East African Medical Journal Vol. 97 No. 12 December 2020
A TREATMENT ALGORITHM FOR EAST AFRICAN SNAKEBITES FOR THE WILDERNESS PROVIDER
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A. Spanier, J. Jude, H. Hiller, A. Ralston and D. Brillhart

ABSTRACT

***Objective*: The aim of this research is to describe a protocol for providers in austere regions of East Africa, in the treatment of patients with snakebites. This research seeks to provide a framework for providers in this area of scarce resources and limited current data on how best to improve patient survival.**

***Design*: A protocol was developed through literature review and examination of available resources provided to austere medical providers.**

***Setting*: This research was developed in East Africa by U.S. providers currently in East Africa.**

***Subjects*: This research does not describe any subjects that the developed protocol and algorithms have been used on, however the research is useful for austere U.S. and East African providers that may have a prolonged extraction time to definitive treatment.**

***Intervention*: The interventions described in this research include the SAIMR polyvalent and SAIMR boomslang antivenoms, as well as adjunct treatments of epinephrine, and neostigmine.**

***Results*: This research outlines an easy-to-use protocol to be utilized in a resource scarce environment with three main steps in treatment and evaluation of patients with snakebite injuries.**

***Conclusions*: The protocol contained within this research is useful to those that do not practice medicine within a hospital in East Africa. New antivenom products are currently under evaluation for use in snake envenomizations within this region, however, they may not be readily available for years to come. This is the first described algorithm for successful treatment that can improve survivability of this life-threatening condition.**

INTRODUCTION

Rural and austere environments across the world present medical providers with difficult medical conditions and treatment plans, and East Africa is no exception. These unique disease patterns and significant logistical limitations make medical care in this region challenging even under ideal conditions, and snake envenomations are among the most challenging of the injuries that may be encountered in this region. Given these challenges, the authors of this paper have developed a protocol regarding the treatment of various snakebites in rural and austere East Africa. High quality medical management of snakebite victims in East Africa is frequently difficult to achieve due to resource limitations and prolonged evacuation times. Given the severe and rapid toxicity of the various East African snake venoms, rapid and exceptional medical care is paramount to maximizing patient outcomes. There is a paucity of literature to guide therapy and management, and there are no established guidelines for the treatment of East African snake envenomation in austere and resource-limited environments. In fact, according to one source, even medical schools in Africa fail to provide adequate instruction on the topic.[1] While case reports have been used as the basis for various treatment regimens and protocols for these envenomations, most of these involve brick and mortar hospital systems and provide little guidance for wilderness medical providers in austere locations without such medical resources and logistic capabilities.[2] This research seeks to provide a framework to operational clinicians in East Africa in regards to evaluation and treatment of these potentially critically ill patients.

The snake responsible for the most deaths throughout Africa is the Puff Adder (*Bitis arietans)*, accounting for a large proportion of the estimated 43,000 yearly African snakebite deaths due to its widespread distribution and aggressive nature.[3,4] Puff adder venom is primarily cytotoxic, and thus painful, progressive swelling (PPS) is by far the most common symptom of puff adder envenomation, though the venom also contains myotoxic, neurotoxic, and hemotoxic components.[3,6] Other possible symptoms include blistering, thrombosis, skin necrosis, disseminated intravascular coagulopathy (DIC), thrombocytopenia, hypotension, and bradycardia.[3] Further complicating this picture is that bites of cytotoxic snakes such as the puff adder are often dry bites, although the exact amount is contested due to the unknown percentage that do not present to a hospital.[6] Death is most commonly due to cardiovascular collapse or complications of DIC.[7] Other snakes with cytotoxic venom covered by the antivenom discussed in this protocol, but not all located in East Africa include the Gaboon Viper (*Bitis gabonica*), Rinkhals *(Hemachatus haemachatus*) and the Spitting Cobras (*Naja spp)*.

While not the most common snakebite encountered, perhaps the most feared and dangerous snake in East Africa is the Black Mamba (*Dendroaspis polylepis*) due to the potency of its venom and highly aggressive and territorial nature.[1] The black mamba is a member of the Elapidae family, which includes other neurotoxic snakes such as coral snakes, kraits, and cobras. The primary components of its venom are dendrotoxin, which prolong the presynaptic action potential and increase acetylcholine release, causing cholinergic symptoms before ultimately progressing to a depolarizing nerve block with fasciculation and paralysis, and α-neurotoxins, which antagonize the post-synaptic nicotinic acetylcholine (ACh) receptors at the muscle motor end-plates, causing a flaccid paralysis. Other components act as acetylcholinesterase inhibitors and calcium channel blockers, which further contribute to cholinergic

symptoms, and cause cardiotoxicity respectively.[1,8,9] As little as 10-15 mg can be fatal to an adult human, and each strike can result in as much as 400 mg of injected venom. Since the Black Mamba frequently strikes repeatedly and quickly, a typical attack results in a massive envenomation, and is almost universally fatal if treatment is delayed.[1,9] While the hallmark of puff adder envenomation is PPS, the pathognomonic symptom of envenomation by Black Mamba (and other neurotoxic snakes of East Africa) is progressive weakness (PW). Symptoms begin rapidly, within 10-15 minutes, and death due to respiratory failure can result within 30-40 minutes[1,9]. Initially victims will develop tingling at the bite site, followed by nausea/vomiting, diaphoresis, hypersalivation, piloerection, and paresthesia. A progressive flaccid paralysis will then develop, often starting with ptosis and weakness of the vocal cords and musculature of the oropharynx before progressing to ultimately include the diaphragm and respiratory muscles. Other reported symptoms include fasciculation, ataxia, tachycardia, bradycardia, hypotension, myocardial infarction, and rhabdomyolysis. Generally swelling is minimal. Death occurs from cardiorespiratory collapse.[11,12,13] Antivenom for neurotoxic snake bites is indicated 50-70% of the time.[6] Other East African snakes with similar yet less potent neurotoxic venoms include the Green and Jameson Mamba, and non-spitting cobras such as the Forest Cobra.

A third East African venomous snake for which an antivenom is available is the Boomslang (*Dispholidus typus*); its venom is directly hemotoxic, which can lead to a consumptive coagulopathy due to activation of factors 9, 10 and prothrombin, resulting in a delayed DIC.[4] Coagulopathy can develop in as little as one hour yet is typically delayed by twelve hours or more. Clinical presentations have included skin necrosis, bruising and purpura, oozing from wounds/gingiva, and spontaneous bleeding.[14,15] While often considered one of Africa's deadliest snakes, envenomation from the Boomslang are actually quite rare.[4] In a five-year retrospective review at a hospital in South Africa, only four envenomation requiring antivenom were reported, out of 879 total cases of venomous snake bite.[5] In fact, since 1957 there have only been nine reported fatalities resulting from Boomslang bite.[14]

METHODS

The purpose of this research was to design a protocol for treating bites from snakes indigenous to the potential operating area of austere providers in the East African region. The protocol was developed through review of collected data from published articles pertaining to snake bites in Africa and Southern Asia. This included case reports, clinical trials and reviews published between 1 January 1980 to 31 December 2019. The review of literature did not include articles on non-human studies, or in vitro studies.

The literature search was performed through the US National Library of Medicine Pubmed Data Base and Google Scholar. Search terms used through Boolean query or individually included: snakebite, snake venom, antivenom, Africa, East Africa, snake bite treatment, anaphylaxis, cytotoxic, hemotoxic, neurotoxic, Bitis, Hemachatus haemachatus, Naja, Dendroaspis, Dispholidus, Elapidae, SAIMR, epinephrine, neostigmine, austere, first aid.

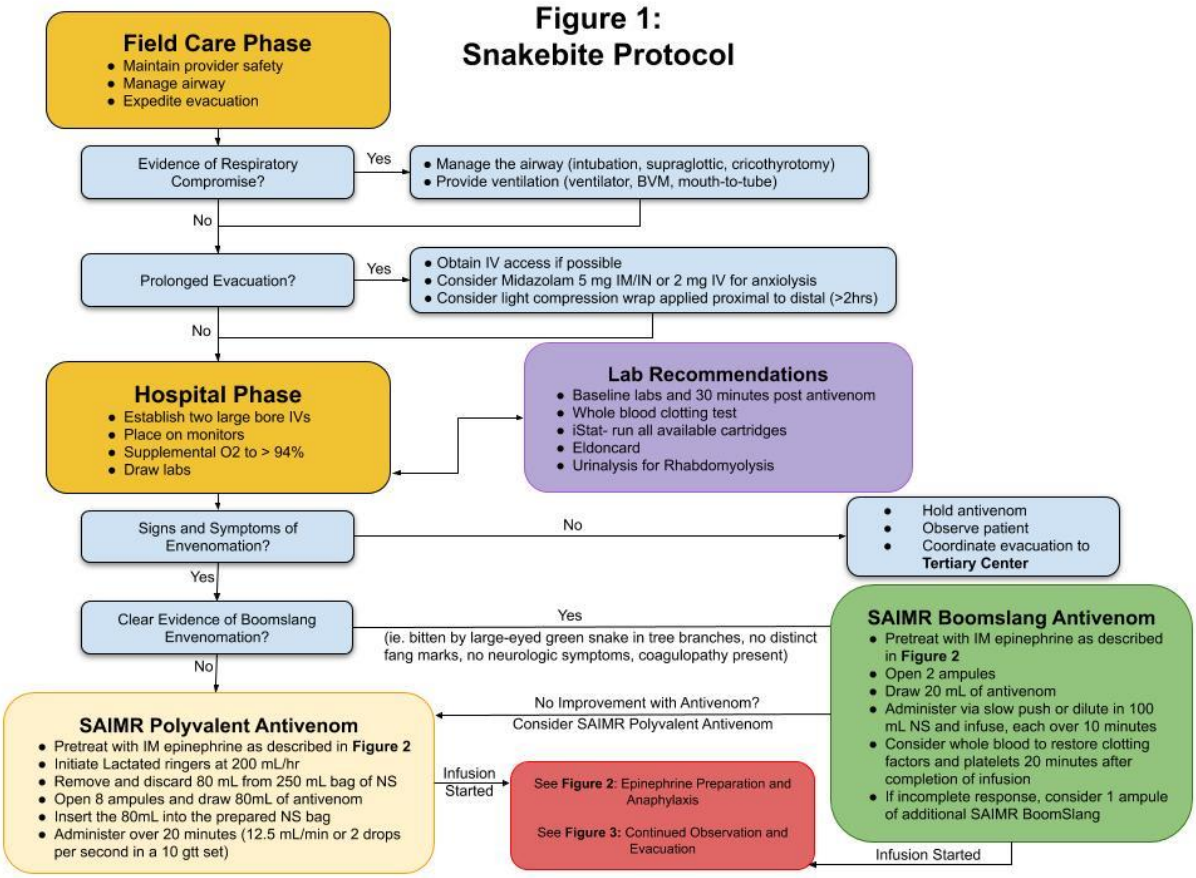
The data from the case reports and antivenom trials were then compiled and crossed with resources available to deployed U.S. Military Providers treating patients. Case reports with documented survival and low adverse reactions, in addition to clinical trials of different antivenoms were utilized to develop the chosen antivenom treatment. Toxicology data from different snake bites were analyzed to develop adjuncts to this

treatment to minimize theoretical risks. Finally, evidence from North American snake antivenom was utilized for development of anaphylaxis treatment, with the available medications to U.S. providers and the expected evacuation times from provided to these providers.

RESULTS

First aid and Point of Snake Bite care: When first responder medical providers are responding to a snake bite, the basics of BLS wilderness medicine must be applied through assessing the scene for safety before rushing to treatment. Except airway management, once at the envenomed patient, there are few interventions at point of injury that are proven to improve morbidity and mortality.[16] Point of injury treatment of snake bites has a long history of ineffective products and superstitious procedures. Most commercial snake bite products advertised to outdoor enthusiasts for first aid at best have shown no benefit, and at worst may be harmful, as in the case of electric shock devices. Tourniquets also have extensive data on the harmful effects, with the WHO and the American Wilderness Medical Society recommending against using these devices at the point of bite. In an East African study, tourniquet use was also associated with greater amounts of antivenom used. This same study showed that any first aid treatment or home remedy is correlated with a longer hospital course.[17] The utility of such devices varies greatly by region, however, as empiric pressure bandage with immobilization at the time of bite is often recommended in Australia due to the high proportion of neurotoxic elapid snakes. Conversely, the American College of Toxicology recommends against pressure immobilization or bandages, as the largest source of envenomation there is from cytotoxic crotaline venoms.[18] Since East African envenomations may be either neurotoxic or cytotoxic, pressure bandages are of limited utility as they likely worsen outcomes for cytotoxic venom and differentiation is incredibly difficult at the point of injury.

Another treatment dependent on early identification of the snake, with limited field data, is the elevation or position of the limb in relation to the heart; cytotoxic envenomations may benefit from elevation of the limb above the heart, while hemotoxic and neurotoxic envenomations should be kept below the heart.[16] The most recommended prehospital treatment is immobilization of the patient, especially the bitten limb, through non constricting splints, and analgesia/anxiolysis if available (See Figure 1). By far the most important aspect of point of injury care is expedient airway management if necessary, followed by rapid evacuation to the location of the closest antivenom.



Current Antivenom Options: One of the most difficult factors in preparing for snakebites in East Africa is the wide range of potentially life-threatening snake species. While in general terms, the venoms fall into three main categories (cytotoxic, neurotoxic, and hemotoxic) in reality each snake has its own venom cocktail, and presentations can be mixed, making symptomatic identification of the specific snake species difficult.6 Fortunately, treatment options are much simpler, and any patient with cytotoxic (PPS) or neurotoxic (PW) symptoms may be treated with a single polyvalent antivenom.6 While at least twelve commercial polyvalent antivenoms covering many combinations of neurotoxic and cytotoxic venoms are on the market, this protocol focuses specifically on SAIMR-Polyvalent Antivenom, (SAIMR-P) distributed by the South African Vaccine Producers, for a number of reasons. As one of the oldest and the best studied antivenoms, it has been consistently reported to be effective against a large number of snake venoms, including the puff adder, Gaboon viper, black and green mambas, and various cobras, and appears to be more effective against the more common envenomation than most of the other options.11 It is recommended by WHO guidelines for use in cytotoxic and neurotoxic envenomation in East Africa.2,11,19

The literature on dosing SAIMR-P is mixed. According to the SAIMR-P package insert, the recommended initial starting dose is AT LEAST 2 vials, or 20 mL given over 10-30 minutes, but that much more may be required by the patient's condition.20 However, the package insert also references certain doses for specific snakes such as initiating 20 vials for the Gaboon adder, and similar dosages for neurotoxic snakes, it is often impractical to identify the snake as already discussed. While in vitro studies have validated that 2-3 vials SAIMR-P should theoretically neutralize the largest venom

loads,7 numerous case reports and protocols written by physicians with extensive experience treating East African snakebites suggest that the actual average dose required to control symptoms may be closer to 5-10 vials, can be as high as 20 vials in severe cases.5,12,13,21,22 Medical providers should be prepared to give additional vials if control of the envenomation is not achieved.1 To our knowledge, no studies have elucidated the appropriate amount of time to observe the patient before determining that the initial dose of SAIMR-P was ineffective and more vials are needed. Based on product recommendations and experience with CroFab® in the United States, observing up to an hour appears reasonable, however this recommendation is obviously limited by extrapolation, and medical providers should use their best clinical judgement when dealing with an acutely worsening patient.23 Our protocol is to start with 8 vials, or 80 mL given over 20 minutes, and re-dose every hour or sooner if toxicity is clearly worsening (See Figure 1).

In a patient who presents with isolated hemotoxic effects in the absence of PPS or PW, it can be assumed that the culprit was the boomslang which has a specific, monovalent antivenom available, SAIMR-Boomslang (SAIMR-B).24 Though less well-studied than SAIMR-P, case reports are less conflicted as to recommended dosing, which 2 vials (20mL) over 30 minutes, with a repeat dose of 1 vial (10mL) if necessary. Despite the paucity of literature, SAIMR-B appears to be consistently effective. 5,11,15

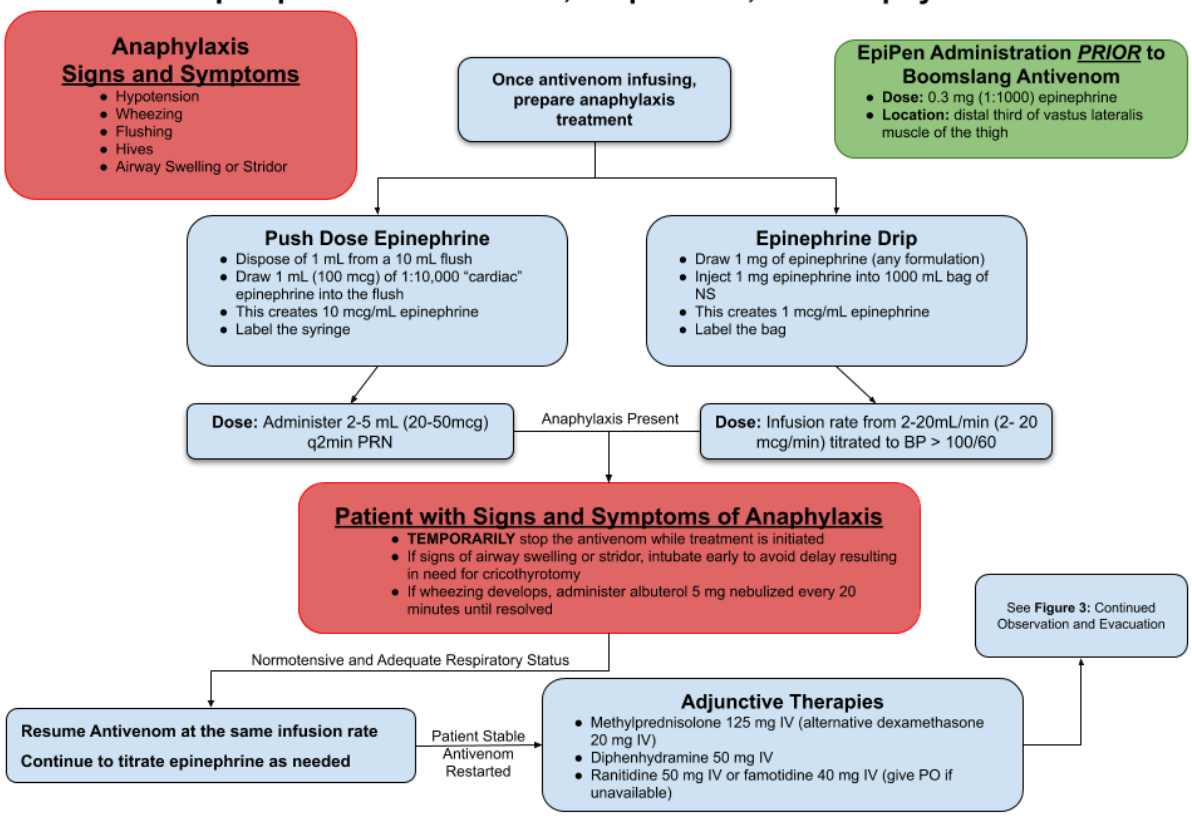
Adverse Effects: The most concerning aspect of antivenom administration is the propensity for early anaphylactoid or anaphylactic reactions, a risk any time an animal serum-derived medication is introduced to a human system. Contrary to popular belief, the majority of early reactions to snake antivenoms are anaphylactoid (MAST cell/Basophil degranulation), rather than true anaphylaxis (Type I hypersensitivity, IgE mediated), as most victims have not been previously sensitized to antivenom.10 However, this is a largely academic distinction as these conditions are clinically indistinguishable and the treatment is the same. Attempts to determine the actual rate of immune reactions to African antivenoms are hampered by a lack of research, however the number appears to be quite high.1,11 Two prospective observational studies in 1998 and 2009 both reported conflicting but high rates of early immune reaction to SAIMR-P, 76% and 38.5% respectively. Both of these studies were small, with 17 patients in the former, and 22 in the latter.22,25 Unfortunately, after an exhaustive review, no published literature appears to analyze adverse reactions of SAIMR-B, however since both SAIMR-P and SAIMR-B are derived from horse serum, containing F(ab')'2 fragments of equine immunoglobulins, and produced by the same company, we feel it is both reasonable and prudent to assume the rates are similar until proven otherwise.

While the literature regarding African antivenom is limited, there has been an extensive amount of research done on North American antivenoms, and some parallels may be drawn to help predict the rate of adverse reaction. The original crotalid antivenom in North America was Antivenin Crotalidae Polyvalent (ACP) and ACP was concentrated equine serum Immunoglobulin G (IgG) with large amounts of extraneous proteins and whole immunoglobulin. Due to the excessive extra protein present, ACP had an estimated incidence of hypersensitivity reactions of 23% to 56%, not outside the realm of what is suggested by the limited SAIMR literature, though with far greater statistical power.26,27,28 While the construct of the two types of antivenoms are very different, whole IgG for ACP and F(ab')'2 for the SAIMR products, in vivo studies have demonstrated no significant difference in immunogenicity between IgG and F(ab')'2 antitoxins when given IV, whereas Fab antitoxins were far less

immunogenic.29 This is supported clinically by a Colombian comparative study of IgG and F(ab')'2 antivenoms that demonstrated no significant difference in the rates of early adverse effects. Likewise, CroFab, a highly purified Fab antivenom, has a well-documented immunologic reaction rate of 5%-9%, much lower than for ACP.26-28,30 It seems reasonable then to assume that the SAIMR antivenoms have a similar, high rate of hypersensitivity reactions, and that a medical provider should both expect and prepare for them when administering the products.

Anaphylaxis Treatment: While common knowledge among medical professionals, it is important to emphasize that intramuscular injection of epinephrine is globally accepted as the first-line treatment for anaphylaxis. For this specific protocol, we recommend a two-tiered approach: first, pretreatment with IM epinephrine before administration of antivenom due to the high incidence of anaphylaxis (See Figure 2). During the preparation of antivenom, push dose epinephrine will also be prepared, to be used with the IV access for faster drug onset.31 Although this is a deviation from current practice in hospitals without supply or evacuation issues, the recommendation of IV epinephrine is for after the prehospital phase, used by skilled medical providers, in the healthier population for whom this protocol is designed. This allows for reduction of morbidity and mortality, while also quickly treating the adverse effects of the antivenom.32 Other second-line medications, such as antihistamines and glucocorticoids, are not lifesaving because they fail to relieve laryngeal edema with resulting upper airway obstruction, hypotension, and shock, but may be administered if time and resources permit. Epinephrine counteracts anaphylaxis through α-adrenergic reversal of peripheral vasodilation and β-adrenergic properties resulting in bronchodilation, increased cardiac output and contractility, and suppresses further mast cell and basophil degranulation.33,34

Figure 2:
Epinephrine Pretreatment, Preparation, and Anaphylaxis



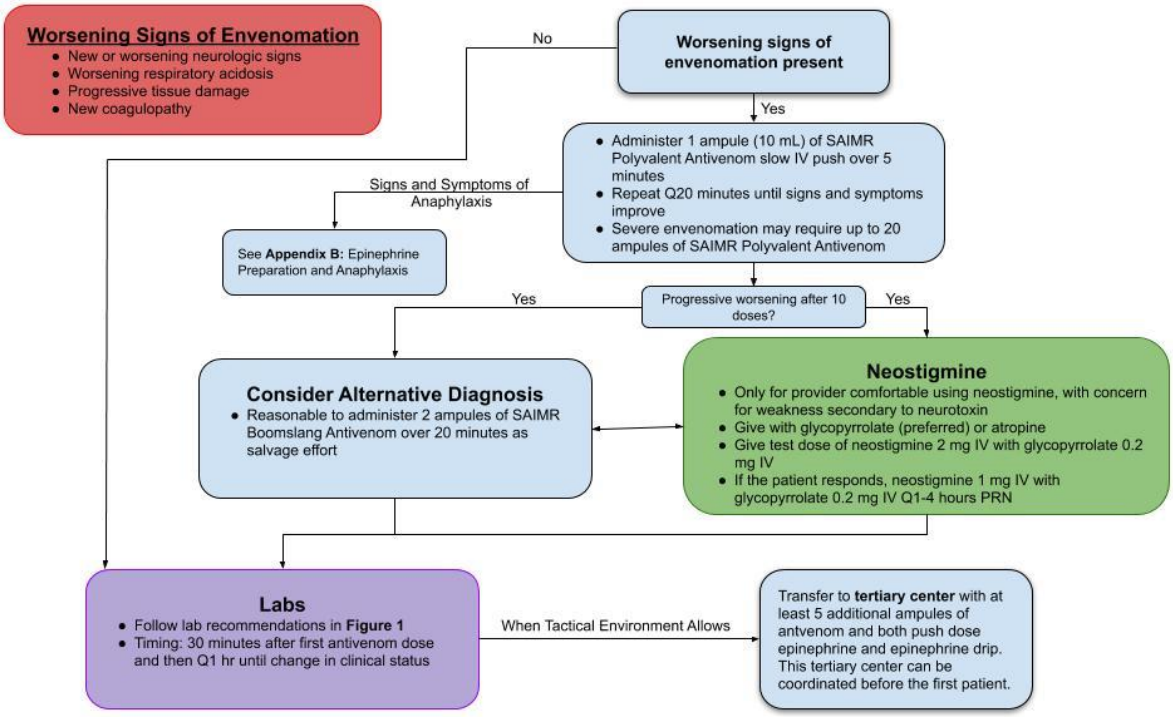
Neostigmine: Neurotoxic envenomation may be rapidly lethal, relying solely on the use of antivenom for treatment of these symptoms may sometimes not be enough to prevent the fatal respiratory paralysis, particularly if there is a delay in administration or a prolonged extrication to a medical facility. This protocol discusses the use of neostigmine, an acetylcholinesterase inhibitor, as an adjunct for the antivenom for prevention of respiratory paralysis. Neostigmine, in addition to atropine or glycopyrrolate to reduce muscarinic effects, is more commonly used for treatment of myasthenia gravis, and reversal of non-depolarizing paralytics during anesthesia. Because neurotoxic venom often has a mixed pre- and post-synaptic mechanism, neostigmine may have an adjunctive role for treatment of elapidae snake bites.

Each genus of the Elapidae family of snakes has a different variant of neurotoxins within their venom, and many contain α-neurotoxins, which competitively inhibit the postsynaptic nicotinic acetylcholine receptors. This postsynaptic blockade leads to a non-depolarizing block similar to Myasthenia gravis, and neostigmine has been used successfully to reverse the paralysis in elapidae snake bites. However, this has been reported primarily in bites from snakes with predominantly post-synaptic venoms such as the Indian Cobra.8 The venom of the black mamba on the other hand contains both the post-synaptic α-neurotoxins and the pre-synaptic dendrotoxins, which may in fact be the primary venom component and responsible for the majority of the symptoms.9 Not only would an anticholinesterase likely be ineffective in this case, this has led to a theoretic concern that it

would exacerbate cholinergic symptoms caused by the increased ACh release.

In addition to worsening the fasciculation and depolarizing paralysis, ACh acts on a wide array of organ systems, including the cardiopulmonary system. The brady dysrhythmias, bronchospasms and bronchorrhea seen in a cholinergic syndrome can lead to further significant instability in these already critical patients.8,35,36 This has led to at least one recommendation that neostigmine NOT be given for a black mamba bite.21 These concerns are purely theoretical, however, and no case reports of adverse effect to an anticholinesterase given for neurotoxic snake bite could be found. Conversely, there is a case report of neostigmine given for black mamba bite in which significant improvement in the patient's paralysis was seen. The authors note though that the patient specifically did not have fasciculation or other cholinergic signs, and so it was felt that the patient was having predominantly post-synaptic symptoms.37 Due to the remote nature of many personnel in East Africa, it is paramount that the patient's ability to breathe be maintained to prevent the complications and possible failure of prolonged artificial respiration while waiting for evacuation to a hospital. As such, we feel it is reasonable and safe to administer a test dose of neostigmine along with glycopyrrolate and monitor closely for improvement of symptoms or adverse effects, and then continue to dose every 4 hours if improvement is seen (See Figure 3), though caution should be taken if the patient is displaying obvious cholinergic symptoms such as fasciculation, salivation, or bradycardia.

Figure 3:
Continued Observation and Evaluation



DISCUSSION

Future Treatment Considerations: While the WHO currently only endorses the SAIMR polyvalent antivenom for most of the snakes in East Africa, a newer antivenom may reduce many of the logistical restraints of treating these patients.5,7 INOSERP Pan-Africa, currently undergoing its third clinical study in Cameroon, is another polyvalent antivenom that covers most of the snakes the SAIMR antivenom does, plus contains antivenom for East African carpet viper (Echis pyramidum).38 While the recommended per vial dosage is the same as SAIMR, it is a third of a cost per vial ($105 vs. $315). The vial is also stored safely at up to 86°F (30°C) for 3 years or 104°F (40°C) for 6 months, which is crucial for austere medical providers, as refrigeration is difficult to obtain and often reserved for blood products.39 While this antivenom may be added to deployment formularies in the future, more data, specifically on snakes also endemic to east Africa, is needed before it can be safely used on envenomed service members. The only two published studies took place in West Africa, encompassing 272 patients, with a total case fatality rate of 6 (2.2%) in those treated with the INOSERP, three of which were possibly undertreated per the study's protocol.11,40 These studies only contributed one case of anaphylaxis to the antivenom, and 17 minor allergic reactions treated with antihistamines and corticosteroids. The preliminary studies for this antivenom show significant potential, however, it has not been tested within the East African habitats and requires further investigation.

CONCLUSION

In conclusion, caring for snake envenomation in austere East Africa is fraught with challenges, but this protocol hopes to aid in the treatment of these often critically ill patients. Due to ready availability in our practice, our protocol relies upon SAIMR Polyvalent and SAIMR Boomslang antivenom although other appropriate antivenom products may be equal or superior to these. However, it is paramount that the medical provider be prepared for the complications of antivenom administration before any treatment, specifically anaphylaxis. Finally, in the rare but highly deadly Elapidae envenomation, neostigmine may have benefit when used by experienced providers. It is our hope that this framework may aid the austere medical provider in providing lifesaving care in difficult situations.

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