Original articles

BITES BY VENOMOUS SNAKES

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GENERAL

There are about 2700 snake species, with only a minority which are potentially lethal. About 30 species pose a frequent threat. Bites are rare in travellers. The risk is higher for the rural population engaged in non-mechanized agriculture, for drunk men who challenge or harrass the animal and for hobbyists who handling captive exotic pet snakes. Beware of decapitated snakes : a bite reflex can persist for more than an hour after decapitation.

TAXONOMY

1. Adders and vipers : Viperidae

Species belonging to this family occur in the Old World, in Africa, Europe and Asia. They are absent from the Americas. There are about 40 species. Vipers have erectile, mobile fangs anterior in the upper part of the mouth. Behind the fangs is a typical diastema (space without teeth). Most vipers have a stout triangular head. Important examples include *Daboia russelli* with five subspecies, *Bitis arietans* (puff viper), *Bitis nasicornis* (rhinoceros snake), Bitis gabonica (gaboon viper), *Bitis caudalis* (a horned adder), Cerastes cerastes (a desert horned adder), *Vipera berus* (mountain asp), *Echis carinatus* and *Echis ocellatus* (carpet vipers).

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2. Pit vipers : Crotalidae

Pit vipers live in the Americas and in much of Asia. There are about 120 species. They have movable fangs on much reduced maxillae, just as vipers. They possess heat-sensing pits between the eyes and nostrils. Important examples include rattlesnakes (*Crotalus* sp. and *Sistrurus* sp), with a typical tailstructure, a warning device. Other important pit vipers are *Agkistrodon contortrix* (copperhead), *A. piscivorus* (cottonmouth mocassin), *Bothrops* sp. (lance head vipers), *Lachesis muta* (bushmaster), *Calloselasma rhodostoma* (Malayan pit viper) and *Trimeresurus* sp. (habus).

3. Elapids : Elapidae

The family of the elapids contain the cobras, mambas, kraits and coral snakes. There are about 180 species. The fangs are rather short and immobile in the front of the mouth, fixed on the maxilla. Cobras (*Naja* sp) often spread their cervical ribs to display their typical hood. Some snakes mimic this behaviour. Some cobras can spit venom up to a distance of 3 meters. If venom enters the eyes, a caustic toxic keratoconjunctivitis will follow. Mambas belong to the genus *Dendroaspis* and live only in sub-saharan Africa. There are several species : *D. polylepis* (black mamba), *D. viridis* (western green mamba), *D. angusticeps* (eastern green mamba), *D. jamesoni* (Jameson's mamba). Kraits (*Bungarus* sp.) live in Asia. Most kraits are quite passive during the day but become active during the night. Their bites often cause remarkebly little pain. Coral snakes exist in the New World and in Asia. Bites are quite rare but have serious consequences.

4. Sea snakes : Hydrophiidae

Problems with sea snakes are limited to Southeast Asian and Australian coastal waters. There are about 50 species. Their fangs are similar to those of the Elapidae, to which they are closely related. The fangs are small and

often cannot penetrate a neoprene diving suit. *Laticauda* sp prefer to live in coral reefs, *Enhydrina schistosa* prefers the murky waters in estuaria and rivermouths and *Pelamis platuris* can be found in open sea.

5. Colubrids : Colubridae

This family contains a large number of species with a worldwide distribution. About 50 species can cause clinical significant symptoms, but few are dangerous. The fangs are in the rear of the mouth. The animal needs a long contact time between teeth and human skin in order to let enough venom penetrate its victim. *Dispholidus typhus,* the boomslang of Southern Africa is a well known example.

6. Burrowing asps - Atractaspididae

These burrowing animals are quite seldom the cause of envenomation (eg. *Atractaspis engaddensis*) . They live in Africa and in limited areas in the Middle East. There are about 15 species. They have large maxillary fangs used singly with a backwards stabbing motion.

7. Boidae - Boas and pythons

None of the species belonging to this family is venomous, but they can bite.

Fangs, teeth and venom glands

There are small teeth on the os dentata ("lower cheek"). There is a double row of small teeth on the upper maxilla (not in vipers) and on the palatine bone. In vipers, hollow fangs are connected to a short mobile maxilla. In these animals, the maxillae rotate on the prefrontal bone so that the fangs can be folded in rest and be erected when needed. In elapids and other snake species, the fangs are grooved and cannot rotate. In colubrids, a modified salivary gland (gland of Duvernoy), will exit nearby the rear fangs. The venom is brought via capillary action into the wound, a slow process. In elapids and vipers, the major venom glands are modified upper labial salivary glands. They can be compressed with the musculus compressor glandulae, which results in fast and forcefull ejection of venom.

Venom

Snake venom contains several components. Cytotoxic enzymes are responsible for proteolysis (trypsine-like), breakdown of membrane phospholipids, cytolysis, blisters, necrosis and gangrene. Neurotoxins can act postsynaptic (competitive inhibition of the acetylcholine receptor) or presynaptic (inhibiting the release of neurotransmitter vesicles). The venom of some species contains anti- and procoagulantia. Several venom proteins activate coagulation factors (eg. ecarine from *Echis carinatus*). They can imitate thrombine and catalyse the conversion of fibrinogen to fibrine (eg. crotalase from rattlesnakes, ancrod from *Calloselasma rhodostoma* or batroxobin from *Bothrops atrox moojeni*). Fibrinolysis can be activated : eg. lebetase from *Vipera lebetina.* Factor V and X can be activated by the venom of the Russell's adder. There can be interference with protein C and S (eg. *Agkistrodon contortrix*). There can be stimulation or inhibition of thrombocyt aggregation. Some venom factors provoke endothelium damage (hemorhagines). Some snakes have endothelin-like molecules (safarotoxines) in their venom, which are among the most powerful vasoconstrictors known. Angiotensin-converting enzym inhibitors were first discovered in the venom of *Bothrops jararaca.* The effect of the venom of this snake can be compared with an overdose of captopril. Rhabdomyolysis is severe after bites by sea snakes and Australian tiger snakes. In general, nephrotoxicity is multifactorial. Some venom components have no known function, such as the nerve growth factor which is present in cobra venom.

Signs and symptoms after snake envenomation

A bite wound can show small scratches from the small teeth and/or puncture wounds from 1, 2, 3 or 4 fangs (reserve fangs are often present). Many snakebites will be dry bites, without injection of venom. In these cases there will be fang marks, but no signs of envenomation.

1. Elapidae

The local symptoms are sometimes minimal, but skin necrosis occurs with some species. There often is significant pain and regional lymphadenopathy. This can also occur after bites by non-venomous snakes and is by itself not an indication for antivenom. Systemic signs and symptoms include neurotoxicity (cranial nerve dysfunction, ptosis, diplopia, swallowing difficulties, slurred speech), peripheral weakness, altered mental status and respiratory failure. There can be an evolution towards cardiovascular failure, myonecrosis and/or renal failure. Bites by spitting cobras often manifest violent local reactions with hemorrhage and necrosis, but rarely neurotoxicity. Bleeding tendencies are rare.

Table 1: Geographical distribution of some important snakes

- Southeast Asia :	Russell's viper *(Daboia russelli)*
	Carpet vipers : *Echis carinatus complex*
	Habus *(Trimeresurus sp)*
	Malayan Pit Viper *(Calloselasma rhodostoma)*
	Several cobras and kraits
- Coastal areas of Southeast Asia and North Australia : sea snakes	
	Laticauda sp (sea kraits)
	Enhydrina sp
	Pelamis sp
- Australia : most problems due to elapids	
	Brown snakes *(Pseudonaja)*
	Black snakes *(Pseudoechis)*
	Taipans *(Oxyuranus)*
	Tiger snakes *(Notechis)*
- Africa :	Carpet vipers *(Echis carinatus / E. ocellatus)*
	Puff viper *(Bitis arietans)*
	Cobras and mambas *(Naja* sp, *Dendroaspis* sp*)*
- South- and Central America :	
	Cascabel *(Crotalus durissus terrificus)*
	Lancehead pit vipers *(Bothrops atrox, B. jararaca)*
	The bushmaster *Lachesis muta* is rather rare.
- North America :	Rattlesnakes (*Crotalus* and *Sistrurus* sp)
	Copperhead and Cottonmouth Mocassin (*Agkistrodon* sp.)
	Coral snakes (*Micrurus* sp)
- Europe :	Only a limited number of endemic viper species. Bites are rare.

2. Sea snakes

The bite of a sea snake often results in trivial local lesions. Fang marks may be difficult to identify. However, there can be an evolution towards neurotoxic symptoms, myotoxicity with muscle pain, tenderness, myoglobinaemia, myoglobinuria and hyperkalemia.

3. Vipers and pit vipers

Bites by vipers and pit vipers result in local pain, soft tissue swelling, regional lymphadenopathy, ecchymosis, bloody exsudate from the fang marks and local skin necrosis. There is a high risk of cardiovascular toxicity (hypotension, pulmonary edema). Neurotoxicity is seen with some species, such as the bergadder (*Bitis atropos*), *Vipera palaestinae,* Russell's viper, some rattlesnakes *(Crotalus scutulatus)* and with South American pit vipers *(Crotalus durissus terrificus).* There is a pronounced hemorrhagic diathesis. Renal failure is common.

4. Burrowing asps

The local symptoms are single fang puncture, pain, some swelling and occasional necrosis. There can be nausea, vomiting, sweating, fever, occasional respiratory distress, AV-block and cardiac ischemia. Fatalities are rare.

5. Colubrids

Colubrid bites result in mild to moderate local swelling, pain, ecchymosis and a bloody exsudate from the fang marks. The patient might develop nausea, vomiting, coagulopathy and renal dysfunction. Since the venom is slow to enter the wound, most colubrid bites do not result in significant envenomation.

Summary : local symptoms after snakebite

- Wounds by teeth (fang marks)
- Local pain
- Local ecchymosis
- Local bleeding
- Local infection
- Lymphangitis
- Lymphadenopathy
- Local inflammation (swelling, redness, warmth)
- Local blister
- Local necrosis

Summary : generalised symptoms after snakebite

- General : nausea, vomiting, malaise, weakness, dizziness
- Cardiovascular : hypotension, shock, arrhythmia, pulmonary edema, cardiac failure
- Hemostasis : bleeding from venepuncture sites, gingiva, nose, vagina, petechiae, hematemesis
- Neurological : paresthesia, ptosis, ophthalmoplegia, dysphagia, aphonia, paralysis, respiratory arrest
- Muscle : generalised myalgia, stiff muscles, trismus, myoglobinuria, oliguria, uremia
- Endocrine (early) : shock and hypoglycemia
- Endocrine (late) : weakness, testis atrophy, amenorrhea, panhypopituitarism, Addison's disease.

Treatment in the field

Many people who are bitten by a snake will have mortal fear. It is important to diminish this fear and to decrease the risk of hyperventilation and vomiting. It is best to reassure the patient, to immobilise the bitten limb if possible (splint). Remove rings, bracelets and similar items. If a neurotoxic snake was responsible for the bite, a compressive elastic bandage can be applied. This should be tight enough to hinder lymphatic drainage, but should not act as an arterial tourniquet. This pressure-immobilisation technique was pioneered for neurotoxic elapid envenomation in Australia. It is controversial for viperid envenomation. Arterial tourniquets, incision, electroshock and cauterisation are to be avoided. The role of sucking by mouth and the commercial available "Extractor" is doubtfull. Some venom can be removed with this last contraption if it is used quickly after the bite, there is a risk of increased damage caused by the vacuum cup. If the venom of a spitting cobra entered the eye, one immediately has to rinse the eye with copious amounts of water or other non-caustic liquids.

Treatment upon arrival in the hospital

First of all, check the vitals : ensure a airway free, check BD and pulse, respiration, pulses in limbs, reflexes. If venom entered the eye, clean again. Local anaesthetic eyedrops can be useful to diminish blepharospasms caused by pain. After rinsing, a steroid and antibiotic containing ointment should be applied and the eye should be bandaged. Prepare two IV lines and apply proper wound care. If an antigen detection kit is available, a skin swab or urine sample can be used to identify the snake (only Australia and Papua New Guinea). In many setting, techniques for the detection of venom in urine or serum will not be available. Take blood for cross matching. A full blood count can show anemia, hemoconcentration, thrombocytopenia and/or leukocytosis. A peripheral smear can show microangiopathic hemolysis with schistocytes. Renal function, ionogram, glucose, coagulation parameters, myoglobin and CK will be determined. A urine sample will be analysed for (pigmented) casts, glucose, blood and myoglobin. Stools will be checked for occult blood. A radiograph of the chest can show pulmonary edema. A radiograph of the bite site can show retained fangs. A CT-scan of the brain will be ordered if there is suspected intracranial hemorrhage. An electrocardiogram will be taken and cardiac monitoring can be started if clinically indicated. ECG changes seen with hyperkalemia include peaked T waves, flat P waves, prolonged PR interval and a widened QRS complex. Plasma-expanders or crystalloids will be infused. Vasopressors will be administered only after restoration of the intravascular volume. There should be adrenaline (ephedrine in case of pregnancy), oxygen, steroids, antihistaminica, atropine and neostigmine in stand by. Prepare an intubation set and a mechanical ventilator. Myoglobinuria should be treated with sodium bicarbonate, mannitol and/or loop diuretics. Dialysis does not remove circulating venom components. Sustained intracompartementeal pressures greater than 30 to 40 mm Hg in a normotensive patient exceeds capillary perfusion pressure in the muscles. The pressure at which ischemia occurs is even lower in a

hypotensive patient. If limb elevation, IV mannitol (1-2 g/kg) and antivenin do not improve the severe ischemia, a fasciotomy might be needed.

If there are signs of paralysis (ptosis, dysphagia), do an edrophonium-test (inject one vial of this short acting acetylcholinesterase inhibitor and check for improvement) or give straight away, without testing :

- Neostigmine : 1 mg vial slow IV, afterwards 25-100 µg/kg/hour and
- Atropine 0,6 mg IV, to be repeated eg. after 4 hours.

Hyperkalemia is a danger, especially with sea snake bites. Give :

- Calcium gluconaat 10% IV, 5-30 ml, provokes a shift of potassium to the intracellular compartment.
- Glucose (eg. 25 gr) + 20 Units Actrapid insuline provokes a shift of potassium to the intracellular compartment. Control glycemia.
- Salbutamol or albuterol (beta-2-agonists) infusion or inhalation provokes a shift of potassium to the intracellular compartment. More study is needed to evaluate this treatment in this setting.
- Eventually IV bicarbonate infusion (100 ml of a 4.2% solution), provokes a shift of potassium to the intracellular compartment.
- Kayexalate (polystyrene sulphonate) is an ion-exchange resin which can be administred by mouth (15g/6h) or rectally (30g enema). Works slowly.
- In severe hyperkalemia hemodialysis or peritoneal dialysis is needed.

Antivenin

A history of snakebite or even the presence of fang marks itself is no indication for treatment with antivenin. Antivenin will be administered in case of local or systemic envenomation symptoms. For a few species of snakes, antivenin should be administered after any bite by an identified specimen regardless of whether symptoms or signs are present. Examples include bites by kraits (*Bungarus* sp) or large coral snakes (*Micrurus* sp. more than 50 cm in length). Once symptoms begin in these scenarios, they may be difficult to stop even with antivenin. Remember that antivenin binds circulating venom. Once the venom has bound to its target, it is difficult to remove. Many viperid bites have laboratory evidence of coagulopathy without significant clinical hemorrhage. Such cases can be treated with or without antivenin, bed rest and close observation. If possible, one is advised to use a narrow spectrum antivenin (monospecific), but this is only possible if one is fairly sure of the identity of the offending snake. Otherwise, polyvalent antivenin will have to be used. It is best to use to local produced antivenin, since antivenin prepared for related species elsewhere might have less cross protection. This is well known for example for the problems with the Russell's vipers in Sri Lanka, India, Myanmar and Thailand and for carpet vipers (*Echis carinatus, E. ocellatus*). However, sometimes there is cross-protection across genera, such as anti-Notechis antivenin which improves the outcome of several sea snake envenomations.

Antivenin : princi ples

All antivenins follow a stepwise production process. First a neutralising antibody is produced by immunisation of a host animal with sublethal doses of venom. Monospecific antivenin is derived from immunizing animals with the venom of a single species, whereas polyspecific antivenin is produced either by inoculating animals with the venom of more than one species or by pooling different monospecific antivenins into a final product. Step two involves isolation and purification of antivenin with reduction in the fraction of nonneutralising proteins. Steps three (for some antivenins) is papain or pepsin digestion followed by further purification (eg. affinity chromatography). Incomplete purification results in the presence of significant amounts of nonneutralising proteins, such as albumin, alpha and beta-globulins and IgM. The purification process results in the denaturation of a fraction of the protective IgG. IgG molecules are large and are primarily confined to the intravascular space. This limits extensive distribution into tissue compartments. Large antivenin proteins exceed the threshold for filtration and excretion by the kidneys and are eliminated primarily by the reticuloendothelial system, a much slower process than renal elimination.

The potency of antivenin is variable and it is difficult to make general recommendations regarding dosages. For many antivenins 20 to 50 ml is a reasonable starting dose. In severe envenomation 100 to 150 ml is more appropiate. Children receive the same or even a higher dose that adults. The total antivenin dose should be added to a bag of diluent (dextrose 5% or crystalloid). The infusion is started at a very slow rate (1 ml per minute) with the physician in attendance. If no allergic reaction occurs after a few minutes, the rate can progressively be increased so that the total dose is administered in 1 hour. Antivenin should not be administered by local or intramuscular injection. If an early reaction occurs, the

antivenin should be stopped and the reaction treated. The infusions can then usually be restarted at a slower rate. Further diluting the antivenin may also be helpful.

Antivenin : side-effects

The immunoglobulines in equine serum can cause anaphylaxis (IgE-mediated), anaphylactoid reactions (non-IgE-mediated) and serum sickness. Anaphylaxis and anaphylactoid reactions are clinically indistinguishable. Pyrogenic reactions and bronchospasms are common. The severity can be diminished by administration of adrenaline. Serum sickness results from deposition of soluble circulating antigen-antibody immune complexes (ICs) in vessels or tissue. Steroids diminish the severity of late onset serum sickness. The risk for late onset serum sickness increases in proportion to the total dose of antivenin administred. It occurs in up to 75% of patients who received more than 5 vials antivenin. It starts 7 to 21 days after administration of the antivenin and may manifest as fever, arthralgias, rash, lymphadenopathy, proteinuria and occasional peripheral neuritis.

Antivenin : Recent improvements

Plasma proteins can be fractionated, purified and isolated via different precipitation techniques and chromatography. Removal of the Fc-fragment of the immunoglobulines can be done via papaine-digestion of pepsine-digestion. In doing so, one obtains 2 Fab-fragments resp. F(ab')2-fragments. These fragments contain the antigen binding site, but lack the Fc-tail, which is responsible for a lot of side-effects. The Fab and F(ab')2 fragments can be lyophilised. They should be slowly and gently reconstituted, in order to avoid denaturation of the fragile molecules. The monomeric Fab is eliminated faster from the human body than the dimeric F(ab')2. Repeated administrations might be necessary. Although Fab complexed to small-molecular weight venom components can be cleared renally, most of the venom proteins have molecular weights greater than 20.000 Dalton and are too large to be filtered and excreted by the kidney when complexed to Fab. This may allow sufficient time for dissociation of the venom-Fab complex, resulting in the release of active venom components. The short halflife of Fab compared with IgG can lead to recurrent signs of envenomation. CroFab® contains Fab-fragments against 4 North American pit vipers : *Crotalus atrox* (western diamondback rattlesnake), *Crotalus adamanteus* (eastern diamondback rattlesnake), *Crotalus scutulatus* (Mojave rattlesnake) and *Agkistrodon piscivorus* (cottonmouth). It is derived from sheep and can be used in persons allergic to horse proteins. For example, four to twelve vials of CroFab® are infused to achieve initial control of the envenomation syndrome, followed by two vials every 6 hours for three additional dosages. The serum sickness rate is about 6% with CroFab®, i.e. superior to the old Antivenin (Crotalidae) Polyvalent Wyeth. ViperaTAb® is made in a similar way and protects against *Vipera berus*. At present it is licenced in Scandinavia. ViperFav® (Aventis Pasteur Mérieux) is a polyvalent but narrow spectrum antivenin against *Vipera berus, V. ammodytes* and *V. aspis*. BothroFav® is a F(ab')2 containing antivenin against *Bothrops lanceolatus,* the fer-de-lance from Martinique Island. EchiTAb® against *Echis ocellatus* is used in Nigeria. We expect further data on BrownTAb® against the Australian Brown snake and PolongaTAb®.

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