Review article

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SNAKE-BITE POISONING IN CHILDHOOD: APPROACH TO DIAGNOSIS AND MANAGEMENT

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This review article examined the epidemiology, pathophysiology, a simple approach to a child allegedly bitten by a snake, and treatment and prevention of snake-bite poisoning. It aims at stimulating the interest of the general paediatrician and raising awareness of health-policy makers of this neglected but important public health issue. Snake bites are most common in tropical countries and in rural areas. Recently, they have been categorized as a Neglected Tropical Diseases (NTDs) to widen its recognition and, more importantly, to improve the allocation of resources given that death from snake-bite poisoning is preventable. The reported prevalence of snake bites in Nigeria is 5 per 1000 persons per year, with the majority of the bites by the African saw-scaled viper (Echis ocellatus). The key to minimizing mortality and severe morbidity is aggressive management of the ABCs of resuscitation, and timely and judicious administration of an adequate dose of antivenom. The health education campaign should emphasize immediate transportation of the victim to an equipped health facility, reassurance, immobilization of the bitten extremity and avoidance of harmful and time-wasting procedures. The paucity of data on the precise incidence of snake-bite poisoning and difficulties in snake identification have led to underestimation of antivenom needs, deficient distribution policies, low antivenom production with an increase in prices of available antivenom, and poor regulation and marketing of inappropriate antivenoms with a general erosion of confidence in antivenom therapy.

Key words: Snake bite ▪ Poisoning ▪ Childhood ▪ Nigeria

Introduction

Snake bites are a neglected public health issue in many tropical and subtropical countries (1). This situation is par-

tly due the fact that the health systems in many of these countries, where snake bites are common, lack the infrastructure and resources to collect the requisite statistical data for assessing the magnitude of the problem (1). This is further compounded by the fact that cases reported to the health ministries by the clinics and hospitals represent a very small proportion of the actual burden, because many victims do not go to health facilities and are therefore not reported. Snake bites are a common emergency among children, especially those living in slums and villages in the tropics. Although snake bites cause considerable morbidity and mortality worldwide, the highest burden exists in Africa, Asia and Latin America, where health systems are also the weakest and medical resources sparse (2). Most deaths and serious complications of snake bites are entirely preventable by making antivenom more widely available, as well as affordable (2). This article reviews the epidemiology, pathophysiology, approach to the child allegedly bitten by a snake, treatment and prevention of snake bites in children, with particular reference to developing countries. The future perspectives are also discussed.

Epidemiology

Gathering data to establish the magnitude of the problem of snake-bite poisoning is a major, difficult undertaking in developing countries, because of under reporting and difficulties associated with identification of snakes. Most victims prefer to be treated by a traditional healer and do not go to hospital (3). For instance, only 8.5% of snake-bite victims attend hospitals in Nigeria (4). Similarly, in Nepal the Ministry of Health reported 480 snake bites with 22 deaths for the year 2000, but a community-based study for Eastern Nepal only, for the same year, reported 4078 snake bites with 396 deaths (5). This paucity of statistical data has led to three interrelated problems: (i) underestimation of antivenom needs by the national health authorities and policy makers in various developing countries; (ii) low demand for manufacturers to produce antivenom products; (iii) the implementation of inappropriate procurement and distribution strategies of antivenom in various countries. Low demand for antivenom has discouraged its production by manufacturers, resulting in an increase in prices, further depressing demand, to the extent that treatment has declined significantly or even disappeared completely in some areas (6). The situation is further compounded by the entry onto the markets of inappropriate, untested or even fake antivenom products which has generally undermined confidence in antivenom therapy among clinicians, health managers and patients, further eroding demand (6). There is a great fear of antivenom supply failure in Africa and in some Asian countries. However, the World Health Organization (WHO) is currently taking some steps to avert such a health catastrophe. In this regard, envisaged strategies include: (i) WHO guidelines for the production, control and regulation of antivenoms and (ii) an online database identifying the worldwide distribution of clinically relevant venomous snakes and their existing antivenoms (6). Estimates indicate that the incidence of snake bites, as well as the resultant mortality, is higher in developing than in developed countries. For instance, it is estimated that per 1000 persons 0.6 to 5 bites occur in Australia compared to 5 bites in Nigeria (7). Approximately 45,000 cases of snake bites are reported annually in the United States (7). The estimated annual snake bite-induced deaths were 23,000 for West Africa and 12 to 15 for the United States (7). In Africa and Asia, case fatality rates up to 15% have been reported among hospitalized patients (7). Annual statistical reports from India have estimated that more than 20,000 deaths

occur annually due to snake bites (8). The estimated mortality figure from Brazil was 2,000 annually (8). The African saw-scaled viper (also referred to as the Nigerian carpet viper), Echis ocellatus, is the most prevalent cause of bites in Nigeria and is associated with the highest mortality rates (9). The four families of venomous snakes found in Nigeria are Viperidae, Elapidae, Colubridae and Atractaspididae (8). In this regard, the three medically most important species are: the Nigerian carpet viper (Echis ocellatus), the black-necked spitting cobra (Naja nigricollis) and the puff adder (Bitis arietans), and they belong to the first two families (9). Bites are most frequent between the months of February and May (10). Children fall victim to snake bites on farms while working with parents, fetching firewood in areas with dense foliage, during play in disused buildings or while exploring holes and crevices in search of rabbits (11, 12). Most bites occur on the foot or hand (11, 12). Prevalence of bites is higher in males than females (10, 11).

Pathophysiology of snake venom

Recent studies have shown that the majority of snake venoms evolved through a process by which genes encoding for a normal body protein, usually involved in regulatory processes or bioactivity, is duplicated and the copy is selectively expressed in the venom gland (13). Studies have revealed that different toxins originated from different protein bodies and evolved through episodes of repeated duplication and recruitment, accounting for their diversity in composition and properties (14), and conferring on the snake the ability to attack a wide range of prey (15). Once toxins have been recruited into the venom proteome, they form large multigene families and evolve via the birth-and-death model of protein evolution (16). This recent finding on the evolution of snake venom strongly challenges previous literature, which stated that snake venoms are modifications of the salivary or pancreatic proteins (17). The composition and toxicity of snake venoms vary with family, genus, species, geographic location, season, diet/habitat, age and sex of the snake (8, 9, 18). Snake venom is a complex mixture of enzymatic and non-enzymatic compounds. Some enzymes identified include phospholipases A2, D-hydrolases, proteases, hydaluronidase, nucleotidase and ATP-ases. The non-enzymatic compounds may have predominantly cytotoxic, neurotoxic, haematotoxic (haemorrhagic or coagulopathies), cardiotoxic or myotoxic effects (19-21). However, this classification is toxicologically misleading as these effects often occur in combination, and pure neurotoxicity, coagulopathy or myotoxicity is rare. The mechanisms of snake venom toxicity are shown in Table 1.

Table 1 Snake venoms and mechanisms of toxicity

Venom action	Clinical effect
Hyaluronidase (all venoms)	Spread of venom
Vasodilators (Kallikrein)	Hypotension
Coagulopathic e. g. Viper, Echis (Activates factors V, X, pro-thrombin)	Consumptive coagulopathy
Haemolysins e. g. Vipers	Bleeding from fang site
Haemorrhagins e. g. Vipers (Inhibit platelet activity. Increase vessel wall permeability)	Bleeding from fang site
Neurotoxins: pre-synaptic e. g. puff Adder. Post-synaptic e. g. Cobras.	Muscular paralysis; respiratory failure
Cardiotoxins e. g. Burrowing Asp, some elapids. Myotoxins e. g. Vipers, Cobras	Local tissue necrosis

Adapted from Jones et al. (21).

The venom of some snakes may contain exogenous pathogenic bacterial flora (22). Vipers and some cobra venoms are chiefly cytotoxic whereas elapid venoms are neurotoxic in nature. Some cobras (Naja naja) and Actractaspididae produce cardiotoxins. Hydrophid venom is chiefly myotoxic. Colubrid venom is haemolytic while some viperidae produce toxins that cause coagulopathy (23). The Echis ocellatus venom contains a zinc metalloproteinase called Ecarin, which acts as a procoagulant by activating prothrombin producing Ecarin-thrombin, which is insensitive to antithrombin III and heparin in the clotting cascade (24). In addition, the venom contains an inhibitor of platelet aggregation called echistatin, a fibrinogen receptor antagonist (25).

Approach to a child allegedly bitten by a snake

The first task of the attending physician is to answer the question, "Is this a poisonous snake bite?" A correct and prompt answer is critical for proper treatment. The task has two parts. First: was the bite due to a venomous or non-venomous snake? Second: if the snake is venomous, is poisoning present or likely? This question may be resolved by:

A. Eliciting focused history (circumstantial evidence). The key questions to ask the victim/relations are:

- Which part of the body was bitten?
- How long ago?
- Under what circumstance were you bitten?
- By what type of snake?
- Was the snake killed? If yes, did you bring the dead snake along with you?

B. Physical examination of the patient.

Evaluation for envenomation depends on the development of local and systemic manifestations.

Local manifestations

The classic local manifestations of inoculation of a potent snake venom in the tissues may be represented by two Ps (puncture and pain) and two Es (edema and erythema). The diagnosis is substantiated if two or more of the four features (i-iv) are present.

- **Puncture:** Presence of one or two fang marks (20). The distance between the two fang marks gives an idea about the size of the snake. Sometimes, no fang mark will be seen.
- **Pain:** Usually develops within 5-10 minutes of the bite (26). In moderate or severe envenomation, the pain is severe and unremitting (8). Non-poisonous snakes do not give rise to intense pain.
- **Edema:** Typically obvious within 5-10 minutes (26). The swelling is progressive, with the overlying skin becoming tense and shiny (intensive cellulitis). If one knows the snake is a viper, and swelling is absent, then poisoning can immediately be excluded (28).
- **Erythema:** Redness is usually visible within 5-10 minutes (26). Later, other types of discoloration appear and eventually become bluish, unlike the typical reaction to a severe insect bite.
- **Haemorrhage:** Oozing from fang marks often continues for several hours in contrast to a wound from non-fang teeth, which cease bleeding promptly. Petechiae and ecchymoses are common (21).
- **Paresthesias:** Often, numbness and/or tingling occur at the site of the bite and around the mouth.
- **Late local signs:** Tissue necrosis and thrombosis may develop, with sloughing of tissues and gangrene in the extremi-

ties. Regional lymphadenopathy may occur (19).

Systemic manifestations

The two major systemic manifestations of snake-bite poisoning occur in the central nervous system and the haematological system.

- **General:** Lassitude, weakness, fatigue, non-whirling dizziness, diaphoresis, sialorrhoea, and sensation of a "full" or "thick" tongue.
- **Haematological system:** Coagulopathy shown clinically by petechiae, ecchymoses, bleeding into the subcutaneous tissues, muscles, viscera and serous cavities. Mucosal bleeding, shown by epistaxis, subconjuctival haemorrhage, haematuria, haematemesis, and melaena are common. Prolonged bleeding from the puncture site is evident (27). Laboratory findings include decreasing fibrinogen, elevated prothrombin and partial prothrombin times, thrombocytopaenia, prolonged bleeding and clotting times (9).
- **Central nervous system:** The early manifestations are ptosis and ophthalmoplegia. Palatal and pharyngeal involvement lead to slurred speech and difficulty in handling oral secretions. Seizures are common in children, occurring 5-10 hours after the bite (23). Typically, the sensorium remains intact with a lucid and oriented patient. Sometimes, somnolence may be a feature. Occasionally, some patients may have euphoria if they have been given a traditional snake bite remedy containing alcohol (19).
- **Renal:** Acute renal failure, haematuria.
- **Cardiac:** Hypotension, congestive cardiac failure, cardiac arrest.
- **Pulmonary:** Oedema, respiratory failure.
- **Gastrointestinal:** Nausea, vomiting, haematemesis, melaena.
- **Death:** May be due to respiratory failure, cardiac failure, acute renal failure, haemorrhage or irreversible shock.

Initial manifestations

The initial manifestations of snake bites arise from fright since systemic effects of even the most poisonous snakes generally take about 30 minutes to appear (23). The initial manifestations include pallor, sweating, fainting, tachycardia, vomiting, abdominal colic, diarrhoea and hypotension, which may be severe enough to result in shock (23). These features usually resolve spontaneously within 30-60 minutes, suggesting activation of the kinin system followed by inhibition by bradykinin rather than a direct venom effect (23). Subsequent manifestations depend on the type of venom inoculated into the victim.

Classification of envenomation severity

The purpose of grading of severity is to determine the quantity of antivenom to be administered to the patient. In this regard, the dose of antivenom is 50 ml for mild, 100 ml for moderate and 150 ml for severe envenomation. The grading is shown in Table 2.

Table 2 Classification of envenomation severity

Grade 0:	No envenomation.
Grade 1:	Mild envenomation (local swelling and pain without progression).
Grade 2:	Moderate envenomation (swelling, pain or ecchymosis progressing beyond site of injury, mild systemic or laboratory manifestations).
Grade 3:	Severe envenomation (marked local response, severe systemic findings and significant alteration in laboratory findings).

Source: Holve (7).

C. Examination of the snake

If the snake has been killed and brought along by the patient's relations, the physician should attempt to assign it to either the poisonous or non-poisonous group. Snakes are best identified by the type and presence of fangs. Only venomous snakes have fangs either in the front or back of their mouths. Non-venomous snakes have no fangs or venom sacs. In general, Viperidae (vipers and adders) have anterior, long curved, mobile fangs (27). Elapidae (cobras and mambas) have anterior, short fixed fangs (27). Colubridae (colubrid, boomslang) have posterior, short, fixed fangs (27). Atractaspididae (burrowing asps or stilleto snakes) have anterior, very long, fangs (29).

D. Simple laboratory tests

A coagulability test of the child's blood (performed 30 minutes or later after the bite) is helpful diagnostically. In Africa, non-clotting blood distinguishes between vipers. For example, Echis ocellatus causes non-clotting blood while Bitis arietans does not (28). If the blood from a finger collected on a clean watch glass coagulates in less than 10 minutes, an Echis ocellatus bite is excluded (23). Similarly microscopic examination of the urine for red blood cells is of diagnostic value.

A rapid enzyme–linked immunosorbent assay (ELISA) test, which can provide accurate diagnosis, has been developed, but it is very expensive and, therefore, not really applicable in most developing countries (28).

Other investigations

The following investigations should be performed: complete blood count, platelet count, clotting time, prothrombin time, partial thrombin time, urea and electrolytes, serum creatinine, electrocardiography ECG) and serum creatinine phosphokinase.

Management of snake-bite poisoning

Broadly, the management of snake-bite poisoning can be subdivided into:

- Pre-hospital care (First aid).
- Supportive therapy.
- Specific therapy.
- Local wound management.

Pre-hospital care (First aid)

- The most important first aid measure is transportation to an equipped health facility as soon as possible, taking the snake along, if killed.
- Avoid harmful and time-wasting procedures such as incisions, suctioning, application of native herbs, ice packs, constricting bands/tourniquets.
- Reassurance, to keep the patient quiet and calm.
- Splint the affected limb and minimize the patient's motion.
- Clean wound with a germicidal preparation.
- All victims of snake bites should be admitted to hospital for at least 24 hours as the course in the early stages is unpredictable.

Supportive therapy

Stabilize the patient by applying the ABCs of resuscitation, depending on the patient's clinical condition. Frequent cardiopulmonary assessment is recommended. An IV line should be established in the unbitten extremity. Blood transfusion (whole blood) is useful in the treatment of shock due to a viper bite, especially if the victim was anaemic before the bite or if an effective antivenom is not available (both of which are common situations in developing countries). Adjustment of fluid and electrolyte balance is indicated in the presence of vomiting, renal insufficiency and shock. A booster of tetanus toxoid is advised. Strictly speaking, antibiotics are not

needed unless clinical signs of infection or necrosis is present. However, in our setting, because of pre-hospital dressing with contaminated materials, I think antibiotics should be given routinely. The antibiotics should cover both aerobic and anaerobic organisms. Analgesics, such as oral paracetamol 15 mg/kg/dose 8 hourly or codeine 1-1.5 mg/kg/dose for pain, are useful. Avoid intramuscular injections. In all venomous snake bites, the victim should be admitted and observed for at least 24 hours. In cases where there is persistence of features of acute snake-venom ophthalmia, treatment with local antibiotics, such as chloramphenicol, is recommended (30). Irrigation with a bland fluid is imperative, but the value of antivenom for ophthalmia appears unproven (30, 31).

Specific therapy

Antivenom therapy: The most appropriate therapy in snake-bite poisoning is timely administration of an adequate dose of the species-appropriate antivenom. Antivenom is indicated only if signs of envenomation are present. The indications are shown in Table 3.

Dose

The ideal dose is not known and dosing depends on the severity of the envenomation (Table 2). The dose is similar for adults and children. The effect of antivenom therapy is judged by the clinical response or clotting time in the case of procoagulant envenomation by E. ocellatus. The initial dose is repeated 6 hourly until clotting occurs at 20 minutes.

Timing of antivenom

The entire initial dose should be given as soon as possible, but preferably within 4 hours of the bite. It is never too late to start, as antivenom given up to 24 hours after a viperine bite has been shown to reverse coagulation deficits (21, 32). Indeed, venom requiring neutralization may be present even 3 weeks after the bite (23).

Preparation and administration of antivenom

The dose of antivenom is diluted 4-5 times with normal saline and infused slowly; about 20 ml is given over the first 30 minutes and, if there is no reaction, the remainder is infused over the next 60 minutes (a total of 90 minutes). Before use, the antivenom should be checked for any opacities which precede loss of potency. A clear antivenom is fully potent. Before the administration of antivenom obtain a history of previous administration of anti-serum, allergies, bronchial asthma and urticaria. In small children, 0.45% saline in 2.5% dextrose should be substituted for 0.9% saline to dilute the antivenom to avoid sodium overload (28). Polyspecific antivenom is mainly used in developing countries, such as in Africa. The advantage is that it eliminates the necessity of the clinician having to make a choice as to which monospecific antivenom

Table 3 Indications for antivenom administration in snake bites (21)

Cardiogenic shock
Spontaneous system bleeding
Incoagulable blood
Neurotoxicity (e. g., ptosis, ophthamoplegia, dysphagia, respiratory paralysis, impaired consciousness)
Haematuria
Evidence of haemolysis
Rapidly progressive extensive local swelling

to administer. But the drawback is that a much larger volume is required in polyspecific than in monospecific antivenom therapy, increasing the risk of occurrence of both immediate and delayed serum reaction (28).

Treatment of serum sensitive individuals
At the first sign of an anaphylactic reaction, the infusion should be temporarily stopped, and 0.01 ml/kg of 1:1000 adrenaline (maximum 0.5 ml) injected intramuscularly. The dose may be repeated. Supplemental oxygen should be provided. Need for intubation should be anticipated. Intravenous chlorpheniramine maleate 0.2 mg/kg/dose and hydrocortisone 2 mg/kg/dose are given. This is almost always quickly effective and the antivenom infusion can then be restarted cautiously over 10-15 minutes with close monitoring of the patient.

Antivenom administration may be complicated by three types of reaction: early (anaphylactic), pyrogenic and late (serum sickness type) (21). Pretreatment with antihistamine, corticosteriod and subcutaneous 0.1% adrenaline reduces the incidence of early or late reaction (19).

Local wound management
The wound is cleaned and left open. Wound debridement may be necessary on the 3rd or 5th day after haemodynamic stabilization. Compartment syndrome should be suspected and surgical assessment requested, if pulses are absent in the bitten limb. Occasionally skin grafting may be required.

Monitoring of the patient
The following parameters should be monitored and charted:

- Hourly blood pressure, pulse rate, respiratory rate.
- Circumference of the bitten extremity is measured at the level of the swelling and hourly progression of swelling is recorded.
- Abnormal bleeding (at injection sites, gums and old wounds).
- Blood clotting time, haemoglobin level, leucocyte count.
- In severe poisoning, urine output, microscopy, specific gravity, serum electrolytes and urea.
- In elapid bites, watch out for neurotoxic features, such as ptosis.
- Daily electrocardiogram and aspartate aminotransferase.
- Frequent evaluation of the patient is critical, especially in the first 3 to 4 days of admission.

Bad prognostic factors (9) This may be related to the dose of venom and the rapidity of its circulation.

- Small, young victims.
- Bites on the trunk, face, neck and blood vessels.
- Bites by large snakes.
- Presence of bacteria in the venom or mouth of the snake.
- Mobilisation or exertion following bite.
- Delay in receiving effective treatment.

Factors contributing to death (9)

- Intracranial haemorrhage.
- Complications of local wound necrosis, including tetanus.
- Acute renal failure.
- Logistic problems regarding cost, availability or efficacy of antivenom.
- Delays between bites and presentation to equipped hospitals.

Prevention

- Children should be cautioned not to explore under ledges or in holes where a snake might be hiding.
- Children should be prevented from playing in disused buildings, rubble and areas overgrown with grass.
- The likelihood of snakes remaining in

the vicinity of dwellings can be reduced by eliminating the rodent population by keeping the surroundings clean and the grass short.
- Protective clothing, boots, socks, long trousers should be worn while working in snake-infested areas.
- Unlit paths and roads are particularly dangerous after heavy rains. Use of a torch light is desirable in such circumstances.
- A health education campaign should emphasize the benefits of orthodox medicine so as to reduce the resultant morbidity and mortality, as only 8.5% of snake bite victims attend hospitals in Nigeria (6). Although the use of first-aid measures following a snake bite, prior to presentation in a health facility, is a common practice in developing countries, these measures are often ineffective, time wasting and, sometimes, harmful (19, 20, 33). In this regard, these harmful practices need to be discouraged.

Future perspectives

Today, although antivenom is the only effective therapy for snake-bite poisoning, it is not only expensive (out of reach of poor tropical countries) but also associated with some adverse reactions. This situation calls for exploration of new technologies and therapies as alternatives to antivenom therapy. In this regard, many plant species are popularly referred to as anti-snake venom. Several of such plant species, such as: Eclipta sp., Curcuma longa, Hibiscus esculentus, Caseaaria sp., Musa paradisiaca, Mucuna pruriens, Bauhinia forficata, Annoma Senegallensis, Mikania glomerata, Piper sp., Cordia verbenacea, Pentaclethra macrolobia, have been scientifically investigated and found to possess some anti-snake venom properties 34-39. Future developments may also involve newer techniques in antivenom production (to minimize adverse reactions) and active immunization against the snake venom itself. The production and modification of venom antigens by genetic engineering is an exciting new development, which could lead to the manufacture of snake-venom vaccines (40). A new antivenom (ECHITAB) specific against the venom of Nigerian Echis ocellatus is undergoing clinical trials. Its effectiveness is being compared with another antivenom (Pasteur Ipser Afrique), which was previously found to be effective against Nigerian E. Ocellatus (41, 42). Research into Nigerian herbal extracts revealed that a number of them have anti-snake venom activity and initial results are encouraging (43-45). There are plans to conduct pre-clinical trials using these herbal extracts. Recently, anti-snake venoms have been included in the WHO list of "Essential Medicines" and should, therefore, be part of any Primary Health Care package in areas where snake bites are common.

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