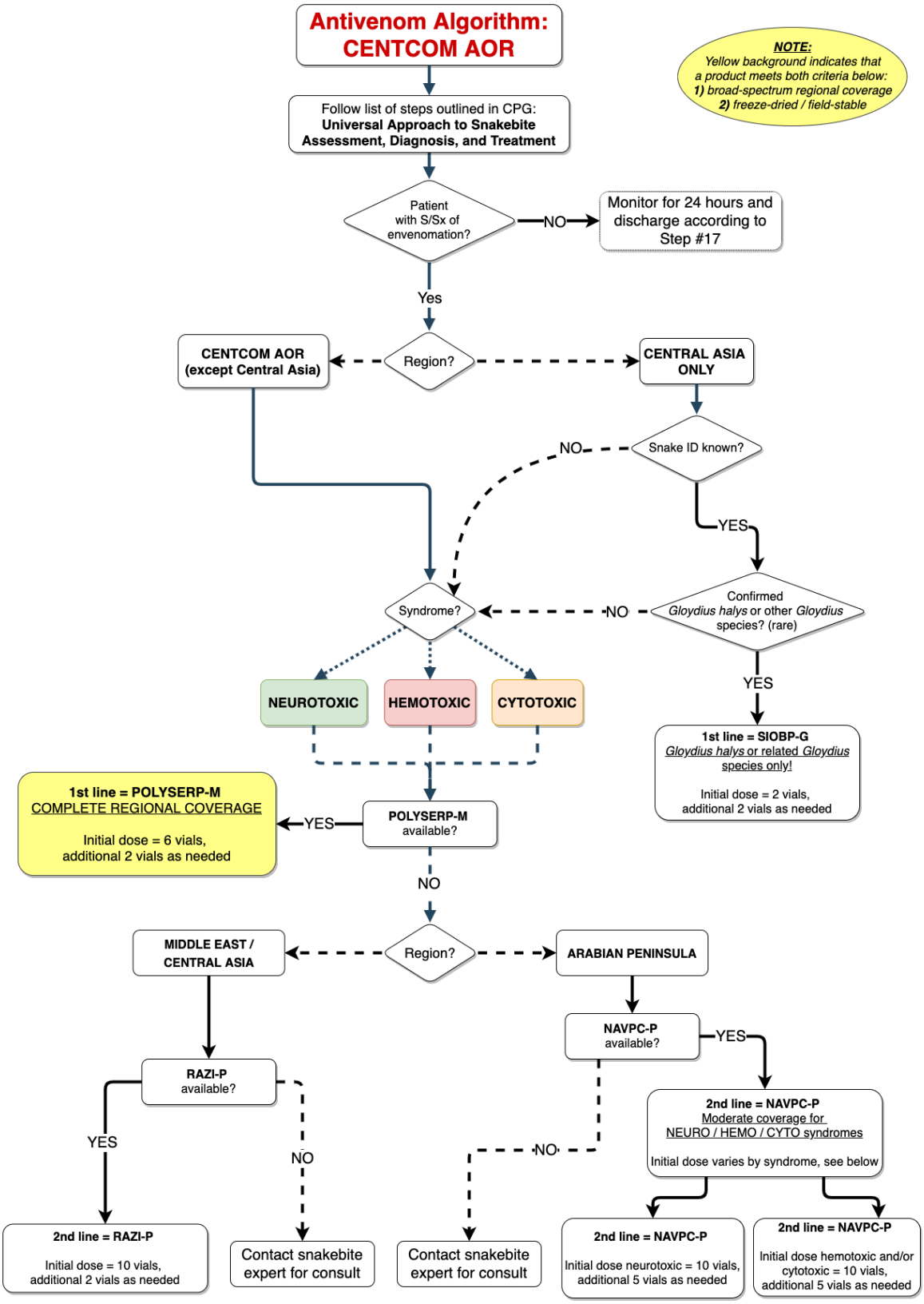
For emergency consultations, call the ADVISOR telemedicine hotline (866-972-9966) and select toxicology from the phone menu.

For additional information about snake bite management or this CPG, email jordan@snakebitefoundation.org or call 415-218-2211.

Table 5. CENTCOM - First Line Antivenoms

	Neurotoxic Syndrome	Hemotoxic Syndrome	Cytotoxic Syndrome
Mild	Local S/Sx (paresthesias; neuropathic pain; piloerection; muscle spasm, fasciculations)	Coagulopathy ± persistence of local bleeding from bite wound > 30 mins after bite	Severe pain; edema below elbow or knee; limited blistering within several inches of the bite wound
Moderate	Systemic S/Sx (bilateral ptosis GI symptoms; visual, auditory, or other sensory disturbances; widespread hyperesthesia)	Moderate systemic bleeding (old scabs, gingival bleeding, epistaxis, etc); bruising distant from the bite wound	Edema above elbow or knee but not beyond shoulder or hip; moderate local blistering along bitten limb segment
Severe	Difficulty speaking; altered mental status; respiratory muscle weakness causing difficulty breathing; shock or otherwise unstable patient	Active GI bleed (usually hematemesis) or other internal bleeding; severe anemia; altered mental status; shock or otherwise unstable patient	Progressive edema beyond shoulder or hip; severe necrosis or widespread blistering; symptomatic bite to head, neck, or torso; altered mental status; shock or otherwise unstable patient
Criteria for additional AV doses at hours 2, 4, 6, 12, 24 (as needed)	Additional doses if: persistence or worsening of systemic neurotoxic S/Sx. Continue to re-administer 2 vial boluses as needed at hours 2, 4, 6, 12, and 24 until indications of improvement begin to appear (↑SBC, ↑LOC, ↑strength, etc.)	Additional doses if: persistence, resumption, or new onset of any active external or internal bleeding **OR** S/Sx of active venom confirmed by secondary recurrence of abnormal WBCT	Additional doses if: significant increase in edema (such as beyond major joint) **OR** significant increase in pain (severity of pain and/or how far pain radiates up the bitten limb)
CENTCOM 1st Line Antivenoms	CENTCOM: Broad-spectrum coverage for all neurotoxic/hemotoxic/cytotoxic snakebite syndromes by known* or unknown species - POLYSERP-M: Initial dose = 6 vials regardless of severity / Additional doses = 2 vials as needed Central Asia: *If patient has a confirmed Gloydius halys bite (rare!), use SIOBP-G as 1st line if available. If unavailable or unconfirmed ID give POLYSERP-M - SIOBP-G: Initial dose = 2 vials / Additional doses = 2 vials as needed		
Antivenom Abbreviations	**POLYSERP-M** = POLYSERP MENA **SIOPB-G** = Gloydius halys monovalent		

Figure 3. Antivenom Algorithm for CENTCOM AOR



FIRST LINE CENTCOM - Arabian Peninsula/Middle East/Central Asia: POLYSERP-M

POLYSERP / Inosan, Spain - POLYSERP MENA Polyvalent (POLYSERP-M) (Freeze dried/Unrefrigerated) [162–172]

1. Field-stable. Broad-spectrum coverage 27+ species of Cyto/Hemo/Neuro.
2. Single source treatment option for all neurotoxic, hemotoxic, and cytotoxic snake envenomations in the Arabian Peninsula, the Middle East, and Central Asia when the causative species is either unknown or among the 27 snakes for which this product is directly indicated. Directly or indirectly covers all WHO category 1 species in the region. Directly or indirectly covers all category 2 snakes in this region for which an antivenom currently exists except for *Gloydius halys*, which is covered by Shanghai SIOBP-G or Iranian RAZI-P. Paraspecific neutralization against *Gloydius* unknown but not anticipated.
3. Initial dose = 6 vials all syndromes, additional doses = 2 vials as needed.

Feasibility of use in austere environments: Recommended for use in operational settings and specifically designed to fill the capability gap for ground medics operating in these areas. Updated version of Inoserp MENA made specifically for the austere and operational medicine environment. Freeze-dried, unrefrigerated, stable at temperatures >100º F for at least 180 days without loss of efficacy. Broad coverage and simple dosing enable administration in the field for any symptomatic snakebite by unknown species in this region. Special operations and conventional units deploying to austere operational environments and areas with critical threat venomous species should carry 8 vials per medic. It is recommended that a reserve quantity is stocked in all role 2 and role 3 facilities in AFRICOM in case additional antivenom is needed upon arrival, and also to restock field medics that have used their supply.

Adverse reactions: High efficacy against all major syndromes and low incidence of serious adverse reactions of approximately 1% based on current publications.

Indications: Broad spectrum polyvalent directly indicated for the treatment of neurotoxic, hemotoxic, and cytotoxic envenomation syndromes caused by 27 different species of Middle Eastern, North African, and Central Asian snakes from the families *Elapidae* and *Viperidae*. First line for snake envenomations in this region when the causative species is unknown or among the species for which the product is directly indicated.

- NEUROTOXIC: Naja haje, N. oxiana; Walterinnesia aegyptia
- CYTOTOXIC and/or HEMOTOXIC: *Bitis arietans; Cerastes cerastes, C. vipera, C. gasperettii; Daboia palestinae, D. mauritanica, D. deserti; Echis. carinatus sochureki, E. coloratus, E. khosatskii, E. leucogaster, E. megalocephalus, E. omanensis, E. pyramidum; Macrovipera lebetina obtusa, M. l. transmediterranea, M. l. turanica; Montivipera bornmuelleri, M. raddei kurdistanica; Naja nubiae, N. pallida; Pseudocerastes persicus persicus, P. fieldi; Vipera latastei*

Pretreatment: Not routinely indicated unless patient is unstable, asthmatic/atopic, known hypersensitivity or other pretreatment criteria met. Low risk of severe allergic reactions and other EARs.

Initial dosing by syndrome:

- NEUROTOXIC initial dose = 6 vials
- HEMOTOXIC initial dose = 6 vials
- CYTOTOXIC initial dose = 6 vials

Additional dosing: Additional doses of 2 vials POLYSERP-M may be given at hours 2, 4, 6, 12, and 24 if needed.

Preparation and administration: Reconstitute every 2 vials of POLYSERP-M in the same 10 mL syringe by mixing the first vial, drawing it back up into syringe, and injecting it into the second vial to yield 2 vials/1 syringe (6 vial dose = 3 syringes total). Administer sequentially via slow, continuous direct IV or IO push over approximately 2

minutes each. If a reaction occurs stop the push, treat the reaction, reassess response to treatment criteria. Dilute remaining dose in a 100 mL bag of isotonic fluids and administer via slow IV or IO infusion over 30 mins if needed.

Direct push is recommended for convenience, but POLYSERP-M may also be administered via IV or IO infusion. Mix in a 50 mL or 100 mL bag of isotonic fluids and administer the entire bag over 5 – 10 mins.

FIRST LINE & SECOND LINE CENTCOM - Middle East/Central Asia: SIOBP-G

Shanghai Institute of Biological Products, China - Agkistrodon (Gloydius) halys Monovalent Antivenom (SIOBP-G): (Liquid/Refrigerated)[194–196]:

NOTE: This product is listed as Agkistrodon halys on the SIOBP website and product packaging but the taxonomy for this species has changed. Agkistrodon halys was moved to the genus *Gloydius* and should be listed as Gloydius *halys* as it is listed elsewhere. The product is abbreviated as SIOBP-G in the CPGs to account for this correction.

1. Not field stable. Not broad-spectrum. Single species coverage.
2. Monovalent for the WHO category 2 species *Gloydius halys*. Indicated as first line only for confirmed envenomation by *Gloydius halys* or related *Gloydius* species. Indicated as second line for unknown cytotoxic and/or hemotoxic envenomation in Middle East or Central Asia with no signs of improvement after 10 vials of POLYSERP-M. Does not provide coverage against any other WHO category 1 or category 2 species.
3. Initial dose = 6 vials hemotoxic/cytotoxic only, additional doses = 2 vials as needed.

First line (CENTCOM - MIDDLE EAST / CENTRAL ASIA): Monovalent for the WHO category 2 species *Gloydius halys.* Indicated only for confirmed envenomation by *Gloydius halys* or related *Gloydius* species. Does not provide coverage against any other WHO category 1 or category 2 species.

Second line (CENTCOM - MIDDLE EAST / CENTRAL ASIA): Indicated for unknown cytotoxic and/or hemotoxic envenomation in Middle East or Central Asia with no signs of improvement ***after 10 vials of POLYSERP-M.***

Feasibility of use in austere environments: Not recommended for operational settings. Requires cold chain refrigeration. Recommend storing small quantities at strategically located Role 2 & 3 facilities in CENTCOM AOR.

Incidence of adverse reactions: Low to moderate rates of EARs and serum sickness are anticipated but clinical evidence is limited.

Indications: This monovalent can be used to treat cytotoxic and hemotoxic envenomations by *Gloydius halys*, a pit viper native to the Middle East and Central Asia. It will most likely neutralize venom from related species in the genus Gloydius through paraspecificity, but this has not been tested in detail. There are several publications indicating that it may also have paraspecificity against some of the Southeast Asian green pit vipers from the genera *Cryptelytrops* and *Trimeresurus.*[196,197] However, it is not currently indicated by the manufacturer for these species.

- HEMOTOXIC AND/OR CYTOTOXIC: *Gloydius halys*

Initial dosing by syndrome:

- NOT INDICATED FOR NEUROTOXIC
- HEMOTOXIC initial dose = 2 vials
- CYTOTOXIC initial dose = 2 vials

Additional dosing: Additional doses of 2 vials SIOBP-G may be given at hours 2, 4, 6, 12, and 24 if needed.

Pretreatment: Not routinely indicated unless patient is unstable, asthmatic/atopic, known hypersensitivity or other pretreatment criteria met.

Preparation and administration: Dilute the entire dose of antivenom in a single 250 - 500 mL bag of isotonic solution and administer by intravenous infusion over 10 - 30 minutes.

SECOND LINE CENTCOM - Middle East/Central Asi): RAZI-P

Razi Serum and Vaccine Research Institute, Islamic Republic of Iran - Polyvalent Snake Antivenom (RAZI-P) (Liquid/refrigerated)[198-205]**:**

1. Not field stable. Broad-spectrum coverage 6+ species Cyto/Hemo/Neuro.
2. Unknown neurotoxic, hemotoxic, or cytotoxic envenomation with no indications of improvement after 10 vials of POLYSERP-M. Directly or indirectly covers all WHO category 1 species in the region. Directly or indirectly covers some of the WHO category 1 and category 2 snakes in this region for which an antivenom currently exists.

Feasibility of use in austere environments: Not recommended for operational settings. Requires cold chain refrigeration. Recommend storing small quantities at strategically located Role 2 & 3 facilities in CENTCOM AOR or selecting alternative second line from this CPG.

Adverse reactions: Limited evidence but appears to be low based on current publications.

Indications: This polyvalent can be used to treat neurotoxic and cytotoxic envenomations by 6 different species of Middle Eastern, North African, and Central Asian snakes. It may be able to neutralize venom from additional species through paraspecific neutralization, but this has not been researched. The 6 species listed below are the official treatment indications recommended by the manufacturer:

- NEUROTOXIC: *Naja oxiana*
- HEMOTOXIC and/or CYTOTOXIC: *Pseudocerastes persicus fieldi, Echis carinatus, Vipera albicornuta, Vipera lebetina obtusa, Agkistrodon (Gloydius) halys*

Pretreatment: Not routinely indicated unless patient is unstable, asthmatic/atopic, known hypersensitivity or other pretreatment criteria met.

Initial dosing by syndrome:

- NEUROTOXIC initial dose = 10 vials
- HEMOTOXIC initial dose = 5 vials
- CYTOTOXIC initial dose = 5 vials

Additional dosing: Additional doses of 5 vials RAZI-P may be given at hours 2, 4, 6, 12, and 24 if needed.

Preparation and administration: Dilute the entire dose of antivenom in a single 250 - 500 mL bag of isotonic solution and administer by intravenous infusion over 10 - 30 minutes.

SECOND LINE CENTCOM - Arabian Peninsula: NAVPC-C

National Antivenom & Vaccine Production Center, Saudi Arabia - Polyvalent Snake Antivenom (NAVPC-P) (Liquid/Refrigerated) [187-192] :

1. Not field stable. Broad-spectrum coverage 6+ species of Neuro/Hemo/Cyto.
2. Unknown neurotoxic, hemotoxic, or cytotoxic envenomation with no indications of improvement after 10 vials of POLYSERP-M. Only for Arabian Peninsula, very limited utility further East. Directly or indirectly covers some of the WHO category 1 and category 2 snakes in this region for which an antivenom currently exists.
3. Initial dose neuro = 10 vials. Initial dose hemo/cyto = 5 vials. All additional doses = 5 vials.

Feasibility of use in austere environments: Not recommended for operational settings. Requires refrigeration, moderate to high rates of adverse reactions are anticipated. Better alternatives exist. If purchased, it should be kept at Role 2 & 3 facilities in the Arabian Peninsula.

Adverse reactions: Insufficient evidence to determine risk of adverse reactions at this time.

Indications: This polyvalent can be used to treat neurotoxic and cytotoxic envenomations by 6 different species of Middle Eastern, North African, and Central Asian snakes. It may be able to neutralize venom from additional species through paraspecific neutralization, but this has not been researched. The 6 species listed below are the official treatment indications recommended by the manufacturer:

- NEUROTOXIC: *Walterinnesia aegyptia, Naja haje*
- HEMOTOXIC and/or CYTOTOXIC: *Bitis arietans, Echis coloratus, Echis carinatus, Cerastes cerastes*

Initial dosing by syndrome:

- NEUROTOXIC initial dose = 10 vials
- HEMOTOXIC initial dose = 5 vials
- CYTOTOXIC initial dose = 5 vials

Additional dosing: Additional doses of 5 vials NAVPC-C may be given at hours 2, 4, 6, 12, and 24 if needed.

Pretreatment: RECOMMENDED for this antivenom due to insufficient evidence for determining risk of EARs. Administer 0.25 mg epinephrine injected SQ prior to beginning antivenom infusion to reduce the risk of a serious reaction. Pediatric doses should be weight based at a dose of 0.01 mg/kg, up to 0.25 mg.

Preparation and administration: Dilute the entire dose of antivenom in a single 250 - 500 mL bag of isotonic solution and administer by intravenous infusion over 10 - 30 minutes.

EUCOM

Treatment Guidelines

Safe and effective broad-spectrum, refrigerated antivenoms are available for all three syndromes of snake envenomation due to European viper species in this AOR and treatment does not require identification of the species responsible. Snakebite treatment at the point of injury is not routinely recommended for EUCOM. This section provides specifics about antivenoms use in this region

ADVERSE REACTION MANAGEMENT

- If a mild or moderate reaction occurs, slow the infusion and treat symptomatically with antihistamines, steroids, and/or antiemetics as needed.
- If a severe reaction such as anaphylaxis occurs, stop the infusion and treat according to the anaphylaxis protocol listed elsewhere in the CPG. Reassess the patient once the reaction has been controlled and resume the infusion at a slower rate if any of the specific criteria for antivenom treatment listed elsewhere in the CPG have not completely resolved.

Sudden Collapse Syndrome Treatment Protocol

Patient presents within 30 minutes of the bite with rapid onset shock ± angioedema, altered mental status, systemic bleeding, and diarrhea.[1]

4. Stabilize with IM or IV epinephrine and fluids as per anaphylaxis protocols
5. Intubate for airway edema not rapidly responsive to epinephrine
6. Follow epinephrine immediately with a high dose of the appropriate regional antivenom given by rapid IV or IO push during the resuscitation
7. Maintain blood pressure with IV or IO fluids and epinephrine until antivenom has taken effect to reverse the hypotension.

See Sudden Collapse Syndrome section for more information.

CONTACT

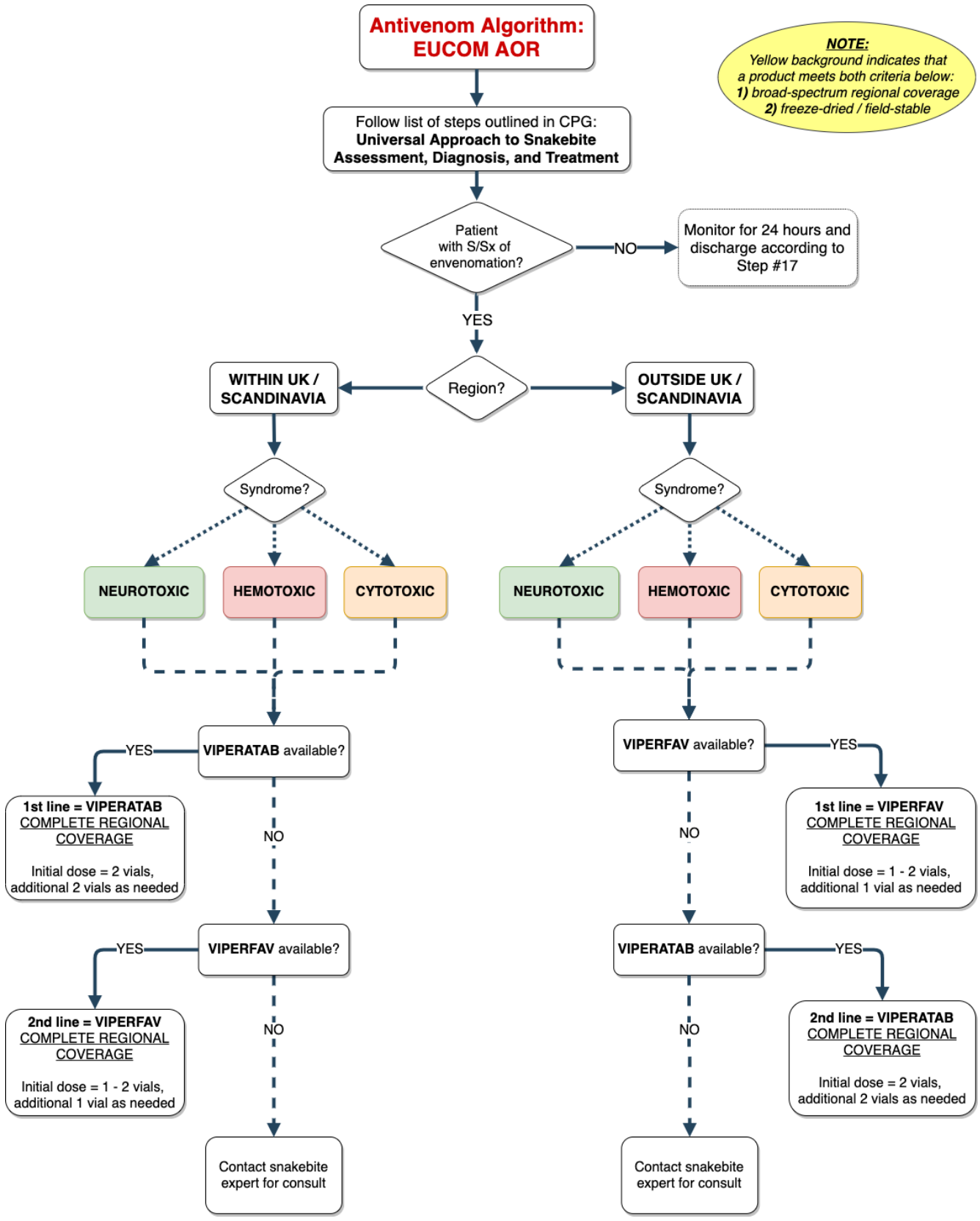
For emergency consultations, call the ADVISOR telemedicine hotline (866-972-9966) and select toxicology from the phone menu.

For additional information about snake bite management or this CPG, email jordan@snakebitefoundation.org or call 415-218-2211.

Table 6. EUCOM First Line Antivenoms

	Neurotoxic Syndrome	Hemotoxic Syndrome	Cytotoxic Syndrome
Mild	Local S/Sx (paresthesias; neuropathic pain; piloerection; muscle spasm, fasciculations)	Coagulopathy ± persistence of local bleeding from bite wound > 30 mins after bite	Severe pain; edema below elbow or knee; limited blistering within several inches of the bite wound
Moderate	Systemic S/Sx (bilateral ptosis GI symptoms; visual, auditory, or other sensory disturbances; widespread hyperesthesia)	Moderate systemic bleeding (old scabs, gingival bleeding, epistaxis, etc.); bruising distant from the bite wound	Edema above elbow or knee but not beyond shoulder or hip; moderate local blistering along bitten limb segment
Severe	Difficulty speaking; altered mental status; respiratory muscle weakness causing difficulty breathing; shock or otherwise unstable patient	Active GI bleed (usually hematemesis) or other internal bleeding; severe anemia; altered mental status; shock or otherwise unstable patient	Progressive edema beyond shoulder or hip; severe necrosis or widespread blistering; symptomatic bite to head, neck, or torso; altered mental status; shock or otherwise unstable patient
Criteria for additional AV doses at hours 2, 4, 6, 12, 24 (as needed)	*Additional doses if:* *persistence or worsening of systemic neurotoxic S/Sx. Continue to re-administer 2 vial boluses as needed at hours 2, 4, 6, 12, and 24 until signs of improvement begin to appear* (↑SBC, ↑LOC, ↑strength, etc.)	*Additional doses if:* *persistence, resumption, or new onset of any active external or internal bleeding* ***OR*** *S/Sx of active venom confirmed by secondary recurrence of abnormal WBCT*	*Additional doses if:* *significant increase in edema (such as beyond major joint)* ***OR*** *significant increase in pain (severity of pain and/or how far pain radiates up the bitten limb)*
EUCOM 1st Line Antivenoms	UK or Scandinavia**:** Broad-spectrum coverage all neurotoxic/hemotoxic/cytotoxic syndromes from European Vipera species - VIPERATAB (1st line): Initial dose = 2 vials (one box), additional doses = 1 – 2 vials as needed - VIPERFAV (2nd line): Initial dose = 1 – 2 vials, additional doses = 1 vial as needed Outside UK/Scandinavia: Broad-spectrum coverage all neurotoxic/hemotoxic/cytotoxic syndromes from European Vipera species - VIPERFAV (1st line): Initial dose = 1 – 2 vials, additional doses = 1 vial as needed - VIPERATAB (2nd line): Initial dose = 2 vials (one box), additional doses = 1 – 2 vials as needed		
Antivenom Abbreviations	**VIPERFAV =** VIPERFAV **VIPERATAB** = ViperaTAb		

Figure 4. Antivenom Algorithm: EUCOM AOR



FIRST LINE EUCOM - Outside UK/Scandinavia: VIPERFAV

SECOND LINE EUCOM - Inside UK/Scandinavia: VIPERFAV

Sanofi-Pasteur, France - Viperfav (VIPERFAV) (Freeze dried/Refrigerated) [206-212]:

1. Not field-stable. Broad-spectrum coverage against multiple European vipers.
2. **First line treatment option (EUCOM - EUCOM OUTSIDE UK / SCANDINAVIA)**: Single-source treatment option for neurotoxic, hemotoxic, and cytotoxic snake envenomations by the most medically and epidemiologically significant species in Europe (*Vipera berus, V. aspis, V. ammodytes*) with paraspecific coverage against other European Vipera species. Can be used in the EUCOM AOR when the causative species is unknown or species for which this product is directly indicated.
3. **Second line treatment option (EUCOM - UK / SCANDINAVIA)** for all neurotoxic, hemotoxic, and cytotoxic snake envenomations within the UK and Scandinavia if first line (VIPERATAB) is not available.
4. Initial dose = 1 – 2 vials all syndromes, additional doses = 1 vial as needed.

Feasibility of use in austere environments: Not recommended for operational settings. Requires cold chain refrigeration between 2 - 8 ºC (35.6 - 46.4 ºF). Recommend storing several vials at a small number of strategically located Role 2 & 3 facilities. Likely to retain efficacy for several weeks in the field but should be disposed of after that duration of time outside refrigeration.

Adverse reactions: High efficacy against all major syndromes and low incidence of serious adverse reactions based on current publications.

Indications: Polyvalent antivenom directly indicated for the treatment of neurotoxic, hemotoxic, and cytotoxic envenomation syndromes caused by *Vipera berus, V. aspis, V. ammodytes* but has demonstrated efficacy against other species of European vipers (genus Vipera) as well.

Pretreatment: Not routinely indicated unless patient is unstable, asthmatic/atopic, known hypersensitivity or other pretreatment criteria met. Low risk of severe allergic reactions and other EARs.

Initial dosing by syndrome:

- NEUROTOXIC initial dose = 2 vials
- HEMOTOXIC initial dose = 1 - 2 vials
- CYTOTOXIC initial dose = 1 - 2 vials

Additional dosing: Additional doses of 1 vial VIPERFAV may be given at hours 2, 4, 6, 12, and 24 if needed.

Preparation and administration: Dilute the entire dose of antivenom in a single 250 - 500 mL bag of isotonic solution and administer by intravenous infusion over 10 - 30 minutes.

FIRST LINE EUCOM – Inside UK/Scandinavia: VIPERATAB

SECOND LINE EUCOM – Outside UK/Scandinavia: VIPERATAB

Micropharm, UK - ViperaTAb (VIPERATAB) (Freeze dried/Refrigerated) [206,210,213–215]:

1. Not field stable. Broad-spectrum coverage against several European vipers.
2. **First line (EUCOM - UK / SCANDINAVIA):-**Single-source treatment option for neurotoxic, hemotoxic, and cytotoxic snake envenomations by the most medically and epidemiologically significant species in the UK and Scandinavia (Vipera berus) with paraspecific coverage against some other European Vipera species.
3. **Second line treatment option (EUCOM - OUTSIDE OF UK / SCANDINAVIA)** for all neurotoxic, hemotoxic, and cytotoxic snake envenomations in the EUCOM AOR outside of the UK and Scandinavia if first line (VIPERFAV) is not available.
4. Initial dose = 2 vials all syndromes, additional doses = 2 vials as needed. Each box = 2 vials.

Feasibility of use in austere environments: Not recommended for operational settings. Requires cold chain refrigeration between 2 - 8 ºC (35.6 - 46.4 ºF). Recommend storing several vials at a small number of strategically located Role 2 & 3 facilities. Likely to retain efficacy for several weeks in the field but should be disposed of after that duration of time outside refrigeration.

Adverse reactions: High efficacy against UK / Scandinavian European viper (*Vipera berus*) envenomations and low incidence of serious adverse reactions based on current publications.

Indications: Polyvalent antivenom directly indicated for the treatment of neurotoxic, hemotoxic, and cytotoxic envenomation syndromes caused by *Vipera berus*. Has demonstrated efficacy against other species of European vipers (*V. aspis, V. ammodytes*) as well but is not directly indicated for these species.

Pretreatment: Not routinely indicated unless patient is unstable, asthmatic/atopic, known hypersensitivity or other pretreatment criteria met. Low risk of severe allergic reactions and other EARs.

Initial dosing by syndrome:

- NEUROTOXIC initial dose = 2 vials
- HEMOTOXIC initial dose = 2 vials
- CYTOTOXIC initial dose = 2 vials

Additional dosing: Additional 2 vials VIPERATAB may be given at hours 2, 4, 6, 12, and 24 if needed.

Preparation and administration: Each box of VIPERATAB comes with two 4 mL vials of antivenom (one box = one dose). Dilute the entire dose of antivenom in a single 100 - 500 mL bag of isotonic solution and administer by intravenous infusion over 10 - 30 minutes.

INDOPACOM
Treatment Guidelines

Safe and effective broad-spectrum, field-stable antivenoms are available for all three syndromes of snake envenomation in Southeast Asia and several other areas within this AOR. Snakebite treatment in INDOPACOM as a whole is more complex than AFRICOM or CENTCOM due to the lack of a truly pan-Asian polyvalent product. Treatment in many places does not require identification of the species responsible, but products are syndrome specific and there is no single product for all 3 syndromes. Snakebite treatment at the point of injury is recommended for areas within the INDOPACOM AOR where field-stable antivenoms are available. This section provides specifics about antivenoms use in this region.

ADVERSE REACTION MANAGEMENT

- If a mild or moderate reaction occurs, slow the infusion and treat symptomatically with antihistamines, steroids, and/or antiemetics as needed.
- If a severe reaction such as anaphylaxis occurs, stop the infusion, and treat according to the anaphylaxis protocol listed elsewhere in the CPG. Reassess the patient once the reaction has been controlled and resume the infusion at a slower rate if any of the specific criteria for antivenom treatment listed elsewhere in the CPG have not completely resolved.

Sudden Collapse Syndrome Treatment Protocol

Patient presents within 30 minutes of the bite with rapid onset shock ± angioedema, altered mental status, systemic bleeding, and diarrhea.[1]

1. Stabilize with IM or IV epinephrine and fluids as per anaphylaxis protocols
2. Intubate for airway edema not rapidly responsive to epinephrine
3. Follow epinephrine immediately with a high dose of the appropriate regional antivenom given by rapid IV or IO push during the resuscitation
4. Maintain blood pressure with IV or IO fluids and epinephrine until antivenom has taken effect to reverse the hypotension.

See Sudden Collapse Syndrome section for more information.

CONTACT

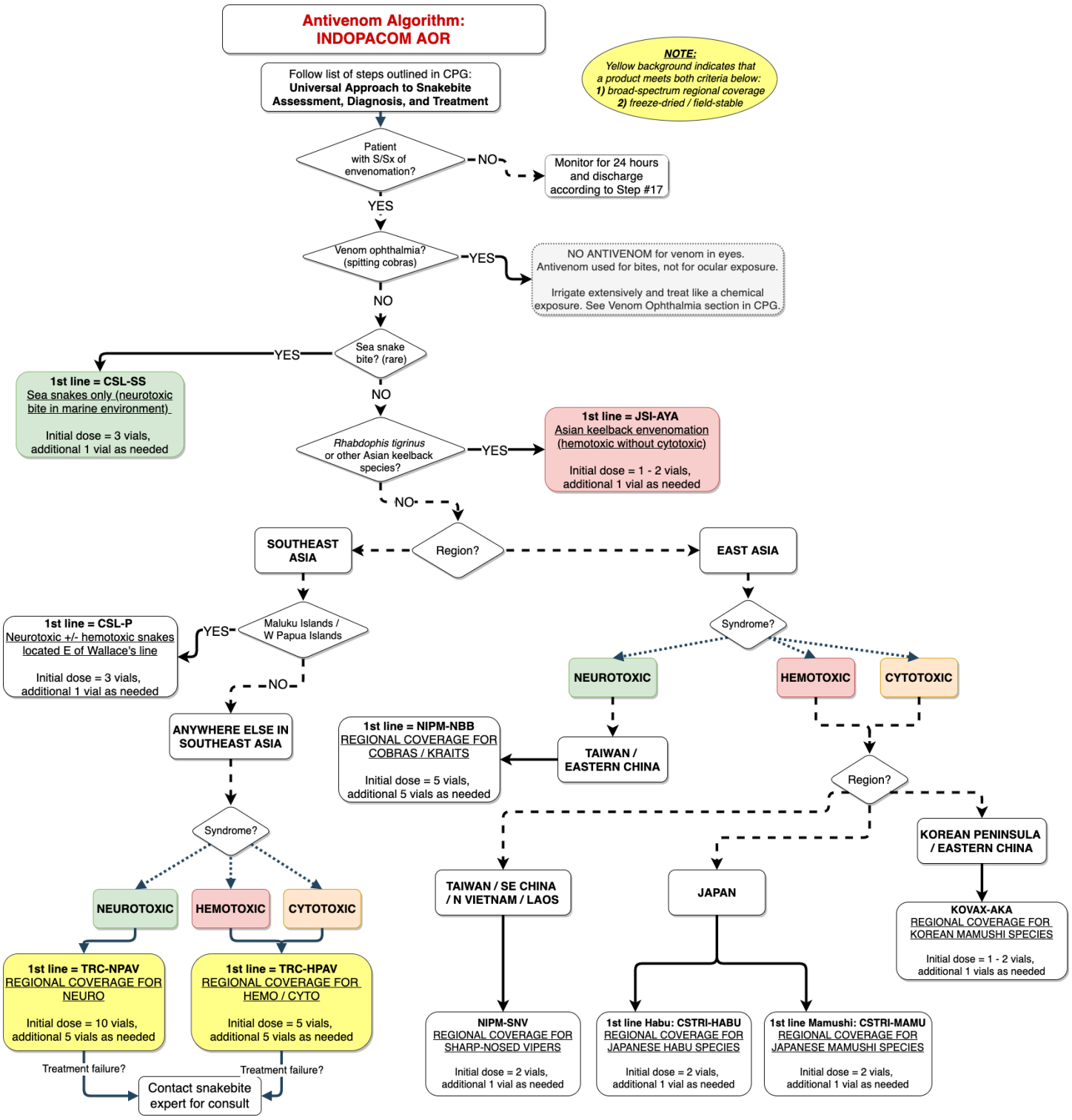
For emergency consultations, call the ADVISOR telemedicine hotline (866-972-9966) and select toxicology from the phone menu.

For additional information about snake bite management or this CPG, email jordan@snakebitefoundation.org or call 415-218-2211.

Table 7. Indo-Pacific Command –First Line Antivenoms

	Neurotoxic Syndrome	Hemotoxic Syndrome	Cytotoxic Syndrome
Mild	Local S/Sx (paresthesias; neuropathic pain; piloerection; muscle spasm, fasciculations)	Coagulopathy ± persistence of local bleeding from bite wound > 30 mins after bite	Severe pain; edema below elbow or knee; limited blistering within several inches of the bite wound
Moderate	Systemic S/Sx (bilateral ptosis GI symptoms; visual, auditory, or other sensory disturbances; widespread hyperesthesia)	Moderate systemic bleeding (old scabs, gingival bleeding, epistaxis, etc); bruising distant from the bite wound	Edema above elbow or knee but not beyond shoulder or hip; moderate local blistering along bitten limb segment
Severe	Difficulty speaking; altered mental status; respiratory muscle weakness causing difficulty breathing; shock or otherwise unstable patient	Active GI bleed (usually hematemesis) or other internal bleeding; severe anemia; altered mental status; shock or otherwise unstable patient	Progressive edema beyond shoulder or hip; severe necrosis or widespread blistering; symptomatic bite to head, neck, or torso; altered mental status; shock or otherwise unstable patient
Criteria for additional AV doses at hours 2, 4, 6, 12, 24 (as needed)	*Additional doses if: persistence or worsening of systemic neurotoxic S/Sx. Continue to re-administer 2 vial boluses as needed at hours 2, 4, 6, 12, and 24 until signs of improvement begin to appear* (↑SBC, ↑LOC, ↑strength, etc.	*Additional doses if: persistence, resumption, or new onset of any active external or internal bleeding OR S/Sx of active venom confirmed by secondary recurrence of abnormal WBCT*	*Additional doses if: significant increase in edema (such as beyond major joint) OR significant increase in pain (severity of pain and/or how far pain radiates up the bitten limb)*
INDOPACOM 1st Line Antivenoms	Southeast Asia: Broad-spectrum for all neurotoxic - *TRC-NPAV: Initial dose 10 vials* - *Additional doses = 5 vials as needed* TRC-NPAV is the 1st line for all neurotoxic bites in SE Asia outside of the circumstances listed below: Marine environments: Sea snake envenomations - *CSL-SS: Initial dose = 3 vials* - *Additional doses = 1 vial as needed* Maluku/West Papua islands: Neurotoxic - *CSL-P: Initial dose = 3 vials* - *Additional doses = 1 vial as needed* Eastern China/Taiwan: Neurotoxic - *NIPM-NBB: Initial dose = 5 vials* - *Additional doses = 5 vials as needed*	Southeast Asia: Broad-spectrum for all hemotoxic/cytotoxic (1st line in SE Asia) - TRC-HPAV: Initial dose = 10 vials, additional doses = 2 vials as needed. TRC-HPAV is the 1st line for all hemotoxic/cytotoxic bites in SE Asia outside of circumstances listed below: Korean Peninsula/Eastern China: Viper envenomations (Cytotoxic +/- Hemotoxic) Korean Mamushi species (Gloydius brevicaudus, G. ussuriensis, G. intermedius) - KOVAX-AKA: Initial dose = 1 - 2 vials, additional doses = 1 vial as needed Taiwan/Se China/N Vietnam/Laos: Sharp-nosed viper (Deinagkistrodon acutus) - NIPB-SNV: Initial dose = 2 vials, additional doses = 1 vial as needed Japan: Viper envenomations (Cytotoxic +/- Hemotoxic) If Japanese Habu (Protobothrops spp.) envenomation: - CSTRI-HABU: Initial dose = 1 -2 vials, additional doses = 1 vial as needed If Japanese Mamushi (Gloydius blomhoffi) envenomation: - CSTRI-MAMU: Initial dose = 1 -2 vials, additional doses = 1 vial as needed Japan/China/N & S Korea Vietnam/E Russia: Rhabdophis spp. - Hemotoxic without Cytotoxic Spontaneous bleeding develops within several days of bite without cytotoxicity. - JSI-AYA: Initial dose = 1 -2 vials, additional doses = 1 vial as needed	
Antivenom Abbreviations	**TRC-NPAV** = Neuro Polyvalent Antivenom **CSL-P** = CSL Polyvalent **CSL-SS** = CSL Sea Snake **NIPM-NBB** = Naja atra - Bungarus multicinctus Bivalent	**TRC-HPAV** = Hemato Polyvalent Antivenom **KOVAX-AKA** = Agkistrodon Mamushi Antivenom **JSI-AYA** = Anti-Yamakagashi Antivenom **CSTRI-HABU** = Kaketsuken Habu Antivenom **CSTRI-MAMU** = Kaketsuken Mamushi Antivenom **NIPM-SNV** = Sharp-nosed Viper Monovalent	

Figure 5. Antivenom Algorithm: INDOPACOM AOR



FIRST LINE INDOPACOM - Southeast Asia: TRC-HPAV

Thai Red Cross, Thailand - Hemato Polyvalent Antivenom (TRC-HPAV) (Freeze dried/Unrefrigerated) [62,196, 197, 216–218]:

1. Field-stable. Broad-spectrum coverage multiple species of Hemo/Cyto.
2. Broad-spectrum treatment option for all hemotoxic and cytotoxic snake envenomations by known or unknown species in Southeast Asia. Best regional polyvalent.
3. Initial dose hemotoxic/cytotoxic only = 10 vials, additional doses = 5 vials as needed.

Feasibility of use in austere environments: Recommended for operational settings. Unrefrigerated storage at ambient tropical temperatures of ≤ 25º C / 77º F. Lyophilized product that likely retains stability at higher temperatures for short excursions (likely up to several months). Recommend carrying full dose into field on extended operations in austere environments and storing larger quantities at strategically located Role 2 & 3 facilities in INDOPACOM AOR.

Adverse reactions: High efficacy against and low incidence of serious adverse reactions based on current publications.

Indications: Polyvalent antivenom directly indicated for the treatment of hemotoxic and cytotoxic envenomation syndromes caused by *Calloselasma rhodostoma, Trimersurus albolabris*, and *Daboia russelli siamensis.* Has demonstrated efficacy against other related species of Asian vipers within the same genera (Crytelytrops, Popeia, Daboia, etc.); is not directly indicated for these species but is the best hemotoxic / cytotoxic polyvalent in the region and should be tried as first line in most cases.

Pretreatment: Not routinely indicated unless patient is unstable, asthmatic/atopic, known hypersensitivity or other pretreatment criteria met. Low risk of severe allergic reactions and other EARs.

Initial dosing by syndrome:

- NOT INDICATED FOR NEUROTOXIC
- HEMOTOXIC initial dose = 10 vials
- CYTOTOXIC initial dose = 10 vials

Additional dosing: Additional 2 vials TRC-HPAV may be given at hours 2, 4, 6, 12, and 24 if needed.

Preparation and administration: Dilute the entire dose of antivenom in a single 250 - 500 mL bag of isotonic solution and administer by intravenous infusion over 10 - 30 minutes.

FIRST LINE INDOPACOM - Southeast Asia Broad Spectrum Neurotoxic: TRC-NPAV

Thai Red Cross, Thailand - Neuro Polyvalent Antivenom (TRC-NPAV) (Freeze dried/Unrefrigerated) [62,196,217,219–221,]:

1. Field-stable. Broad-spectrum coverage multiple species of Neuro.
2. Broad-spectrum treatment option for all neurotoxic snake envenomations by known or unknown species in Southeast Asia. Best regional polyvalent.
3. Initial dose = 10 vials neurotoxic only, additional doses = 5 vials as needed.

Feasibility of use in austere environments: Recommended for operational settings. Unrefrigerated storage at ambient tropical temperatures of ≤ 25º C / 77º F. Lyophilized product that likely retains stability at higher temperatures for field excursions (likely stable for several months at higher temps based on data from similar

products). Recommend carrying full dose into field on extended operations in austere environments and storing larger quantities at strategically located Role 2 & 3 facilities in INDOPACOM AOR.

Adverse reactions: High efficacy and low incidence of serious adverse reactions based on current publications.

Indications: Polyvalent antivenom directly indicated for the treatment of hemotoxic and cytotoxic envenomation syndromes caused by *Ophiophagus hannah, Naja kaouthia, Bungarus candidus,* and *B. fasciatus candidus*. Has demonstrated efficacy against other related species of Asian cobras and kraits; is not directly indicated for these species but is the best hemotoxic / cytotoxic polyvalent in the region and should be tried as the first line in most cases.

Pretreatment: Not routinely indicated unless patient is unstable, asthmatic/atopic, known hypersensitivity or other pretreatment criteria met. Low risk of severe allergic reactions and other EARs.

Initial dosing by syndrome:

- NEUROTOXIC initial dose = 10 vials
  ***NOTE**: King cobra (O. hannah) bites likely to require much higher doses of antivenom due to massive venom yield; it is not unusual to require dozens of vials in these cases.*
- NOT INDICATED FOR HEMOTOXIC
- NOT INDICATED FOR CYTOTOXIC

Additional dosing: Additional 5 vials TRC-NPAV may be given at hours 2, 4, 6, 12, and 24 if needed. Bites from large king cobras may require several dozen vials or more due to massive venom yield.

Preparation and administration: Dilute the entire dose of antivenom in a single 250 - 500 mL bag of isotonic solution and administer by intravenous infusion over 10 - 30 minutes.

FIRST LINE INDOPACOM – Taiwan/Southeast China/N Laos/N Vietnam: NIPM-NBB

National Institute Preventative Medicine, Taiwan - *Naja atra* / *Bungarus multicinctus* Bivalent (NIPM-NBB) (Freeze dried/Refrigerated) [222–230]:

1. Liquid product but field-stable for short excursions. Broad-spectrum coverage multiple species of Neuro.
2. Bivalent treatment option for neurotoxic cobra and krait envenomations in East Asia.
3. Initial dose = 5 vials neurotoxic only, additional doses = 5 vials as needed.

Feasibility of use in austere environments: Conditionally recommended for operational settings during short excursions. Lyophilized but requires cold chain refrigeration below 10ºC (50 ºF); however, testing by Taiwanese CDC showed no loss of potency after 30 days of incubation at 35º C / 95º F and also after it was returned to refrigerated storage for 4 months thereafter. Recommend carrying full dose into field on extended operations in austere environments and storing larger quantities at regional Role 2 & 3 facilities.

Adverse reactions: High efficacy and low incidence of serious adverse reactions based on current publications.

Indications: Polyvalent antivenom directly indicated for the treatment of hemotoxic and cytotoxic envenomation syndromes caused by *Naja atra* and *Bungarus multicinctus.* Has demonstrated efficacy against other related species of Asian cobras and kraits but is not directly indicated for these species.

Pretreatment: Not routinely indicated unless patient is unstable, asthmatic/atopic, known hypersensitivity or other pretreatment criteria met. Low risk of severe allergic reactions and other EARs.

Initial dosing by syndrome:

- NEUROTOXIC initial dose = 5 vials
- NOT INDICATED FOR HEMOTOXIC
- NOT INDICATED FOR CYTOTOXIC

Additional dosing: Additional 5 vials NIPM-NBB may be given at hours 2, 4, 6, 12, and 24 if needed.

Preparation and administration: Dilute the entire dose of antivenom in a single 100 – 500 mL bag of isotonic solution and administer by intravenous infusion over 10 – 30 minutes.

FIRST LINE INDOPACOM - Japan: CSTRI-HABU

Chemo-Sero Therapeutic Research Institute, Japan - Kaketsuken Habu Antivenom (CSTRI-HABU)
(Freeze dried/Refrigerated) [231–235]:

1. Not field-stable. Not broad-spectrum. Habu coverage only.
2. First line treatment option for Habu envenomation (Protobothrops spp.).
3. Initial dose = 1 – 2 vials, additional doses = 1 vial as needed

Feasibility of use in austere environments: Not recommended for operational settings. Lyophilized but requires cold chain refrigeration below 10ºC (50 ºF); likely to retain efficacy for short excursions lasting several weeks in the field but should be disposed of and replaced after extended time outside refrigeration. Recommend storing several vials at a small number of strategically located Role 2 & 3 facilities.

Adverse reactions: High efficacy and low incidence of serious adverse reactions based on current publications.

Indications: Directly indicated for the treatment of hemotoxic and cytotoxic envenomation syndromes caused by the Japanese Habu (*Protobothrops [Trimeresurus] flavoviridis*)

Pretreatment: Not routinely Indicated unless patient is unstable, asthmatic/atopic, known hypersensitivity or other pretreatment criteria met; however, total reactions (~11% overall; ~25% serum sickness) higher than other regional products. Consider pretreatment on an individual basis.

Initial dosing by syndrome:

- NOT INDICATED FOR NEUROTOXIC
- HEMOTOXIC = 1 - 2 vials
- CYTOTOXIC = 1 - 2 vials

Additional dosing: Additional 1 vial CSTRI-HABU may be given at hours 2, 4, 6, 12, and 24 if needed.

Preparation and administration: Dilute the entire dose of antivenom in a single 250 - 500 mL bag of isotonic solution and administer by intravenous infusion over 10 - 30 minutes.

FIRST LINE INDOPACOM - Japan: CSTRI-MAMU

Chemo-Sero Therapeutic Research Institute, Japan - Kaketsuken Mamushi Antivenom (CSTRI-MAMU)
(Freeze dried/Refrigerated) [231–235]:

1. Not field stable. Not broad-spectrum. Japanese Mamushi coverage only.
2. First line treatment option for hemotoxic and cytotoxic envenomation syndromes caused by the Japanese Mamushi (*Gloydius blomhoffi*).

3. Initial dose = 1 – 2 vials, additional doses = 1 vial as needed

Feasibility of use in austere environments: Not recommended for operational settings. Lyophilized but requires cold chain refrigeration below 10ºC (50 ºF); likely to retain efficacy for short excursions lasting several weeks in the field but should be disposed of and replaced after extended time outside refrigeration. Recommend storing several vials at a small number of strategically located Role 2 & 3 facilities.

Adverse reactions: High efficacy and low incidence of serious adverse reactions based on current publications.

Indications: Directly indicated for the treatment of hemotoxic and cytotoxic envenomation syndromes caused by the Japanese Mamushi, *Gloydius blomhoffi*.

Pretreatment: Not routinely indicated unless patient is unstable, asthmatic/atopic, known hypersensitivity or other pretreatment criteria met. Low risk of severe allergic reactions and other EARs.

Initial dosing by syndrome:

- NOT INDICATED FOR NEUROTOXIC
- HEMOTOXIC = 1 - 2 vials
- CYTOTOXIC = 1 - 2 vials

Additional dosing: Additional 1 vial CSTRI-MAMU may be given at hours 2, 4, 6, 12, and 24 if needed.

Preparation and administration: Dilute the entire dose of antivenom in a single 250 - 500 mL bag of isotonic solution and administer by intravenous infusion over 10 - 30 minutes.

FIRST LINE (INDOPACOM – Japan/China/N Korea/S Korea/Vietnam/E Russia): JSI-AYA

Japan Snake Institute, Japan - Anti-Yamakagashi Antivenom (JSI-AYA) (Freeze dried/Refrigerated) [231–233]:

1. Not field stable. Not broad-spectrum. Keelback coverage only.
2. First line treatment option for hemotoxic and cytotoxic envenomation syndromes caused by the Tiger Keelback (*Rhabdophis tigrinus*) and other East Asian keelback species.
3. Initial dose = 1 – 2 vials, additional doses = 1 vial as needed

Feasibility of use in austere environments: Not recommended for operational settings. Lyophilized but requires cold chain refrigeration below 10ºC (50 ºF); likely to retain efficacy for short excursions lasting several weeks in the field but should be disposed of and replaced after extended time outside refrigeration. Recommend storing several vials at a small number of strategically located Role 2 & 3 facilities.

Adverse reactions: High efficacy and low incidence of serious adverse reactions based on current publications.

Indications: Directly indicated for the treatment of hemotoxic and cytotoxic envenomation syndromes caused by the Tiger Keelback (*Rhabdophis tigrinus*) and other East Asian keelbacks.

Pretreatment: Not routinely indicated unless patient is unstable, asthmatic/atopic, known hypersensitivity or other pretreatment criteria met. Low risk of severe allergic reactions and other EARs.

Initial dosing by syndrome:

- NOT INDICATED FOR NEUROTOXIC
- HEMOTOXIC = 1 - 2 vials
- CYTOTOXIC = 1 - 2 vials

Additional dosing: Additional 1 vial JSI-AYA may be given at hours 2, 4, 6, 12, and 24 if needed.

Preparation and administration: Dilute the entire dose of antivenom in a single 250 - 500 mL bag of isotonic solution and administer by intravenous infusion over 10 - 30 minutes.

FIRST LINE (INDOPACOM - N Korea/S Korea/E. China): KOVAX-AKA

Korea Vaccine, Korea - Agkistrodon Mamushi Antivenom (KOVAX-AKA) (Freeze dried/Refrigerated) [234–240]:

1. Not field stable. Not broad-spectrum. Korean Mamushi coverage only.
2. First line treatment option of hemotoxic and cytotoxic envenomation syndromes caused by the major species of Mamushi in the Korean Peninsula (*Gloydius brevicaudus, G. ussuriensis, G. intermedius*). May neutralize other related species.
3. Initial dose = 1 – 2 vials, additional doses = 1 vial as needed

Feasibility of use in austere environments: Not recommended for operational settings. Lyophilized but requires cold chain refrigeration below 10ºC (50 ºF); likely to retain efficacy for short excursions lasting several weeks in the field but should be disposed of and replaced after extended time outside refrigeration. Recommend storing several vials at a small number of strategically located Role 2 & 3 facilities.

Adverse reactions: High efficacy and low incidence of serious adverse reactions based on current publications.

Indications: Directly indicated for the treatment of hemotoxic and cytotoxic envenomation syndromes caused by the major species of Mamushi in the Korean Peninsula (*Gloydius brevicaudus, G. ussuriensis, G. intermedius*). May neutralize other related species.

Pretreatment: Not routinely indicated unless patient is unstable, asthmatic/atopic, known hypersensitivity or other pretreatment criteria met. Low risk of severe allergic reactions and other EARs.

Initial dosing by syndrome:

- NOT INDICATED FOR NEUROTOXIC
- HEMOTOXIC = 1 - 2 vials
- CYTOTOXIC = 1 - 2 vials

Additional dosing: Additional 1 vial KOVAX-AKA may be given at hours 2, 4, 6, 12, and 24 if needed.

Preparation and administration: Dilute the entire dose of antivenom in a single 250 - 500 mL bag of isotonic solution and administer by intravenous infusion over 10 - 30 minutes.

FIRST LINE (INDOPACOM - Taiwan/SE China/N Vietnam/Laos): NIPM-SNV

National Institute Preventative Medicine, Taiwan - Sharp-nosed Viper Monovalent (NIPM-SNV) (Freeze dried/Refrigerated) [223,235–240:]

1. Freeze-dried product requiring cold chain but likely to be field-stable for short excursions. Not broad-spectrum. Sharp-nosed viper only.
2. First line monovalent antivenom directly indicated for the treatment of hemotoxic and cytotoxic envenomation syndromes caused by the sharp-nosed viper (*Deinagkistrodon acutus*).
3. Initial dose = 2 vials, additional doses = 1 vial as needed

Feasibility of use in austere environments: Conditionally recommended for operational settings during short excursions. Lyophilized but requires cold chain refrigeration below 10ºC (50 ºF); however, testing by Taiwanese

CDC showed no loss of potency after 30 days of incubation at 35º C / 95º F and also after it was returned to refrigerated storage for 4 months thereafter. Recommend carrying full dose into field on extended operations in austere environments and storing larger quantities at regional Role 2 and 3 facilities.

Adverse reactions: High efficacy and low incidence of serious adverse reactions based on current publications.

Indications: Monovalent antivenom directly indicated for the treatment of hemotoxic and cytotoxic envenomation syndromes caused by *Deinagkistrodon acutus*.

Pretreatment: Not routinely indicated unless patient is unstable, asthmatic/atopic, known hypersensitivity or other pretreatment criteria met. Low risk of severe allergic reactions and other EARs.

Initial dosing by syndrome:

- NOT INDICATED FOR NEUROTOXIC
- HEMOTOXIC initial dose = 2 vials
- CYTOTOXIC initial dose = 2 vials

Additional dosing: Additional 1 vials NIPM-SNV may be given at hours 2, 4, 6, 12, and 24 if needed.

Preparation and administration: Dilute the entire dose of antivenom in a single 250 - 500 mL bag of isotonic solution and administer by intravenous infusion over 10 - 30 minutes.

FIRST LINE (INDOPACOM – Marine Environments Only): CSL-SS

Commonwealth Serum Laboratories, Australia - Sea Snake (CSL-SS) (Liquid/Refrigerated) [231-245] :

1. Not field stable. Broad-spectrum coverage against Indo-Pacific sea snakes only.
2. Neurotoxic envenomation in INDOPACOM by sea snakes or unknown species occurring in a strictly marine environment.
3. Initial dose = 3 vials, additional doses = 1 vial as needed

Feasibility of use in austere environments: Not recommended for operational settings. Requires cold chain refrigeration between 2 - 8 ºC (35.6 - 46.4 ºF). Recommend storing several vials at a small number of strategically located Role 2 & 3 facilities. Likely to retain efficacy for several weeks in the field but should be disposed of after that duration of time outside refrigeration.

Adverse reactions: High-quality product with low rates of reactions anticipated.

Indications: This polyvalent can be used to treat neurotoxic envenomations by most major species of sea snakes in Australasia.

Initial dosing by syndrome:

- NEUROTOXIC syndrome initial dose = 3 vials
- NOT INDICATED for hemotoxic envenomations
- NOT INDICATED for cytotoxic envenomations

Additional dosing: Additional doses of 1 vials CSL-SS may be given at hours 2, 4, 6, 12, and 24 if needed.

Pretreatment: Not routinely indicated unless patient is unstable, asthmatic/atopic, known hypersensitivity or other pretreatment criteria met. Low risk of severe allergic reactions and other EARs.

Preparation and administration: Dilute the entire dose of antivenom in a single 250 - 500 mL bag of isotonic solution and administer by intravenous infusion over 10 - 30 minutes.

FIRST LINE (INDOPACOM – Maluku/West Papua Islands only): CSL-P

Commonwealth Serum Laboratories, Australia - Polyvalent (CSL-P) (Liquid/Refrigerated) [61, 241, 245-248]:

1. Not field stable. Broad-spectrum coverage.
2. First line antivenom indicated for neurotoxic/hemotoxic envenomation in INDOPACOM by Australasian elapids or unknown species occurring East of Wallace's line.
3. Initial dose = 3 vials, additional doses = 1 vial as needed

Feasibility of use in austere environments: Not recommended for operational settings. Requires cold chain refrigeration between 2 - 8 ºC (35.6 - 46.4 ºF). Recommend storing several vials at a small number of strategically located Role 2 & 3 facilities. Likely to retain efficacy during short excursion at higher temperatures for several weeks in the field but should be disposed of and replaced afterwards.

Adverse reactions: High-quality product with low rates of reactions anticipated.

Indications: This polyvalent can be used to treat neurotoxic envenomations by the most medically significant species of Australasian elapid snakes found East of Wallace's line.

Initial dosing by syndrome:

- NEUROTOXIC syndrome initial dose = 3 vials
- HEMOTOXIC syndrome initial dose = 3 vials
- NOT INDICATED FOR CYTOTOXIC ENVENOMATIONS

Additional dosing: Additional doses of 1 vials CSL-P may be given at hours 2, 4, 6, 12, and 24 if needed.

Pretreatment: Not routinely indicated unless patient is unstable, asthmatic/atopic, known hypersensitivity or other pretreatment criteria met. Low risk of severe allergic reactions and other EARs.

Preparation and administration: Dilute the entire dose of antivenom in a single 250 - 500 mL bag of isotonic solution and administer by intravenous infusion over 10 - 30 minutes.

NORTHCOM
Treatment Guidelines

Safe and effective antivenoms are available for all neurotoxic/hemo/cytotoxic pit viper envenomations and for neurotoxic coral snake envenomations in this AOR. Treatment does not require identification of the species responsible. Snakebite treatment at the point of injury is not routinely recommended for NORTHCOM.

For all NORTHCOM antivenoms, refer to the package insert in the antivenom box for specific usage instructions as per FDA regulations for domestically approved products. Also see Unified treatment algorithm for the management of crotaline snakebite in the U.S. (Lavonas et al. 2011) for dosing and management guidelines on pit viper bites.[101] This section provides specifics about antivenoms use in this region.

Adverse Reaction Management

- If a mild or moderate reaction occurs, slow the infusion, and treat symptomatically with antihistamines, steroids, and/or antiemetics as needed.
- If a severe reaction such as anaphylaxis occurs, stop the infusion, and treat according to the anaphylaxis protocol listed elsewhere in the CPG. Reassess the patient once the reaction has been controlled and resume the infusion at a slower rate if any of the specific criteria for antivenom treatment listed elsewhere in the CPG have not completely resolved.

Sudden Collapse Syndrome Treatment Protocol

Patient presents within 30 minutes of the bite with rapid onset shock ± angioedema, altered mental status, systemic bleeding, and diarrhea.[1]

1. Stabilize with IM or IV epinephrine and fluids as per anaphylaxis protocols
2. Intubate for airway edema not rapidly responsive to epinephrine
3. Follow epinephrine immediately with a high dose of the appropriate regional antivenom given by rapid IV or IO push during the resuscitation
4. Maintain blood pressure with IV or IO fluids and epinephrine until antivenom has taken effect to reverse the hypotension.

See Sudden Collapse Syndrome section for more information.

CONTACT

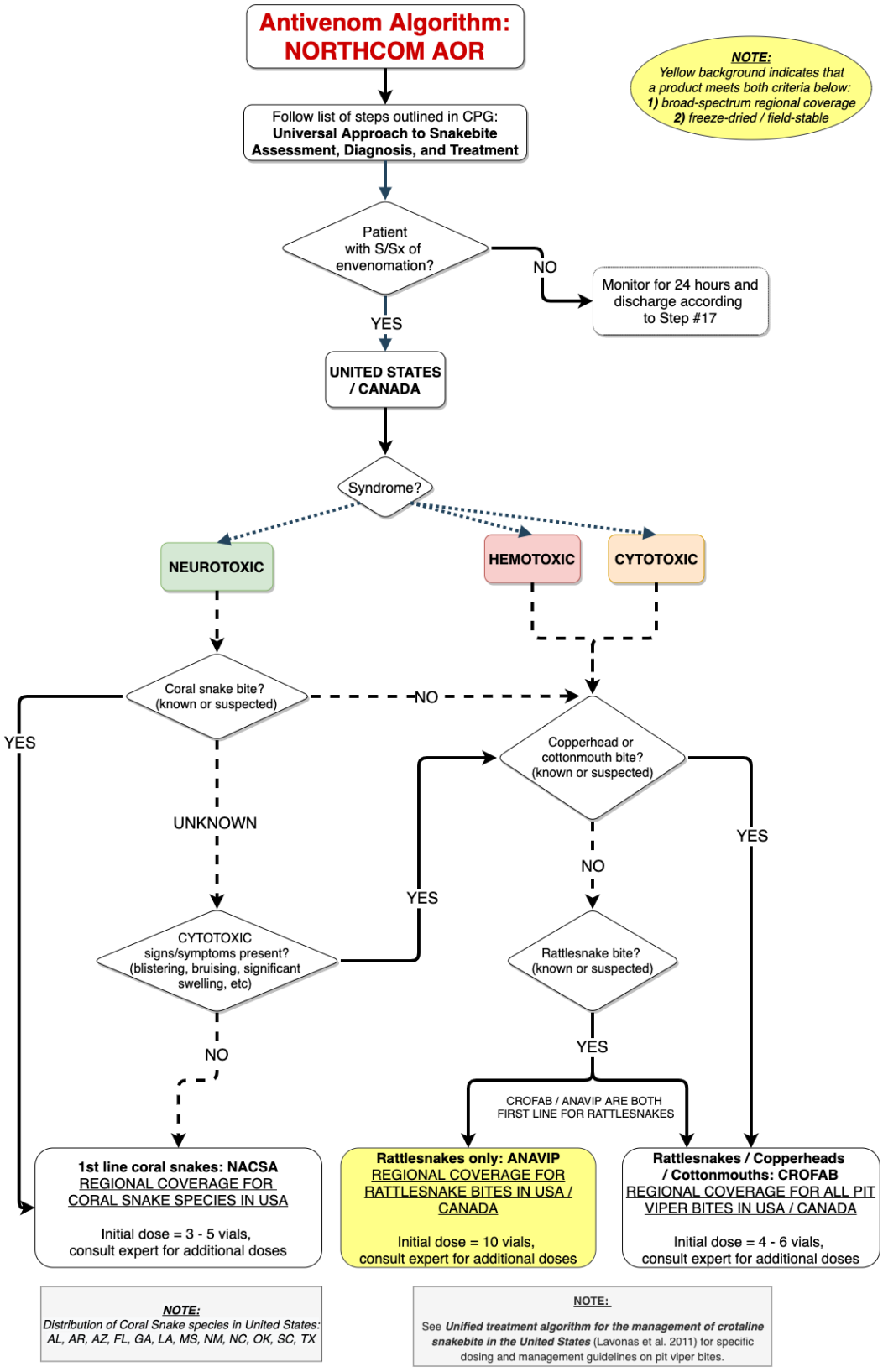
For emergency consultations, call the ADVISOR telemedicine hotline (866-972-9966) and select toxicology from the phone menu.

For additional information about snake bite management or this CPG, email jordan@snakebitefoundation.org or call 415-218-2211.

Table 8. NORTHCOM- First Line Antivenoms

	Neurotoxic Syndrome	Hemotoxic Syndrome	Cytotoxic Syndrome
Mild	Local S/Sx (paresthesias; neuropathic pain; piloerection; muscle spasm, fasciculations)	Coagulopathy ± persistence of local bleeding from bite wound > 30 mins after bite	Severe pain; edema below elbow or knee; limited blistering within several inches of the bite wound
Moderate	Systemic S/Sx (bilateral ptosis GI symptoms; visual, auditory, or other sensory disturbances; widespread hyperesthesia)	Moderate systemic bleeding (old scabs, gingival bleeding, epistaxis, etc.); bruising distant from the bite wound	Edema above elbow or knee but not beyond shoulder or hip; moderate local blistering along bitten limb segment
Severe	Difficulty speaking; altered mental status; respiratory muscle weakness causing difficulty breathing; shock or otherwise unstable patient	Active GI bleed (usually hematemesis) or other internal bleeding; severe anemia; altered mental status; shock or otherwise unstable patient	Progressive edema beyond shoulder or hip; severe necrosis or widespread blistering; symptomatic bite to head, neck, or torso; altered mental status; shock or otherwise unstable patient
Criteria for additional AV doses at hours 2, 4, 6, 12, 24 (as needed)	Additional dose if: persistence or worsening of systemic neurotoxic S/Sx. Continue to re-administer 2 vial boluses as needed at hours 2, 4, 6, 12, and 24 until signs of improvement begin to appear (↑SBC, ↑LOC, ↑strength, etc.)	Additional doses if: persistence, resumption, or new onset of any active external or internal bleeding **OR** S/Sx of active venom confirmed by secondary recurrence of abnormal WBCT	Additional doses if: significant increase in edema (such as beyond major joint) **OR** significant increase in pain (severity of pain and/or how far pain radiates up the bitten limb)
NORTHCOM **1st Line Antivenoms**	U.S: Coral snake envenomations Initial 3-5 vials NACSA, additional doses not needed if 5 vial initial dose given U.S./Canada: Pit viper envenomations* - CROFAB: Initial dose = 4-6 vials, additional doses = 4-6 vial as needed - ANAVIP (rattlesnakes only): Initial dose = 10 vials, - additional doses = 10 vials as needed *Follow unified treatment algorithm	U.S./Canada: Broad spectrum coverage all hemotoxic/cytotoxic syndromes* Any pit viper envenomation (rattlesnake, copperhead, cottonmouth): - CROFAB: Initial dose = 4-6 vials, additional doses = 4-6 vials as needed Rattlesnake envenomations only: - ANAVIP: Initial dose = 10 vials, additional doses = 10 vials as needed NOTE: Anavip is only indicated by FDA for rattlesnake envenomations; not for copperheads or cottonmouths at this time; however, it is likely effective against all North American pit vipers. Follow Unified treatment algorithm for the management of crotaline snakebite in the U.S. (Lavonas et al. 2011) for dosing and management guidelines on pit viper bites.	
Antivenom Abbreviations	**CROFAB** = CroFab **ANAVIP** = ANAVIP **NACSA** = North American Coral Snake Antivenin		

Figure 6. Antivenom Algorithm: NORTHCOM AOR



BTG Therapeutics, USA – CroFab

(Freeze-dried/Refrigerated) [94,95,101,249-250] :

- **Indications:** Envenomation by all Pit Viper species (rattlesnakes, copperheads, cottonmouths) in North America. Freeze-dried; requires refrigeration but one study has demonstrated that it will maintain efficacy under field conditions for ≥ 90 days if needed.
- **Initial dosing:** 4 – 6 vials

RDT/Instituto Bioclon, USA/Mexico – ANAVIP

(Freeze-dried/Unrefrigerated) [92]

- **Indications:** Currently only indicated by FDA for rattlesnake envenomations.
- **Not currently indicated for copperhead or cottonmouth envenomations**, although this may change in the near future depending on results of upcoming studies. Freeze dried and field-stable at room temperature of 25º C / 77º F.
- **Initial dosing:** 10 vials

Pfizer, USA – North American Coral Snake Antivenom (NACSA)

(Freeze-dried/Refrigerated) [251]

- **Indications:** Indicated for neurotoxic envenomations by North American coral snake (NACSA) species in the United States including Eastern coral snake *(Micrurus fulvius)* and Texas coral snake *(Micrurus tener)*. Store between 2 – 8º C / 35.6 - 46.4 ºF; however, likely retains stability for short excursions in the field.
- **Initial dosing:** 5 vials

SOUTHCOM

Treatment Guidelines

Safe and effective antivenoms are available for all hemo/cytotoxic pit viper envenomations and for neurotoxic coral snake envenomations in this AOR. Treatment does not require identification of the species responsible but does require identification of the syndrome. Snakebite treatment at the point of injury is recommended for SOUTHCOM. This section provides specifics about antivenoms use in this region.

Adverse Reaction Management

- If a mild or moderate reaction occurs, slow the infusion, and treat symptomatically with antihistamines, steroids, and/or antiemetics as needed.
- If a severe reaction such as anaphylaxis occurs, stop the infusion, and treat according to the anaphylaxis protocol listed elsewhere in the CPG. Reassess the patient once the reaction has been controlled and resume the infusion at a slower rate if any of the specific criteria for antivenom treatment listed elsewhere in the CPG have not completely resolved.

Sudden Collapse Syndrome Treatment Protocol

Patient presents within 30 minutes of the bite with rapid onset shock ± angioedema, altered mental status, systemic bleeding, and diarrhea.[1]

5. Stabilize with IM or IV epinephrine and fluids as per anaphylaxis protocols
6. Intubate for airway edema not rapidly responsive to epinephrine
7. Follow epinephrine immediately with a high dose of the appropriate regional antivenom given by rapid IV or IO push during the resuscitation
8. Maintain blood pressure with IV or IO fluids and epinephrine until antivenom has taken effect to reverse the hypotension.

See Sudden Collapse Syndrome section for more information.

CONTACT

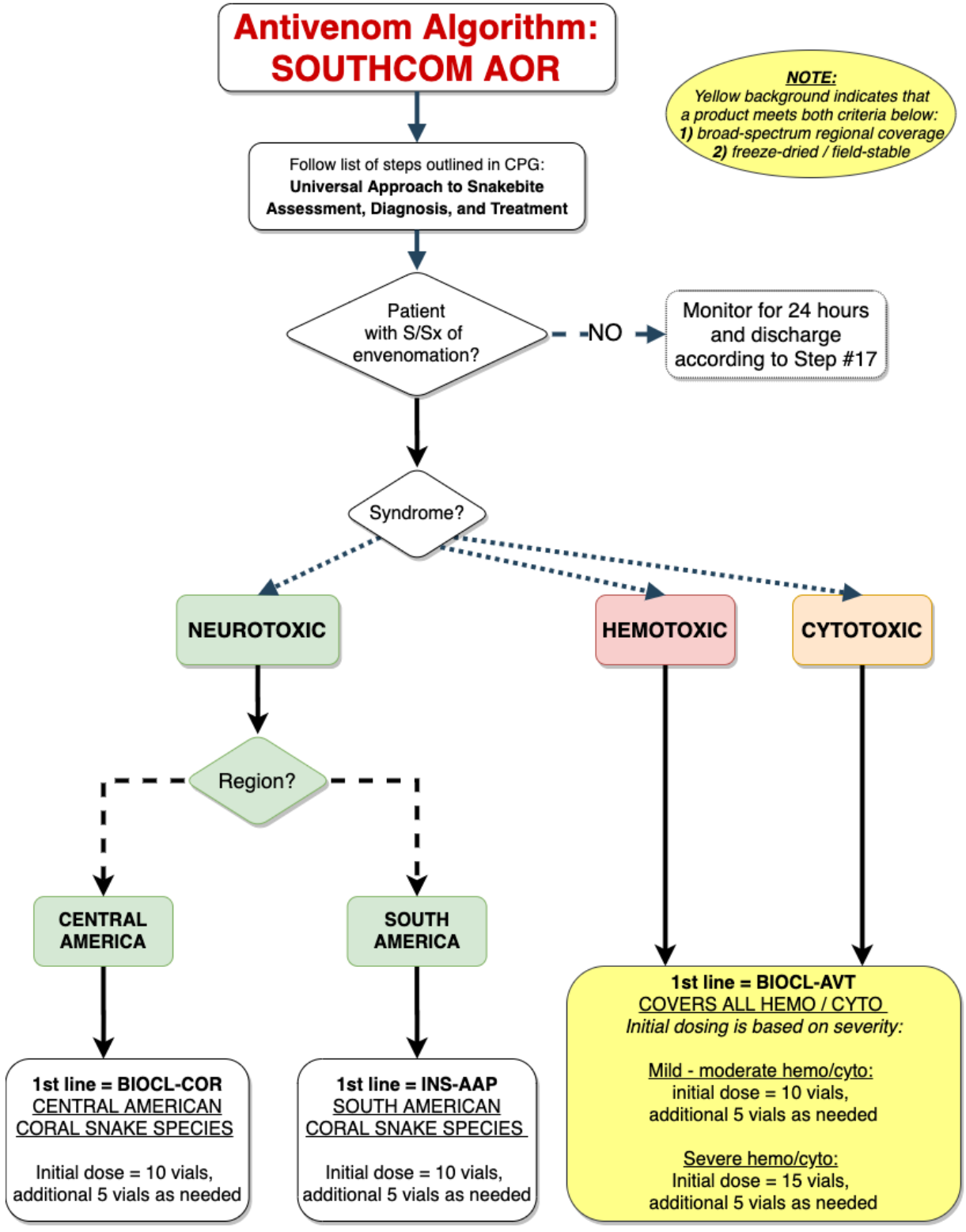
For emergency consultations, call the ADVISOR telemedicine hotline (866-972-9966) and select toxicology from the phone menu.

For additional information about snake bite management or this CPG, email jordan@snakebitefoundation.org or call 415-218-2211.

Table 9. SOUTHCOM - First line antivenoms

	Neurotoxic Syndrome	Hemotoxic Syndrome	Cytotoxic Syndrome
Mild	Local S/Sx (paresthesias; neuropathic pain; piloerection; muscle spasm, fasciculations)	Coagulopathy ± persistence of local bleeding from bite wound > 30 mins after bite	Severe pain; edema below elbow or knee; limited blistering within several inches of the bite wound
Moderate	Systemic S/Sx (bilateral ptosis GI symptoms; visual, auditory, or other sensory disturbances; widespread hyperesthesia)	Moderate systemic bleeding (old scabs, gingival bleeding, epistaxis, etc.); bruising distant from the bite wound	Edema above elbow or knee but not beyond shoulder or hip; moderate local blistering along bitten limb segment
Severe	Difficulty speaking; altered mental status; respiratory muscle weakness causing difficulty breathing; shock or otherwise unstable patient	Active GI bleed (usually hematemesis) or other internal bleeding; severe anemia; altered mental status; shock or otherwise unstable patient	Progressive edema beyond shoulder or hip; severe necrosis or widespread blistering; symptomatic bite to head, neck, or torso; altered mental status; shock or otherwise unstable patient
Criteria for additional AV doses at hours 2, 4, 6, 12, 24 (as needed)	<u>Additional doses if:</u> persistence or worsening of systemic neurotoxic S/Sx. Continue to re-administer 2 vial boluses as needed at hours 2, 4, 6, 12, and 24 until signs of improvement begin to appear (↑SBC, ↑LOC, ↑strength, etc.)	<u>Additional doses if:</u> persistence, resumption, or new onset of any active external or internal bleeding **OR** S/Sx of active venom confirmed by secondary recurrence of abnormal WBCT	<u>Additional doses if:</u> significant increase in edema (such as beyond major joint) **OR** significant increase in pain (severity of pain and/or how far pain radiates up the bitten limb)
SOUTHCOM 1st Line Antivenoms	Central America: Neurotoxic polyvalent - *BIOCL-COR: Any severity = initial 10 vials* - *Additional 5 vials as needed* South America: Neurotoxic polyvalent - *INS-AAP: Any Severity = 10 vials* - *Additional 5 vials as needed*	Central and South America: Broad-spectrum all hemotoxic/cytotoxic syndromes *BIOCL-AVT: Initial dosing is based on severity* - *<u>Mild – moderate:</u> Initial dose = 10 vials BIOCL-AVT* - *Additional doses = 5 vials as needed* - *<u>Severe:</u> Initial dose = 15 vials BIOCL-AVT* - *Additional doses = 5 vials as needed*	
Antivenom Abbreviations	**BIOCL-COR** = CORALMYN **INS-AAP** = Antiveneno Anticoral Polivalente **BIOCL-AVT** = Antivipmyn Tri		

Figure 7. Antivenom Algorithm: SOUTHCOM AOR



FIRST LINE (Entire SOUTHCOM AOR): BIOCL-AVT

Instituto Bioclon, Mexico – ANTIVIPMYN-TRI (BIOCL-AVT) (Freeze dried/Unrefrigerated) [251-255]:

1. Field-stable. Broad-spectrum coverage 14 species Hemo/Cyto.
2. First line treatment option for all hemotoxic and cytotoxic snake envenomations anywhere in the SOUTHCOM AOR when the causative species is either unknown or among the ≥ 14 snakes for which this product is directly indicated. Directly or indirectly covers most of the WHO category 1 and category 2 snakes in this region.
3. Initial dose = 10 vials hemotoxic/cytotoxic only, additional doses = 5 vials as needed.

Feasibility of use in austere environments: Recommended for operational settings. Unrefrigerated storage at ambient tropical temperatures of ≤ 37º C / 98.6º F. Lyophilized product that likely retains stability at higher temperatures for short excursions. Recommend carrying full dose or loading dose (≥ 5 vials) into field on extended operations in austere environments and storing larger quantities at strategically located Role 2 & 3 facilities in SOUTHCOM AOR.

Adverse reactions: High-quality product with low rates of reactions anticipated.

Indications: This broad-spectrum polyvalent can be used to treat hemotoxic and cytotoxic envenomations by more than 14 different species of Central and South American snakes. It may be able to neutralize venom from additional species through paraspecific neutralization, but this has not been officially determined. The species listed below are the official treatment indications recommended by the manufacturer:

- HEMOTOXIC and/or CYTOTOXIC: *Crotalus durissis terrificus; Bothrops asper, B. atrox, B. neuwiedii, B. alternatus, B. jararacussu, B. venezulensis, B. pictus, B. brazili; Lachesis muta muta, L. m. stenophyrs; Sistrurus spp.; Agkistrodon spp*.

Pretreatment: Not routinely indicated unless patient is unstable, asthmatic/atopic, known hypersensitivity or other pretreatment criteria met.

Initial dosing by syndrome:

- NOT INDICATED FOR NEUROTOXIC
- HEMOTOXIC initial dose = 10 vials
- CYTOTOXIC initial dose = 10 vials

Additional dosing: Additional doses of 5 vials BIOCL-AVT may be given at hours 2, 4, 6, 12, and 24 if needed.

Pretreatment: Not routinely indicated unless patient is unstable, asthmatic/atopic, known hypersensitivity or other pretreatment criteria met. Low risk of severe allergic reactions and other EARs.

Preparation and administration: Dilute the entire dose of antivenom in a single 250 - 500 mL bag of isotonic solution and administer by intravenous infusion over 10 - 30 minutes.

FIRST LINE (SOUTHCOM – Central America/South America): BIOCL-COR

SECOND LINE (SOUTHCOM – South America): BIOCL-COR

Instituto Bioclon, Mexico - CORALMYN (BIOCL-COR) (Liquid/Refrigerated) [256-262]:

1. Not field stable. Broad-spectrum coverage neuro in Central America.
2. First line treatment option for neurotoxic envenomation in Central America by coral snakes or unknown species (coral snakes are only strictly neurotoxic snakes in SOUTHCOM AOR). Second line treatment option for coral snake / unknown neurotoxic envenomation in South America if first line (INS-AAP) is not available.
3. Initial dose = 10 vials neurotoxic only, additional doses = 5 vials as needed.

First Line (SOUTHCOM – Central America): Neurotoxic envenomation in Central America by coral snakes or unknown species (coral snakes are only strictly neurotoxic snakes in SOUTHCOM AOR).

Second Line (SOUTHCOM – South America): May treat some coral snakes in South America but major coverage gaps in that region compared to the first line for South America (INS-AAP).

Feasibility of use in austere environments: Not recommended for operational settings. Requires cold chain refrigeration between 2 - 8 ºC (35.6 - 46.4 ºF). Recommend storing several vials at a small number of strategically located Role 2 & 3 facilities in South America. Likely to retain efficacy for several weeks in the field but should be disposed of after that duration of time outside refrigeration.

Adverse reactions: High-quality product with low rates of reactions anticipated.

Indications: This polyvalent can be used to treat neurotoxic envenomations by most major species of Central American coral snakes from the genus *Micrurus*.

- NEUROTOXIC: Central American coral snakes (*Micrurus spp*.)

Initial dosing by syndrome:

- NEUROTOXIC syndrome initial dose = 10 vials
- NOT INDICATED FOR HEMOTOXIC ENVENOMATIONS
- NOT INDICATED FOR CYTOTOXIC ENVENOMATIONS

Additional dosing: Additional doses of 5 vials BIOCL-COR may be given at hours 2, 4, 6, 12, and 24 if needed.

Pretreatment: Not routinely indicated unless patient is unstable, asthmatic/atopic, known hypersensitivity or other pretreatment criteria met. Low risk of severe allergic reactions and other EARs.

Preparation and administration: Dilute the entire dose of antivenom in a single 250 - 500 mL bag of isotonic solution and administer by intravenous infusion over 10 - 30 minutes.

FIRST LINE (SOUTHCOM – South America): INS-AAP

SECOND LINE (SOUTHCOM – Central America): INS-AAP

Instituto Nacional de Salud, Colombia - Antiveneno Anticoral Polivalente (INS-AAP) (Liquid/Refrigerated) [260-2]:

1. Not field stable. Broad-spectrum coverage Neuro in South America.
2. First line treatment option for neurotoxic envenomation in South America by coral snakes or unknown species (coral snakes are only strictly neurotoxic snakes in SOUTHCOM AOR). Second line treatment option for coral snake / unknown neurotoxic envenomation in Central America if first line (INS-AAP) is not available.
3. Initial dose = 10 vials neurotoxic only, additional doses = 5 vials as needed.

First Line (SOUTHCOM – South America): Broadest efficacy against neurotoxic snake bites by coral snakes or unknown species in South America. Coral snakes are the only strictly neurotoxic species in SOUTHCOM.

Second Line (SOUTHCOM – Central America): Should treat most coral snake species in Central America but will have some coverage gaps compared to the first line for Central America (BIOCL-COR).

Feasibility of use in austere environments: Not recommended for operational settings. Liquid product that requires cold chain refrigeration between 4 - 8 ºC / 39.2 - 46.4 ºF. Recommend storing several vials at a small number of strategically located Role 2 & 3 facilities in South America. Likely to retain efficacy for several weeks in the field but should be disposed of after that duration of time outside refrigeration.

Adverse reactions: High-quality product with low rates of reactions anticipated.

Indications: This polyvalent can be used to treat neurotoxic envenomations by most major species of South American coral snakes from the genus *Micrurus* as well as some Central American species.

- NEUROTOXIC: South American coral snakes (*Micrurus spp.)* including *Micrurus dumerilii, M. mipartitus, M. surinamensis, M. isozonus, M. lemniscatus, M. spixi, M. Medemi*

Initial dosing by syndrome:

- NEUROTOXIC syndrome initial dose = 10 vials
- NOT INDICATED FOR HEMOTOXIC ENVENOMATIONS
- NOT INDICATED FOR CYTOTOXIC ENVENOMATIONS

Additional dosing: Additional doses of 5 vials INS-AAP may be given at hours 2, 4, 6, 12, and 24 if needed.

Pretreatment: Not routinely indicated unless patient is unstable, asthmatic/atopic, known hypersensitivity or other pretreatment criteria met. Low risk of severe allergic reactions and other EARs.

Preparation and administration: Dilute the entire dose of antivenom in a single 250 - 500 mL bag of isotonic solution and administer by intravenous infusion over 10 - 30 minutes.

PERFORMANCE IMPROVEMENT (PI) MONITORING

POPULATION OF INTEREST

All patients injured by snakes.

INTENT (EXPECTED OUTCOMES)

1. All snakebite patients should be managed according to the steps outlined in the Universal Approach to Snakebite Assessment, Diagnosis, and Treatment section.
2. Assessment, diagnosis, and treatment of snakebite patients should be based on the clinical syndrome of envenomation and not the identity of the snake species responsible for the bite.

   When a broad-spectrum antivenom does not exist for a given syndrome in a given area, follow the steps outlined in the regional algorithms to determine the most appropriate antivenom therapy for the patient.
3. Snakebites are dynamic events and patients must be frequently reassessed for signs of neurotoxic, hemotoxic, and cytotoxic syndromes throughout the course of care as some syndromes will develop than others.
4. There are no absolute contraindications to antivenom administration for a patient with a symptomatic snake envenomation.
5. Antivenom administration should be performed by medical providers capable of providing advanced life support and trained to a minimum level of paramedic (or DoD equivalent) and higher (i.e. SOCM, 18D, PJ, IDC, IDMT, RN, PA, MD or DO, etc.)
6. Early antivenom treatment is the standard of care for snake envenomations worldwide. Whenever possible, the appropriate antivenom should be administered in the field prior to medevac to neutralize circulating venom before significant and potentially irreversible damage has occurred.
   - Field-stable, broad-spectrum antivenom options are included in this CPG for all combatant commands except for EUCOM.
   - Appropriate regional products listed in the CPG should be stocked in Role 2 and Role 3 medical facilities. Far-forward units with paramedic level providers should be equipped with field-stable, broad-spectrum antivenoms that can be stocked in the aid station and carried into the field for extended periods of times at high temperatures without loss of efficacy.
7. If antivenom is not available, the patient should be transferred to a facility that maintains a stock of the appropriate antivenom. Confirm that the receiving facility has the correct antivenom in stock prior to transfer. If the receiving facility does not have the correct product(s) in stock, then that facility should be bypassed for a facility that is stocking the appropriate products.
8. Antivenom dosage, preparation, and administration procedures for each product should be performed as detailed for each specific product.
9. Tetanus prophylaxis should be given prior to discharge when needed.
10. Fasciotomy is contraindicated for snakebite and all cases of suspected compartment syndrome should be managed with additional doses of antivenom and elevation ≥ 60 degrees to reduce oncotic pressure in the bitten limb.

11. Initiate a telemedicine consult with a qualified snakebite expert for any questions, concerns, or unusual manifestations that arise.
12. Do not attempt to kill or capture the snake for identification purposes as treatment is based on clinical findings. If a photo of the snake is available it can be sent to an expert for identification, but this should not delay antivenom treatment in a symptomatic patient with signs and symptoms of any envenomation syndrome.

PERFORMANCE/ADHERENCE METRICS

1. Administration of antivenom to any patients with clinical signs and symptoms of neurotoxic, hemotoxic, or cytotoxic envenomations
2. Early administration of appropriate antivenoms to symptomatic patients in the field
3. Rapid transfer of patients to a facility stocking the appropriate antivenom if not available on site
4. Antivenom administration should be performed by an advanced life support qualified provider trained to the paramedic level (or DoD equivalent) or higher
5. Tetanus prophylaxis as needed
6. Manage elevated intracompartmental pressures with antivenom and do not perform fasciotomies.

DATA SOURCES

- 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 Joint Trauma System (JTS) Chief, JTS Program Manager, 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.

REFERENCES

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APPENDIX A: WHOLE BLOOD CLOTTING TEST

Whole Blood Clotting Test for Venom-Induced Consumptive Coagulopathies

The whole blood clotting test (WBCT) is a simple but critical bedside gross examination used in the assessment, diagnosis, and therapeutic monitoring of snakebite patients in the developing world and remote environments.[1-10] Refer to the diagram below regarding instructions for performing the test. At minutes 20 and 30, the tube is gently picked up and tilted 90 degrees; a stable solid clot retained within the tube is scored "Grade 0" and indicates normal coagulation. Abnormal results are scored "Grade 1" for a partial, semisolid clot that breaks apart and detaches from the glass tube shortly after it is turned or "Grade 2" for completely incoagulable liquid blood that pours out of the tube immediately. Attempting to score the test earlier than 20 minutes will not yield accurate results due to the consumptive mechanism of the coagulopathy. Using a healthy donor as a control is ideal to confirm questionable findings.

Continue WBCT testing throughout the course of care to monitor for secondary resumption of venom-induced consumptive coagulopathy.[11-13] After control of the envenomation has been achieved, reassess WBCT every 24 hours throughout the course of hospitalization. It is important to remember that the WBCT must be interpreted in the context of the larger clinical picture. If a patient has improved in all parameters except for a persistent abnormal WBCT, it may reflect an inertia in replenishment of depleted clotting factors after a severe hemotoxic envenomation.[1] If the venom is active then hematocrit should continue to decrease or signs of ongoing hemolysis or bleeding should be present.

Whole Blood Clotting Test (WBCT)

Draw 2 mL of venous blood and transfer directly into a clean and dry glass tube. Leave it upright, open, undisturbed for 20 and/or 30 minutes at room temp.

Collection: a blood sample for WBCT testing immediately after collection.

After exactly 20 minutes, pick up the tube and invert it. If a solid clot is retained, the test indicates normal coagulation.

Normal: a solid clot is retaining upon inversion of the tube at 20 or 30 minutes (Grade 0, no coagulopathy).

If clot breaks down quickly upon inversion of the tube or fails to coagulate, the test indicates a coagulopathy.

Abnormal: clot degrades rapidly (Grade 1, friable clot) or fails to coagulate whatsoever (Grade 2).

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APPENDIX B: 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 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.