

Snake Bite: A review of Current Literature

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Snake bite is a significant public health problem in rural areas of many parts of the world¹. Venomous snakes are found worldwide, except for a few islands and the frozen environments. Snake bite most commonly affects those living in the tropical and sub-tropical areas of Africa, Asia, the Americas and Oceania. The morbidity and mortality resulting from bites are significant. Huge variation in management, coupled with many patients' traditional cultural beliefs and lack of resources contribute to a huge disease burden from snake bites². The World Health Organisation (WHO) recently recognised snake bite as a neglected tropical disease and this has led to a global snake bite initiative to improve clinical outcome following snake bites³.

The aim of this paper is to review current literature on the incidence, pathophysiology and management of snake bite. The aim is to help clinicians to a better understanding of the management of bites, especially when in situations with minimal resources and lack of anti-venom, which is where most snake bites occur. This review discusses a safe approach to clinical management in a field with limited evidence. A treatment guide to use of anti-venom is included to facilitate rapid decision making in stressful clinical situations.

Surgeons in rural hospitals in low and middle income countries are often involved in the management of snake bite patients due to the nature of tissue damage caused by venom or wrong primary management, or because surgeons might be amongst the more senior staff available to help manage critically ill patients in such district hospitals. Most surgeons are outside their comfort zone, however, when they have to manage a snake bite patient, and this paper attempts to provide a structured approach to management.

Burden of Disease

Snake bite has recently been recognised by the World Health Organisation as a neglected tropical disease¹. An exact estimation of the incidence of snake bite has not yet been achieved and remains an epidemiological challenge^{2,4}. Estimates vary greatly and no accurate morbidity and mortality data exist. Swaroop and Grabb⁵ first attempted to quantify the global burden of snakebite but admitted that their data was flawed. Their study suggested that the global annual mortality from snakebite is between 30 000 and 40 000. This was calculated mostly from hospital data and the authors recognised the gross inaccuracy from these results since most bites go unreported or take place in regions where data is not accurately collected⁵.

More recent attempts to determine the annual global deaths from snake bite vary between 20 000 and 125 000^{1,6,7}. Estimates are that the number of bites may be around 5 million per year with more than 2.5 million envenomings^{6,7}. The highest incidences appear to be in Latin America, sub-Saharan Africa, South and South-East Asia^{6,7}. Interestingly, mortality rates were less in Latin American countries than Africa and Asia with similar incidences of bites⁷. The reason for this is unclear, but has been suggested to be due to increased availability and better developed local anti-venom, or better local guidelines on management of bites⁷.

There remains very little evidence detailing the extent of morbidity, long term disability and major psychological impact from snakebite. This is of particular importance since many victims are agricultural workers and a return to work will likely provide significant psychological stress. Disability may also hamper the victim's functional ability to work.

Some studies suggest permanent disfigurement or disability in 18-19% of victims^{8,9}. This is mostly due to local tissue necrosis resulting in debridement, amputation or permanent scarring. Hypoxic brain injury secondary to neurotoxic bites or haemorrhagic complications from envenoming are also causes of long term disability². Significant renal injury can lead to dependence on dialysis following envenoming and is common after bites from Russell's viper in South Asia¹⁰. Permanent disability and disfigurement is of particular concern to the majority of snakebite victims, since most bites occur in regions with poor access to healthcare or income support such as Sub-Saharan Africa and South East Asia⁷.

Pathophysiology

Bites occur most commonly on the lower extremity as a result of accidentally stepping close to the snake¹¹. This is particularly so in low and middle income countries where victims use rural footpaths, often at night. In regions where it is customary to sleep on the ground or on low beds, bites occur at night as cold blooded snakes search for a warm environment. There has been growing reports of exotic venomous snake bites in the Western world due to increasing numbers being kept as pets. Here victims are often bitten on the upper extremity when attempting to handle the snake, often while intoxicated¹¹.

Most venomous bites occur from species with anteriorly located fangs, such as the *Viperidae* and *Elapidae* species. Envenoming from posterior fanged snakes is rare, yet can be highly dangerous, as with bites from species such as the boomslang (*Dispholidus typus*). Snake venoms are complex collections of peptides, enzymes and other toxins that vary greatly even amongst sub-species^{2,11}. This allows the venom to induce several systemic responses in potential prey. The most clinically significant toxins are those that cause tissue necrosis and adversely affect the neurological, cardiovascular and coagulation systems².

Snake venoms contain multiple compounds that cause systemic effects. These vary from neurotoxic pre- and post synaptic blockers, to cytotoxic compounds such as Phospholipase A2 that cause severe local necrosis^{2,12,13}. The toxicology of snake venom is complex and there remains great heterogeneity amongst species, making development of anti-venom difficult and challenging¹⁴.

Probably the most common clinical effect of snake bite is tissue necrosis that can cause extensive soft tissue destruction. Envenoming by a wide range of species, particularly the *Viperidae* such as the puff-adder and rattlesnake species are responsible for tissue necrosis through cytotoxic compounds. Cell lysis, increased vascular permeability and thrombosis within the micro-circulation lead to cell death, severe local inflammation and ischaemia^{2,12}. The systemic inflammatory response syndrome is triggered to varying degree and can result in severe local and systemic sepsis. Debridement is often required^{2,11,12}. Compartment syndrome and the requirement for fasciotomy are not as common as previously thought, and can be prevented by good medical management¹⁵. Snake bite induced nephropathy is a common sequel to cytotoxic envenoming leading to acute renal failure¹². Rhabdomyolysis, cardio-vascular compromise, changes within the micro-circulation and coagulopathy all contribute to nephropathy¹². Pathological changes that can be seen in the kidney include acute tubular necrosis, glomerulonephritis and vasculitis, producing a range of clinical manifestations¹².

Snake venom is thought to cause neurotoxicity exclusively by affecting the peripheral nervous system with almost no penetrance into the central nervous system^{2,16}. Toxicology is complex, affecting both pre- and post-synaptic receptors. The clinical effects vary greatly, with the most feared that of respiratory depression and neurogenic shock². In certain species such as the black mamba (*Dendroaspis polylepis*), symptoms of neurotoxicity start with metallic taste, ptosis and gradual bulbar paralysis^{2,15}. These patients carry a high risk of death and should be treated with great urgency (see management section).

Patients with significant envenoming can have profound cardio-vascular compromise leading to a variety of clinical manifestations with multi-factorial causes. Increased vascular permeability and

dilatation is thought to be implicated, and may be due to the release of cytokines such as bradykinin^{2,17}. Cardiogenic shock is seen in severe bites secondary to cardiac specific myotoxic compounds and venom induced conduction defects. This can be further complicated by ischaemia secondary to coronary artery thrombosis secondary to coagulopathy¹⁸.

Snake bite induced coagulopathy is a complex and diverse clinical problem. It is responsible for a large proportion of snake bite mortality and can be lethal due to complex pathophysiology which is often only reversed with anti-venom^{13,15}. Venom heterogeneity results in disruption of the coagulation pathway at various stages. A range of haemostatic disturbances can be seen due to vessel damage due to cytokines and trauma, reduced coagulability, disseminated intravascular coagulation and the development of pro-thrombotic states¹³. Disintegrins, lectins and phospholipases are examples of substances that are thought to inhibit haemostasis^{2,13}. In some species snake venom contain pro-coagulant factors, such as factor V, X, XIII and pro-thrombin activators resulting in a pro-thrombotic state^{2,13}. Platelet aggregation can be either inhibited or induced depending on the venom sub-type. Laboratory results of patients are often dramatically deranged without correlating clinical manifestation¹³. It is important that snake bite coagulopathy is managed differently to the more common causes of deranged clotting, as usual treatments can be ineffective and dangerous (see management section).

Management

The management of venomous snake bite remains a challenge for even the experienced clinician. Lack of emergency transport and rural location of most bites result in patients often presenting late after the clinical effects of envenoming is well established^{2, 19}. The cultural beliefs of many rural populations further exacerbate the problem with traditional healers often attempting to manage the bite using traditional methods^{2, 8}. Poor education amongst rural populations and healthcare professionals alike result in poor first aid measures that often worsen the effects of envenoming^{8, 19}. Some studies in Africa have suggested that late presentation is not associated with worse outcome^{4, 8}. These conclusions can be challenged: with neurotoxic bites late presentation can result in respiratory failure and hypoxic death while haemotoxic envenoming can lead to fatal coagulopathy if untreated.

A major obstacle in snake bite treatment is the correct identification of the responsible snake. Snake bite species vary greatly from one geographic region to another, even within countries. This makes developing a national or regional treatment strategy problematic. In 40% of cases the patient does not identify the snake and mistaking for a different species is common^{15, 20}. Even expert herpetologists can misidentify the snake, resulting in inappropriate treatment with anti-venom^{2, 20}. Attempting to kill or capture the snake that caused the bite further endangers the individual attempting this, as well as being detrimental to the local eco-system. Capturing the snake responsible for identification should therefore be discouraged.

The difficulties facing clinicians treating snake bite is further exacerbated by the lack of availability of anti-venom and modern medical equipment. Most bites occur in the rural tropics and sub-tropics in low and middle income countries where access to health care is difficult and resources are limited⁷. Clinicians often face treating patients with advanced stages of envenoming without anti-venom. A systematic approach to managing the clinical syndromes resulting from snake bite is an effective and safe strategy for clinicians even with limited resources^{15, 20}.

First Aid

Suggestions for initial treatment of snake bite vary greatly^{2, 15}. Most important are to avoid the use of a tourniquet and transport the patient to medical care as soon as possible^{2, 15}. Attempts to clean or incise the wound and to suck out any venom are ineffective and should be discouraged¹⁵. The Sutherland technique of pressure immobilisation involves compression bandaging of the affected limb along a splinted support²¹. This has been widely taught to reduce venom transport but there is no evidence that

this is indeed successful^{10, 15, 22, 23}. It may be effective in treatment of bites in which the venom is mainly transported via the lymphatics¹⁵. Direct pressure pad application, on the other hand, has been shown to reduce venom uptake in experimental settings, although the evidence for the clinical benefit of this technique is limited^{10, 23}. Educating health care professionals and first aiders in these techniques is fraught with difficulty and inaccuracy; patients are more likely to be harmed by over-tight bandaging resulting in a tourniquet effect^{15, 23}. Tourniquets should be discouraged for use in immediate care except for bites with neurotoxic venom (e.g. mamba species) that are confidently identified; tourniquets should be removed within 90 minutes of application^{15, 24, 25}. Tourniquet use as a first aid measure is associated with increased hospital stay and worse outcome⁸. The ischaemic effects of tourniquet use can greatly increase the tissue damage resulting from cytotoxic envenoming which accounts for 90% of bites in Africa¹⁵.

All patients that suffer venomous snake bite should be resuscitated as per Advanced Trauma Life Support (ATLS®) guidelines²⁶. The most rapid threat to life is with neurotoxic bites in which respiratory depression secondary to muscle paralysis is a frequent cause of mortality^{2, 15}. The airway must be secured while ensuring adequate oxygenation. Patients may become hypotensive due to direct neurotoxicity, cardiogenic shock, bleeding or sepsis. Shock must be urgently treated with IV fluid therapy with appropriate monitoring. Avoiding hypoglycaemia and hypothermia are important resuscitative adjunct measures prior to definitive treatment. All patients should receive tetanus vaccination.

Syndromic Management

The shortage of anti-venom globally, particularly in the rural tropics, provides a major challenge to snakebite management. Management of the specific clinical syndrome caused by envenoming can be effective, whether anti-venom is available or not^{15, 20}. As described previously, snake venom produces different clinical syndromes depending on the venom constituents and varies greatly^{14, 15}.

Local Necrosis / Painful Progressive swelling

Bites from *Viperidae* (e.g. puff-adder, diamondback rattlesnake) and some *Elapidae* (e.g. kraits, cape cobra) species are associated with severe cytotoxic effects^{14, 15}. This is the most common presentation associated with snake bite in many parts of the world, particularly Africa. The cytotoxic effects of the venom progress rapidly and may be severe in patients presenting late. Due to local tissue necrosis and the chemical nature of cytotoxic venom, the administration of anti-venom can be fairly ineffective once tissue damage has occurred¹⁴. Clinical management of these bites can be very effectively dealt with in a systematic fashion¹⁵.

Patients presenting with progressive tissue necrosis should be resuscitated as stated above. It is worth keeping in mind that some snakes such as the African spitting cobras can have neuro- and cytotoxic venom and progressive paralysis is a greater initial threat to life¹⁵.

The affected limb should be elevated and patients should receive adequate analgesia. Fluid resuscitation is an important aspect of management. The cytotoxic effects of the venom can cause fluid loss and patients are at risk of acute kidney injury from processes causing myoglobinuria¹⁴. The affected limb should be monitored closely for tissue necrosis. If debridement is required, it is recommended that this is performed 5-7 days after the bite¹⁵. This allows adequate demarcation margins to develop and can avoid unnecessary returns to the operating theatre in an unstable patient. Anti-biotic therapy is only indicated if signs of sepsis are present.

Complications of cytotoxic envenoming include compartment syndrome, rhabdomyolysis, myoglobinuria and acute renal failure. Compartment syndrome is uncommon and should be managed with fasciotomy, if required on clinical grounds¹⁵. Femoral vessel entrapment by the inguinal ligament can occur rarely, resulting in an ischaemic lower limb²⁷. Carpal tunnel syndrome from bites to the upper limb usually recovers with elevation and analgesia¹⁵.

Not all patients suffering from cytotoxic bites require anti-venom. The indications include compartment syndrome or serious associated complications such as coagulopathy or adult respiratory distress syndrome (*Table 1*). This is required in less than 10% of cytotoxic bites¹⁵.

Table 1

Indications for Anti-Venom
Always use anti-venom with appropriate medical staff and monitoring available. Treat reactions appropriately and ensure adrenaline, cortico-steroid and anti-histamine are available prior to administration
Airway/Breathing
<ul style="list-style-type: none"> • Swelling affecting airway • Bulbar paralysis affecting breathing / swallowing • Respiratory distress (ARDS) after cytotoxic bite
Circulation
<ul style="list-style-type: none"> • All confirmed envenoming from species with haematotoxic venom e.g. boomslang • Systemic bleeding • Signs of intra-cerebral bleeding • Significant deranged clotting measurements eg APTT/PT, TEG • Shock not responsive to fluid therapy • Cardiac arrhythmias
Disability
<ul style="list-style-type: none"> • Triad of Pins and needles, profuse sweating and excessive salivation with metallic taste [suggest severe neurotoxic envenomation] • Evidence of severe/progressive neurotoxicity (low threshold in species known for neurotoxicity such as black mamba) • Seizures / reduced conscious level / severe headache [suggesting intra-cerebral haemorrhage] • Severe local swelling <ul style="list-style-type: none"> ▪ More than ½ of limb within 24 hours ▪ Significant swelling involving digits ▪ Rapid extension within few hours ▪ Compartment syndrome / vessel entrapment
Repeating Anti-Venom
<ul style="list-style-type: none"> • Continued bleeding 1-2 hours after initiating anti-venom • Deteriorating neurological function after 1-2hours • Continued coagulopathy as per laboratory measurements after 6 hours

Progressive Paralysis

Neurotoxic envenoming can cause rapid deterioration and death. This is commonly caused by *Elapidae* such as the black mamba in southern Africa and cobra species^{14, 15, 20}. Some patients may have minor local tissue damage or they may have severe necrosis and associated coagulopathy.

In neurotoxic envenoming the application of an arterial tourniquet is indicated whilst awaiting hospital transfer, as the initial risk to life is much greater from neurotoxicity than tissue necrosis¹⁵. Initial

management of neurotoxic envenoming is appropriate resuscitation with primary attention to Airway and Breathing. This is crucial in order to prevent respiratory failure secondary to bulbar and respiratory paralysis. Patients with severe envenoming will require intubation and full respiratory support and this should not be delayed if indicated during primary survey. Muscle-relaxants should be avoided, unless absolutely required for initial intubation¹⁵.

These patients require anti-venom in almost all cases. Lack of information regarding the snake responsible should not delay anti-venom administration if clinical signs and symptoms are highly suggestive of neurotoxicity. This includes difficulty in swallowing, peri-oral paraesthesiae, metallic taste, excessive salivation and respiratory failure. If patients are supporting their own respiratory function but a rapid onset generalised weakness occur, then anti-venom administration is required to prevent respiratory complications¹⁵. Early intubation should be considered as this allows respiratory support prior to inevitable respiratory failure. Unlike in cytotoxic envenoming, anti-venom is very successful in reversing synaptic neurotoxicity^{14, 24}. If patients are ventilated and anti-venom administered then recovery can be excellent, unless the venom also had significant cytotoxic or coagulopathic effects.

Coagulopathy

Coagulopathy can be the primary venomous effect of some bites, or in conjunction with neurotoxic or cytotoxic venom. The coagulopathic effects vary greatly depending on the venom and the haematological interference it produces. It is worth remembering that even if the coagulopathic effects of venom can produce extremely abnormal laboratory results, these do not always transpire into clinical morbidity or mortality. Most snake bite coagulopathy result in haemorrhagic tendency, but can rarely result in pro-thrombotic events and overall is a major source of snakebite mortality globally, causing as many as 50% of deaths¹³.

As discussed previously, underlying mechanisms of coagulopathy vary greatly. Unlike other more common clinical causes of coagulopathy, those resulting from snake bite are not successfully treated using standard treatment strategies. The only successful treatment is administration of anti-venom. The indications for anti-venom include persistent bleeding from minor skin wounds, clinical evidence of intra-cranial haemorrhage, systemic bleeding or significantly deranged laboratory measurements of coagulation^{13, 15}. Patients may require repeated administration of anti-venom depending on clinical response. Blood coagulation profiles should be rechecked six hours after administration of anti-venom and, if still abnormal, a repeat dose is indicated². The clinician should keep in mind that coagulopathy is often associated with concurrent cyto- or neurotoxic envenoming. These patients should be resuscitated and managed as required for all the clinical sequelae of the bite.

Anti-venom

Anti-venom was first developed by Calmette in the late 19th century^{2, 14}. Immunoglobulins are extracted and purified, usually from animal serum after previous immunization to that specific venom. Anti-venom can be mono- or polyspecific, depending on whether it is effective against a single or multiple species' venom. Polyvalent anti-venom is usually created geographically to cater specifically for the most common bites in that particular region. The large variability in inter- and intra-species venom constitution makes development of anti-venom challenging. This is compounded by the requirement of having venom from all the particular species available to manufacturing companies. Economical and distribution difficulties result in anti-venom being unavailable to large populations that are at particular risk of snake bite.

Anti-venom reactions are common, with more than 10% of patients developing a reaction. These vary from early Type I hypersensitivity reactions to late serum sickness type reactions. Hypersensitivity is due to the use of animal serum and patients with previous exposure to animal serum are at particular risk. The use of pre-administration sensitivity testing is inaccurate, wastes time in patients that are critically ill and should therefore be avoided². Anti-venom should always be administered, resources

permitting, with suitable monitoring and resuscitation equipment available. Intra-muscular adrenaline is the treatment of choice in patients with immediate reactions. Corticosteroids and anti-histamines are indicated as in other causes of anaphylaxis. Patients who receive anti-venom must be monitored for at least 2 hours post-administration.

The lack of anti-venom availability and the risks of its administration must always be considered by the clinician treating a patient with snakebite. The majority of bite victims can be managed safely and successfully without anti-venom. Administration must, however, not be delayed in cases in which anti-venom is indicated (Table 1). Clinicians must familiarise themselves with regional anti-venom availability and whom to contact to obtain these in case of a venomous bite.

Conclusions

Snake bite is a huge public health concern, mostly affecting those in rural areas in low and middle income countries with poor access to healthcare. This is further complicated by a lack of availability of anti-venom, and no good quality evidence base on how to manage bites most effectively. This paper helps to provide clinicians who might have to treat snake bite patients with information on the identification and management of the syndromic sequelae of snake bites, with or without the availability of anti-venom. It is essential that the evidence base for effective snake bite treatment is expanded in order to reduce the devastating public health impact of this neglected tropical disease.

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