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Antivenom: Can We Apply More than One in the Same Patient?

Numila Maliqari[1], Loreta Teneqexhi[2], Albana Haxhiu[3], Alba Dokaj[4], Asfloral Haxhiu[5]

[1, 2, 3, 4] General Pediatric Department, University Hospital Centre "Mother Theresa" Tirana Albania

[5]General Surgery Department, University Hospital Centre "ShefqetNdroqi" Tirana Albania

Abstract: ***Snake - bite is an important medical emergency and cause of hospital admission. In this article we will present 2 reported cases of snake bitten children in Albania focusing in the management of the patient, especially in the use of the antivenom and the criteria we should follow. Antivenom is the only effective antidote for snake venom. It is an essential element of treatment of systemic envenoming but may be insufficient on its own to save the patient's life.***

Keywords: snake bite, children, management, antivenom.

1. Introduction

In Albania we have nearly 17 species of snakes but only a few serious studies are made about them. Viperaammodytes is the most harmful snake in Albania. It has a wide spread from the seaside areas to the 1800 m over the sea level. Its status of protection in global level refering to IUCN is LC.[2, 15]

More than 90% of snake venom (dry weight) is protein. Each venom contains more than a hundred different proteins: enzymes (constituting 80 - 90% of viperid and 25 - 70% of elapid venoms), non - enzymatic polypeptide toxins, and non - toxic proteins such as nerve growth factor.[30, 38.40, 42, 43]

The quantity of venom injected at a bite is very variable, depending on the species and size of the snake, the mechanical efficiency of the bite, whether one or two fangs penetrated the skin and whether there were repeated strikes. Either because of mechanical inefficiency or the snake's control of venom discharge, a proportion of bites by venomous snakes does not result in the injection of sufficient venom to cause clinical effects.

The incidence of snake - bites depends critically on the frequency of contact between snakes and humans. The peak age for bites is children (WHO UNICEF, 2008) and young adults.

Factors identified as contributing to a fatal outcome included problems with antivenom use (inadequate dose or use of a monospecific antivenom of inappropriate specificity), delayed hospital treatment resulting from prolonged visits to traditional healers and problems with transportation, death on the way to hospital, inadequate artificial ventilation or failure to attempt such treatment, failure to treat hypovolemia in shocked patients, airway obstruction, complicated infections, and failure to observe patients closely after they were admitted to hospital.

Although very rapid death after snake - bite has rarely been reported, it is clear from studies of large series of snake - bite deaths that many hours usually elapse between bite and death in the case of elapid envenoming and several days in the case of viper envenoming (Reid 1968; Warrell 1995).

Symptoms and signs of snake - bite

When venom has not been injected: some people who are bitten by snakes or suspect or imagine that they have been bitten, may develop quite striking symptoms and signs even when no venom has been injected. This results from an understandable fear of the consequences of a real venomous bite. (Harris et al., 2010).

When venom has been injected

Early symptoms and signs: following the immediate pain of mechanical penetration of the skin by the snake's fangs, there may be increasing local pain (burning, bursting, throbbing) at the site of the bite, local swelling that gradually extends proximally up the bitten limb and tender, painful enlargement of the regional lymph nodes draining the site of the bite (in the groin - femoral or inguinal, following bites in the lower limb; at the elbow – epitrochlear - or in the axilla following bitesin the upper limb).

Local symptoms and signs in the bitten part: fang marks, local pain, local bleeding, bruising, lymphangitis (raised red lines tracking up the bitten limb), lymph node enlargement, inflammation (swelling, redness, heat), blistering, local infection, abscess formation, necrosis.

Systemic symptoms and signs: general: nausea, vomiting, malaise, abdominal pain, weakness, drowsiness, prostration, cardiovascular (Viperidae), bleeding and clotting disorders (Viperidae), cerebral arterial thrombosis (western Russell's viper Daboia russelii) (Gawarammana et al., 2009), neurological (Elapidae, Russell's viper), renal (Viperidae, sea snakes) (Tin - Nu - Swe et al.1993), endocrine (acute pituitary/adrenal insufficiency from infarction of theanterior pituitary) (Russell's viper in Myanmar and South India) (Tun - Pe et al., 1987).

Management of snake - bite

First aid treatment - Aims:
Attempt to retard systemic absorption of venom. Preserve life and prevent complications before the patient can

receivemedical care. Control distressing or dangerous early symptoms of envenoming. Arrange the transport of the patient to a place where they can receivemedical care.

ABOVE ALL, AIM TO DO NO HARM!

MOST TRADITIONAL FIRST AID METHODS SHOULD BE DISCOURAGED: THEY DO MORE HARM THAN GOOD!

Recommended first - aid methods:
Reassure the victim who may be very anxious. Immobilize the whole of the patient's body by laying him/her down in a comfortable and safe position and especially immobilize the bitten limb with a splint or sling. Any movement or muscular contraction increases absorption of venom into the blood stream and lymphatics.

If the necessary equipment and skills are available, consider pressure - immobilization or pressure pad unless an elapid bite can be excluded.

Avoid any interference with the bite wound (incisions, rubbing, vigorous cleaning, massage, application of herbs or chemicals) as this may introduce infection, increase absorption of the venom and increase local bleeding.

Tight (arterial) tourniquets are not recommended! To be effective, these had to be applied around the upper part of the limb so tightly that the peripheral pulse gets occluded. This method can be extremely painful and very dangerous if the tourniquet was left on for too long (more than about 40 minutes), as the limb might be damaged by ischemia.

The patient must be transported to a place where they can receive medical care as quickly, but as safely and comfortably, as possible.

Physical examination
This should start with careful assessment of the site of the bite and signs of local envenoming.

Examination of the bitten part: The extent of swelling, which is usually also the extent of tenderness to palpation (start proximally), should be recorded. Lymph nodes draining the limb should be palpated and overlying ecchymoses and lymphangitic lines noted. A bitten limb may be tensely edematous, cold, immobile and with impalpable arterial pulses. If possible, intercompartmental pressure should be measure and the blood flow and patency of arteries and veins assessed. Early signs of necrosis may include blistering, demarcated darkening or paleness of the skin, loss of sensation and a smell of putrefaction (rotting flesh).

General examination: Measure the blood pressure (sitting up and lying to detect a postural drop indicative of hypovolemia) and heart rate. Examine the skin and mucous membranes for evidence of petechiae, purpura, discoid hemorrhages, ecchymoses and, in the conjunctivae, for hemorrhages and chemosis. Thoroughly examine the gingival sulci, using a torch and tongue depressor, as these may show the earliest evidence of spontaneous systemic bleeding. Examine the nose for epistaxis. Abdominal tenderness may suggest gastrointestinal or retroperitoneal bleeding. Loin (low back) pain and tenderness suggests acute renal ischemia (Russell's viper bites). Intracranial hemorrhage is suggested by lateralising neurological signs, asymmetrical pupils, convulsions or impaired consciousness.

Investigations/laboratory tests
20 - minute whole blood clotting test (20WBCT). Hemoglobin concentration/hematocrit may decrease, platelet count also may be decreased in some cases, in the white blood cell count early neutrophil leukocytosis is evidence of systemic envenoming from any species, fragmented red cells ("helmet cell", schistocytes) are seen when there is microangiopathic hemolysis, plasma/serum may be pinkish or brownish if there is gross hemoglobinemia or myoglobinemia.

Biochemical abnormalities like elevated aminotransferases and muscle enzymes if there is severe local muscle damage or particularly if there is generalized muscle damage. Mild hepatic dysfunction is reflected in slight increases in other serum enzymes. Bilirubin is elevated following massive extravasation of blood. Potassium, creatinine, urea or blood urea nitrogen levels are raised in the renal failure. Early hyperkalemia may be seen following extensive rhabdomyolysis. Bicarbonate will be low in metabolic acidosis (e. g. renal failure).

Arterial blood gases and pH may show evidence of respiratory failure (neurotoxic envenoming) and acidemia (respiratory or metabolic acidosis). Desaturation can be assessed non - invasively in patients with respiratory failure or shock.

The color of the urine should be noted and the urine should be tested by dipsticks for blood or hemoglobin or myoglobin. Red cell casts indicate glomerular bleeding. Massive proteinuria is an early sign of the generalized increase in capillary permeability and an early indicator of acute kidney injury.

Antivenom treatment
Antivenom is the only specific antidote to snake venom. A most important decision in the management of a snake - bite victim is whether or not to administer antivenom.

Antivenom treatment for snake - bite was first introduced by Albert Calmette at the Institut Pasteur in Saigon in the 1890s (Bon and Goyffon 1996).

Antivenom is immunoglobulin [usually pepsin - refined F (ab') 2 fragment of whole IgG] purified from the plasma of a horse, mule or donkey (equine) or sheep (ovine) that has been immunized with the venoms of one or more species of snake.

"Specific" antivenom, implies that the antivenom has been raised against the venom of the snake that has bitten the patient and that it can therefore be expected to contain specific antibody that will neutralize that particular venom and perhaps the venoms of closely related species (paraspecific neutralization).

Monovalent (monospecific) antivenom neutralizes the venom of only one species of snake. Polyvalent (polyspecific) antivenom neutralizes the venoms of several different species of snakes, usually the most important species, from a medical point of view, in a particular geographical area.

Antivenom should be given only to patients in whom its benefits are considered likely to exceed its risks. The risk of reactions should always be taken into consideration.

A proportion of patients, usually more than 10%, develop a ***reaction*** either early (within a few hours) or late (five days or more) after being given antivenom. The risk of reactions is dose - related, except in rare cases in which there has been sensitization (IgE - mediated Type I hypersensitivity) by previous exposure to animal serum, for example, to equine antivenom, tetanus - immune globulin or rabies - immune globulin.

Early anaphylactic reactions: Usually within 10 - 180 minutes of starting antivenom, the patient begins to itch (often over the scalp) and develops urticaria, dry cough, fever, nausea, vomiting, abdominal colic, diarrhea and tachycardia. A minority of these patients may develop severe life - threatening anaphylaxis: hypotension, bronchospasm and angioedema.

Fatal reactions have probably been under - reported as death after snake - bite is usually attributed to the venom and patients may not be monitored carefully after treatment.

In most cases, these reactions are not truly “allergic”. They are not IgE - mediated type I hypersensitivity reactions to horse or sheep proteins as there is no evidence of specific IgE, either by skin testing or radioallergosorbent tests (RAST). Complement activation by IgG aggregates or residual Fc fragments or direct stimulation of mast cells or basophils by antivenom protein are more likely mechanisms for these reactions.

Pyrogenic (endotoxin) reactions: Usually these develop 1 - 2 hours after treatment. Symptoms include shaking chills (rigors), fever, vasodilatation and a fall in blood pressure. Febrile convulsions may be precipitated in children. These reactions are caused by pyrogen contamination during the manufacturing process. They are commonly reported.

Late (serum sickness type) reactions: Develop 1 - 12 (mean 7) days after treatment. Clinical features include fever, nausea, vomiting, diarrhea, itching, recurrent urticaria, arthralgia, myalgia, lymphadenopathy, periarticular swellings, mononeuritis multiplex, proteinuria with immune complex nephritis and, rarely, encephalopathy. Patients who suffer early reactions and are treated with antihistamines and corticosteroid are less likely to develop late reactions.

There is no absolute contraindication to antivenom treatment, but patients who have reacted to horse (equine) or sheep (ovine) serum in the past and those with a strong historyof atopic diseases (especially severe asthma) are at high risk of severe reactions and should therefore be given antivenom only if they have signs of systemic envenoming.

In the absence of any prophylactic regimen that has proved effective in clinical trials, these high risks patients may be pre - treated empirically with subcutaneous epinephrine (adrenaline), intravenous antihistamines (both anti - H1, such as promethazine or chlorphenamine; and anti - H2, such as cimetidine) and corticosteroid.

In asthmatic patients, prophylactic use of an inhaled adrenergic β2 agonist such as salbutamol may prevent bronchospasm.
Antivenom should be given by the intravenous route whenever possible.

All patients should be watched carefully for two hours after the completion of antivenom administration and should be treated with epinephrine/adrenaline at the first sign of a reaction.

Antivenom should never be injected into the gluteal region (upper outer quadrant of the buttock) as absorption is exceptionally slow and unreliable and there is always the danger of sciatic nerve damage when the injection is given by an inexperienced operator.

Snakes inject the same dose of venom into children and adults. Children must therefore be given exactly the same dose of antivenom as adults.

2. Reported Cases

Case 1
The patient Xh. C., male, 13 years old, was bitten by a snake on the dorsum of his leftfoot while playing on a grass field, (figure 1).

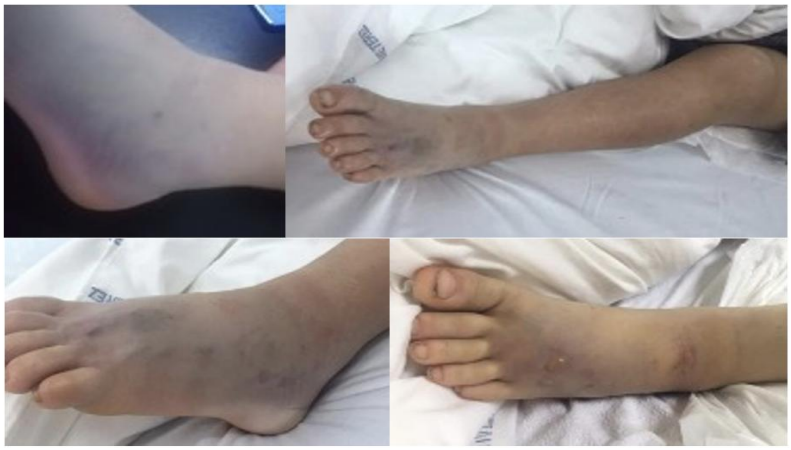

Figure 1: Snake bitted foot, case 1

As first aid, Antivenom (1) was administered in the regional hospital of the nearest area and after some hours the patient was transported with an ambulance at QSU "Nënë Tereza" Tiranë.

After 12 hours, he was hospitalized in our pediatric service with the following complains: edema of the right lower limb at the level of the coxofemoraljoint; severe leg pain with clear evidence of the sign of snake bite; nausea; altered psychological status.

He was strictly monitored and treated with supportive care: liquids, Fresh Frozen Plasma, prednisolone, SAT, AIJS, gastroprotector.

During the passing hours the situation got worst:

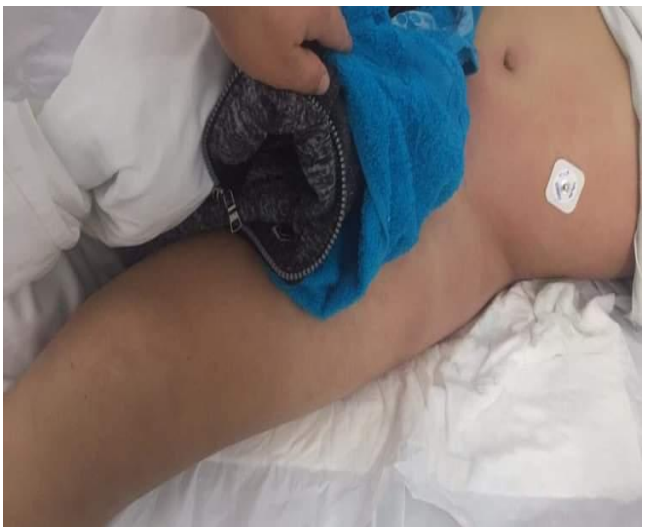

Figure 2: The progression of edema, case 1

He had the progression of the edema at the level of the thorax causing difficulty in breath. The bitten limb was showing necrotic areas. General condition was comprimised. Started the signs of hypovolemic shock with hypotension, oliguria, filiform pulses. The patient was almost in total immobilization. The laboratory findings are mentioned in the table.

Facing this situation we applied the Antivenom (2) for the second time and also continued with aggressive supporting care. After some hours we saw clear clinical improvement: regression of the edema, improvement of neurological and cardiovascular pattern and diuresis. The laboratory findings are mentioned in the table below:

Table 1: Laboratory findings

	In admission	*After first administration of antivenom*	*After second administration of anivenom*
Leukocyte count (/mm^3)	16 000	6 600	12 300
Red blood cell count (/mm^3)	5 510 000	2 570 000	3 250 000
Hemoglobin (g/dL)	13.8	6.8	8.4
Hematocrit (%)	41.9	19	24.3
Platelet count (/mm^3)	444 000	180 000	418 000
ESR (mm/h)	19	55	26
Blood Urea (mg/dL)	54	121	37
Creatininemia (mg/dL)	1.1	1.4	0.6
CK (U/L)	710	1916	820
CK - MB (U/L)	33	44	29
Prothrombin time (%)		35.5	64
Fibrinogen (mg/dL)		199	298

After that, under strictly medical monitoring, the progression was excellent.

The patient has been discharged from hospital in very good condition, supervised by parents, instructed and given a time table of rehabilitation activities.

Case2

The patient E. M, male, 5 years old, was snake bitten on the fingers of his left hand, (figure 3).

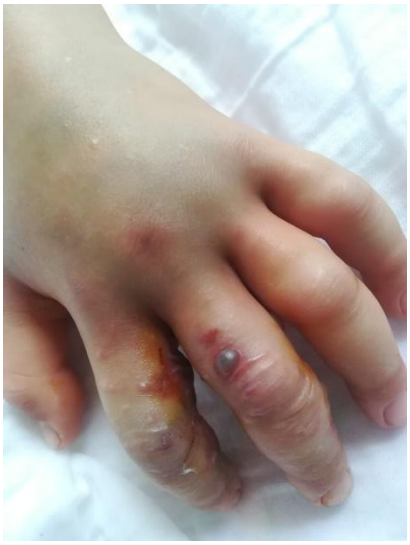

Figure 3: Snake bitten hand, case 2

The first Antivenom (1) was administrated immediately on the regional hospital near the area, after this the patient was transferred with the ambulance on QSU "Nënë Tereza", Tiranë.

The edema was present in a larger area and during the monitoring it spread further the scapulohumeral joint so was applied the second Antivenom (2) with supportive care additionally.

The patient had a temporary improvement.

During the monitoring the edema continued spreading in both hemithoraxes and the head. The general condition was stable. Laboratory findings are mentioned in table 2.

Table 2: Laboratory findings

	In admission	*After third administration of antivenom*
Leukocyte count (/mm^3)	17 700	9 700
Red blood cell count (/mm^3)	4 350 000	3 460 000
Hemoglobin (g/dL)	13.8	9.7
Hematocrit (%)	41.2	25.8
Platelet count (/mm^3)	290 000	237 000
ESR (mm/h)	19	12
Blood Urea (mg/dL)	23	16
Creatininemia (mg/dL)	0.5	0.4
CK (U/L)	368	340
Prothrombin time (%)	64.5	80.3
Fibrinogen (mg/dL)	237	211

Referring to the conditions we decided to apply the third dose of Antivenom (3).

The results were spectacular in the edema regress. Laboratory findings are mentionedin table 2.

After that, under strictly medical monitoring, the progression was excellent. The patient has been discharged from hospital in very good condition, supervised by parents, instructed and given a time table of rehabilitation activities.

3. Discussion

Indications for antivenom
Antivenom treatment is recommended when a patient with proven or suspected snake - bite develops one or more of the following signs:

Systemic envenoming:
Haemostatic abnormalities: Spontaneous systemic bleeding (clinical), coagulopathy (20WBCT or other laboratory tests such as prothrombin time) or thrombocytopenia (<100 x 109/litre or 100 000/cu mm) (laboratory).

Neurotoxic signs: ptosis, external ophthalmoplegia, paralysis etc (clinical).

Cardiovascular abnormalities: hypotension, shock, cardiac arrhythmia (clinical), abnormal ECG. *Acute kidney injury (renal failure):* oliguria/anuria (clinical), rising blood creatinine/ urea (lab).

(Haemoglobin - /myoglobin - uria:) dark brown urine (clinical), urine dipsticks, other evidence of intravascular haemolysis or generalised rhabdomyolysis (muscle aches and pains, hyperkalaemia) (clinical, laboratory).

***Local envenoming*:**
Local swelling involving more than half of the bitten limb (in the absence of a tourniquet) within 48 hours of the bite.

Swelling after bites on the digits (toes and especially fingers).

Rapid extension of swelling (for example, beyond the wrist or ankle within a few hours of bite on the hands or feet).

Development of an enlarged tender lymph node draining the bitten limb.

Antivenom treatment should be given as soon as it is indicated. It may reverse systemic envenoming even when this has persisted for several days or in the case of haemostatic abnormalities for two or more weeks.

It is, therefore, appropriate to give antivenom for as long as evidence of the coagulopathy persists.

Whether antivenom can prevent local necrosis remains controversial, but there is some clinical evidence that, to be effective in this situation, it must be administered within the first few hours after the bite (Warrell et al., 1976; Tilbury 1982).

Deciding whether further dose (s) of antivenom are needed
In patients envenomed by vipers, after an initial response to antivenom signs of systemic envenoming may recur within 24 - 48 hours. This is attributable to:

- Continuing absorption of venom from the "depot" at the site of the bite, perhaps assisted by improved blood supply following correction of shock, hypovolemia etc., after elimination of antivenom (range of elimination half - lives: IgG 45 hours; F (ab') 2 80 - 100 hours; Fab12 - 18 hours) (Ho et al., 1986; Ho et al., 1990)

- Redistribution of venom from the tissues into the vascular space, as the result of antivenom treatment (Rivière et al., 1997).

***Criteria for giving more antivenom*:**
Persistence or recurrence of altered blood coagulability after 6 hours or persistence ore recurrence of bleeding after 1 - 2 hours. Deteriorating neurotoxic or cardiovascular signs after 1 - 2 hours.

If the blood remains incoagulable (as measured by 20WBCT) six hours after the initial dose of antivenom, the same dose should be repeated. This is based on the observation that if a large dose of antivenom (more than enough to neutralize the venom procoagulant enzymes) is given initially, the time taken for the liver to restore coagulable levels of fibrinogen and other clotting factors is 3 - 9 hours. In patients who continue to bleed briskly, the dose of antivenom should be repeated within 1 - 2 hours. In case of deteriorating neurotoxicity or cardiovascular signs, the initial dose of antivenom should be repeated after 1 - 2 hours, and full supportive treatment must be considered.

Supportive/ancillary treatment
Antivenom treatment can be expected to neutralize free circulating venom, prevent progression of envenoming and allow recovery. However, theseprocesses take time and the severely envenomed patient may require life support systems such as treatment of shock, assisted ventilation and renal dialysis until the severely damaged organs and tissues have had time to recover.

Treatment of the bitten part
The bitten limb, which may be painful and swollen, should be nursed in the most comfortable position, but not excessively elevated as this may reduce arterial perfusion pressure in a tensely swollen limb and increase the risk of intra - compartmental ischemia. Bullae may be large and tense but they should be aspirated only if they seem likely to rupture.

Rehabilitation
In patients with severe local envenoming, the limb should be maintained in a functional position. Functional effects of local envenoming range from persistent stiffness and induration due to sclerosis of veins, lymphatics and tissue planes through which the venom has spread, to severe deformity, tissue loss, especially dermonecrosis, and requiring skin grafting and gangrene requiring debridement and amputation. Restoration of normal function in the bitten part should be started by simple exercises while the patient is still in hospital. After the patient has been discharged from hospital rehabilitation is rarely supervised but relatives can be instructed and given a time table of rehabilitation activities. Conventional physiotherapy may accelerate functional recovery of the bitten limb.

References

[1] A. Warrell. Guidelines for the management of snake - bites David A Warrell, WHO, WHO Library Cataloguing - in - Publication data Warrel, David A. Guidelines for the management of snake - bites.1. Snake Bites – education - epidemiology – prevention and control – therapy.2. Public Health.3. Venoms – therapy.4. Russell's Viper.5. Guidelines.6. South - East Asia.7. WHO Regional Office for South - East Asia ISBN 978 - 92 - 9022 - 377 - 4 (NLM classification: WD 410)
[2] Belt PJ. Russell's viper in Indonesia: snakebite and systematics. In: Thorpe RS, Wüster W, Malhotra A (eds). Venomous snakes: ecology, evolution, and snake bite. Symposia of the Zoological Society of London. Oxford: Oxford University Press, 1997. p.219 - 234.
[3] Bon C, Goyffon M. Envenomings and their treatments. Lyon: Editions Fondation Marcel Mérieux, 1996.
[4] Canale E, Isbister GK, Currie BJ. Investigating pressure bandaging for snakebite in a simulated setting: bandage type, training and the effect of transport. Emerg Med Australas.2009; 21: 184 - 90.
[5] Caron EJ et al. Apparent marked reduction in early antivenom reactions compared to historical controls: was it prophylaxis or method of administration? Toxicon.2009.54: 779 - 83.
[6] Chippaux JP. Snake - bites: appraisal of the global situation. Bull World Health Organ.1998; 76: 515 - 24.
[7] Chu ER, Weinstein SA, White J, Warrell DA. Venom ophthalmia caused by venoms of spitting elapid and other snakes: report of nine cases with review of epidemiology, clinical features, pathophysiology and management. Toxicon (2010), doi: 10.1016/j. toxicon.2010.02.023
[8] Dassanayake AS et al. Safety of subcutaneous adrenaline as prophylaxis against acute adverse reactions to anti - venom serum in snakebite. Ceylon Med J.2002; 47: 48 - 9.
[9] de Silva, H. A et al. Prevention of acute adverse reactions to snake antivenom after snakebite: multi - centre, randomized, controlled clinical trial. In: Presented at the Global Issues in clinical toxinology 2008 Conference, 23–28 November 2008, University of Melbourne, Australia.
[10] Fox S, Rathuwithana A, Kasturiratne A, Lalloo D, de Silva H. Underestimation of snakebite mortality by hospital statistics in the Monaragala District of Sri Lanka. Trans R Soc Trop Med Hyg.2006 (7); 100: 693 - 5.
[11] Gawarammana IB et al. Parallel infusion of hydrocortisone +/ - chlorpheniramine bolus injection to prevent acute adverse reactions to antivenom for snakebites. Med J Aust.2004; 180: 20 - 3. Erratum in: Med J Aust.2004 Apr 19; 180 (8): 428.
[12] Gawarammana I, Mendis S, Jeganathan K. Acute ischemic strokes due to bites by Daboia russelii in Sri Lanka - first authenticated case series. Toxicon.2009: 54: 421 - 8.
[13] Gopalakrishnakone P, Chou LM. Eds. Snakes of medical importance (Asia - Pacific region). Singapore: National University of Singapore, 1990.
[14] Ha - Tran - Hung, Höjer, J., Nguyen - Thi - Du. Clinical features of 60 consecutive ICUtreated patients envenomed by Bungarusmulticinctus. SE Asian J. Trop. Med. Publ. Hlth.2009; 40, 518 - 524.
[15] https: //has - org. al/sq/zvarraniket - e - shqiperise/gjarperinjte - e - shqiperise/neperka/

[16] Junghanss T. Bodio M. Notfall - HandbuchGifttiere. Diagnose, Terapie, Biologie (GebundeneAusgabe). Stuttgart: G. Thieme, 1996.
[17] Kasturiratne al. The global burden of snakebite: a literature analysis and modeling based on regional estimates of envenoming and deaths. PLoS Med.2008; 5 (11): e218.
[18] Lalloo D et al. Neurotoxicity and haemostatic disturbances in patients envenomed by the Papuan black snake (Pseudechispapuanus). Toxicon.1994; 32: 927 - 936.
[19] Lalloo DG et al. Snake bites by the Papuan taipan (Oxyuranus scutellatus canni). Paralysis, hemostatic and electrocardiographic abnormalities, and effects of antivenom. American J Trop Med Hyg.1995; 52: 525 - 31.
[20] Lalloo DG et al. Neurotoxicity, anticoagulant activity and evidence of rhabdomyolysis in patients bitten by death adders (Acanthophis sp.) in southern Papua New Guinea. QJM.1996; 89: 25 - 35.
[21] Nuchprayoon I, Garner P. Interventions for preventing reactions to snake antivenom. Cochrane Database of Systematic Reviews.1999; Issue 4. Art. No.: CD002153. DOI: 10.1002/14651858. CD002153.
[22] Nuchprayoon I, Pongpan C, Sripaiboonkij N. The role of prednisolone in reducing limb oedema in children bitten by green pit vipers: a randomized, controlled trial. Ann Trop Med Parasitol.2008; 102: 643 - 9.
[23] Reid HA, Thean PC, Chan KE, BaharomAR. Clinical effects of bites by Malayan viper (Ancistrodonrhodostoma). Lancet.1963; i: 617 - 21.
[24] Rivière G et al. Effect of antivenom on venom pharmacokinetics in experimentally envenomed rabbits: toward an optimization of antivenom therapy. J Pharmacol Exp Ther.1997; 281: 1–8
[25] Rojnuckarin P et al. A randomized, double - blind, placebo - controlled trial of antivenom for local effects of green pit viper bites. Trans R Soc Trop Med Hyg.2006; 100: 879 - 84.
[26] Rusznak C, Peebles RS. Anaphylaxis and anaphylactoid reactions. A guide to prevention, recognition, and emergent treatment. Postgrad Med.2002; 111: 101 - 4, 107 - 8, 111 - 4.
[27] Sano - Martins IS et al. Reliability of the simple 20 minute whole blood clotting test (WBCT20) as an indicator of low plasma fibrinogen concentration in patients envenomed by Bothrops snakes. Toxicon.1994; 32: 1045 - 50.
[28] Sarkar MSU, Sarkar NJ, Patwary MS. Epidemiological survey of snakebite in Bangladesh. Report submitted to Ministry of Science and Technology, Government of the People's Republic of Bangladesh. Dhaka: Ministry of Science and Technology, 1999.
[29] Sawai Y. Clinical problem of snakebites in Southeast Asia. In: AT Tu. Ed. Toxin - related diseases. New Delhi: Oxford and IBH Publishing Co, 1993. p.445 - 69
[30] Theakston RDG. Warrell DA. Antivenoms: a list of hyperimmune sera currently available for the treatment of envenoming by bites and stings. Toxicon.1991; 29: 1419 - 70.
[31] Theakston RDG et al. Envenoming by the common krait (Bungarus caeruleus) and Sri Lankan cobra (Najanajanaja): efficacy and complications of theray with Haffkine antivenom. Transactions Roy Soc Trop Med Hyg.1990; 84: 301 - 308.
[32] Thein - Than et al. Development of renal function abnormalities following Russell's viper (Viperarussellisiamensis) bite in Myanmar. Trans Roy Soc Trop Med Hyg.1991; 85: 404 - 409.
[33] Tun - Pe et al. Bites by Russell's viper (Daboia russeliisiamensis) in Myanmar: effect of snake's length and recent feeding on venom antigenaemia and severity of envenoming. Trans Roy Soc Trop Med Hyg.1991; 85: 804 - 8.
[34] Warrell DA. Treatment of snake bite in the Asia - Pacific Region: a personal view. In: Gopalakrishnakone P, Chou LM (eds). Snakes of medical importance (Asia - Pacific region). Singapore: National University of Singapore Press, 1990. p 641 - 670.
[35] Warrell DA. The global problem of snake bite: its prevention and treatment. In: Gopalakrishnakone P, Tan CK. Eds. Recent advances in toxinology research. Vol 1. Singapore: National University of Singapore, 1992. p 121 - 153.
[36] Williams DJ et al. Antivenom use, premedication and early adverse reactions in the management of snake bites in rural Papua New Guinea. Toxicon.2007; 49: 780 - 92.
[37] Williams DJ, Jensen SD, O'Shea M. Snake bite management in Cambodia: towards improved prevention, clinical treatment and rehabilitation. Manila: WHO Regional Office for the Western Pacific, 2009.
[38] Williams D et al. The Global Snake Bite Initiative: an antidote for snake bite. Lancet.2010; 375: 89–91.
[39] Win - Aung, et al. Clinical trial of intramuscular anti - snake venom administration as a first aid measure in the field in the management of Russell's viper bite patients. Southeast Asian J Trop Med Public Health.1996; 27: 494 - 7.
[40] World Health Organization. Progress in the characterization of venoms and standardization of antivenoms. WHO Offset Publication No.58. Geneva: WHO, 1981.
[41] World Health Organization. Rabies and envenomings: a neglected public health issue. Report of a consultative meeting, WHO, Geneva, 10 January 2007. Geneva: WHO, 2007. (http: //www.who. int/bloodproducts/animal_sera/Rabies. pdf - accessed 08 February 2010).
[42] World Health Organization. WHO guidelines for the production, control and regulation of snake antivenom immunoglobulins. Geneva: WHO, 2010. http: //www.who. int/ bloodproducts/snake_antivenoms/snakeantivenomguide/en/
[43] WHO Antivenoms website http: //apps. who. int/bloodproducts/snakeantivenoms/ database/
[44] World Health Organization - United Nations Children's Fund. World report on child injury prevention. WHO Geneva 2008: 128 - 9.
[45] Wüster W et al. Redescription of Najasiamensis (Serpentes: Elapidae), a widely overlooked spitting cobra from South East Asia: geographic variation,

medical importance and designation of neotype. J ZoolLond.1997; 243: 771 - 88.
https: //www.who. int/teams/control - of - neglected - neglected - tropical - diseases/snakebite envenoming/treatment
[47] Longbottom J, Shearer FM, Devine M, et al. Vulnerability to snakebite envenoming: a global mapping of hotspots. Lancet.2018; 392 (10148): 673–684. doi: 10.1016/S0140 - 6736 (18) 31224 - 8
[48] Chippaux J - P. Snakebite envenomation turns again into a neglected tropical disease! J Venom Anim Toxins Incl Trop Dis.2017; 23 (1): 38. doi: 10.1186/s40409 - 017 - 0127 - 6
[49] World Health Organization. Snakebite envenoming; 2018.
[50] de la Hoz F, Duran ME, García OE, et al.1. Snakebite, Public Health Surveillance Protocol. Instituto Nacional de Salud; 2017.
[51] World Health Organization. Guidelines for the production, control and regulation of snake antivenoms immunoglobulins (WHO); 2018.
[52] Otero - Patino R, Cardoso JL, Higashi HG, et al. A randomized, blinded, comparative trial of one pepsin - digested and two whole IgG antivenoms for Bothrops snake bites in Uraba, Colombia. The Regional Group on Antivenom Therapy Research (REGATHER). Am J Trop Med Hyg.1998; 58 (2): 183–189. doi: 10.4269/ajtmh.1998.58.183
[53] Gutiérrez JM. Improving antivenom availability and accessibility: science, technology, and beyond. Toxicon.2012; 60 (4): 676–687. doi: 10.1016/j. toxicon.2012.02.008
[54] Wakefield J. Ecologic studies revisited. Annu Rev Public Health.2008; 29 (1): 75–90. doi: 10.1146/annurev. publhealth.29.020907.090821
[55] Morgenstern H. Ecologic studies in epidemiology: concepts, principles, and methods. Annu Rev Public Health.1995; 16 (1): 61–81. doi: 10.1146/annurev. pu.16.050195.000425
[56] Chippaux J - P. Incidence and mortality due to snakebite in the Americas. PLoSNegl Trop Dis.2017; 11 (6): e0005662. doi: 10.1371/journal. pntd.0005662