Snakebites in Africa and Europe: a military perspective and update for contemporary operations

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ABSTRACT

Snakebite envenoming is rare among military patients, with few cases reported in recent years. Increasingly, however, military operations are taking place in remote parts of Africa, which are inhabited by numerous species of venomous snake, and in Europe, where dangerous species exist but are less common. Bites from a venomous snake may prove fatal, and therefore military medics must be adequately prepared to manage them. This paper reviews the most medically significant species of venomous snake present in Africa and Europe, before suggesting an evidence-based approach to snakebite prevention and management, including possible changes to the UK's Clinical Guidelines for Operations.

Key messages

- Snakebites in the military are rare.
- Bites can lead to risk to life if not managed correctly.
- This review asseses the guidance on how to manage snakebites in Africa and Europe.

INTRODUCTION

Snakebite is a rare, but potentially significant, risk to British service personnel deployed on operations worldwide. Recent case reports involving UK troops include a British soldier envenomed, probably by a viper, on the Iraq/Iran border in 2004. He did not require antivenom.[1] In 2017 a British soldier was envenomed by a horned viper (*Vipera ammodytes*) in Croatia and was treated with antivenom. At Camp Bastion, Afghanistan, a case series of two Afghan children and two Afghan National Security Force personnel were treated for snakebite,[2] all of whom required antivenom and survived. In a 2-year review of medical admissions to the Role 3 hospital at Camp Bastion, envenoming did not feature in the top 20 diagnoses among UK military patients.[3] However, among non-UK military and civilian patients treated by military clinicians, 15 cases of envenoming were admitted in the same 2-year period, proving to be the fifth most common diagnosis on discharge.

Two cases of snakebite were treated during a recent medical exercise, ASKARI SERPENT,[4] aimed at the local community in Kenya. Historically, this trend is borne out by substantial case series of, largely civilian, snakebites treated by military medical staff in Nepal[5] and West Africa.[6] In recent years, UK service personnel have deployed on exercises and operations to countries throughout Africa, with a permanent base and frequent large training exercises taking place in Kenya.[7] There have been smaller short-term training programmes taking place throughout Africa,[8 9] as well as a recent operational deployment in support of the United Nations Mission in South Sudan.[10]

Venomous snake species are present throughout Africa, where they are a significant cause of morbidity and mortality in the local population,[11] and therefore may also pose a risk to our deployed population.[12 13] A previous military-orientated review is now nearly 10 years old and had an emphasis on the Middle East and Afghanistan, then the focus of operations.[14] This paper aims to provide an evidence-based guide to the most medically important snake species found in Africa and Europe, and the management of snakebite in the deployed settings, from initial treatment at Role 1 to further management in a hospital.

SNAKEBITE ENVENOMING

Snakes have evolved their bite and highly complex venoms to immobilise, kill and begin digestion of prey, and for self-defence. Snakes are secretive animals, they avoid contact with predators and large animals, including humans, and, given the opportunity, will avoid confrontation and slither away. However, when startled or frightened, snakes may bite defensively. Not all bites from a venomous snake will result in envenoming: in around 50% of bites there is failure to inoculate sufficient venom to cause a noticeable effect, so-called 'dry bites'.[15] Effects of envenoming may take several hours to become evident, and, therefore, all bite victims should be admitted to hospital and observed for at least 24 hours before a 'dry bite', a bite by a non-venomous snake or non-snakebite can be diagnosed. It is important to bear in mind that, even in the absence of envenoming, fear and anxiety may produce symptoms such as feeling flushed, dizzy, breathless and sweaty, with chest tightness, palpitations, acroparaesthesiae and carpopedal spasm.[14]

During a bite, venom is delivered by powerful muscular compression of the venom-producing glands situated behind the eyes. Venom is directed through venom ducts to the base of the fangs through which venom is conducted through a groove or venom canal to the tips of the fangs and inoculated subcutaneously, intramuscularly or, in rare cases, intravascularly, by the snake's fangs. The dose of venom inoculated is affected by numerous factors including snake species,

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Table 1 Clinical syndromes of snake envenoming

Syndrome	Features	Main species
1. Mild local envenoming	Mild pain and swelling	Night adders Burrowing asps
2. Severe local envenoming	Severe pain Swelling, bruising and blistering Necrosis Lymphadenopathy ±Hypovolaemic shock Rarely: compartment syndrome	Puff adders Cytotoxic cobras
3. Bleeding and coagulopathy	Spontaneous systemic bleeding from, gums, gastrointestinal and genitourinary tracts, intracranial, and elsewhere; post-traumatic bleeding from fang punctures, recent wounds, venepunctures, etc. Risk of acute kidney injury	Boomslang
4. Severe local envenoming, and bleeding and coagulopathy	Features as above for syndrome 2 and 3	*Echis* vipers ? Puff adder (outside of West Africa)
5. Neurotoxic	Local features less prominent Progressive descending paralysis Life-threatening respiratory failure Lymphadenitis	Mambas Neurotoxic cobras

size and maturity; whether one or two fangs were engaged in the bite and for how long; and whether there were repeated strikes. Larger adult snakes tend to inject more venom, but smaller juveniles of the same species may secrete venom that is richer in some dangerous components, such as pro-coagulant enzymes, so bites from small snakes should not be trivialised. Even after several bites snakes do not exhaust their venom and they remain just as dangerous.[15]

Venom composition

Snake venom is the most complex of all animal toxins. The dry weight is >90% protein, and enzymes and toxic polypeptides are the most important components. Snake venom composition varies by species, but also within each species with variation due to geographical and seasonal factors, and snake maturity.[16] Venom contains around a hundred toxic and non-toxic proteins, along with carbohydrates, lipids, amines and other small molecules.[17] The most important venom components are pro-coagulant enzymes leading to consumption coagulopathy that contributes to bleeding; cytolytic toxins, digestive enzymes that destroy cell membranes; haemolytic and myolytic phospholipases, causing widespread effects including neurotoxicity and rhabdomyolysis; neurotoxins that act both presynaptically and postsynaptically at neuromuscular junctions leading to paralysis; and haemorrhagings which damage vascular endothelium and cause spontaneous bleeding.[15] Variation in these venom components leads to the different clinical syndromes of envenoming (Table 1).

VENOMOUS SNAKES IN AFRICA AND EUROPE

Background

Africa provides a home to >400 different species of snake, around 100 of which are venomous and around 30 have been known to cause deaths in humans.[15] Venomous snakes can be grouped into two main taxonomic families: the Viperidae, which includes vipers and adders, and the Elapidae, such as cobras, mambas and sea snakes. In addition, two medically less important venomous families also exist. The first are the *Colubridae* or rear-fanged snakes, including the Boomslang, which rarely bite humans but may cause bleeding and acute kidney injury (AKI). The second are the *Atractaspidinae*, the burrowing asps, whose bites are common and often cause local necrosis. In Africa, many cases of mild envenoming, involving only local pain and swelling, are caused by night adders (*Causus* spp.). Broadly speaking, venoms of Viperidae have predominantly local and haemotoxic effects, leading to tissue necrosis, lymphadenitis and derangement of haemostatic mechanisms. The Elapidae, however, possess neurotoxic venoms, leading to descending paralysis and life-threatening bulbar and respiratory muscle impairment, and in the case of spitting cobras, cytotoxic effects causing tissue damage. Most Viperidae are relatively short and thick-bodied snakes, with a clearly demarcated wide head and distinctive dorsal pattern, while most Elapidae are relatively long, slender and uniformly coloured. However, reliable identification is challenging for the non-expert. The key snakes of medical importance, based on the frequency and severity of their bites, are summarised by African region in Figure 1. Europe is inhabited by several species of viper (*Vipera, Macrovipera* and *Montivipera* spp.) and a mildly venomous colubrid (*Malpolon monspessulanus*).

Snake species of concern

Viperidae

Saw-scaled or carpet vipers (Echis)

The seven or more African species of saw-scaled or carpet vipers, belonging to the genus *Echis,* are indigenous to parts of North, East, West and Central Africa, north of the equator. They are of great medical importance and are responsible for most fatal and debilitating snakebites in savanna areas of the northern third of Africa.[18] They are generally small and slender snakes, averaging 30–70 cm in length with a small, short and wide head. Colouring varies by species but is generally grey or reddish-brown, with distinctive oval or undulating dorsal patterns (Figure 2). The snake's rough, keeled lateral scales produce a distinctive warning rasping sound when the snake feels threatened and rubs its coils together.

In one large case series, carpet vipers had the lowest recorded 'dry bite' frequency of all venomous snakes.[18] Envenoming leads to both local and systemic effects, including blistering and necrosis, extensive swelling and bruising, and coagulopathy. Spontaneous bleeding is most commonly evident from the nose and gums. Victims also bleed from sites of trauma such as venepuncture and other recent wounds. Cerebral or widespread internal and external haemorrhages are common causes of death.[15]

Puff adder (Bitis arietans)

Puff adders are large, heavy-bodied snakes, whose total length may exceed 130 cm. The body is brownish or grey, with distinctive U-shaped or V-shaped 'chevron' dorsal markings, a broad head and narrow neck (Figure 3). Puff adders are generally sluggish, but when agitated, they inflate their bodies and produce a loud hissing sound by blowing air through large nostrils on the top of the snout. The puff adder is widely distributed throughout savanna regions of sub-Saharan Africa and some North African and Arab countries. Considering Africa as a whole, it is probably responsible for more venomous bites than any other snake.[15]

Envenoming causes local swelling, which may progress to include the entire affected limb and adjacent areas of the trunk; blistering and necrosis. Extravasation of plasma into the envenomed limb leads to hypovolaemia and shock is a common feature

Figure 1 Summary of snakes of medical importance by African region.

at presentation.[19] On rare occasions, swelling of muscles within tight fascial compartments (eg, anterior tibial compartment following bites on the foot or lower leg) may raise compartment pressures sufficiently to cause a compartment syndrome. Thrombocytopenia and other anti-haemostatic effects may occur in some geographical areas. In West Africa, envenoming causes bleeding and bruising resulting from thrombocytopenia,[20] whereas in East and South Africa coagulopathy without thrombocytopenia may occur.[21]

Other medically important African vipers

In North Africa, Saharan horned vipers, blunt-nosed vipers and Moorish vipers are of medical importance. The Saharan horned viper (*Cerastes cerastes*) lives in arid, desert environments of North Africa, where it is the most common cause of snakebite.[15] This viper averages 30–60 cm in length, with a thick body and, in most cases, distinctive supraorbital horns. Like carpet vipers, they produce a rasping sound by forming S-shaped coils and rubbing their scales together. Envenoming usually results in local pain, swelling and necrosis. Haemolysis, coagulopathy and AKI have also been observed.[22] The blunt-nosed viper (*Macrovipera lebetina*) and the Moorish viper (*Macrovipera mauritanica*), the most common cause of snakebite in Morocco,[23] are larger snakes, reaching 100–180 cm in length, greyish or reddish brown, with distinctive dorsal markings. Bites result in local envenoming and coagulopathy. Several species of night adders (*Causus*) occur throughout Africa. They are common causes of bites with mild

Figure 2 Saw-scaled or carpet viper. (Copyright DA Warrell).

Figure 3 Puff adder (*Bitis arietans*) Watamu, Kenya (copyright DA Warrell).

Figure 4 Horned or long-nosed viper (*Vipera ammodytes*) (copyright DA Warrell).

local envenoming (local swelling and pain) but have not been responsible for any human deaths.

European vipers

The familiar British adder (*Vipera berus*) is widely distributed across Northern Europe, including Scandinavia. The asp viper (*Vipera aspis*) is found in France, south of Paris, Switzerland and Italy. Probably the most dangerous species is the horned or nose-horned viper (*V ammodytes*) of Austria, Northeast Italy, Hungary, Croatia, Slovenia, Bosnia and Herzegovina, Monte Negro, Macedonia, Serbia, Romania, Bulgaria, Albania, Greece and Turkey (Figure 4).

Elapidae

Spitting (cytotoxic) cobras

Several species of spitting cobra belonging to the genus *Naja* are indigenous to savanna regions of Africa, with a wide geographical range. Appearance varies by species, ranging from uniformly black for the black spitting cobra (*Naja nigricincta woodi*), black with pink throat markings for the black-necked spitting cobra (*Naja nigricollis*), to red-orange for the red spitting cobra (*Naja pallida*), and black with white stripes for the zebra spitting cobra (*N nigricincta*). Adult length varies from 50 to 200 cm, with most adults exceeding 100 cm in length. All share the ability to raise the front of their body from the ground and spread their neck hoods to appear larger to enemies, a key aid to identification of cobras (Figure 5).

Spitting cobras are distinct from the other elapids as their bites cause a clinical syndrome of predominantly local features, without neurological effects. Pain is almost immediate, followed by vomiting, and extensive swelling and blistering in around 60% of bites, and necrosis of the skin and subcutaneous tissues in 70% causing extensive damage.[24] Necrotic lesions may have long-term complications including scarring, chronic ulceration and malignant transformation years later (Marjolin's ulcer). Defensive spitting of cytotoxic venom into the eyes causes venom ophthalmia, which is a syndrome of intense pain, blepharospasm, lacrimation, leucorrhoea, palpebral oedema and corneal ulceration with anterior uveitis. Prompt treatment reduces the risk of complications such as secondary infection, blindness and the need for enucleation.[25] The rinkhals (*Hemachatus haemachatus*) is a small black and white southern African spitting elapid.

Neurotoxic cobras

The neurotoxic cobras also belong to the genus *Naja* and therefore share a number of characteristics with the spitting cobras, with

Figure 5 Egyptian cobra (*Naja haje*) Kenya (copyright DA Warrell).

variable appearance and size between species. One species with a particularly characteristic appearance is the snouted 'banded' cobra (*Naja annulifera*) with a blue-black and yellow-brown banded pattern found in South East Africa. Neurotoxic cobra bites may cause local swelling, but this is less marked than with spitting cobras, and necrosis does not develop. The predominant effect of envenoming is a progressive descending flaccid paralysis, starting within 30 min. Bilateral ptosis, ophthalmoplegia and weakness in muscles innervated by the cranial nerves affecting speech, swallowing, chewing and airway reflexes are affected first, eventually progressing to respiratory failure within 2–16 hours.[26]

Mambas

The mambas, genus *Dendroaspis,* are long, thin, agile snakes, with long coffin-shaped heads. They are nervous and highly dangerous. All but the black mamba are tree-dwelling. The eastern green mamba (*Dendroaspis angusticeps*) and western green mamba (*Dendroaspis viridis*) are uniformly predominantly bright green in colour while Trail's mamba (*Dendroaspis jamesoni*) has some faint darker banding. All may exceed 2 m in length. The black mamba (*Dendroaspis polylepis*) is more heavily built and longer than the other mambas, sometimes reaching >4 m in length, and, despite its name, is coloured greyish-brown, with a black buccal lining (Figure 6). In defence the mambas may rear and hiss, and the black mamba may spread a narrow hood.

The effects of mamba envenoming are due to unusual neurotoxic dendrotoxins, which bind to voltage-gated potassium channels and induce acetylcholine release from the presynaptic neuron. These toxins produce a clinical syndrome of paraesthesia, autonomic overactivity, fasciculations, and rapidly progressive descending paralysis (the effects of which may be present within 15 min), and advancing to fatal respiratory muscle failure. Local effects are variable, but not usually prominent.[15]

Figure 6 Black mamba (*Dendroaspis polylepis*), inset showing black buccal lining (copyright DA Warrell.

Other medically important snakes

Burrowing asps (also known as stiletto snakes, burrowing or mole vipers) (Atractaspis)

These nocturnal, burrow-dwelling snakes are neither vipers nor elapids. One of their long, partially erectile fangs is protruded from the corner of the mouth to inflict side-stabbing bites. They are a common cause of nocturnal bites, especially after heavy rains that force them from their burrows. The venom produces local necrosis especially after bites on fingers or toes. Bites by several different species have been responsible for the few reported acute cardiorespiratory deaths. No antivenoms are available.

Colubridae (back-fanged tree snakes)

Boomslangs (*Dispholidus typus;* Figure 7) and the four species of tree, bird, vine or twig snakes (*Thelotornis*) have small grooved fangs situated at the back of the maxillae. They inflate their throats when threatened. Envenoming requires a sustained bite. Local effects are minimal, but delayed coagulopathy and bleeding can be fatal and haemolysis may lead to AKI. A boomslang monospecific antivenom is manufactured in South Africa.

PREVENTION AND TREATMENT OF SNAKEBITE

Prevention

Personnel deployed in Africa or Europe should adopt simple common sense measures to avoid disturbing snakes and minimise the risk of being bitten. These include wearing boots and long trousers or socks, especially at night and when in undergrowth; sleeping off the ground, or in a tent with sewn-in ground sheet, or under a well tucked-in mosquito net; wearing gloves when collecting firewood or disturbing undergrowth, and using a light at night whenever possible and compatible with military operations. A fuller list of precautions is included in a previous supplement to the journal.[14]

Figure 7 Boomslang (*Dispholidus typus*).

Treatment

Treatment of snakebite can be divided into the prehospital management at Role 1, performed typically by a Combat Medical Technician or Medical Officer (MO) with a focus on first aid measures to prevent harm; and the hospital management at Role 2 or 3 (or possibly a host nation hospital facility in some cases), where decisions about use of antivenom are key. It should be noted that in isolated settings MOs at Role 1 may have to care for patients for a prolonged time, including making judgements about the use of antivenom.

Prehospital management

Snakebite is a medical emergency, and safe, timely evacuation of the patient is critical. Prehospital management of snakebite should focus on evaluating danger to the patient and rescuers while being careful not to further threaten venomous snakes in the area that may bite again if provoked. The patient should be lain flat, ideally in the recovery position, and kept still. Many symptoms following snakebite will be driven by fear and anxiety, and these may settle down with reassurance and relaxation techniques. Immobilisation of the patient, and the affected limb in a splint or sling, combined with use of a pressure pad over the bite wound, may delay systemic absorption of venom. Urgent evacuation to a suitable medical facility should follow rapidly (Figure 8). If possible, attempts should be made to identify the snake species, but this should not be at the expense of delaying evacuation or endangering rescuers. No attempt should be made to catch or kill the snake, but if it does happen to have been killed it should be taken safely to medical care with the victim, or several close-up mobile phone images taken to allow eventual expert identification.

Pressure immobilisation

For definitely neurotoxic bites, such as by identified mambas or neurotoxic cobras, where respiratory paralysis requiring artificial ventilation is the mode of death, simple techniques to delay the systemic absorption of venom may allow time for the victim to be evacuated to medical care before respiratory failure develops. These methods rely on compression of veins and lymphatics draining the site where venom has been inoculated, to delay systemic spread of larger molecular weight neurotoxins.[17] There are no dangerously neurotoxic snakes in Europe and so pressure-immobilisation methods are not needed here. In almost all cases of snakebite on a military deployment in Africa, it is unlikely that the snake species will be identified reliably, and, therefore, the need for identification should be de-emphasised, with a much greater emphasis placed on the rapid application of these techniques before timely evacuation to hospital. Two techniques have been suggested for reducing systemic spread of lethal venom components from the bite site: pressure-pad immobilisation and pressure-bandage immobilisation (Table 2).

The older and better established pressure bandage immobilisation technique involves firmly bandaging the entire limb with elastic (not crepe) bandages to obstruct venous and lymphatic flow without causing ischaemia. Promising results

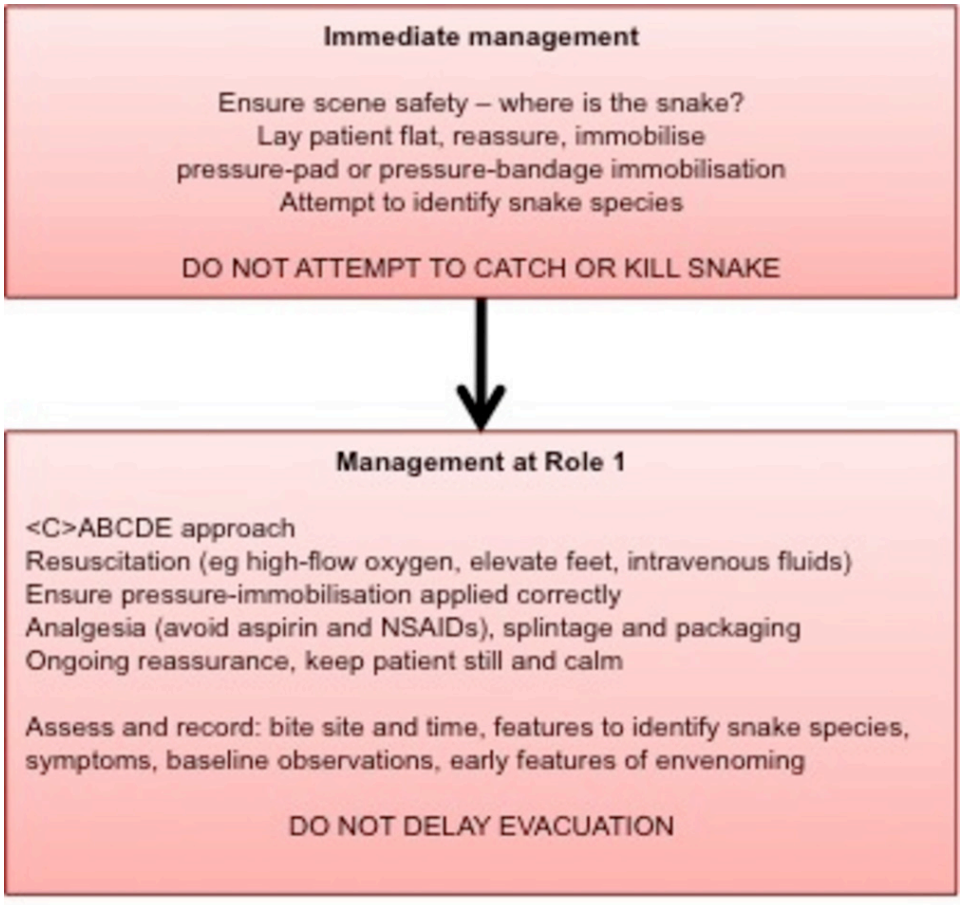

Figure 8 Summary of prehospital management of snakebite. NSAID, non-steroidal anti-inflammatory drugs. FBC, full blood count; PT, prothrombin time; APTT, activated Partial thromobplastin time; FDP, fibrin degradation products; CK, creatinine kinase; LFT, liver function tests.

were seen in laboratory studies in monkeys[27] and, although never rigorously studied in humans, anecdotal case reports of rapid deterioration after removal of the dressing have been published.[28–30] However, frequent reports also exist of inadequate application, loosening in transport and difficulties in training and effective application, even in Australia, where the method has been officially recommended since the 1970s.[31–33] In a military environment, the use of emergency bandages and malleable aluminium splints for the application of pressure immobilisation has been advocated.[34] These are commonplace on military deployments and military medics are familiar with their use and thus this seems a sensible and pragmatic technique, with a minimal training requirement. The effectiveness of this technique is yet to be studied.

An alternative, much simpler, method is pressure-pad immobilisation. This involves applying a small firm pad of any compressible material such as bandage, cloth or foam rubber (approximately 6×6×3 cm) directly over the bite site and tightly bandaging it in place. In comparative mock venom studies in human volunteers, this technique was shown to be superior to pressure-bandage immobilisation, and limb immobilisation alone.[35] Promising results have also been seen in one prospective study of cases of viper bite in Myanmar.[36] A recent systematic review concluded that there was insufficient evidence to firmly recommend one technique over another and that further trials were warranted.[37]

The pressure-bandage immobilisation technique is advocated in the UK Clinical Guidelines for Operations (CGOs), however, only in the case of confirmed elapid bite,[38] presumably fuelled by the theoretical risk of worsening local effects in the case of cytotoxic envenoming. However, no evidence has been published to confirm the risk that local pressure methods increase the extent or severity of local necrosis. In the case of a bite by an unidentified snake species (the likely scenario on military deployments), we therefore propose that the unproven risk of exaggerating local venom effects is outweighed by the potential benefit of delaying respiratory paralysis until the patient can be evacuated to a hospital facility and that the technique should be used immediately in all snakebite cases unless elapid envenoming can confidently be excluded. This is in line

Table 2 Comparison of the two pressure methods for snakebite first aid

	Pressure pad immobilisation	Pressure bandage immobilisation
Technique	Easy to learn	Difficult to learn and to judge tightness
Materials	Readily available	Scarce and expensive
Dangers	Negligible	Tourniquet effect if applied too tightly
Evidence—animal/simulation	Mock venom studies in human volunteers	Studies in monkeys and simulation studies in human volunteers
Evidence—clinical	One field study—venom antigenaemia	Anecdotal cases of deterioration after release

with the WHO guidelines for snakebite management in Africa[14] and South East Asia,[39] and as previously recommended in this journal.[15 34]

Further Role 1 management

After the immediate management steps above, snakebite victims should be rapidly evacuated to hospital care where antivenom may be administered if indicated. Depending on evacuation timelines, further management at Role 1 should focus on resuscitation, supportive management, including administration of analgesia and assessment for developing signs of envenoming. In the case of venom ophthalmia, the eyes should be thoroughly irrigated with generous volumes of bland clean fluid, before using empirical topical antimicrobials (such as chloramphenicol), cautious single instillation of local anaesthetic drops to control the intense pain, eye patching and evacuating to specialist care to exclude corneal abrasions and intraocular complications that may threaten vision.

Hospital management

The focus of hospital management should be on resuscitation, supportive management, searching for evidence of clinically significant envenoming and attempts to determine the species involved with a view to administering antivenom. All victims of snakebite should be admitted to hospital and observed and investigated for signs of envenoming for at least 24 hours before envenoming can be excluded. Mild or absent signs of envenoming on admission and the use of fashionable but arbitrary severity grading scales may be highly misleading, as deterioration may be rapid and unpredictable. Patients must therefore be closely monitored and regularly re-examined for early signs of toxicity, such as gingival bleeding, ptosis, ophthalmoplegia and shock. Baseline investigations should be conducted on admission to hospital (Figure 9), and should include routine haematology and biochemistry, and the 20 min whole blood clotting test (20WBCT). The 20WBCT is a simple test in which whole blood is placed in a new, clean, dry, glass test tube (plastic tubes and glass tubes that have been cleaned with detergent/soap or coated with silicon will not stimulate clotting, producing a false positive result) and checked for clotting after 20 min (Figure 10). Failure to clot warrants use of antivenom.

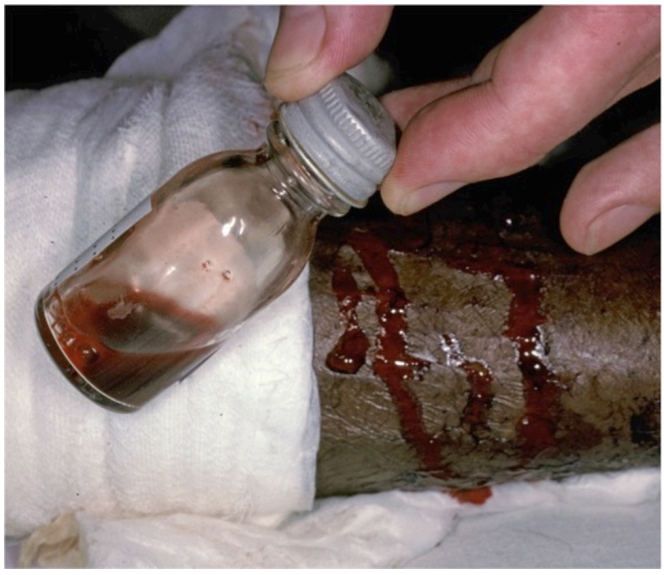

Figure 10 The 20 min whole blood clotting test (copyright DA Warrell).

Vomiting is a common symptom of systemic envenoming and airway management should be considered early to avoid aspiration in patients with incipient bulbar paralysis. Invasive procedures should be avoided in patients with incoagulable blood, unless haemostasis can be achieved with simple pressure dressings. Tetanus risk should be considered in all patients, particularly non-military personnel whose vaccination history may be unknown, and a tetanus toxoid booster is appropriate for all bite victims, even those without envenoming. Prophylactic antibiotics (such as co-amoxiclav) should be reserved for patients whose bites have been incised (as part of ill-advised first aid) or those with obvious tissue necrosis.[15] Secondary infection must be distinguished from local inflammatory effects of envenoming

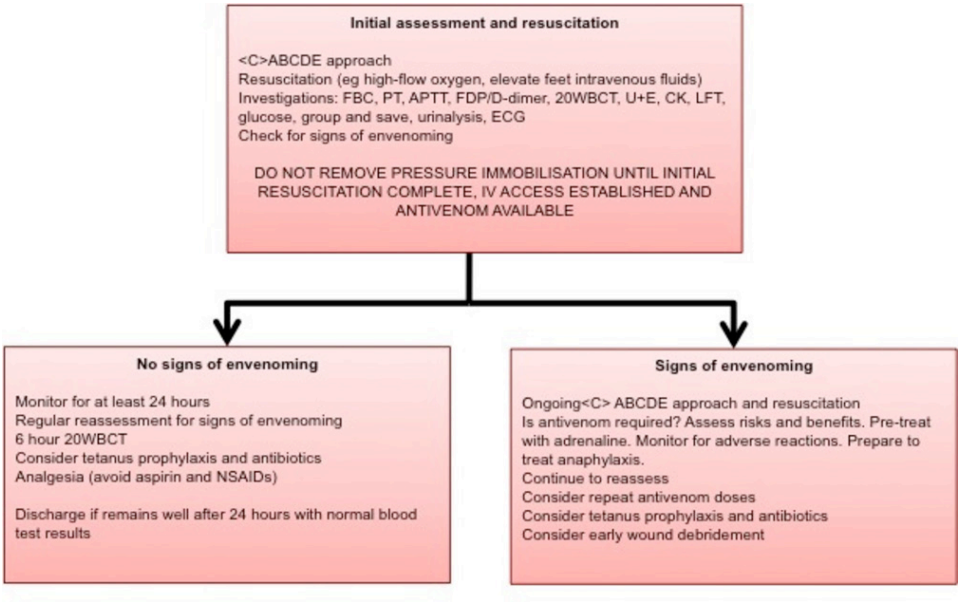

Figure 9 Summary of hospital management. 20WBCT, 20-minute whole blood clotting test; NSAID, non-steroidal anti-inflammatory drugs.

and antibiotic treatment based on results of bacterial cultures (eg, of wound abscess aspirates).

Antivenom

The only specific antidote to snake venom is the immunoglobulin from an animal (usually horse or sheep) that has been hyperimmunised with the venom in gradually increasing doses.[40] Antivenoms can either be monovalent, by which they cover only one species, or polyvalent, by which they cover the most medically important species in a particular region. Monovalent antivenoms are only of use in areas where there is only one species of venomous snake (eg, adder *Vipera berus* in the UK, Scandinavia, the Netherlands, Belgium) or when the species can be identified unambiguously; all African countries are inhabited by several medically important snake species whose identification is challenging, so the use of polyvalent antivenoms is recommended except in the case of boomslang envenoming.[40] Liquid antivenom must be stored refrigerated. Lyophilised antivenoms have longer shelf lives and are easier to store, but they are more costly and must be reconstituted prior to administration.[15] European *Vipera* envenoming is covered by several antivenoms, including MicroPharm ViperaTAb, the one used for treating British adder bites.[41–43]

Indications for antivenom use

Antivenom should not be used routinely for all cases of snakebite but reserved for when clinically indicated: it is expensive, has a limited shelf life, and in the developing world is a scarce commodity. Furthermore, antivenom carries a risk of life-threatening anaphylactic reactions.[15] Antivenom is not required for bites from non-venomous snakes, and in around 50% of cases the bite may be 'dry'. Whether monovalent or polyvalent all antivenoms have a defined range of snake venoms that they will neutralise, outside which they are useless. For certain snake species no antivenoms exist at all and conservative treatment must be employed. Clinical indications for antivenom use are listed in Box 1.

Dosage and administration of antivenom

The dosage of antivenom is based on the amount required to neutralise a set quantity of venom, and not patient size; therefore, adults and children should receive the same dose. Antivenom should be administered as soon as features of severe envenoming are identified. It has proved effective in reversing coagulopathy up to 10 days following bite.[15] The type of antivenom used will depend on likely species. The minimal initial dose should, ideally, be based on clinical dose-finding studies and clinical severity. Otherwise, manufacturer's recommendations, based on lethality tests in rodents, must be used. Doses required are usually between 1 and 20 vials (10–200 mL). Administration can be via slow intravenous injection or infusion over 30–60 min. The incidence and severity of adverse reactions depends on the level of refinement of the antivenom and the dose, but not on the technique or duration of intravenous administration.[44] If intravenous administration is impossible, antivenom can be given intraosseously. Intramuscular injection results in very slow and unreliable absorption, and large volumes cannot be administered this way. It should be used only as a last resort.[15]

Early adverse reactions with antivenom administration are common. Some reactions are pyrogenic, involving teeth-rattling rigours, fever and falling BP, attributable to pyrogen (endotoxin) contamination during manufacture. They are treated by physical cooling (sponging and fanning) and an antipyretic drug such as paracetamol. Most early anaphylactic reactions are relatively mild (urticaria, nausea, vomiting and fever), but severe anaphylactic reactions are seen in 5%–10% of patients and may be life-threatening.[45 46] Most acute anaphylactic reactions result from complement activation triggered by immunoglobulin aggregation.[47] Type 1 hypersensitivity from previous exposure to equine/ovine serum is very rare. Early antivenom reactions are not reliably predicted by skin tests or test doses of antivenom.[4 14]

Despite lack of evidence, pre-medication with antihistamines and corticosteroids is widespread,[47] and is also included in current edition of CGOs.[38] Traditionally there has been a reluctance to use prophylactic epinephrine. However, two small studies demonstrated benefit in preventing acute severe reactions.[48 49] Finally, in 2011, a powerful placebo-controlled double-blinded randomised control trial was conducted, demonstrating that 250 μg subcutaneous epinephrine pretreatment was safe and effective, reducing the incidence of acute severe adverse reactions by 43%, which was sustained at 48 hours in 38%.[50] Pretreatment with low-dose epinephrine has subsequently been recommended in the most recent WHO guidelines at a dose of 0.25 mL of 0.1% solution by subcutaneous injection, except where an antivenom has a low incidence of reactions (<5%), or in older patients with a suspicion of underlying cerebrovascular diseases.[39] In the same trial, neither corticosteroids nor antihistamines had any benefit in preventing acute reactions, and interestingly when epinephrine and hydrocortisone were co-administered, the beneficial effect of epinephrine was not observed. We recommend that premedication with antivenom is used as per the WHO guidelines, and that while antivenom is being administered and for the period immediately after suitably trained staff and equipment (including epinephrine) are readily available in case of severe adverse reaction.

Following antivenom administration, patients must be monitored closely for at least 2 hours. In the event of severe adverse reactions, the antivenom administration should be paused pending aggressive resuscitation, prior to reinitiating the infusion when the patient's condition permits.[15 47] Dose-related late serum sickness-type reactions may occur after 5–10 days, involving urticaria, arthralgias, periarticular swellings, fever, lymphadenopathy and sometimes neurological complications.

Clinical response to antivenom treatment

Administration of appropriate antivenom can lead to rapid correction of cardiovascular effects (often within 10–20 min), cessation of bleeding (within 15–30 min) and resolution of coagulopathy

Box 1 Clinical indications for snakebite antivenom administration in Africa[6]

Systemic envenoming

- Neurotoxicity (eg, bilateral ptosis, ophthalmoplegia, etc)
- Spontaneous systemic bleeding (eg, from gums, nose, Gastrointestinal (GI) and genitourinary, (GU) tracts)
- Incoagulable blood (20-min whole blood clotting test +ve, ie, non-clotting)
- Cardiovascular abnormality (shock, arrhythmia, abnormal ECG)

Local envenoming by species known to cause necrosis

- Extensive swelling (more than half of the bitten limb)
- Rapidly progressive swelling
- Bites on the fingers and toes

within 6 hours. If after 6 hours the blood remains incoagulable, the initial dose of antivenom should be repeated. Postsynaptic neurotoxicity (eg, after bites by neurotoxic cobras) is reversible by antivenom within 30 min to a few hours. Progression to respiratory muscle paralysis may not be preventable and so artificial ventilation is a crucial life-saving treatment. However, antivenom may hasten recovery from paralysis. In the case of cytotoxic envenoming, antivenom will not reverse damage, but may prevent or limit the progress of tissue destruction if given within a few hours of the bite.[15]

After initial treatment, patients may exhibit signs of recurrent envenoming, when further doses of antivenom may be clinically indicated.[51 52] This can be caused by rapid clearance of antivenom[51 53 54] while venom continues to be absorbed from a depot at the bite site.[55] This is possibly enhanced by resuscitation and correction of shock, and redistribution of venom to the intravascular space.[56]

When considering aeromedical evacuation, the destination of a patient and platform used should take into account any ongoing features of envenomation, particularly coagulopathy or neurotoxicity, including the potential for ongoing absorption of antivenom requiring repeat antivenom dosing, adverse reactions from antivenom administration, and any requirements the patient may have for ongoing care, particularly where there is extensive local necrosis or ongoing neurotoxicity. Where the patient is receiving high-quality hospital care, delaying evacuation until a patient is stable and >24 hours from envenomation or last antivenom administration may be prudent depending on the military context.

MEDICAL PLANNING CONSIDERATIONS

When conducting medical planning for a deployment to an African or European country, consideration of likely species, differential diagnoses for envenoming syndromes, availability of antivenom and training requirements should all be considered. As an example, some planning considerations for a deployment to South Sudan are shown in Box 2.

SUMMARY

A change in the pattern of current and future operations, with the likely deployment of small groups of service personnel to remote locations within Africa and Europe, demands an update to the current guidance on the management of snakebites to refresh awareness and reflect new evidence and practices.[14 38] This review article aims to provide a summary of the clinically important venomous snake species encountered in Africa and Europe and the management of their bites from Role 1 to 3. There have been suggestions made to amend previous guidance, now nearly 10 years out of date, which includes the addition of the pressure pad immobilisation technique and the administration of epinephrine immediately prior to antivenom use. Following the publication of this article, the authors will suggest amendments to the current CGOs (dated 2012). Snakebite outside of Africa or Europe is outside the scope of this article but it is recommended that groups deploying to these areas develop an awareness of local snake species, clinical effects of envenomation and the selection and availability of appropriate antivenom prior to travel. Reference to appropriate local guidance such as Southeast Asia,[39] North America[57] or Australia[58] regional guidelines is recommended.

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Box 2 Medical planning considerations for South Sudan

Medically important snake species:

Highly venomous snakes which are common or widespread and cause numerous snakebites, resulting in high levels of morbidity, disability or mortality.

- Elapidae: cobras (*Naja haje, Naja nigricollis*)
- Viperidae: puff adder (*Bitis arietans*), Egyptian carpet viper (*Echis pyramidum*)

Category 2: secondary medical importance

Highly venomous snakes capable of causing morbidity, disability or death, but for which:

- *exact epidemiological or clinical data may be lacking and/or*
- *are less frequently implicated*
  - Atractaspidinae: burrowing asps (*Atractaspis fallax, Atractaspis irregularis*)
  - Colubridae: boomslang (*Dispholidus typus*)
  - Elapidae: mambas (*Dendroaspis jamesoni, D polylepis*), cobras (*Naja melanoleuca, Naja nubiae, Naja pallida*)
  - Viperidae: Gaboon viper (*Bitis gabonica*), rhinoceros viper (*Bitis nasicornis*)

Differential diagnosis for clinical syndromes of envenoming:

- Severe local envenoming alone—puff adder, cytotoxic cobras
- Bleeding/clotting disorders alone—boomslang
- Severe local envenoming+bleeding/clotting disorders—Egyptian carpet viper
- Neurotoxic—neurotoxic cobras, mambas

Available antivenom:

(WHO Guidelines for the Production, Control and Regulation of Snake Antivenom Immunoglobulins 2nd ed 2016[59])

- South African vaccine producers (SAVP) polyvalent covers the most important/most likely biting species (puff adder, Gaboon viper, mambas, neurotoxic cobras but not Egyptian carpet viper, and boomslang).
- In patients with systemic bleeding and coagulopathy (20-min whole blood clotting test+ve non-clotting), the differential diagnosis would be between Egyptian carpet viper and Boomslang, for which SAVP produces two separate monovalent antivenoms.
- Costa Rican 'EchiTAb PLUS ICP' will cover puff adder, *Echis* vipers and spitting cobras.
- No antivenom is available for burrowing asp bites.

Training requirements:

- Pressure-immobilisation techniques for all suspected snakebites, as several neurotoxic species are present
- Snakebite envenoming syndrome recognition and antivenom use for deployed hospital staff

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Snakebites in Africa and Europe: a military perspective and update for contemporary operations

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Notes