GUIDELINES

FOR THE

MANAGEMENT OF SNAKEBITES

World Health Organization

Regional Office for South-East Asia

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Contents

Foreword

Snakebites are well known medical emergencies and a cause of hospital admission in many countries. The true scale of this problem however is unknown because of inadequate reporting in almost every part of the world. The South-East Asia Region is one of the world's most affected regions, due to its high population density, widespread agriculture activities, presence of numerous venomous snakes and lack of necessary community awareness to address the problem.

Regardless of the increasing knowledge about the composition of snake venom and its mode of action, and a sound understanding of clinical features of envenoming, management of snakebites remains a challenge in the Region. Appropriate and timely use of anti-snake venom reduces morbidity and mortality. Although in the last few years production of anti-venom has increased, it is still well below the current estimated annual requirement of 10 million vials. In addition, available anti-venoms do not cover all the important venomous snakes of the Region. Mechanisms need to be developed to ensure timely access and availability of anti-venom to all needy persons. Public-private partnerships, intercountry support, involvement of national, regional, and global agencies are vital to effectively meet the challenge.

The WHO Regional Office for South-East Asia had developed and published Guidelines for the Management of Snakebites as a special issue of the South East Asian Journal of Tropical Medicine and Public Health in 1999 followed by publication of the guidelines as independent regional document in 2011. Considering the new technical advances in the field, the guidelines have been revised with the help of regional and global experts. The geographical area specifically covered by this publication includes the South-East Asia Region of WHO. The venomous snake fauna of the South East Asia Region is rich and diverse. It varies within and between countries. Countries such as Malaysia, Singapore, Cambodia, Lao People's Democratic Republic, Republic of Korea, Philippines, Pakistan and Afghanistan may share many of the same medically-important species of snakes that occur in the South-East Asia Region and may find these guidelines useful. This publication aims to pass on a digest of available knowledge about all clinical aspects of snake-bite to medically trained personnel.

I am confident that these revised guidelines will help Member States to improve the management of snakebites in the peripheral health services and thereby reduce the morbidity and mortality due to snakebites.

Dr Poonam Khetrapal Singh
Regional Director

Acknowledgements

Preface

Geographical coverage

The geographical area specifically covered by this publication includes the South-East Asia Region of WHO including eleven Member States (Bangladesh, Bhutan, Democratic People's Republic of Korea, Maldives, Myanmar, Nepal, India, Indonesia, Sri Lanka, Thailand, Timor-Leste). Countries such as Malaysia, Singapore, Cambodia, Lao People's Democratic Republic, Republic of Korea, Philippines, Pakistan and Afghanistan may share many of the same medically important species of snakes that occur in the South-East Asia Region. It is interesting to note that snakes inhabiting the Indonesian islands East of Wallace's line (West Papua and Maluku Islands) are part of the Australasian elapid fauna, differing from those West of this line.

Antivenoms are essential drugs

The only specific antidotes to snake venoms are immunoglobulin antivenoms (WHO, 2010), which are recognized as essential drugs. see http://www.who.int/medicines/publications/essentialmedicines/EML_2015_FINAL_amended_NOV2015.pdf?ua=1.

Target readership

This publication aims to pass on a digest of available knowledge about all clinical aspects of snakebites to medically trained personnel. The guidelines are intended for medical doctors, nurses, paramedics, dispensers and community health workers who have the responsibility of treating victims of snakebites, and also for medical and nursing students and postgraduates as an educational resource. They aim to provide sufficient practical information to allow medically trained personnel to assess and treat patients with snakebites at all the different levels of the health service.

Levels of evidence

Recommendations are based largely on observational studies ("O" see below), expert opinion ("E") and, in some cases, comparative trials ("T"), but in only one case on formal systematic reviews ("S").

Symbols for the evidence used as the basis of each recommendation (in order of level of evidence) are:

S formal systematic reviews, such as Cochrane Reviews of which there is only one in the field of snakebites. These include more than one randomized controlled trial;

T comparative trials without formal systematic review;

O observational studies (e.g. surveillance or pharmacological data);

E expert opinion/consensus.

EXECUTIVE SUMMARY
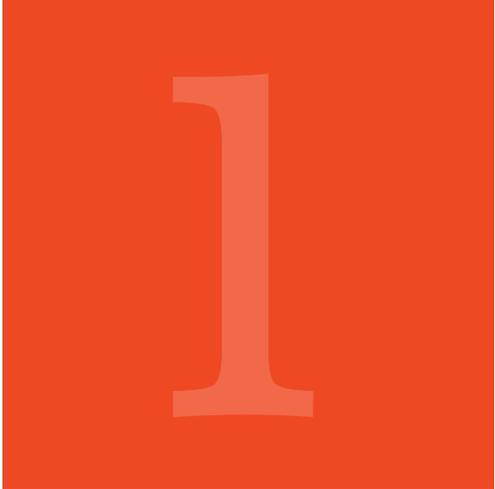
Executive Summary

Epidemiology

The venomous snake fauna of the South-East Asia Region is rich and diverse. It varies within and between countries. Widely distributed species of major medical importance, such as Russell's vipers, show geographical intra-species variation in their venom composition. In many countries, snakebite is an important medical emergency and cause of hospital admission, demanding urgent attention by adequately trained medical staff. It results in the death or chronic disability of tens of thousands of active younger people, especially those involved in farming and plantation work. The true scale of mortality and acute and chronic morbidity from snakebite is only just beginning to be recognized, based on large well-designed community-based studies (Mohapatra et al., 2011; Rahman et al., 2010; Ediriweera et al, 2016). Persisting or permanent physical and psychological disability in snakebite survivors may confer social stigma. The full burden of human suffering remains uncertain because of inadequate reporting in almost every part of the Region. To remedy this deficiency, it is strongly **recommended** that snakebite be made a specific notifiable disease in all countries in the South-East Asia Region (E).

Snakebite is predominantly a rural problem that has important implications for the nutrition and economy of the countries where it occurs commonly, since it is largely an occupational disease of food-producers such as farmers, plantation workers, herdsmen, and fishermen, and also of wild life park rangers, military personnel, snake restaurant workers, snake handlers and collectors of snake skins. It is **recommended** that snakebite should be formally recognized by the International Labour Office as an important occupational disease in the South-East Asia Region (E).

Prevention

Detailed consideration of community education on venomous snakes and snakebite is outside the scope of this publication. However, it is clear that this is a most powerful tool and essential component in any campaign to address the public health challenge posed by snakebite. It is strongly **recommended** as the method most likely to succeed in reducing the risk of snakebites (E).

Health system strengthening, education and training

Some ministries of health in the Region have begun to organise training of doctors and other medical workers in the clinical management of snakebite patients. However, medical personnel throughout the Region would benefit from more formal instruction on all aspects of this subject. This should include the

Most of the familiar methods for first-aid treatment of snakebite, both western and "traditional/herbal", have been found to result in more harm (risk) than good (benefit) and should be firmly discouraged.

identification of medically important species of snake, clinical diagnosis and the appropriate use of antivenoms and ancillary treatments. It is **recommended** that education and training in the prevention and management of snakebite should be included in the curriculum of medical and nursing schools and should be addressed specifically through the organization of special training courses and other educational events based on nationally agreed guidelines (E). These measures should be supported by improvements in hospital accommodation of snake-bitten patients (ideally in specialized units staffed by specially trained teams), basic laboratory and diagnostic facilities, supply, deployment and conservation/storage of antivenoms, ambulance services and general community awareness of the problem and its potential solutions.

Management

First-aid: most of the familiar methods for first-aid treatment of snakebite, both western and "traditional/herbal", have been found to result in more harm (risk) than good (benefit) and should be firmly discouraged. However, in many communities, traditional therapists and their practices are respected and it is important to initiate a dialogue with these practitioners, perhaps through anthropologists, to encourage their understanding and cooperation in the timely referral of envenomed patients to

medical care at the hospital or dispensary. **Recommended** first-aid methods emphasise reassurance, application of a pressure-pad over the bite wound, immobilization of the bitten limb and transport of the patient to a place where they can receive medical care without delay (O).

Diagnosis of the species of snake responsible for the bite is important for optimal clinical management. This may be achieved through expert identification of the dead snake or a (mobile-phone) image of it, or by inference from the resulting "clinical syndrome" of envenoming. It is **recommended** that syndromic approaches and algorithms for diagnosing the species responsible for snakebites be developed in different parts of the Region (E).

Treatment: antivenom (species-specific hyperimmune immunoglobulin), a life-saving, WHO-recognized, essential medicine, is the only effective antidote for envenoming. However, there are challenges surrounding its design, production, distribution, conservation, safety, initial dosage and effectiveness. It is **recommended** that a critical appraisal of all aspects of antivenom production should be carried out in South-East Asia Region countries. Although antivenom is an essential element of the treatment of systemic envenoming, it may be insufficient on its own to save the patient's life. Antivenoms are generally expensive and in short supply. It is **recommended** that antivenom should be used in all patients with signs of systemic and/or severe local envenoming in whom the benefits of treatment are judged to exceed the risks of antivenom reactions (E). It should not be used in the absence of evidence of envenoming. Skin/conjunctival hypersensitivity testing does not predict early or late antivenom

reactions and it is **recommended** that these tests should not be carried out (T). Prophylactic subcutaneous adrenaline has proved effective in reducing the frequency and severity of early antivenom reactions and its routine use is, therefore, **recommended** unless the risk of reactions associated with a particular antivenom is low (less than a few %) (T). It is **recommended** that whenever possible antivenom should be given by slow intravenous injection or infusion (O). Adrenaline should always be available in readiness at the bedside in case of an early anaphylactic antivenom reaction. When no appropriate specific antivenom is available, judicious conservative treatment can in many cases save the life of the patient. In the case of neurotoxic envenoming with bulbar and respiratory paralysis, antivenom alone cannot be relied upon to prevent early death from asphyxiation. Artificial ventilation is essential in such cases. In the case of acute kidney injury associated particularly with envenoming by Russell's vipers, hump-nosed pit-vipers and sea snakes, conservative management and, in some cases renal replacement therapy (dialysis), is an effective supportive treatment. It is **recommended** that fasciotomy should never be carried out in snakebite patients unless or until

haemostatic abnormalities have been corrected, clinical features of an intra-compartmental syndrome are present and a consistently raised intra-compartmental pressure has been confirmed by direct measurement (E). Before discharge from the medical facility, patients should be given explanation, reassurance, and advice about avoiding future bites, and the opportunity for follow-up and further rehabilitation/counselling in case of late antivenom reactions and persistent physical or psychological sequelae.

Research: there have been fewer proper clinical studies of snakebite than of almost any other tropical disease, despite its causing more deaths and chronic disability in the Region than all the other so-called Neglected Tropical Diseases combined. It is **recommended** that governments, academic institutions, pharmaceutical, agricultural and other industries and other funding bodies, should actively encourage, sponsor and invest in properly designed clinical studies of all aspects of snakebite, especially community-based, nation-wide epidemiological studies, correlation of clinical syndromes with envenoming by defined species, and antivenom dose-finding studies (E).

Prevention

Prevention

Essentials:

Snakebites are environmental, occupational and climatic hazards, predominantly of rural areas. Bites are usually inflicted on lower legs, ankles and feet of agricultural workers and their families. Know your local snakes, their favourite habitats, and times of day and seasons when they are most active. Never handle, threaten or attack snakes. Do not attract snakes to homes by keeping livestock indoors or leaving food unprotected, encouraging rodents. Sleep under a well-tucked–in mosquito net, ideally on a raised bed. Clear rubbish and undergrowth from around the house. Always use a light and prod with a stick when walking outside at night, visiting the latrine or relieving yourself in the open. Solid shoes or boots are recommended especially during agricultural activities. Fishermen should avoid touching sea snakes caught in their nets.

Community education reduces the risk of snakebites. Involve all community workers, traditional healers and villagers. Distribute leaflets, banners and posters. Reformat these SEARO recommendations for national or local use as guidelines, training modules, leaflets, video clips or posters, displayed in hospital and clinic waiting areas and disseminate them via radio, TV and social networks.

2.1 Reducing the risk of snakebites

Snakebite is an environmental, occupational and climatic hazard in rural and urban areas of many South-East Asian countries where most bites are inflicted on the lower legs, ankles and feet of agricultural workers and their families. Attention to the following recommendations for community education will reduce the risk of bites. Snakes have adapted to a wide range of habitats and prey species. All snakes are predatory carnivores, none is vegetarian although some eat birds' eggs. Since snakes are preyed upon by other animals, they tend to be secretive and have evolved many survival strategies, including camouflage, making them difficult to see. By understanding something about snakes' habits, simple precautions can be adopted to reduce the chance of encounters, and consequently bites. Know your local snakes, the sorts of places where they prefer to live and hide, the times of year and times of day and night, and the kinds of weather when they are most likely to be active. Many species are mainly nocturnal (night hunters) (e.g. kraits) while other species (e.g. Australasian brown snakes) are mainly diurnal (daylight hunters). Be particularly vigilant about the risk of snakebites after rains, during flooding, at harvest time and at night and when

walking to and from the fields before dawn and after dusk. Snakes prefer not to confront large animals such as humans, and so avoid cornering them and give them every opportunity to escape.

Inside the house, where snakes may enter in search of food or to find hiding places, do not keep livestock, especially chickens, as they are potential prey for larger snakes and they may attract rodents upon which many species of snakes will prey. Store food in rodent-proof containers. Regularly check houses for snakes and, if possible, avoid types of house construction that will provide snakes with hiding places (e.g. thatched roofs with open eaves, mud and straw walls with large cracks and cavities, large unsealed spaces beneath floorboards). In South Asia, almost all krait **(Bungarus)** bites are inflicted on people sleeping in their homes, usually on the floor but sometimes even in beds and under pillows

(e.g. in the Sundarbans). Ideally, avoid sleeping unprotected on the ground, but if you do choose, or are forced, to sleep on the ground, or are able to sleep on a raised bed, use an insecticide-impregnated mosquito net that is well tucked-in under the mattress or sleeping mat. This will protect against mosquitoes and other biting insects, centipedes, scorpions, and snakes (Chappuis et al., 2007). **(Fig 001)** No chemical has yet been discovered that is effectively repellent to snakes without being so toxic as to threaten the life of children and domestic animals.

In the farm yard, compound, or garden: Try not to provide hiding places for snakes. Clear away termite mounds, heaps of rubbish, building materials etc. from near the house. Do not have tree branches touching the house. Keep grass short or clear the ground around your house and clear underneath low bushes so that snakes cannot hide close to the

खाट व मच्छरदानी वापरल्यास.
डासामुळे होणारे मलेरीया,फिलेरीया(हत्ती रोग), डेंग्यू ताप, चिकन गुनिया व मेंदूज्वर टाळता येतो.
व
विंचु व मणेर दंशाने येणारा जीवघेणा प्रसंग हेही टाळता येतो.

सौजन्यः डॉ.बावस्कर हॉस्पिटल अॅन्ड रिसर्च सेंटर
महाड–रायगड

Figure 001: Protection from sleeping under a mosquito net (H Bawaskar)

GUIDELINES FOR THE MANAGEMENT OF SNAKEBITES

house. Keep your granary away from the house (it may attract rodents that snakes will hunt). Water sources, reservoirs, ponds and puddles may also attract prey animals such as frogs and toads. Listen to wild and domestic animals, especially birds, as they mob snakes and warn of a snake nearby. Use a light when you walk outside the house, visit the latrine at night, or relieve yourself in the open.

In the countryside: firewood collection at night is a high risk activity. Watch where you walk. The value of wearing protective clothing is widely accepted, but there are many practical difficulties, including cost, habit, inconvenience and discomfort in a tropical climate as well as cultural and superstitious objections making this seem impracticable. However, in Myanmar, a specially developed light-weight boots proved acceptable to farmers for use during the high risk rice harvesting season, although these would be impracticable during rice planting when the fields are inundated (Tun Pe et al., 2002). Rather than walking bare-footed or wearing sandals, use proper shoes or boots and long trousers, especially when walking in the dark or in undergrowth. This advice may not be immediately acceptable in some communities because of cost, cultural attitudes, comfort and convenience. However, use of protective clothing (boots and gloves) should be promoted as the most obvious means of reducing occupational risk of snakebite. Step on to rocks or logs rather than straight over them – snakes may be sunning themselves on the sides. Do not put hands into holes or nests or any hidden places where snakes might be resting. Young boys often do this while hunting for rodents. Use a light (torch, flashlight or lamp) when walking at night especially after heavy rains and prod the ground ahead of you with a stick. Lamps placed at strategic locations such as at

Lamps placed at strategic locations such as at the entrance to the house, in passages between houses, in front of the latrine outside the house or within the courtyard are valuable, provided that they are positioned so as to avoid casting shadows over corners and niches where snakes may be concealed.

the entrance to the house, in passages between houses, in front of the latrine outside the house or within the courtyard are valuable, provided that they are positioned so as to avoid casting shadows over corners and niches where snakes may be concealed. Be careful when handling dead or apparently dead snakes – even an accidental scratch from the fang of a snake's severed head may inject venom. Snake restaurants pose a threat of bites to staff and customers. Many snakebites occur during ploughing, planting and harvesting and in the rainy season. Rain may wash snakes and debris into gutters at the edges of roads, and flush burrowing species out of their burrows, so be careful when walking on roads after heavy rain especially after dark.

On the road: Drivers or cyclists should never intentionally run over snakes on the road. The snake may not be instantly killed and may lie injured and pose a risk to pedestrians. The snake may also be injured and trapped under the vehicle, from where it will crawl out once the vehicle has stopped or has been parked in the house compound or garage.

In rivers, estuaries and the sea: To prevent sea snakebites, fishermen should avoid touching sea snakes caught in nets

and on lines. The head and tail are not easily distinguishable. Sea snakes are air-breathing and are therefore drowned if caught in drift or trawl nets, but, unlike fish, may survive if laid on the beach. There is a risk of bites to bathers and those washing clothes in the muddy waters of estuaries, river mouths and some coastlines.

General: Avoid snakes as far as possible, including those displayed by snake charmers, who are frequently bitten. Displays by performers such as Austin Stevens and the late Steve Irwin on TV and social media have encouraged people to risk pursuing, attacking and handling wild snakes. This should be actively discouraged. Never handle, threaten or attack a snake and never intentionally trap or corner a snake in an enclosed space. In many parts of the Region there are dedicated snake catchers who will remove snakes found in houses and gardens. For example, in New Delhi, "if you find a snake hissing inside your house, just don't panic or cause it any harm. All you need to do is dial a helpline (9871963535) and dedicated snake trappers will be at your doorstep to help you" Wildlife SOS (WSOS). Keep young children away from areas known to be snake-infested. In occupations that carry a high risk of snakebite, such as rice farming and fish farming, employers might be held responsible for providing protective clothing (boots). In Myanmar, farmers can take out special low-cost insurance to cover them specifically against snakebite, and India's National Health Assurance Mission envisages free treatment for snakebite.

2.2 Implementing preventive strategies for community education

Community education has been proved to be an effective strategy for preventing snakebites. In the Terai region of Nepal, a group of villages was targeted for snakebite awareness sessions, involving political leaders, female health volunteers, community health workers, social workers, traditional healers and other villagers. Many leaflets, banners and posters were distributed. As a result, snakebite incidence decreased from 502 bites to 315 bites/100 000 population in targeted villages (relative risk reduction 0.373 (95% CI = 0.245–0.48) but it remained constant in the control untargeted villages (Sharma et al., 2013). A similar scheme in West Bengal, India involved the training of 800 health workers (Vishal Santra, Simultala Conservationists). Such programmes should be repeated every year, using well-designed posters with colour photographs of the medically significant snakes of the Region combined with clear recommendations for preventing snakebite. In Indonesia, since 2013, medical staff have collaborated regularly with herpetologists in learning about snake identification and snakebite management, while in West Papua, church and other religious organizations have an important role in education campaigns on snakebite. Designers of Information, Education and Communication (IEC) activities for preventing snakebites, should bear in mind local infrastructure, demography and topography. An example is given in **Figure 01** from Duncan Hospital, Raxaul, Bihar, India (Longkumer et al., 2016).

Recommendations for health care workers

	Recommendation for health care workers	Rationale
1	Use the moths of April and May to • Procure the necessary stocks of ASV • Train health care workers in snakebite prevention and first aid	80% of bites occur during the months of June-September so preparedness and prevention need particular attention in the time leading up to this "edidemic" season.
2	Envenomation should not be excluded by the absence of fang marks.	3.8% of people without fang marks were envenomed. Krait bites, in particular, can be hard to visualise, even a short time after the bite.
3	Consider snakebite in the differential diagnosis of unexplained altered sensorium, alteration to speech and swallowing, and abdominal pain, especially during the rainy season.	Patients can present with symptoms of envenomation, without any history of being bitten by a snake.
4	Bites by an unknown predator need to be taken seriously and observed for signs of envenomation.	14% of people, who were unable to identify what predator bit them were envenomed.
5	Don't rely on the ability of patients or relatives to identify snakes.	Identification of snake species is poor, although it is better for cobras.
6	Antivenom should only be given to patients showing symptoms of envenomation	Envenomation of patients only occurred in 63.6% of the cases where cobras were brought. To give anti venom without symptoms of envenomation express people to the risk of adverse reactions and is costly, especially in a setting where demand exceeds supplies.
7	Consider the production of a bivalent ASV for regions of north India and Nepal.	Saw scaled and Russells vipers are not present in this region and a bivalent anti venom is likely to cause less adverse reactions.

Recommendations for Community Education

	Recommendation for health care workers	Rationale
1	A large part of the public health education needs to be directed to children and young people to both genders.	The 10-19 year old age group is the peak age interval for bites. Numbers of males and females bitten are almost equal.
2	Encourage the use of footwear and long pants/trousers.	67% of bites occur on the feet and legs.
3	The use of a stick to sacare away snakes, prior to working in an area wth ones hands.	This would decrease the number of bites where hands are put into snake micro habitats without prior visualisation of the area.
4	Improved fighting using: • Torches when walking outside • Lighting in and around houses.	40% of bites occur between 1700-2200 hours. 59.2% of bites occur in and around the house. Lighting will enable better visualisation of snakes.
5	Provision of toilets and education regarding their use.	8% of bites occurred when people were going to the fields for the purpose of open defecation.
6	Encourage people to sleep on a bed and under a well fucked-in mosquito net.	10% of people were bitten while they were sleeping. Sleeping on the ground, inceases your risk of envenomation, sixfold. Sleeping under a mosquito net, decreases your risk of envenomation, six fold.
7	Provision of buffer zones between fields and housing areas.	59.2% of bites occur in and around the house. Snakes are attracted to the rodents who come for grain being grown. Keeping these distances separate may help in decreasing the encroachment of snakes in housing areas.
8	Make sleeping areas separate from food storage, preparation and sonsumption areas.	The presence of rodents in food related areas is prone to attract snakes. If people sleep in places away from areas of the house connected with food, theis may decrease the risk of people connecting with snakes.

Figure 01: Community Education: recommendations for health-care workers and community education from Duncan Hospital, Raxaul, Bihar, India (see Longkumer et al., 2016)

Raising community awareness about prevention of snakebites is the most effective strategy for reducing snakebite morbidity and mortality.

The above recommendations for preventing snakebite could be reformatted for national or local use as guidelines, training modules, leaflets, video clips and posters **(Fig 001)** that can be displayed on the walls of hospital and clinic waiting areas for the attention of patients and their families. At the village level, role-playing, drama and puppets have been used successfully to portray snakebite scenarios. Media such as radio and TV can be used for health promotion and advantage can be taken of FM radio phone-ins to publicise the problem. Increasingly, young people and advertisers use social networking (YouTube, Twitter) to communicate information and mobile phone messaging might also be employed.

Religious organizations and charities such as Rotary and Lions Clubs might be persuaded to promote snakebite awareness. It is especially valuable to win the support of high profile media figures such as sporting heroes, film stars, pop stars and politicians. Education departments should incorporate appropriate first-aid for snakebite in school textbooks.

2.3 Conclusion

Raising community awareness about prevention of snakebites is the most effective strategy for reducing snakebite morbidity and mortality. The current burden of snakebite morbidity can also be mitigated by providing region-specific guidelines and training protocols for effective case management. Support materials for health-care providers at all levels of the health service could help to disseminate appropriate scientific knowledge about snakebite management. Ensuring an efficient supply-chain for antivenom and other supplies can reduce preventable deaths from snakebite.
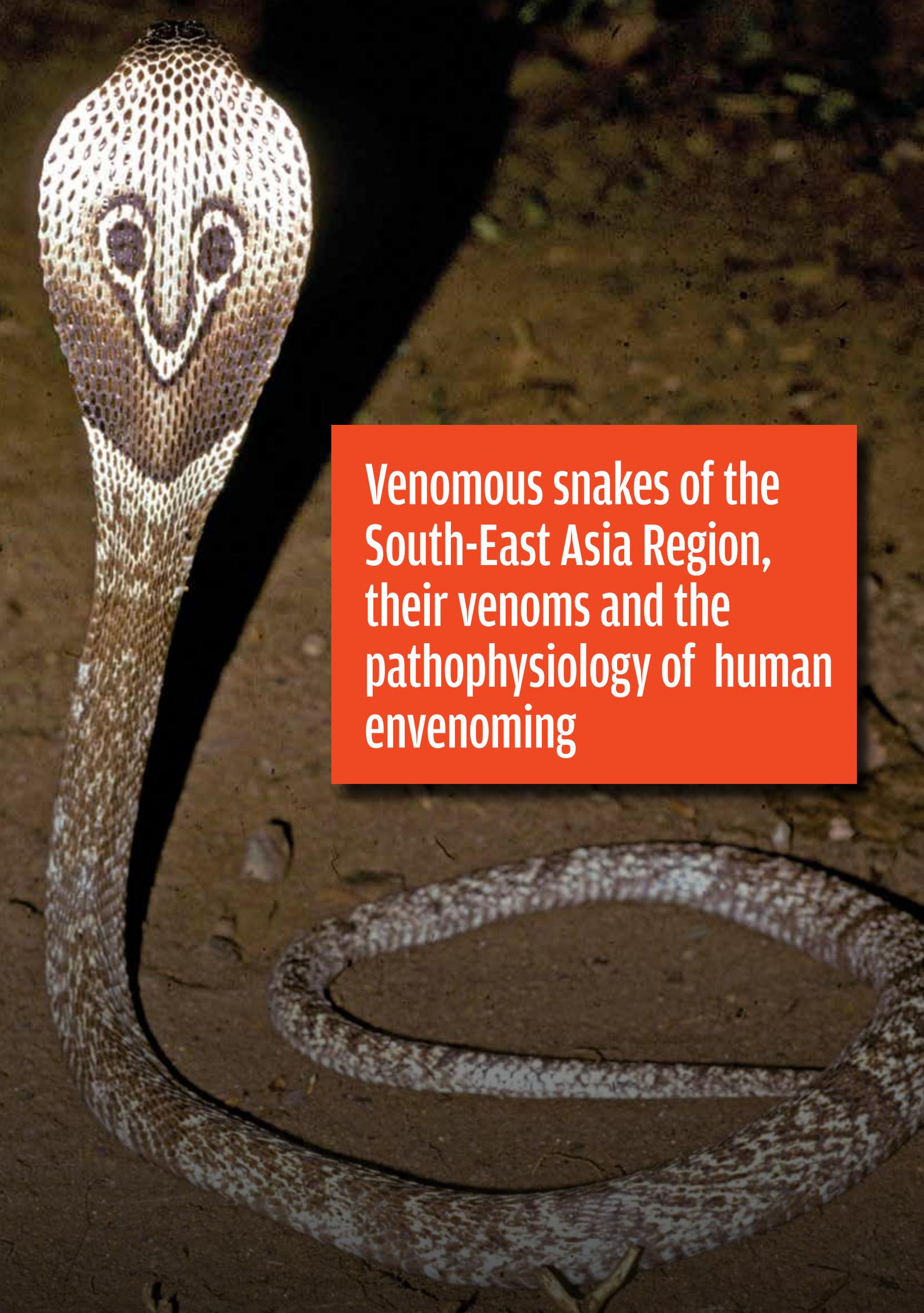
Venomous snakes of the South-East Asia Region, their venoms and the pathophysiology of human envenoming

Venomous snakes of the South-East Asia Region, their venoms and the pathophysiology of human envenoming

Essentials:

The venom apparatus: venom glands of Elapidae and Viperidae are situated behind the eye, surrounded by compressor muscles. The venom duct opens at the base of the fang, conducting venom to its tip through a groove or canal. In Viperidae, but not Elapidae or Colubridae, fangs are mounted on a rotatable maxilla, making them erectile. In Colubridae, venom secreted by Duvernoy's (supralabial) glands tracks down grooves in posterior maxillary fangs. Spitting cobras squeeze venom forward from tips of their fangs in a fine spray directed towards the eyes of an aggressor.

Classification/taxonomy: there are three families of venomous snakes in South East Asia, Elapidae, Viperidae and Colubridae.

Elapidae are relatively long, thin, usually uniformly-coloured snakes with large smooth symmetrical scales on the top of the head. Cobras, raise the front part of their body off the ground and spread a hood. Venomous sea-snakes have flattened paddle-like tails. The most important species medically are cobras (Naja), kraits (Bungarus), death adders, taipan, black and brown snakes (Acanthophis, Oxyuranus, Pseudechis, Pseudonaja) and sea-snakes.

Viperidae (vipers) are divided into typical vipers (Viperinae) and pit-vipers (Crotalinae) that have a heat-sensitive loreal pit organ situated between nostril and eye. Vipers are relatively short, thick-bodied, short-tailed snakes with many small rough scales on the top of the head and characteristic patterns of coloured markings on their backs. The most important species are: Russell's vipers (Daboia), saw-scaled vipers (Echis), Malayan pit viper (Calloselasma), mamushis (Gloydius), hump-nosed pit- vipers (Hypnale), Chinese habu (Protobothrops mucrosquamatus), and green pit vipers (Trimeresurus).

Among Colubridae, red-necked keelback (Rhabdophis subminiatus) and yamakagashi (R. tigrinus) are dangerous. More than a dozen other species can cause mild local envenoming (e.g. cat snakes - Boiga).

Composition and antigenicity of snake venoms varies greatly between and within species, as snakes mature, seasonally, between sexes, and throughout the geographical range.

Many bites are inflicted by non-venomous or minimally-venomous species of medical importance because they may be mistaken for venomous species, resulting in unnecessary, expensive, risky and wasteful antivenom treatment. Large pythons (Boidae), occasionally attack and even swallow humans.

Identification: posters and picture cards, with vernacular names are useful. Expert identification of the snake responsible, or of a photo image, is recommended.

Snake venoms 90% of dry weight comprises >100 different proteins: enzymes, non-enzymatic polypeptide toxins, and non-toxic proteins. Enzymes are digestive hydrolases, hyaluronidase (spreading factor), yellow L-amino acid oxidases, phospholipases A_2, and peptidases. Snake venom metalloproteases (SVMPs) damage basement membranes, causing endothelial cell damage and spontaneous systemic bleeding. Procoagulant enzymes are thrombin-like, splitting fibrinogen, or activators of factors V, X, prothrombin and other clotting factors, causing DIC, consumption coagulopathy and incoagulable blood. Phospholipases A_2 damage mitochondria, red blood cells, leucocytes, platelets, peripheral nerve endings, skeletal muscle, vascular endothelium, and other membranes, producing presynaptic neurotoxic activity, cardiotoxicity, myotoxicity, necrosis, hypotension, haemolysis, anti-coagulation,

haemorrhage, plasma leakage (oedema-formation) and autopharmacological release of histamine and other autacoids.

Polypeptide postsynaptic (α) neurotoxins bind to acetylcholine receptors at the motor endplate. Presynaptic (β) neurotoxins are phospholipases that damage nerve endings irreparably.

Composition and antigenicity of snake venoms varies greatly between and within species, as snakes mature, seasonally, between sexes, and throughout the geographical range. Thus, envenoming by a particular species in one part of its geographical range may not be responsive to an antivenom raised against venom from this same species in another area.

"Dry bites": about 50% of venomous snakebites do not result in envenoming.

Pathophysiology of human envenoming Swelling and bruising result from venom-induced increased vascular permeability and ischaemia caused by thrombosis, tight tourniquets applied as first-aid, or swollen muscle within tight fascial compartments. Hypotension and shock often results from hypovolaemia caused by leakage of plasma or blood into the bitten limb and elsewhere, vasodilatation and myocardial damage. Oligopeptides (ACE inhibitors and BPPs) and vasodilating autacoids cause early transient hypotension. Procoagulant enzymes cause defibrinogenation, DIC and consumption coagulopathy. Venom phospholipases are anticoagulant. Platelet activation/inhibition and sequestration causes thrombocytopenia. Spontaneous systemic bleeding is attributable to Zn metalloproteases haemorrhagins. Complement activation affects platelets, blood coagulation and other humoral mediator. With elapid and some colubroid venoms the alternative pathway is triggered by

"cobra venom factor", while viperid venoms activate the classical pathway. Neurotoxic polypeptides and PLA$_2$s cause paralysis by blocking transmission at neuromuscular junctions, but do not cross the blood-brain-barrier; there are no direct CNS effects. Descending paralysis affects bulbar and respiratory muscle causing fatal upper airway obstruction, aspiration, or respiratory paralysis. Anticholinesterase drugs (e.g. neostigmine) prolong activity of ACh at neuromuscular junctions, improving paralytic symptoms when postsynaptic neurotoxins are involved. PLA$_2$ myotoxins and metalloproteases in venoms of sea snakes, terrestrial Australasian elapids and some kraits and Russell's vipers cause generalized rhabdomyolysis, myoglobinaemia, myoglobinuria and acute kidney injury. Acute kidney injury is associated with histopathological evidence of acute tubular necrosis, proliferative glomerulonephritis, bilateral renal cortical necrosis, acute interstitial nephritis, toxic mesangiolysis with platelet agglutination, fibrin deposition and ischaemic changes. Causes include prolonged hypotension, hypovolaemia, DIC, direct nephrotoxicity, haemoglobinuria, myoglobinuria, and hyperkalaemia. Antivenom can cause immune-complex-mediated kidney injury. DIC may result in deposition of fibrin on vascular endothelium that has been activated by metalloproteases, producing microangiopathic haemolysis and thrombotic microangiopathy, resembling haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP), but ADAMTS 13 levels are not depleted. Generalized increase in capillary permeability in Russell's viper envenoming is attributable to metalloproteases that damage vascular endothelium.

3.1 The venom apparatus

(Fig 1) (Gans and Gans 1978; Junghanss and Bodio 1995; Weinstein et al. 2009)

The ability to inject venom into prey animals by means of cannulated, modified teeth evolved over 140 million years ago in bird-like dinosaurs and later in snakes (Gong et al., 2010). The venom glands of Elapidae and Viperidae are situated behind the eye, surrounded by compressor muscles (**Fig 1**). The venom duct opens within the sheath at the base of the fang and venom is conducted to its tip through a groove or canal, as through a hypodermic needle. In Elapidae, the (proteroglyph) fangs are mounted on a relatively fixed maxilla at the front of the mouth (**Fig. 2a**). In Viperidae, the (solenoglyph) fangs are mounted on a rotatable maxilla so that they can be folded flat against the roof of the mouth (**Fig. 2b**). In Colubridae (used here in the broad sense, including some subfamilies such as Natricinae, considered by some taxonomists to be separate families), venom secreted by Duvernoy's (supralabial) glands tracks down grooves in the anterior
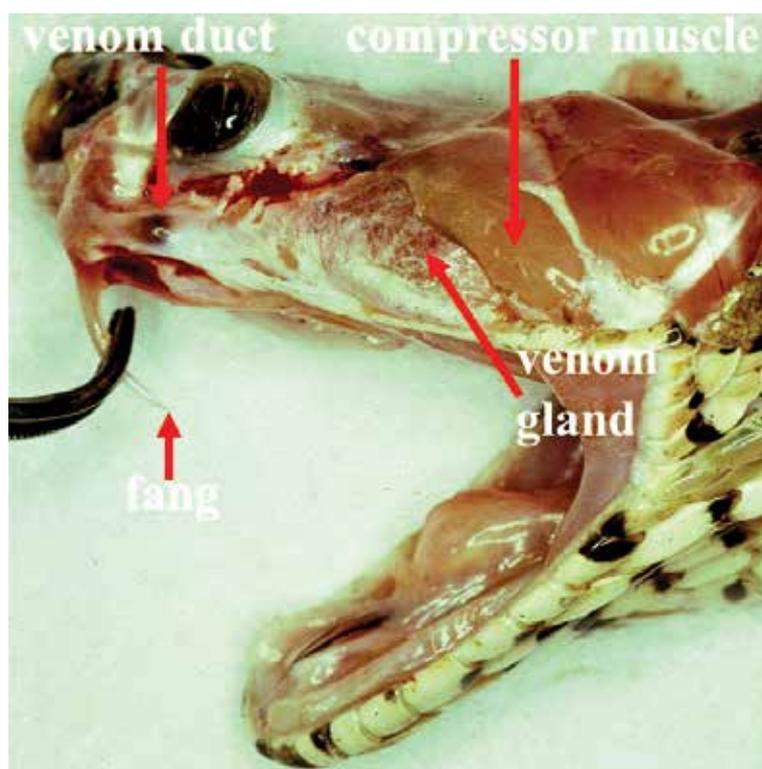
Figure 1: Venom apparatus of an eastern Russell's viper (Daboia siamensis) *(Copyright DA Warrell)*

Figure 2a: Short, permanently erect, front fangs of a typical elapid (Sri Lankan cobra - Naja naja) *(Copyright DA Warrell)*

Figure 2c: Rear fangs of a dangerously venomous Colubrid snake, the red-necked keelback (Rhabdophis subminiatus)) (Copyright DA Warrell)

Figure 2b: Long, hinged, front fangs of a typical viper (Thailand Russell's viper Daboia russelii) *Copyright DA Warrell)*

surfaces of (opisthoglyph) fangs at the posterior end of the maxilla (**Fig 2c**) (Weinstein et al., 2011) . Fangs allow the snake to introduced venom deep into the tissues of its natural prey. If a human is bitten, venom is usually injected subcutaneously or intramuscularly. Spitting cobras can squeeze the venom out of the tips of their fangs producing a fine spray directed towards the eyes of an aggressor.

3.2 Classification of venomous snakes

3.2.1 Medically important species in South-East Asia Region countries
(Gopalakrishnakone and Chou 1990; Williams et al., 2009; WHO 2010)

There are three families of venomous snakes in South-East Asia, Elapidae, Viperidae and Colubridae.

Figure 3: Absent loreal scale in Elapid snakes: above - Rat snake *Ptyas mucosus* – non-venomous family Colubridae, showing 3 loreal scales (red arrows) between pre-ocular (p) and nasal (n) scales (Copyright Mark O'Shea); below - Sind krait *Bungarus sindanus – venomous* family Elapidae, showing no loreal scale between pre-ocular (p) and nasal (n) scales *(Copyright Rom Whitaker)*

Elapidae: have relatively short fixed front (proteroglyph) fangs **(Fig 2a)**. This family includes cobras, king cobra, kraits, coral snakes, Australasian snakes and sea snakes. Elapidae are relatively long, thin, uniformly-coloured snakes with large smooth symmetrical scales (plates) on the top (dorsum) of the head **(Fig 3 and Fig 9)**. There is no loreal scale between the pre-ocular and nasal scales **(Fig 3)**. Some, notably cobras, raise the front part of their body off the ground and spread and flatten the neck to form a hood **(Figs 4-9)**. Several species of cobra can spit their venom for one metre or more towards the eyes of perceived enemies. Venomous sea snakes have flattened paddle-like tails and their ventral (belly) scales are greatly reduced in size or lost **(Figs 20-24)**.

Some important examples of the Elapidae inhabiting South-East Asia Region countries (References to reports or reviews of bites by these species are given in parenthesis):

- Cobras (genus *Naja*):

- Common spectacled (Indian) cobra *N. naja* **(Fig 4)** (Theakston et al., 1990)

- North Indian or Oxus cobra *N. oxiana* **(Fig 5)**

- Monocellate cobra *N. kaouthia* **(Fig 6a-c)** (Reid 1964; Warrell 1986; Viravan et al., 1992)

- Andaman cobra *Naja sagittifera* **(Fig 6d)**

- Spitting cobras: *N. siamensis* **(Fig 7)** (Warrell 1986; Wüster et al., 1997),

- *N. sumatrana* **(Fig 8)**, *N. sputatrix, N. mandalayensis* etc

- King cobra: *Ophiophagus hannah* **(Fig 9)** (Tin-Myint et al., 1991)

- Kraits (genus *Bungarus*):

- Common krait *B. caeruleus* **(Fig 10)** (Theakston et al., 1990; Ariaratnam et al., 2009)

- Malayan krait *B. candidus* **(Fig 11)** (Warrell et al., 1983; Kiem-Xuan-Trinh et al., 2010)

- Ceylon krait B. ceylonicus **(Fig 12)** (de Silva et al., 1993)

- Banded krait *B. fasciatus* **(Fig 13)**

- Red-headed krait *B. flaviceps* **(Fig 14)**

- Lesser black krait *B. lividus* (Kuch et al., 2011)

- Chinese krait *B. multicinctus* **(Fig 15)**

(Tun- Pe et al., 1997; Ha-Tran-Hung et al., 2010)

- Greater black krait *B. niger* **(Fig 16)** (Faiz et al., 2010)

- Sind krait *B. sindanus* (Pillai et al., 2012; in press) **(Fig 17)**

- Wall's krait *B. walli*

- Spotted coral snake *Calliophis maculiceps* **(Fig 18)**

- MacClelland's coral snake *Sinomicrurus maclellandi* (Kramer 1977)

- Australasian elapids inhabiting Eastern Indonesia (Maluku and West Papua):

- Death adders (Genus Acanthophis): *A. rugosus* **(Fig 19a)** (Lalloo et al., 1996)

- New Guinea small-eyed snake *Micropechis ikaheka* **(Fig 19b)** (Warrell et al., 1996)

- Papuan Taipan *Oxyuranus scutellatus canni* **(Fig 20)** (Lalloo et al., 1995)

- Papuan black snake *Pseudechis papuanus* **(Fig 21)** (Lalloo et al., 1994)

- Brown snakes (Genus *Pseudonaja*) **(Fig 22)**

- Sea snakes (Reid 1975, 1979; Reid and Lim 1957; Warrell 1994): important species include *Enhydrina schistosa* (*Hydrophis schistosus*) **(Fig 23)** (Kularatne et al., 2014), *Hydrophis sp.* **(Fig 24)** (Amararasekara et al., 1994; Watt and Theakston 1985), *Lapemis curtus* **(Fig 25)**, *Pelamis platura* **(Fig 26)** and *Laticauda colubrina* **(Fig 27)**.

Figures 4: Common spectacled cobra *(Naja naja):* (a) Sri Lanka;
(b) Pune; (c) Kolkata; (d) Bardia, Nepal (a-c Copyright DA Warrell;
d Copyright Mark O'Shea)

Figure 5: North Indian or Oxus cobra *(Naja oxiana)* (Copyright DA Warrell)

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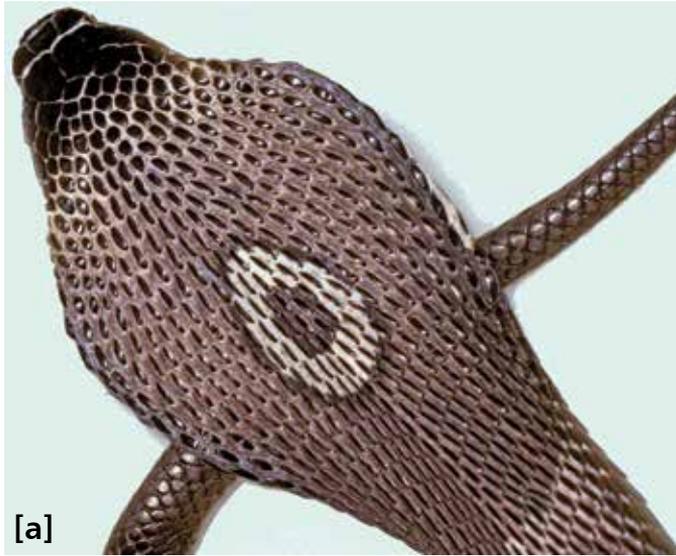
Figures 6: Monocellate cobra *(Naja kaouthia)*: (a) Thailand nuchal pattern; (b) Thailand; (c) West Bengal (Fig a-c: Copyright DA Warrell); (d) Andamans cobra *(Naja sagittifera)* juvenile specimen (Fig d: Copyright Ashok Captain)

Figures 7: Indo-Chinese spitting cobra *(Naja siamensis)* Thailand: (a) Black and white specimen with ill-defined spectacle marking on hood; (b, c) Brown-coloured specimen showing spectacle marking on hood (Copyright DA Warrell)

Figures 8: Sumatran spitting
cobra *(Naja sumatrana)*:
(a) black phase Singapore
(b) golden phase Thailand
(Copyright DA Warrell)
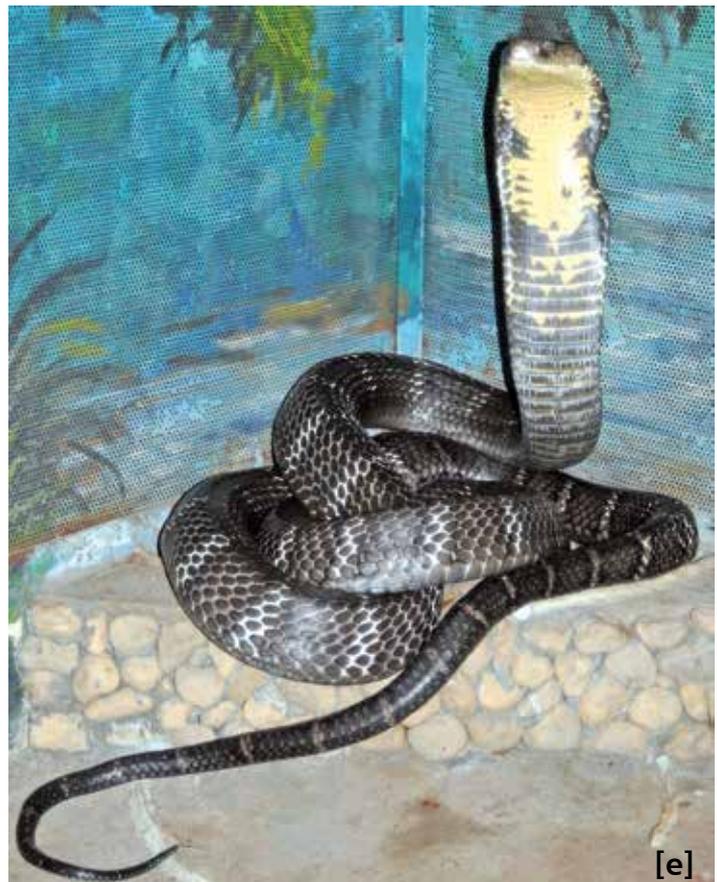
Figures 9: King cobra or hamadryad *(Ophiophagus hannah)* (Copyright DA Warrell)
(a) The famous king cobra dance in Yangon, Myanmar; (b) Specimen from Trang, southern Thailand more than 3.5 metres in total length; (c, d) Dorsal and lateral views of head of Thai specimens showing the two large occipital scales which distinguish this species from cobras *(Naja)*; (e) Pune, India (Copyright DA Warrell)

Figures 10: Common krait *(Bungarus caeruleus)*: (a) Sri Lankan specimen showing narrow white dorsal bands; (b) Indian specimen showing pure white ventrals (Copyright DA Warrell)

Figures 11: Malayan krait *(Bungarus candidus)* Thai specimen: (a) Showing dorsal black saddle-shaped markings; (b) Showing pure white ventrals (Copyright DA Warrell).

Figures 12: Ceylon krait *(Bungarus ceylonicus)*: (a) showing incomplete white bands (spots); (b) head; (c) showing white bands and dark ventral scales. Perideniya, Sri Lanka (Copyright DA Warrell)

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Figures 13: Banded krait *(Bungarus fasciatus)* Thai specimens: (a) Showing black and yellow bands; (b) Showing circumferential black bands and blunt-tipped tail (Copyright DA Warrell)

Figure 14: Red-headed krait *(Bungarus flaviceps)* Thailand (Copyright DA Warrell)

Figure 15: Chinese krait (*Bungarus multicinctus*) (Copyright DA Warrell)

Figure 16: Greater black krait (*Bungarus niger*) Nepal (Copyright F. Tillack)

[a]

Figures 17: Sind krait (*Bungarus sindanus*): (a) specimen from Bikaner (Copyright Rom Whitaker); (b) head of specimen from Maharashtra, India (Copyright DA Warrell)

[b]

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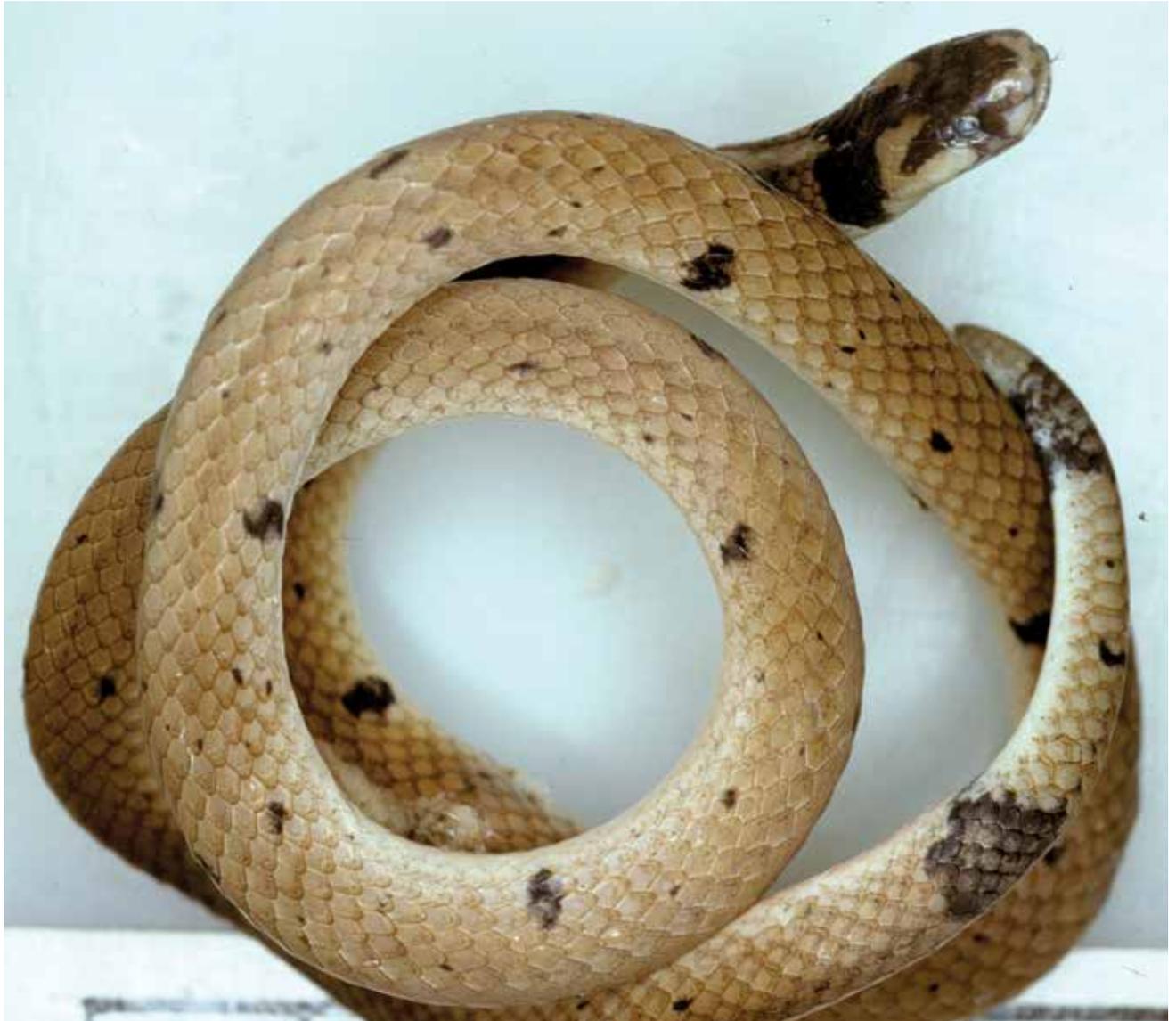
Figure 18: Spotted coral snake *(Calliophis maculiceps)* Thai specimen (Copyright DA Warrell)

[a]

[b]

Figures 19: Death adders *(Acanthophis rugosus):* (a) Specimen from West Irian, Indonesia; (b) Specimen from Seram, Indonesia

Figure 19c: New Guinea small-eyed snake *(Micropechis ikaheka)*. Specimen from Arso, West Irian, Indonesia 1.69m in total length responsible for a case of envenoming (see Warrell et al., 1996).; (Copyright DA Warrell)

Figure 20: Papuan taipan *(Oxuyuranus scutellatus)* SaiBai Island, Torres Strait Islands (Copyright DA Warrell)

Figure 21: Papuan black snake *(Pseudechis papuanus)* SaiBai Island, Torres Strait Islands (Copyright DA Warrell)

Figure 22: Eastern brown snake *(Pseudechis textilis)* Australia (Copyright DA Warrell)

Figure 23: Beaked sea snake *(Enhydrina schistose or Hydrophis schistosus)* Bunapas Mission, Ramu River, Papua New Guinea (Copyright DA Warrell)

Figure 24a: Blue spotted sea snake *(Hydrophis cyanocinctus)* Thailand (Copyright DA Warrell)

Figure 24b: Banded sea snake *(Hydrophis fasciatus atriceps)* Thailand (Copyright DA Warrell)

Figure 24c: Flattened paddle-like tail of sea snakes: *Hydrophis cyanocinctus* (above); *Lapemis curtus* (below) Thailand (Copyright DA Warrell)

Figure 25: Hardwick's sea snake *(Lapemis curtus)* showing tiny fangs (Copyright DA Warrell)

Figure 26: Yellow-bellied sea snake *(Pelamis platurus)* Watamu, Kenya (Copyright Royjan Taylor)

Figures 27: Sea krait *(Laticauda colubrina)* Madang, Papua New Guinea: (a) Showing blue and banded pattern and amphibious behaviour; (b) Showing fangs (Copyright DA Warrell)

Viperidae have relatively long fangs (solenoglyph) which are normally folded flat against the upper jaw but, when the snake strikes, are erected **(Fig 2b)**. There are two subfamilies, typical vipers (Viperinae) and pit-vipers (Crotalinae). The Crotalinae possess a special infra-red heat-sensing organ, the loreal pit organ, to detect their warm-blooded prey. This is situated between the nostril and the eye **(Fig. 28)**. Viperidae are relatively short, thick-bodied snakes with many small rough scales on the top (dorsum) of the head and characteristic patterns of coloured markings on the dorsal surface of the body **(Fig 29)**.

Pit Viper (Trimeresurus T. Macrops)
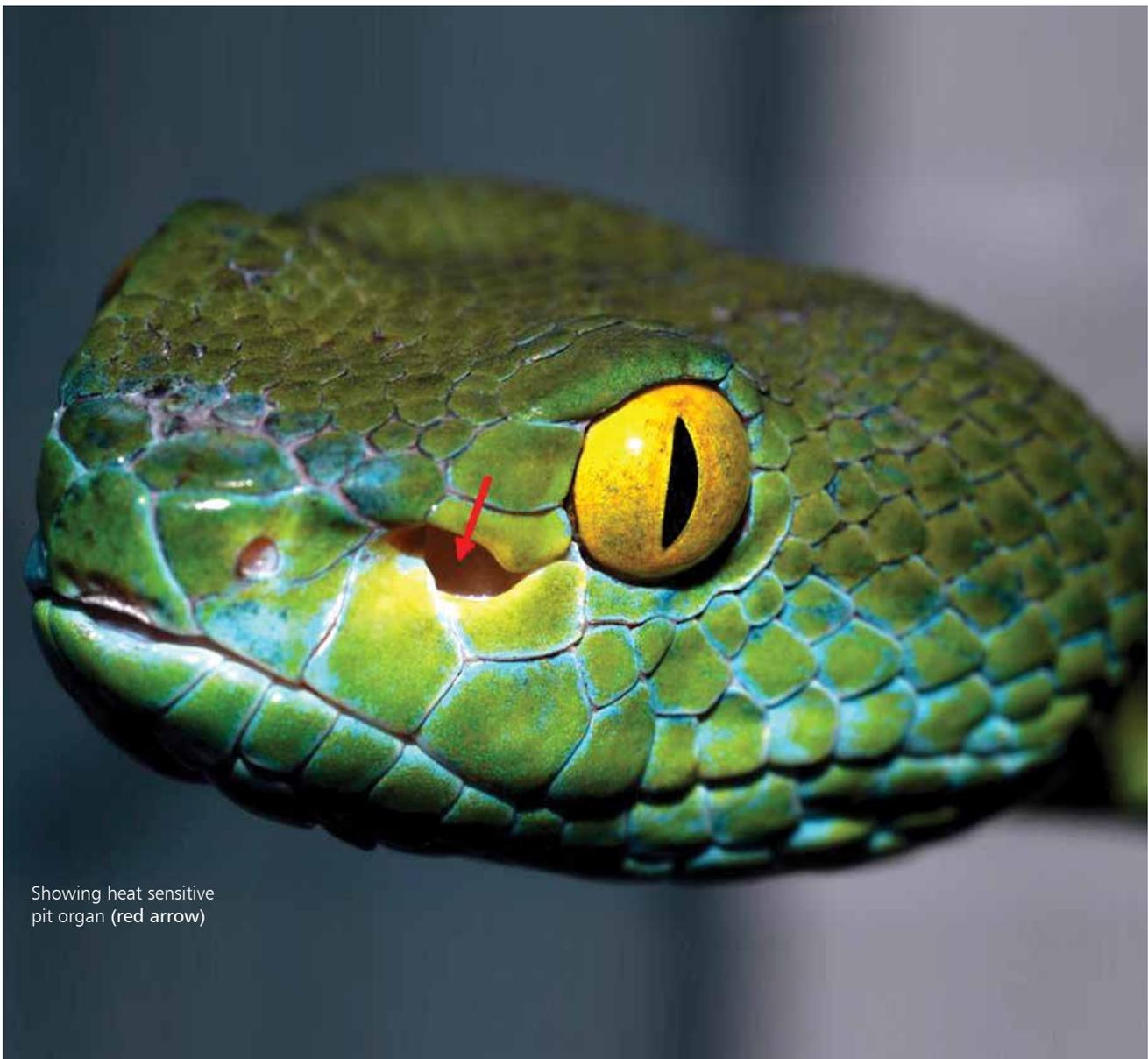
Showing heat sensitive pit organ **(red arrow)**

Figure 28: Head of a typical pit viper - dark green pit viper *(Trimeresurus T. macrops)* showing the pit organ situated between the nostril and the eye (red arrow) (Copyright DA Warrell)
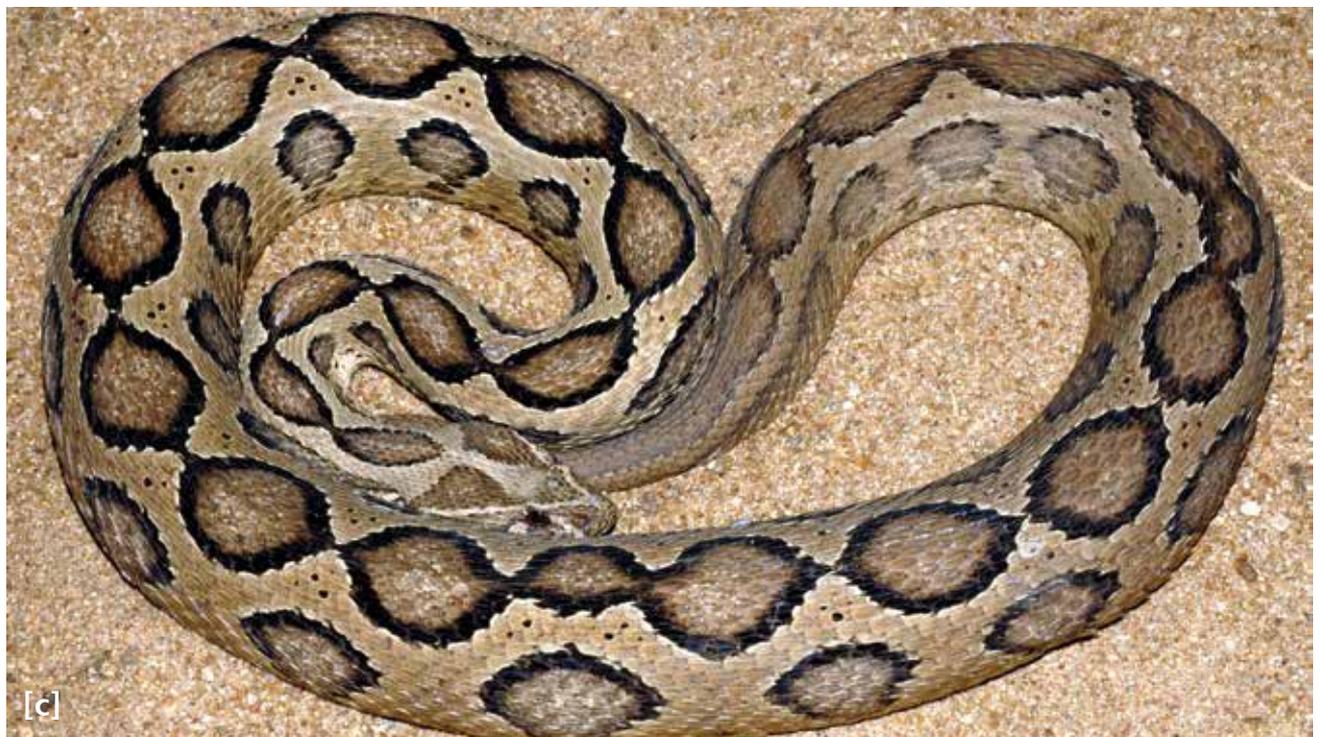
Figures 29: Western Russell's viper *(Daboia russelii)*: (a) Specimen from Sri Lanka; (b, c) Specimens from Tamil Nadu, southern India; (d, e) specimens from Pune, India (Copyright DA Warrell)

Some important examples of the Viperidae inhabiting South-East Asia Region countries (References to reports of reviews of bites by these species are given in parenthesis):

Typical vipers (subfamily Viperinae): Russell's vipers, Western, *Daboia russelii* *(Fig 29 a-e)* (Phillips et al., 1988; Warrell 1989; Gawarammana et al., 2009); and Eastern, *D. siamensis* **(Fig 30)** (Myint-Lwin et al., 1985; Tun-Pe et al., 1987; Than-Than et al., 1987; Than-Than et al., 1988; Warrell 1989; Than- Than et al., 1989; Thein-Than et al., 1991; Tin-Nu-Swe et al., 1993; Belt et al., 1997)

Saw-scaled or carpet vipers *Echis c. carinatus* **(Fig 31)** (Bhat 1974; Warrell and Arnett 1976) and *E. c. sochureki* **(Fig 31c)** (Kochar et al., 2007).

Levantine or blunt-nosed viper *Macrovipera lebetina* **(Fig 32)** (Sharma et al., 2008)

Pit vipers (subfamily Crotalinae):

Malayan pit viper *Calloselasma rhodostoma* **(Fig 33)** (Reid et al., 1963a; Reid et al., 1963b;

Reid 1968; Warrell et al., 1986)

Mount Kinabalu pit viper *Garthia chaseni* **(Fig 34)** (Haile 1963; Warrell 1995)

Mamushis *(Genus Gloydius): G. brevicaudus* **(Fig 35)** (Warrell 1995)

Hump-nosed pit viper *Hypnale hypnale* **(Fig 36)** (de Silva et al., 1994; Joseph et al., 2007;

Ariaratnam et al., 2008; Premawardhena et al, 1998) and other *Hypnale* species (Maduwage et al., 2011).

Chinese habu *Protobothrops mucrosquamatus* **(Fig 37)** (Warrell 1995)

Green pit vipers, bamboo vipers, palm vipers and habus (formerly all *genus Trimeresurus)*

Indian bamboo viper *Trimeresurus*

(Craspedocephalus) gramineus **(Fig 38)**

Malabar rock pit viper *Trimeresurus (Crapedocephalus) malabaricus* **(Fig 39)** (Gowda et al., 2006)

Palm viper *Trimeresurus (Craspedocephalus) puniceus* **(Fig 40)**

Sri Lankan viper *Trimeresurus (Craspedocephalus) trigonocephalus* **(Fig 41)** (Warrell 1995)

Hagen's pit viper *Trimeresurus (Parias) hageni* **(Fig 42)**

Pope's pit viper *Trimeresurus (Popeia) popeiorum* **(Fig 43)**

Chinese bamboo viper *Trimeresurus (Viridovipera) stejnegeri* **(Fig 44)** (Warrell 1995)

White-lipped green pit viper *Trimeresurus (Trimeresurus) albolabris* **(Fig 45)** (Hutton et al., 1990; Rojnuckarin et al., 1998)

Dark green pit viper *Trimeresurus (Trimeresurus) macrops* **(Fig 28, 46)** (Hutton et al., 1990; Warrell 1990b)

Spot-tailed green pit viper *Trimeresurus (Trimeresurus) erythrurus* **(Fig 47)** (Warrell 1995)

White-lipped island viper *Trimeresurus (Trimeresurus) insularis* **(Fig 48)**

Kanchanburi pit viper *Trimeresurus (Trimeresurus) kanburiensis* (Warrell et al., 1992)

Mangrove pit viper *Trimeresurus (Trimeresurus) purpureomaculatus* **(Fig 49)** (Warrell 1995)

Northern white-lipped pit viper *Trimeresurus (Trimeresurus) septentrionalis* (Whitaker)

Beautiful pit viper *Trimeresurus (Trimeresurus) venustus* **(Fig 50)**

Wagler's (temple) pit viper *Tropidolaemus wagleri* **(Fig 51a)** (Reid 1968)

Banded temple viper *Tropidolaemus subannulatus* **(Fig 51b)**

Figures 30: Eastern Russell's viper *(Daboia siamensis):* (a) Specimen from Myanmar; (b) Specimen from Thailand; (c) Specimen from East Java, Indonesia; (d) Specimen from Flores, Indonesia (Copyright DA Warrell)

Figures 31: Saw-scaled viper *(Echis carinatus):* (a) *Echis carinatus carinatus* Specimen from southern India; (b) *Echis carinatus carinatus* Specimen from Sri Lanka; (c) *Echis carinatus sochureki* Specimen from Chhattagharh Rajisthan (Copyright DA Warrell)

Figure 32: Levantine viper *(Macrovipera lebetina)* Specimen from Cyprus (Copyright DA Warrell)

[a]

[b]

Figures 33: Malayan pit viper *(Calloselasma rhodostoma)* Thai specimens: (a) Showing characteristic posture and triangular dorsal markings; (b) Showing supralabial markings (Copyright DA Warrell)

Figure 34: Mount Kinabalu pit viper *(Garthia chaseni)* (Copyright Prof RS Thorpe)

Figure 35: Mamushi or Fu-she *(Gloydius brevicaudus)* from China (Copyright DA Warrell)

Figures 36 a-d: Hump-nosed viper *(Hynpale hypnale)* (Copyright DA Warrell)
a) Specimen from Sri Lanka; (b) Specimen from Sri Lanka showing long fangs; (c) Specimen from south western India;
(d) Specimen from south western India showing upturned snout

Figure 37:
Chinese habu
*(Protobothrops
mucrosquamatus)*
Specimen from
China (Copyright
DA Warrell)

Figure 38: Indian bamboo viper *(Trimeresurus Craspedocephalus gramineus)* (Copyright DA Warrell)

[a]

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Figures 39 a, b: Malabar rock pit viper *(Trimeresurus Craspedocephalus malabaricus)* (Copyright DA Warrell)

Figure 40: Palm viper *(Trimeresurus Craspedocephalus puniceus)* Specimen from Cilacap, West Java, Indonesia (Copyright DA Warrell)

Figure 41: Sri Lankan pit viper *(Trimeresurus Craspedocephalus trigonocephalus)* (Copyright DA Warrell

Figure 42: Hagen's pit viper *(Trimeresurus Parias hageni)* Trang, Thailand (Copyright DA Warrell)

Figure 43: Pope's pit viper *(Trimeresurus Popeia popeiorum)* Thailand (Copyright DA Warrell)

Figure 44: Chinese bamboo viper *(Viridovipera stejnegeri)* Specimen from China (Copyright DA Warrell)

[a]

[b]

Figures 45 a,b: White-lipped green pit viper *(Cryptelytrops albolabris)* Thai specimen: (a) Showing colouring and distinctive brown-topped tail; (b) Showing details of the head: note smooth temporal scales (Copyright DA Warrell)

Figure 46: Dark green pit viper (Trimeresurus T. macrops) Thai specimen (Copyright DA Warrell)

Figures 47 a, b: Spot-tailed green pit viper *(Cryptelytrops erythrurus)* Specimen from near Yangon, Myanmar: (a) Showing colouring and brown spotted tail; (b) Showing details of head; note keeled temporal scales (Copyright DA Warrell)

Figure 48: White-lipped island viper *(Trimeresurus T. insularis)* specimen from Tutuala Sub-district Lautem District Timor-Leste (Copyright Mark O'Shea)

Figures 49 a,b:
Mangrove pit viper
(Trimeresurus T. purpureomaculatus):
(a) Specimen from
Kanchanburi, Thailand;
(b) Specimen from
upper Myanmar
(Copyright DA Warrell)

Figure 50: Beautiful
pit viper *(Cryptelytrops venustus)* specimen from
Thung Song, Thailand
(Copyright DA Warrell)

Figure 51a: Wagler's pit
(temple) viper *(Tropidolaemus
wagleri)* specimens in the
snake temple, Penang,
Malaysia
(Copyright DA Warrell)
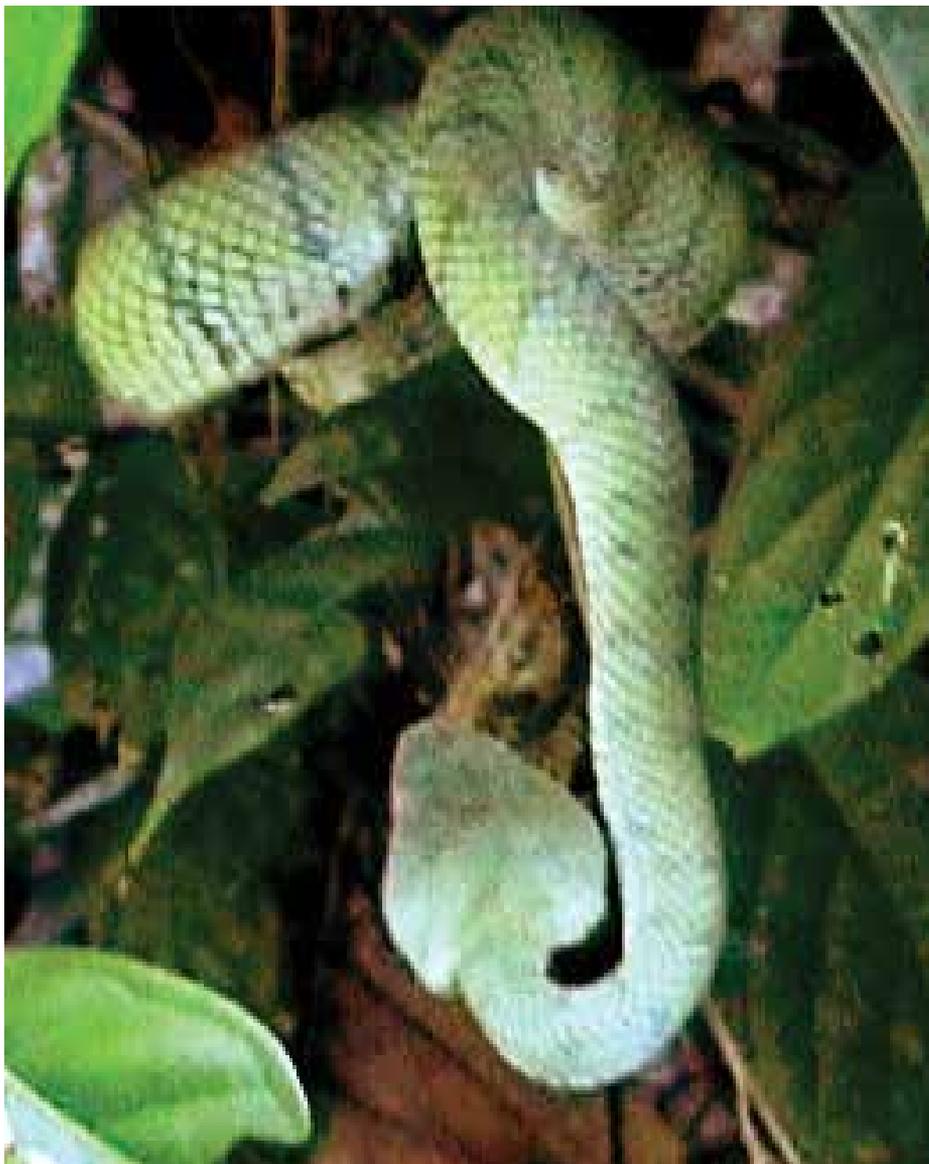
Figure 51b:
Banded temple viper
*(Tropidolaemus
semiannulatus)* Borneo

3.2.2 Other medically important venomous snakes

Several species of medically important Colubridae (sensu lato) have been identified in the South-East Asia Region. The red-necked keelback *Rhabdophis subminiatus* **(Fig 2c and 52a)** and yamakagashi *R. tigrinus* **(Fig 52b)** (Warrell 1995) can cause severe life-threatening anti-haemostatic disturbances and acute kidney injury **(Fig 52c, 52d)**. A case of systemic envenoming by the Sri Lankan keelback *(Balanophis ceylonicus)* with similar features has also been reported

Figure 52a: Red-necked keelback (Rhabdophis subminiatus) Thai specimen (Copyright DA Warrell)

Figure 52b: Yamakagashi *(Rhabdophis tigrinus)* (Copyright S Mishima The Snake 1974 6-1 Courtesy of Dr Y Sawai)

(Fernando et al 2015). More than a dozen other species have proved capable of causing local envenoming [e.g. mangrove snake *(Boiga dendrophila)* (Weinstein et al., 2014) Warrell, 1995) and other cat snakes *(Boiga species)*; long-nosed whip snake *(Ahaetulla nasuta)* **(Fig 52e)**; dog-faced water snake *(Cerberus rhynchops)*; and water snakes/paddy field snakes *(Enhydris* species) **(Fig 52f and 53c)**. Undoubtedly more will be described as the concept of "non-venomous" is further reviewed (Weinstein et al., 2011)

Figure 52c: Extensive bruising from envenoming by *R. tigrinus* in Japan
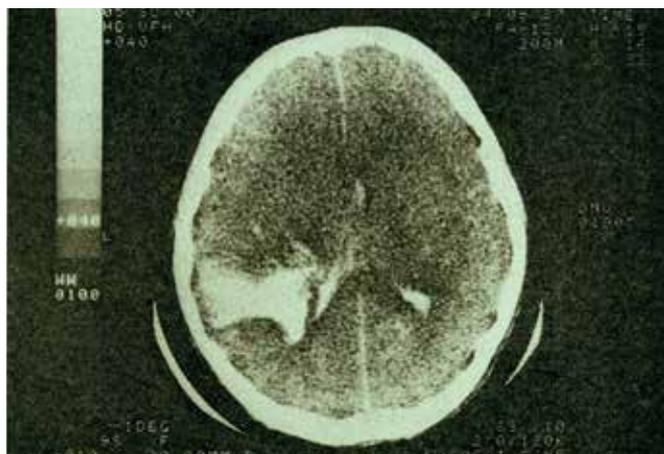
CT scanning of the head: Hemorrhage in the left temporal and occipital perforative hemorrhage into the ventricle.

Figure 52d: Intracerebral haemorrhage
(Courtesy of the late Dr Y Sawai)

Figure 52f: Paddy field snake *(Enhydris plumbea)*

Figure 52e: Long-nosed whip snake *(Ahaetulla nasuta)* Sri Lanka (Copyright DA Warrell)

3.2.3 Non-venomous snakes

Many species of non-venomous or only trivially-venomous species are responsible for bites, especially those that are aggressive, irritable or prone to strike at humans who approach to closely or that commonly inhabit urban and rural gardens and compounds.

Apart from the taxa mentioned above, these include paradise or flying snakes *(Chrysopelea species)* **(Fig 52g)**, striped keelbacks (*Amphiesma* species) **(Fig 52h)**, kukri snakes *(Oligodon species)* **(Fig 52i)**, checkered keelbacks or Asian water snake (*Xenochrophis* species) **(Fig 52j)**, wolf snakes (*Lycodon* or *Dinodon* species) **(Fig 52k)**, bridle snakes *(Dryocalamus)* **(Fig 52m)** and rat snakes *(Ptyas, Elaphe, Coelognathus, Goniosoma etc.)* **(Fig 52n)**. Their medical importance is that they may be mistaken for venomous species (notably the krait mimics *Lycodon* and *Dryocalamus*), resulting in unnecessary and wasteful antivenom treatment (Viravan et al., 1992; Ariaratnam et al., 2009).

Large pythons (Boidae), notably the reticulated python *Python reticularis* in Indonesia, have been reported to attack and even ingest humans, usually inebriated farmers **(Fig 52o)**.

Figure 52g: Paradise or flying snakes *(Chrysopelea ornata)* (Copyright Mark O'Shea)

Figure 52h: Striped keelbacks *(Amphiesma stolatum)* (Copyright Mark O'Shea)

Figure 52i: Kukri snakes *(Oligodon cyclurus)* (Copyright DA Warrell)
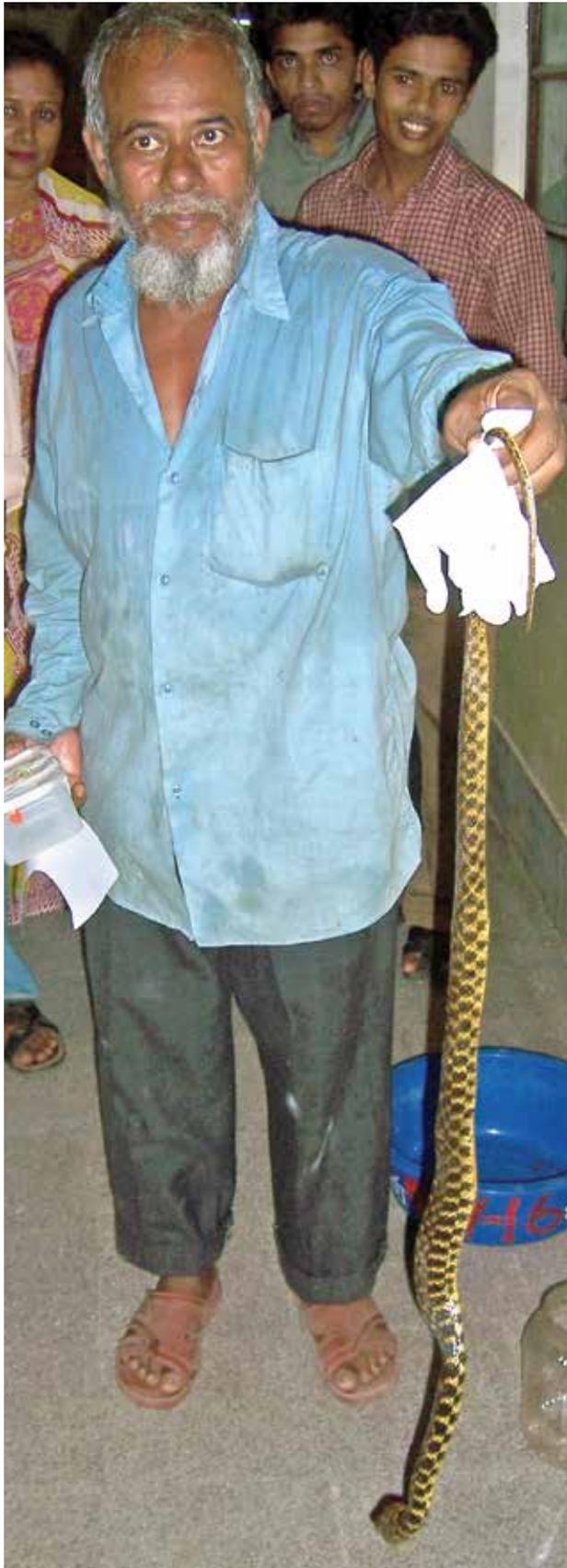
Figure 52j: Chequered keelback *(Xenochrophis piscator)* brought by bite victim Chittagong Bangladesh

Figure 52k: Wolf snakes *(Lycodon aulicus)* (Copyright DA Warrell)

Figure 52l: Yellow-necked wolf snake *(Lycodon flavicollis)* biting (Copyright DA Warrell)

Figure 52m: Bridle snake (Dryocalamus davisoni) (Copyright DA Warrell)

Figure 52n: Rat snake *(Ptyas mucosus)* (Copyright Marl O'Shea)

Figure 52o: Reticulated python *(Python reticularis)* containing the body of a farmer it had swallowed at Palu, Sulawesi, Indonesia (Copyright Excel Sawuwu)

3.3 Identification of venomous snakes

Unfortunately, there is no simple rule for identifying a dangerous venomous snake. However, public educational materials such as posters and cards with pictures of medically significant species of that region with short one line or two line notes of identifying features below the pictures in the local language will be very useful. In a dead snake, a needle may be drawn along the upper jaw from the angle of the jaw to the snout to snag and reveal the fangs. Some harmless snakes have evolved to look almost identical to venomous ones. Examples are various species of *Lycodon, Dryocalamus* and *Cercaspis* that mimic the appearance of the kraits *B. candidus, B. caeruleus* and *B. ceylonicus; Cylindropis ruffus,* whose tail raising display and colouring may mimic coral snakes (*Calliophis* species*), and Boiga multomaculata that mimics Daboia siamensis*. However, some of the most notorious venomous snakes can be recognized by their size, shape, colour, pattern of markings, behaviour and the sound they make when they feel threatened. For example, the defensive behaviour of the cobras is well known **(Fig 4-9)**: they rear up, spread a hood, hiss and make repeated strikes towards the aggressor. Colouring can vary enormously. However, some patterns, like the longitudinal rows of large, dark-rimmed, pale-centred spots of the Russell's vipers **(Figs 29, 30)**, or the alternating black and yellow circumferential bands of the banded krait **(Fig 13)**, are distinctive. The blowing hiss of the Russell's viper and the grating rasp of the saw-scaled viper are warning and identifying sounds, even in the dark.

3.4 Snake venoms

(Bucherl et al., 1968,1971; Gans and Gans 1978; Lee 1979; Harvey 1991; Ménez 2003; Mackessy 2009; Warrell 2010)

3.4.1 Venom composition

Modern techniques of "venomics" (proteomics as applied to venoms) such as high performance liquid chromatography, SDS-PAGE, and mass spectrometry are revealing the enormous complexity of snake venoms (Warrell et al., 2013). 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. Nonprotein ingredients include carbohydrates and metals (often part of glycoprotein metalloprotein enzymes), lipids, free amino acids, nucleosides, and biogenic amines such as serotonin and acetylcholine.

Venom enzymes

These include digestive hydrolases (proteinases, exopeptidase, endopeptidases, phosphodiesterases, metalloproteinases, and phospholipases), hyaluronidase (spreading fator), and activators or inactivators of physiological processes, such as kininogenases. Most venoms contain L-amino acid oxidase (containing a riboflavin 5'-phosphate prosthetic group that confers the yellow colour of many venoms), phospho mono- and di- esterases, 5'-nucleotidase, DNAase, NAD-nucleosidase, phospholipase A_2, and peptidases.

Zinc metalloproteinases/ metalloproteases (metalloproteinase-like, disintegrin-like, cysteine-rich) haemorrhagins (snake venom metalloproteinases, SVMPs): degrade basement membrane components, leading to endothelial cell damage and contributing to spontaneous systemic bleeding.

Procoagulant enzymes: venoms of Viperidae and some Elapidae and

Envenoming by juvenile and adult snakes may cause qualitatively different clinical effects

Colubridae contain serine proteases and other procoagulant enzymes that are thrombin-like or activate factors V, X, prothrombin and other clotting factors. These enzymes stimulate blood clotting with formation of fibrin in the blood stream. Paradoxically, this process results in incoagulable blood because most of the fibrin clot is broken down immediately by the body's own plasmin fibrinolytic system. Sometimes within 30 minutes of the bite, the levels of clotting factors have been so depleted that the blood will not clot ("consumption coagulopathy"). Some venoms contain multiple anti-haemostatic factors. For example, Russell's viper venom contains toxins that activate factors II (prothrombin), V, X, IX and XIII, fibrinolysis and protein C, and cause platelet aggregation, anticoagulation and haemorrhage.

Phospholipases A$_2$ (lecithinase): are most widespread and extensively studied of all venom enzymes. They damages mitochondria, red blood cells, leucocytes, platelets, peripheral nerve endings, skeletal muscle, vascular endothelium, and other membranes, producing presynaptic neurotoxic activity, cardiotoxicity, myotoxicity, necrosis, hypotension, haemolysis, haemorrhage, plasma leakage (oedema-induction), opiate-like sedative effects and autopharmacological release of histamine and other autacoids. They are anti-coagulant, either by hydrolysing plasma or platelet membrane phospholipids, or by interacting with different coagulation factors.

Acetylcholinesterases: although found in most elapid venoms, may cause fasciculation.

Hyaluronidase: promotes the spread of venom through tissues by increasing permeability but can also contribute to tissue damage.

Proteolytic enzymes (metalloproteinases, endopeptidases or hydrolases) and polypetide cytotoxins ("cardiotoxins"): increase vascular permeability causing oedema, blistering, bruising and necrosis at the site of the bite.

Venom polypeptide toxins ("neurotoxins")

Postsynaptic (α) neurotoxins such as α-bungarotoxin and cobrotoxin, consist of 60-62 or 66- 74 amino acids. They bind to acetylcholine receptors at the motor endplate. Presynaptic (β) neurotoxins such as β-bungarotoxin, and taipoxin, contain 120-140 amino-acids and a phospholipase A subunit. These release acetylcholine at the nerve endings at neuromuscular junctions and then damage the endings, preventing further release of transmitter.

Variation in venom composition within species

The composition of snake venoms, and hence their antigenicities in inducing specific neutralizing antibodies during antivenom manufacture, varies greatly between different species, but also within an individual species, as the snake matures (ontogenic variation), seasonally, between sexes, and throughout the geographical range (Warrell, 1997; Mackessy et al., 2003). The two important implications of venom variation are 1- envenoming by juvenile and adult snakes may cause qualitatively different clinical effects and 2- envenoming by a snake in one part of its geographical range may not be neutralized

by an antivenom raised using venom from another part of the range.

3.4.2 Quantity of venom injected at a bite, "dry bites"

This 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. The average dry weight of venom injected at a strike is approximately 60 mg in *N. naja*, 13 mg in *E. carinatus* and 63 mg in *D. russelii*. In the case of *D. siamensis* in Myanmar, the total yield of desiccated venom extracted by milking ranged from 21-268 mg (127 +/- 13 mg, mean +/- 1SE) in adults (mean total length 111 +/- 1.8 cm) and 8-79 mg (45 +/- 7 mg) in juveniles (mean total length 79 +/- 2.8 cm). Adults inject 45% of the venom glands' content in the first bite (Tun-Pe and Khin-Aung Cho, 1986). 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. About 50% of bites by Malayan pit vipers and Russell's vipers, 30% of bites by cobras and 5-10% of bites by saw-scaled vipers do not result in any symptoms or signs of envenoming. Snakes do not exhaust their store of venom, even after several strikes, and they are no less venomous after eating their prey (Tun-Pe et al., 1991).

3.4.3 Variations in venom composition within individual species of snakes

Although large snakes tend to inject more venom than smaller specimens of the same species, the venom of smaller, younger vipers may be richer in some dangerous components, such as those affecting haemostasis because venom composition varies (ontogenically) with the snake's age and hence size (Tun-Pe et al., 1995a).

Recommendations: Bites by small snakes should not be ignored or dismissed. They should be taken just as seriously as bites by large snakes of the same species (O). Design and manufacture of antivenoms should take account of geographical and ontogenic variation in venom composition within individual species (O).

3.5 Pathophysiology of human envenoming

Local envenoming

Swelling and bruising result from increased vascular permeability attributable to venom endopeptidases, metalloproteinase hemorrhagins, membrane-damaging polypeptide toxins, phospholipases, and endogenous autacoids released by the venom, such as histamine, 5-HT, and kinins. Local tissue necrosis results from the direct action of myotoxins and cytotoxins, and ischemia caused by thrombosis; compression of blood vessels by first-aid methods such as tight tourniquets; or by swollen muscle within a tight fascial compartment. Myotoxins damage the muscle cell plasma membrane directly. Most are PLA2s, either enzymatically active (aspartate-49) or enzymatically inactive (lysine-49). Cobra cardiotoxins are low-molecular weight polypeptides with cytotoxic action.

Hypotension and shock

After viper bites, leakage of plasma or blood into the bitten limb and elsewhere, or massive gastrointestinal haemorrhage, may cause hypovolaemia. Vasodilation, especially of splanchnic vessels, and a direct effect on the myocardium may contribute to hypotension. Profound hypotension

is part of the autopharmacological syndrome that occurs within minutes of bites by D. siamensis, D. russelii, and Australasian elapids, attributable to oligopeptides (ACE inhibitors and BPPs) and vasodilating autacoids. In some cases, direct myocardial effects of venom may be suggested by electrocardiographic (ECG) changes and autopsy findings of epicardial or endocardial haemorrhages and histopathological evidence of cardiac myonecrosis.

Bleeding and blood clotting disturbances

Snake venoms affect haemostasis in several ways. Procoagulant enzymes activate intravascular coagulation, producing consumption coagulopathy and incoagulable blood. Procoagulants of Colubridae, Australasian Elapidae, *Echis*, and *Daboia* species activate prothrombin, whereas those in venoms of *Daboia russelii* and *D. siamensis* also activate factors V and X. Thrombin-like enzymes in pit-viper venoms have a direct action on fibrinogen. Some venoms cause defibrinogenation by activating the endogenous fibrinolytic (plasmin) system. Anticoagulant activity is attributable to venom phospholipases. Platelet activation or inhibition results in thrombocytopenia in victims of *Trimeresurus* and *Viridovipera* species, *Calloselasma rhodostoma, Deinagkistrodon acutus,* and *Daboia siamensis*. Potentially lethal spontaneous systemic bleeding is attributable venom haemorrhagins (Zn metalloproteases).

Complement Activation

Elapid and some colubroid venoms activate complement via the alternative pathway ("cobra venom factor" is the snake's C3b), whereas some viperid venoms activate the classic pathway. Complement activation affects platelets, the blood coagulation system, and other humoral mediators.

Neurotoxicity

Neurotoxic polypeptides and PLA2s of snake venoms cause paralysis by blocking transmission at the neuromuscular junction. Patients with paralysis of the bulbar muscles may die of upper airway obstruction or aspiration, but the most common mode of death after neurotoxic envenoming is respiratory paralysis. By prolonging activity of ACh at neuromuscular junctions, anticholinesterase drugs may improve paralytic symptoms in patients bitten by snakes with neurotoxins that are predominantly postsynaptic in their action (e.g., cobras and Australasian death adders [genus Acanthophis]). Some patients bitten by elapids or vipers are drowsy in the absence of respiratory or circulatory failure. This is unlikely to be an effect of neurotoxic polypeptides, which do not cross the blood-brain barrier.

Myotoxicity

PLA_2 myotoxins and metalloproteinases are principally responsible. They are present in venoms of most species of sea snakes, many terrestrial Australasian elapids, some species of krait (Bungarus), and Viperidae, such as the Sri Lankan Russell's viper (D. russelii). Release into the bloodstream of myoglobin, muscle enzymes, uric acid, potassium, and other muscle constituents is an effect in humans of presynaptic neurotoxins. Patients may die of bulbar and respiratory muscle weakness, acute hyperkalaemia, or acute kidney injury.

Acute kidney injury

A wide range of renal histological changes has been described after snakebite. Acute tubular necrosis is the most common, but proliferative glomerulonephritis, interstitial nephritis, toxic mesangiolysis with platelet agglutination, fibrin deposition, ischaemic changes, and distal tubular damage ("lower nephron nephrosis"), suggesting direct venom nephrotoxicity attributable

to venom PLA$_2$ and metalloproteases , and bilateral renal cortical necrosis with subsequent calcification are also reported. Antivenom can cause immune-complex-mediated kidney injury. Acute tubular necrosis may result from prolonged hypotension and hypovolaemia, DIC, direct toxic effect of the venom on the renal tubules, haemoglobinuria, myoglobinuria, and hyperkalaemia. Russell's viper venom produces hypotension, DIC, direct nephrotoxicity, and, in Sri Lanka and India, intravascular haemolysis and rhabdomyolysis.In Burmese patients envenomed by Russell's vipers *(D. siamensis)*, high urinary concentrations of β2-microglobulin, retinal binding protein, and N-acetyl glucosaminidase suggested failure of proximal tubular reabsorption and tubular damage. High plasma concentrations of active renin suggested that renal ischaemia with activation of the renin-angiotensin system was involved in development of renal failure. A massive but transient capillary and glomerular leak of albumin was an early sign of oliguric renal failure. Snake venom–induced DIC may result in deposition of fibrin on vascular endothelium that has been activated by, for example, metalloproteinases, producing microangiopathic haemolysis. Although the clinical picture is reminiscent of haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP), there is no evidence of depleted ADAMTS-13 levels and, therefore no justification for cryosupernatant plasmapheresis (Ho et al., 2010).

Generalized increase in capillary permeability

Venoms of some Viperidae, such as *D. russelii* and *D. siamensis*, can cause a generalized increase in vascular permeability, resulting in pulmonary oedema, serous effusions, conjunctival, periorbital, facial and retinal oedema, bilateral parotid enlargement, albuminuria, and haemoconcentration. The likely cause is metalloproteases that damage vascular endothelium.

Epidemiology of snakebite in South-East Asia Region countries

Epidemiology of snakebite in South-East Asia Region countries

Essentials:

Most published data, based on hospital returns, are incomplete because many patients are treated by traditional healers. However, three large, well-designed, national, community-based studies from Bangladesh, India and Sri Lanka have produced reliable estimates. Data are inadequately reported and so snakebite should be made a notifiable disease in all South-East Asia Region countries. Death certification should use International Classification of Diseases code T63.0 (Toxic effect of contact with venomous animals – snake venom and sea-snake venom) (ICD-10 Version:2015 http://apps.who.int/classifications/icd10/browse/2015/en#/T63.0)

Incidence of snakebite varies diurnally and seasonally. It is highest during agricultural activities and seasonal rains. Most bites are inflicted on the feet and ankles of bare-footed agricultural workers who tread on snakes inadvertently while walking in the dark or working in fields and plantations. Snake species differ in their inclination to strike when disturbed. Notoriously "irritable" species include Russell's and saw-scaled vipers. Cobras and kraits enter human dwellings. Kraits bite people who are asleep on the ground at night. On average, about 50% of bites by venomous snake cause no envenoming ("dry bites"), a figure ranging 5-80% with different species.

Snakebite epidemics follow flooding, cyclones and invasion of snakes' habitats for road building, irrigation schemes and logging. These activities cause long term changes in climate and ecology and encourage influx of human settlers.

Males are more often bitten than females. Peak incidence is in children and young adults. Pregnant women and their fetuses are at increased risk of dying. Snakebite is an occupational disease of farmers, plantation workers, herders, hunters, fishermen, fish farmers, snake restaurant workers and snake charmers. Factors contributing to fatal snakebite include problems with choice and dosage of antivenom, delay from visiting traditional healers, transportation difficulties, death in transit, airway obstruction, failure to attempt assisted ventilation or problems in carrying it out, failure to treat hypovolaemia, complicating infections, failure to observe deterioration in hospital. Hours usually elapse between bite and neurotoxic deaths from elapid envenoming and several days or longer, from viper envenoming.

Snakebite in different South-East Asia Region countries

Bangladesh: *medically important species include B. caeruleus, B. niger, B. walli; N. kaouthia, N. naja; D. russelii and T. (T.) erythrurus.*

In 2009, 9000 people were questioned in about 4000 randomly selected households throughout all 6 administrative divisions. 589,919 snakebites and 6,041 deaths per year were estimated in rural areas (case-fatality 1%).

Green pit vipers cause many bites, some morbidity but few deaths. D. russelii is restricted to western and southern areas. B. niger, previously unknown in Bangladesh, has caused deaths. N. kaouthia causes most cobra bites.

Bhutan: *medically-important species include cobras, kraits and pit-vipers. No recent data on bites.*

Democratic People's Republic of Korea: *medically-important species include adders (Vipera berus and V. sachalinensis), several species of mamushi (genus Gloydius) and Rhabdophis tigrinus. No recent data on bites.*

India: *medically important species include N. naja, N. kaouthia; B. caeruleus; D. russelii, E. carinatus; Hypnale hypnale, Trimeresurus. Registrar General of India's "Million Death Study" assigned causes of all deaths in about 7000 randomly chosen sample areas, each with a population of about 1000 throughout the whole country. Verbal autopsy (questioning bereaved relatives and neighbours about the circumstances of the deceased's death), proved reliable for an event as distinctive, dramatic and memorable as snakebite fatality. Results were independent of hospital underreporting and were nationally representative.*

Direct estimate of deaths attributable to snakebite in 2005 was 46 000 (99%CI 41 000-51 000), (1 snakebite death for every 2 HIV/AIDS deaths). Snakebites caused 0.5% of all deaths, 3% in 5-14 year-olds. 97% died in rural areas, only 23% in health facilities. The highest numbers of deaths were in Uttar Pradesh (8,700), Andhra Pradesh (5,200), and Bihar (4,500).

Indonesia: *medically important species throughout the >18 000 islands include B. candidus, N. sputatrix, N. sumatrana, C. rhodostoma , T. (T.) albolabris; D. siamensis and, in West Papua and Maluku, Acanthophis laevis. Hundreds of bites each year are treated in Sumatra, Java, East Kalimantan, Sulawesi, Wetar and West Papua.*

Maldives: *there is one species of sea snake but no terrestrial venomous snake. No recent data on bites.*

Myanmar: *medically important species include B. magnimaculatus, B. multicinctus; N. kaouthia, N. mandalayensis; Trimeresurus (T.) albolabris, T. (T.) erythrurus; D. siamensis In 2014, 15,080 bites with 305 deaths were reported to the Ministry of Health (case-fatality 2.02%). D. siamensis causes 90% of bites.*

Nepal: *medically important species include B. caeruleus, B. niger, B. walli; N. naja, N. kaouthia; D. russelii and Ovophis monticola. In the Eastern Terai, there were 162 snakebite deaths/100 000/year. Only 20% of deaths occurred in hospitals. Most were attributed to krait. National totals of between 1000 bites and 200 deaths and 20 000 bites and 1000 deaths/year have been suggested. In 2000, the Ministry of Health reported 480 bites with 22 deaths, while 4,078 bites with 81 deaths were recorded at 10 hospitals in eastern Nepal (case-fatality 3-58%).*

Sri Lanka: medically important species include B. caeruleus; N. naja; D. russelii, Echis carinatus and Hypnale hypnale. Bites are caused by D. russelii, (30%), H. hypnale (22%), N. naja (17%) and B. caeruleus. A recent community-based, countrywide survey of snakebite included nearly 1% of the country's population. The incidence of bites, envenoming and mortality from snakebite was found to be 398 (95% CI: 356–441), 151 (130–173) and 2.3 (0.2– 4.4)/100 000/year, respectively, amounting to more than 80 000 bites, 30 000 envenomings and 400 deaths in the country each year.

Thailand: medically important species include B. candidus; N. kaouthia, N. siamensis; C. rhodostoma; Trimeresurus (T.) albolabris and D. siamensis. Incidence of bites has declined from 9,071 bites (14.5/100 000) in 2002 to 457 (0.7/100 000) in 2015. Mortality has declined from an average of 178/year in the 1950s to fewer than 2/year since 2008 (case-fatality <0.5%). Calloselasma rhodostoma causes 38% of attributable bites, Trimeresurus (T.) albolabris and T. (T). macrops 30 %, Naja kaouthia and N. siamensis 23% and Daboia siamensis 2%. B. candidus causes as many fatalities as the far better recognized Calloselasma rhodostoma).

Timor-Leste: T. (T.) insularis causes bites and a few fatalities.

4.1 Introduction

It is generally recognized that the epidemiology of snakebite in the South-East Asia Region has not been adequately studied and that the published data, based almost exclusively on hospital returns to ministries of health, are likely to be unreliable and therefore misleading. One reason is that many snakebite victims are treated not in hospitals but by traditional healers (Warrell, 1992). In the past half century, only three attempts have

The total number of snakebites each year might exceed 5 million with a snakebite mortality of 125 000 each year in the world as a whole. (Chippaux,1998)

been made to assess global snakebite mortality. In 1954, Swaroop and Grab of the Statistical Studies Section, WHO, estimated that among half a million snakebites and between 30 000 and 40 000 snakebite deaths each year in the world as a whole, with between 25 000 and 35 000 deaths in Asia. Their analysis was based on registration of deaths in different countries, but they recognized the following deficiencies in this method:

1. "Available statistical data are known to be unreliable and, at best, can serve to provide only an approximate and highly conservative estimate of the relative magnitude of the snakebite problem."

2. "The chance of snakebite deaths being missed are perhaps even greater than for deaths occurring from several other causes."

3. "The recorded figures of snakebite deaths may therefore be regarded as underestimates of the total fatality from this cause, the degree of underrecording varying from place to place."

In 1998, Chippaux published an appraisal of the global situation, again based mainly on hospital records or health authority statistics, quoting 114 publications. He speculated that the total number of snakebites each year might exceed 5 million with a snakebite mortality of 125 000 each year in the world as a whole, including 4 million snakebites, 2 million

snakebite envenomings, and 100 000 snakebite deaths each year in Asia.

In 2008 Kasturiratne et al estimated 237 379–1 184 550 envenomings with 15 385 - 57 636 deaths in the Asia-Pacific region (South 14 112-33 666 – rate 0.912- 2.175/100 000/year; East 462-4 829 – rate 0.033- 0.347/100 000/year). Their most conservative estimate of the highest number of deaths due to snake bite was 14 000 in South Asia. Various studies suggest that bites with envenoming constitute 12-50% of the total number of bites in Asia and 18-30% in India and Pakistan.

A fundamental problem throughout much of the Region is that snakebite treatment has remained in the domain of traditional, herbal or ayurvedic practitioners, so that the majority of snakebite victims are not seen or recorded in western-style hospitals or dispensaries. For example, in Wat Promlok, Nakorn Srithamarat, Thailand, one "moor glang baan" (traditional therapist) treated 72-393 snakebite victims each year between 1985 and 2002.

In the Terai of Nepal, a community-based study established the high fatality rate of 161/100 000/year, attributable mainly to krait bites (Sharma et al., 2004). Few other community studies have been attempted (Hati et al 1992). In some countries, such as Sri Lanka, there has, over the last two decades, been a dramatic shift in patients' preference for treatment from ayurvedic to western medicine.

The true scale of mortality from snakebite is just beginning to be revealed, thanks to three large, well-designed, community-based studies that have recently been published from India (Mohapatra et al., 2011), Bangladesh (Rahman et al., 2010) and Sri Lanka (Ediriweera et al, 2016).

The continuing inadequacies in the reporting of snakebite incidence, morbidity and mortality, prompts the following recommendation.

Recommendation: To remedy the deficiency in reliable snakebite data, it is strongly recommended that snakebites should be made a specific notifiable disease in all countries in the South-East Asia Region and that death certification should use the specific International Classification of Diseases code T63.0 (Toxic effect of contact with venomous animals – snake venom and sea-snake venom) (ICD-10 Version:2015 http://apps.who.int/classifications/icd10/browse/2015/en#/T63.0 (E) (T63.0) Snake venom

4.2 Determinants of snakebite incidence and severity of envenoming

The incidence of snakebites depends critically on the frequency of contact between snakes and humans. Except at times of flooding, snakes are elusive and reclusive and so contact with humans is likely only when humans move into the snakes' favoured habitat (rice fields in the case of Russell's vipers and cobras; rubber and coffee plantations in the case of Malayan pit vipers) or when nocturnally active snakes are trodden upon by people walking along paths in the dark. Seasonal peaks of snakebite incidence are usually associated with increases in agricultural activity or seasonal rains, perhaps coinciding with unusual movements and activity by the snakes. Different species of snake vary in their willingness to strike

when disturbed. Typically "irritable" species are Russell's vipers (*Daboia russelii and D. siamensis*) and saw-scaled vipers (*Echis*). Bites may be inflicted in the home by peri-domestic species such as cobras (*Naja*) which may live in roof spaces or under the floor and by kraits (*Bungarus*) which enter human dwellings at night in search of their prey and may bite people who move in their sleep. Bites in which a venomous snake's fangs pierce the skin but no envenoming results are known as "dry bites". The incidence of dry bites varies with the species, from 5-80%, average about 50% (Reid et al., 1963a; de Rezende et al., 1998; Silveira and Nishioka, 1995). The explanation for dry bites is either mechanical inefficiency of the venom apparatus striking at an unnatural angle or through clothing, or perhaps voluntary defensive retention (metering) of venom by the snake.

Snakebite epidemics follow flooding (India, Bangladesh, Myanmar and Indonesia), cyclones and invasion of snakes' habitats for road building, irrigation schemes (e.g. Mahaweli Ganga Irrigation Project in Sri Lanka) and logging. These activities cause long-term changes in climate and ecology that may encourage influx of venomous snakes and human settlers into deforested areas that have been developed for farming and plantations. There was no immediate increase in snakebites in Myanmar after Cyclone Nargis, but there was in the aftermath 9-12 months later.

4.3 Epidemiological characteristics of snakebite victims

Males are more often bitten than females, except where the work force is predominantly female (e.g. tea and coffee picking). The peak age for bites is in children and young adults. There is some evidence that peak case fatality is in young children and the elderly. In pregnant women, snakebite carries definite but largely unquantified risks to mother (perhaps 4-5% case-fatality) and fetus (perhaps 20% case-fatality), mainly from bleeding and stillbirth/abortion (Seneviratne at al, 2002; Langley, 2010). Most snakebites are inflicted on the feet and ankles of agricultural workers.

4.4 Circumstances of snakebites

Most snakebites happen when the snake is trodden on, either in the dark or in undergrowth, by someone who is bare-footed or wearing only sandals. The snake may be picked up, unintentionally in a handful of foliage or intentionally by someone who is unwise or boastful. Some bites occur when the snake (usually a krait) comes in to the home at night in search ofits prey (other snakes, lizards, frogs, mice) and someone sleeping on the floor rolls over onto the snake in their sleep. Not all snakebites happen in rural areas. For example, in some large cities, such as Jammu in India, people who sleep in small huts (jhuggies) are bitten by kraits during the night and wake with paralysis (Saini et al., 1986). In parts of India, Hindu pilgrims travel bare-footed though overgrown and mountainous areas in the dark of early morning to reach a holy place and are at increased risk of snakebites (e.g. Sabarimala in the Periyar Tiger Reserve, Kerala, India). Sea snakebites usually occur when fishermen pick the animals out of their hand nets or when people are bathing or washing clothes in estauaries.

4.5 Snakebite as an occupational disease

In South-East Asia Region countries, the risk of snakebite is strongly associated with occupations: farming (rice), plantation work (rubber, coffee), herding, hunting, fishing and fish farming,

catching and handling snakes for food (in snake restaurants), displaying and performing with snakes (snake charmers), manufacturing leather (especially sea snakes), and in the preparation of traditional (Chinese) medicines.

SNAKEBITE:
an occupational disease in South-East Asia

- Farmers (rice, etc.,)
- Plantation workers (rubber, coffee, cacao, oil palm etc.)
- Herdsmen
- Hunters
- Snake handlers (snake charmers and in snake restaurants and traditional Chinese
- pharmacies)
- Fishermen and fish farmers
- Sea-snake catchers (for sea-snake skins, leather)

4.6 Death from snakebite
4.6.1 Factors contributing to fatal snakebite
Few attempts have been made to examine the factors responsible for death in cases of bites by identified species of snakes. In a study of 46 cases of identified snakebite in Thailand, the three species causing most deaths were Malayan krait (*Bungarus candidus*), Malayan pit viper

(*Calloselasma rhodostoma*) and cobras (*Naja species*) (Looareesuwan et al., 1988). Factors identified as contributing to a fatal outcome included problems with antivenom use (inadequate dose or use of a monospecific antivenom for a bite by a different species), 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 hypovolaemia in shocked patients, airway obstruction, complicating infections, and failure to observe patients closely after they had been admitted to hospital. Inadequacies in ambulance transport from rural locations to properly equipped hospitals is an important cause of death (Gimkala et al., 2016). In India, the majority of deaths occur outside a hospital facility (Mohapatra et al. 2011). Peripheral hospitals often have inadequate medical and nursing staffing. It is very important that relatives be effectively deployed to monitor snakebite victims, particularly those with neurotoxic envenoming, to detect progression of weakness and early signs of respiratory paralysis.

4.6.2 Time between snakebite and death
Although very rapid death after snakebite has, rarely, been reported (e.g. reputedly "a few minutes" after a bite by the king cobra *Ophiophagus hannah*), it is clear from studies of large series of snakebite deaths that many hours usually elapse between bite and death in the case of elapid envenoming, and several days, or even longer, in the case of viper envenoming (Reid 1968; Warrell 1995).

4.7 Snakebite in different South-East Asia Region countries
For each South-East Asia Region country, some information about the estimated

incidence of snakebite is reviewed below, based on published and unpublished reports. The most important snake species from a medical point of view are given in the boxes, according to the following definitions (WHO, 2010):

CATEGORY 1: Highest Medical Importance - highly venomous snakes that are common or widespread and cause numerous snakebites, resulting in high levels of morbidity, disability or mortality.

CATEGORY 2: Secondary Medical Importance - highly venomous snakes capable of causing morbidity, disability or death, but for which (a) exact epidemiological or clinical data are lacking or (b) are less frequently implicated because of their behaviour, habitat preferences or occurrence in areas remote from large human populations.

Bangladesh: In 2003, about 170 000 households were surveyed in 12 randomly selected districts. A national total was estimated of 15 372 bites and 1709 deaths (Case Fatality 11%). The risk in rural areas was 10.54 times that in urban areas. 94% victims lived under poor socioeconomic conditions and 61% sought immediate treatment from traditional healers (Hossain et al., 2016). In 2009, a survey, funded by the government and World Bank, questioned 9000 people questioned in about 4000 randomly selected households throughout all 6 administrative divisions. Results suggested an incidence of 623.4 (95% CI 513.4–789.2) snakebites per 100 000 person-years. There were an estimated 710 159 episodes of snakebites occur annually in rural Bangladesh. An estimated 589 919 individuals are bitten by snakes and 6041 die from snakebites every year in rural (Case Fatality 1%) (Rahman et al., 2010). This is a much higher incidence than formerly had been imagined. The

large disparities between the results of these two surveys must be explained by their design and assumptions made in calculating the national estimates.

In 1988-1989, a study had discovered records of 764 bites and 168 deaths (22% case fatality). 34% were cobra *(Naja naja, N. kaouthia)* bites, carrying a 40% case fatality. A total of 8000 bites per year across Bangladesh was estimated (Sarkar et al., 1999). A postal survey suggested 4.3 bites/100 000/year, rising to 7 per 100 000 in areas like Chittagong Division, with an overall case fatality of 20% (Huq et al., 1995). Forty-five percent of victims are said to be farmers and 23% housewives. Most patients are treated by traditional healers ("ozhas") and 20% of fatal cases receive no conventional medical treatment (Ali Reza Khan. Indo-Asian News Service, Dhaka October 12, 2001). In one five-year study of 336 cases of snakebite at Mymensingh Medical College Hospital, 70% of cases were aged 11-30 years and 75% were males (Bhuiyan WHO New Delhi 1981, unpublished). During the severe flooding of July-August 2007, there were 76 cases of snakebite with 13 deaths.

Only 3% of bite victims attend hospital or seek help from a trained doctor, 6% seek assistance from village doctors and most of the rest used traditional healers "Ojhas". About 75 % of snakebite victims receive some kind of treatment within two hours of being bitten. Peak snakebite incidence is during May-October. It was highest in Barisal (2667/100 000/year) and lowest in Sylhet (321/100 000/year). In Dhaka, incidence was 440/100 000/year. A study carried out in 4 tertiary referral hospitals estimated the economic cost of snakebite to the victims' families. The total expenditure related to snakebite was mean US$124 (4 – 2294) with a mean income loss of US$93. Cost of a venomous snakebite was US$231, 7 times higher

than for a non-venomous snakebite. Treatment imposes a major economic burden on affected families, especially in venomous snakebite cases (Hasan et al., 2012).

Green pit vipers *Trimeresurus (Trimeresurus) erythrurus* cause many bites and some morbidity but few if any fatalities. Russell's Viper *(Daboia russelii)* appears to be rare. It is restricted to western and southern parts of the country. There are recent reports of envenoming in the Rajshahi area (Ghose and Faiz, 2015; Ghose et al., 2015). Kraits are responsible for many bites and fatalities. The importance of the greater black krait *(Bungarus niger)*, a species previously unreported from Bangladesh, has only recently emerged. Based on their frequencies among proven krait bites in Bangladesh and their geographical distribution, it is estimated that Wall's krait *(Bungarus walli)* causes about 40% of all krait bites in the country, greater black krait *(B. niger)* and common krait *(B. caeruleus)* about 28% each, and banded *(B. fasciatus)* and lesser black kraits *(B. lividus)* very few. In Bangladesh, *B. lividus* is known only from the northwest, B. *walli* and *B. caeruleus* are absent from southeastern Bangladesh, but *B. fasciatus* and *B. niger* occur throughout the country. Monocled cobras *Naja kaouthia* occur throughout the country and cause most cobra bites. They are the only cobras found in southeastern Bangladesh (including Chittagong, Cox's Bazar and Chittagong Hill Tract Districts). Spectacled cobras *Naja naja* occur around Dhaka and to the west and north of the capital. King cobras *(Ophiophagus hannah)* occur wherever relatively undisturbed bamboo stands and forests remain in Bangladesh, but have not caused documented bites in recent years.

Cat 1: *Elapidae: Bungarus caeruleus, Bungarus niger, Bungarus walli; Naja kaouthia;* **Viperidae:** *Daboia russelii, Trimeresurus (T.) erythrurus*

Cat 2: *Elapidae: Bungarus fasciatus, Bungarus lividus; Naja naja; Ophiophagus hannah;* **Viperidae:** *Trimeresurus (T.) purpureomaculatus, Trimeresurus (T.) septentrionalis*

Bhutan: In 2000, 2085 bites and stings were reported. Five elapid species have been reported from lowland regions of Bhutan (less than 500 metres above mean sea level): cobra *(Naja naja)*, king cobra *(Ophiophagus hannah)* and two species of krait *(Bungarus niger* and *B. fasciatus)*. Other venomous species such as *N. kaouthia, Sinomicrurus macclellandi, Daboia russelii* ("Bhutan Hills" according to MA Smith 1943), and several pit vipers may well occur there as well. There is no published information on snakebites in Bhutan but there are said to be many bites causing local pain and swelling and there were a minimum of 2 fatalities in one year. Antivenom is imported from India (200 vials each year). No recent data on bites.

Cat 1: *Elapidae: Bungarus niger; Naja naja*

Cat 2: *Elapidae: Bungarus fasciatus; Ophiophagus hannah;* **Viperidae:** *Trimeresurus (T.) erythrurus; Daboia russelii*

Democratic People's Republic of Korea: Two species of adders

(Vipera berus and *V. sachalinensis)*, several species of mamushi (genus Gloydius) and the yamakagashi *(Rhabdophis tigrinus)* occur in North Korea but there is no information on snakebites.

Published data are restricted to the Republic of (South) Korea (eg Soh et al., 1978; Sawai,1993). No recent data on bites.

> **Cat 1:** *Gloydius brevicaudus*
>
> **Cat 2:** *Gloydius intermedius; Gloydius ussuriensis; Vipera berus*

India: the numbers of snakebite fatalities in India has long been controversial. The Government of India's web-site reported an average of only 1350 deaths/year between 2003 and 2008, whereas Kastururatne et al., 2008 estimated about 11 000 deaths/year. Estimates as low as 61 507 bites and 1124 deaths in 2006 and 76 948 bites and 1359 deaths in 2007 and as high as 50 000 deaths each year have been published. The Registrar General of India's "Million Death Study", 2001-2003, assigned causes of all deaths, using verbal autopsy, in about 7000 randomly chosen sample areas, each with a population of about 1000 throughout the whole country. Verbal autopsy (questioning bereaved relatives and neighbours about the circumstances of the deceased's death), proved reliable for an event as distinctive, dramatic and memorable as snakebite fatality (Mohapatra et al., 2011). The results were independent of hospital underreporting and were nationally representative. The direct estimate of deaths attributable to snakebite in 2005 was 46 000 (99%CI 41 000-51 000), or 1 snakebite death for every 2 HIV/AIDS deaths. This figure was more than 20 times higher than Government of India's

The direct estimate of deaths attributable to snakebite in India in 2005 was 46 000 (99%CI 41 000-51 000), or 1 snakebite death for every 2 HIV/AIDS deaths.

figure from health facilities and more than 4 times higher than WHO-sponsored guesstimate (Kasturiratne et al, 2008). Snakebites caused 0.5% of all deaths, but 3% in the age group 5-14 years. The proportion of victims dying in rural areas was 97%. Only 23% had died in a health facility. The highest number of deaths were in Uttar Pradesh (8700), Andhra Pradesh (5200), and Bihar (4500).

Previous studies had included a field survey in randomly selected villages in Barddhaman (Burdwan) District, West Bengal that suggested that among the total population of nearly 5 million people, nearly 8000 were bitten and 800 killed by snakes each year, an average incidence of 16.4 deaths/100 000/year (Hati et al., 1992). In Maharashtra State, between 1974 and 78, there was an average of 1224 deaths/year (2.43 deaths/100 000/year). "The big four" medically important species had been considered to be *Naja naja, Bungarus caeruleus, Daboia russelii* and *Echis carinatus* but other species have now been proved important in particular areas, such as *Naja oxiana* (north), *N. kaouthia* (north east), *Hypnale hypnale* (south-west coast and Western Ghats (Joseph et al., 2007)), *Echis carinatus sochureki* (Rajisthan) (Kochar et al., 2007) and *Trimeresurus (Craspedocephalus) malabaricus* (Hassan District, Mysore, Karnataka). Bites by non-venomous species such as checkered keelback/Asiatic water snake *(Xenochrophis piscator)* are common and may cause confusion among medical staff and lead to inappropriate

antivenom treatment. There is variation in the pattern of syndromes across India, with predominance of haemotoxic viper bites in south India and neurotoxic elapid bites in north India. Syndrome-species correlation studies in Tamil Nadu suggest the validity of the main syndromes in identifying the four main venomous snakes in this geographical region: haemotoxicity without acute kidney injury *(Echis carinatus)*; haemotoxicity and neurotoxicity with or without renal failure *(Daboia russelii)*; neurotoxicity with local swelling *(Naja naja)*; and neurotoxicity without local swelling *(Bungarus caeruleus)*.

Cat 1: *Elapidae: Bungarus caeruleus; Naja kaouthia* (east)*, Naja naja* (throughout)*;*
Viperidae: *Daboia russelii; Echis carinatus; Hypnale hypnale* (south-west)

Cat 2: *Elapidae: Bungarus fasciatus, Bungarus niger, Bungarus sindanus, Bungarus walli; Naja oxiana* (north west)*, Naja sagittifera* (Andaman Islands)*; Ophiophagus hannah* (south, north-east, Andaman Islands)*;*
Viperidae: *Trimeresurus (T.) albolabris* (northeast)*; Trimeresurus (T.) erythrurus* (northeast)*; Trimeresurus (T.) purpureomaculatus* (east)*; Trimeresurus (Craspedocephalus) malabaricus* (south-west)*, Trimeresurus (Craspedocephalus) gramineus* (south India, Andaman & Nicobar Islands)*, Macrovipera lebetina* (north)

Indonesia: Although fewer than 20 snakebite deaths are registered each year in this vast archipelago of more than 18 000 islands, several thousand deaths are suspected to occur. Species responsible for most bites include *Trimeresurus*

(Trimeresurus) albolabris, Bungarus candidus (Kuch and Mebs 2007), spitting cobras *(Naja sumatrana and N. sputatrix)*, *Calloselasma rhodostoma* (Java, Madura), *Daboia siamensis* (East Java, Komodo, Flores and Lomblen) and death adders *(Acanthophis* spp.)(West Irian). The national antivenom producer BioFarma manufactures a trivalent antivenom against *Naja sputatrix, Bungarus fasciatus* and *Calloselasma rhodostoma*. No cases of *B. fasciatus* bites are known but deaths from *B. candidus* (Java), *D. siamensis* (Java, Flores, Komodo) and *Acanthophis* (West Irian) have been reported.

Sumatra: in Bengkulu, 2-4 case of snakebite /week; Java (West): in Semarang 1-3 case/week, in Serang, 5-8 case /week, in Madiun 1-3 case/week, in Jogjarkarta 5-6 case/week; Java East: in Surabaya and Sidoarjo 2-5 case/week, in Bondowoso, 148 cases of snakebite were treated between March 2015 and May 2016 (15 months): *Trimeresurus (T.) insularis* - 85 cases, *Bungarus* sp – 5, *Naja* sp -15, *Calleselasma rhodostoma* – 2, non-venomous snakes - 5, unidentified snakes – 36; Lombok: 5-8 case/week; East Kalimantan, Borneo: in Samarinda 1-4 case/week; Sulawesi: in Palu 1-2 case/week; Weta: 5-8 case/week; West Papua: in Timika 1-3 case/week (Dr Tri Maharani, personal communication).

Indonesia (Sumatra, Java, Borneo, Sulawesi & Lesser Sunda Islands but West of Wallace's line i.e. excluding West Papua and Maluku Islands):

Cat 1: *Elapidae: Bungarus candidus* (Sumatra, Java, east to Bali)*; Naja sputatrix* (Java & Lesser Sunda Islands)*, Naja sumatrana* (Sumatra & Borneo)*;*

> **Viperidae:** *Calloselasma rhodostoma* (Java, Madura)*; Trimeresurus (T.) albolabris* (Java, Sumatra, Borneo)*; Daboia siamensis* (formerly D. s. limitis and D.s . sublimitis)

> **Cat 2: Elapidae:** *Bungarus fasciatus, Bungarus flaviceps* (Sumatra & Borneo)*; Calliophis bivirgatus; Ophiophagus hannah* (Sumatra, Borneo & Java)*;*
> **Viperidae:** *Trimeresurus (T.) insularis* (Java, Bali, Komodo, Wetar, Bangka, Sumatra, Sulawesi)*, Trimeresurus (T.) purpureomaculatus* (Sumatra)

Indonesia (East of Wallace's line, i.e. West Papua and Maluku):

> **Cat 1: Elapidae: Acanthophis laevis**

> **Cat 2: Elapidae:** *Acanthophis rugosus; Micropechis ikaheka; Oxyuranus scutellatus; Pseudechis papuanus, Pseudechis rossignolii; Pseudonaja textilis*

Maldives: Only one species of sea snake *(Pelamis platurus)* and two species of harmless land snakes *(Lycodon aulicus* or *L. capucinus* and *Typhlops brahminus)* occur. There have been no reports of bites. A living specimen of *Naja kaouthia* was found in the wild. It had presumably been imported in cargo from South Asia. No recent data on bites.

Myanmar: In the 1930s the annual snakebite mortality reported in Burma exceeded 2000 (15.4/100 000/year). Thirty years later it was still estimated to exceed 1000 (3.3/100 000/year). Russell's viper *(Daboia siamensis)* bite was once the 5th

and is now the 12th leading cause of death in this country. In 1991, there were 14 000 bites with 1000 deaths and in 1997, 8000 bites with 500 deaths. From 2005 until 2008, 8994-11172 bites were reported annually with 748-794 deaths. In 2012, there were 13 867 snakebites in the whole country with 285 deaths (case-fatality 2.06%). In 2014, there were 15 080 bites with 305 deaths (case-fatality 2.02%). Russell's vipers *(Daboia siamensis)* cause 90% of bites. Other important species are cobras *(Naja kaouthia and N. mandalayensis)*, kraits (Bungarus spp.) and green pit vipers [*Trimeresurus (T.) erythrurus*]. In the recent past, antivenom has been imported from Thailand and India to supplement national production. However, the latest annual production by Myanmar Pharmaceutical Factory (Insein) is 73 000 vials of Russell's viper and 7000 vials of Cobra antivenom, with a predicted production of 100 000 vials of antivenom in 2016-2017 financial year that will fulfil national requirements.

> **Cat 1: Elapidae:** *Bungarus magnimaculatus, Bungarus multicinctus; Naja kaouthia, Naja mandalayensis;*
> **Viperidae:** *Trimeresurus (T.) albolabris, Trimeresurus (T.) erythrurus; Daboia siamensis*

> **Cat 2: Elapidae:** *Bungarus candidus; Ophiophagus hannah;*
> **Viperidae:** *Calloselasma rhodostoma (southern Peninsula); Trimeresurus (T.) purpureomaculatus; Ovophis monticola, Protobothrops kaulbacki, Protobothrops mucrosquamatus*

Nepal: Sixteen species of known or potential medical importance occur in Nepal (Sharma et al, 2013). The highest

recorded focal incidence, for Nepal or for the whole world, was 162 snakebite deaths/100 000/year, determined in the Eastern Terai (Sharma et al., 2004). In this study, only 20% of the deaths occurred in hospitals. Increased risk of fatality was associated with being bitten inside the house while resting between 2400 and 0060 hr, suggesting bites by the common krait *(Bungarus caeruleus)* (see below). Other risk factors were an initial visit to a traditional healer and delayed transport to hospital. Medically important species include *Naja naja, Bungarus caeruleus, B. walli* and *Daboia russelii*. In the Kathmandu valley and foothills of the Himalaya, *Ovophis monticola* and *Trimeresurus* pit-vipers cause some bites. Russell's viper *(D. russelii)* causes bites in a few parts of the Terai (e.g. Nawalparasi). In the country as a whole, 1000 bites and 200 deaths have been estimated but one survey suggested 20 000 bites and 1000 deaths/ year (Bhetwal et al., 1998). In 2000, the Ministry of Health reported 480 bites with 22 deaths, while 4078 bites with 81 deaths were recorded at 10 hospitals in eastern Nepal. The case-fatality varied from 3 to 58% in different hospitals (Sharma, 2003).

Cat 1: *Elapidae: Bungarus caeruleus, Bungarus niger; Naja naja; Naja kaouthia*
Viperidae: *Daboia russelii*

Cat 2: *Elapidae:* Elapidae: *Bungarus bungaroides, Bungarus*

fasciatus; Bungarus lividus; Bungarus walli; Ophiophagus hannah; Hemibungarus (Sinomicrurus) *macclellandii*
Viperidae: *Trimeresurus (T.) septentrionalis; Cryptelytrops Trimeresurus (T.) albolabris; Trimeresurus (T.) erythrurus; Trimeresurus* (Crapedocephalus) *gramineus; Gloydius himalayanus; Ovophis monticola; Himalayophis tibetanus; Protobothrops jerdonii; Trimeresurus* (Viridovipera) *stejnegeri; Trimeresurus* (Viridovipera) *yunnanensis*

Sri Lanka: According to the Epidemiology Unit, Ministry of Health, reported snakebite numbers increased from 12 175 per year in 1991 to peak at 37 244 in 2002 and 36 861 in 2005. Fatalities peaked at 194 in 2000 and there were 134 in 2005. There are currently 30 000 – 35 000 bites and 100-150 deaths each year. In hospitals, case fatality decreased from 3.5% in 1985 to 0.2% in 2006. However, these data are based on hospital returns which are likely to miss at least 5% of deaths. Comparison of hospital data with death certifications in Monaragala District during a 5-year period (1999-2003) revealed a 63% underestimate by hospital records of the true number of snakebite deaths (Fox et al., 2006), partly explained by the fact that 36% of snakebite victims did not seek or achieve hospital treatment. In Kandy district, snakebite fatality based on death certification was 2/100 000/year during the period 1967-1987, amounting to about 0.5% of all deaths. Bites are caused by *Daboia russelii*, (30%), hump-nosed viper *(Hypnale hypnale)* (22%), *Naja naja* (17%) and kraits (mainly *Bungarus caeruleus* but a few *B. ceylonicus*) (15%).

A recent community based, countrywide survey of snakebite included nearly 1% of the country's population. The incidence of bites, envenoming and mortality from snakebite was found to be 398 (95% CI: 356–441), 151 (130–173) and 2.3 (0.2– 4.4)/100 000/year, respectively. This amounts to more than 80 000 bites, 30 000 envenomings and 400 deaths in the country each year (Ediriweera et al, 2016).

Cat 1: *Elapidae:* *Bungarus caeruleus; Naja naja;* ***Viperidae:*** *Daboia russelii; Hypnale hypnale*

Cat 2: *Elapidae:* *Bungarus ceylonicus;* ***Viperidae:*** *Echis carinatus; Hypnale nepa, Hypnale walli; Trimeresurus trigonocephalus*

Thailand: Improved surveillance explained the reporting of increasing numbers of snakebite cases from an average of 2316/year in the 1950s to 9071 (14.5/100 000) in 2002 and 8299 (13.25/100 000) in 2006. Cases have subsequently declined from 7835 (12.35/100 000) in 2008 to 5077 (7.9/100 000) in 2012, 1962 (3.06/100 000) in 2013, 1219 (1.88/100 000) in 2014 and 457 (0.7/100 000) in 2015. Mortality has declined from an average of 178/year in the 1950s to fewer than 2/year since 2008. Over the last 5 years, both incidence and case fatality have declined to 500–5000 bites/year (1-10/100 000/year) with an admirably low case fatality less than 0.05%. *Calloselasma rhodostoma* causes 38% of attributable bites, *Trimeresurus (T.) albolabris* and *T. (T). macrops* 30 %, *Naja kaouthia* and *N. siamensis* 23% and *Daboia siamensis* 2%. However, Bungarus candidus causes as many fatalities as the far better recognized *Calloselasma rhodostoma)* (Looareesuwan et al., 1988).

Cat 1: *Elapidae:* *Bungarus candidus; Naja kaouthia, Naja siamensis;* ***Viperidae:*** *Calloselasma rhodostoma; Trimeresurus (T.) albolabris; Daboia siamensis*

Cat 2: *Elapidae:* *Bungarus fasciatus, Bungarus flaviceps; Naja sumatrana; Ophiophagus hannah;* **Viperidae:** *Trimeresurus (T.) macrops, Trimeresurus (T.) purpureomaculatus*

Timor-Leste: *the white-lipped island viper Trimeresurus (T.) insularis* is very common on the main island of Timor, on the small Ataúro Island to the north and on at least 18 other islands in Indonesia. On Timor L'Este, it does cause bites including a few fatalities. The spitting cobra *(Naja sputatrix)* is still unconfirmed but suspected and ophthalmic injuries from spitting have been rumoured (http://www.markoshea.info/timor.php) No recent data on bites.

Cat 1: *Viperidae:* *Trimeresurus (T.) insularis*

Cat 2: *Elapidae:* *Naja sputatrix (unconfirmed)*

Summary: There is great diversity of venomous snake species in the Region. There are in excess of one million envenomings and 75 000 deaths/year in the Region. Important species include Naja naja, N. kaouthia, N. oxiana, Bungarus caeruleus, B. multicinctus, Daboia russelii, D. siamensis, Echis carinatus, Calloselasma rhodostoma, Hypnale hypnale, Trimeresurus (T.) albolabris and Trimeresurus (Craspedocephalus) gramineus. (O)

Clinical effects of snakebite

Clinical effects of snakebite

Essentials:

In patients with suspected snakebite there may be 1-Puncture mark(s) only, caused by "dry bite" from venomous snake, bite by non-venomous snake, bite/scratch by another animal (lizard, fish, rodent, spider etc.), or puncture by sharp vegetation; 2-Local pain/swelling at bite site that may be transient, persistent or complicated by necrosis or infection leading to permanent disability; 3-Local and/or systemic envenoming affecting organs and tissues distant from bite site that may be transient, persistent, life-threatening or permanently debilitating; 4-Signs of extreme anxiety prompted by the frightening experience: hyperventilation, acroparaesthesiae, tetany, dizziness/syncope, vasovagal shock with profound bradycardia, diarrhoea and vomiting, agitation, irrational behaviour, hypertension, tachycardia, sweating, trembling that may mislead medical staff and lead to persistent psychological morbidity; 5-Effects of first-aid and other pre-hospital treatments such as pain, swelling and congestion from tight tourniquet and effects of herbal and other traditional remedies.

Summary of symptoms and signs
General: *fear and foreboding are very common*

Local envenoming: *increasing local pain at the site of the bite (krait bites*
usually painless), local swelling spreading proximally, tender, painful swelling of regional lymph nodes draining bite site. Other signs: fang mark, persistent local bleeding, bruising, lymphangitis, inflammation (swelling, redness, heat), blistering (blebs, bullae, vesicles), infection, abscess formation, necrosis.

Systemic envenoming: nausea, vomiting, malaise, abdominal pain, weakness, drowsiness, prostration.

Cardiovascular (Viperidae): visual disturbances, dizziness, faintness, collapse, shock, hypotension, cardiac arrhythmias, myocardial damage. Generalized increase in capillary permeability: facial, periorbital, conjunctival oedema (chemosis), bilateral parotid enlargement, pleural and pericardial effusions, pulmonary oedema, massive albuminuria, haemoconcentration. Bleeding and clotting disorders (Viperidae): local traumatic bleeding from recent and partly-healed wounds and venepuncture sites; spontaneous systemic bleeding (gums, epistaxis, haematemesis, meningism from subarachnoid haemorrhage, lateralising signs and/ or coma from cerebral haemorrhage/ thrombosis), haemoptysis, haematemesis, rectal bleeding or melaena, haematuria, vaginal bleeding, subconjunctival haemorrhages, skin petechiae, purpura, discoid haemorrhages, ecchymoses.

Neurological (Elapidae, Viperidae eg Russell's viper D. russelii, Gloydius species): bilateral ptosis, external ophthalmoplegia, descending paralysis progressing to generalized flaccid paralysis. Generalized rhabdomyolysis: muscles stiff, tender, painful on passive stretching, trismus, dark brown urine. Acute kidney injury: loin (lower back) pain, haematuria, haemoglobinuria, myoglobinuria, oliguria/anuria, uraemia (acidotic breathing, hiccups, nausea, pleuritic chest pain, encephalopathy).

Acute pituitary insufficiency (Russell's viper): acute - shock, hypoglycaemia; chronic - weakness, loss of secondary sexual hair, loss of libido, amenorrhoea, testicular atrophy, hypothyroidism etc.

Clinical syndromes of snakebite in South-East Asia: although there may be overlap of clinical features caused by venoms of different species of snake, especially as knowledge advances, a "syndromic approach" is useful, especially when the snake has not been identified and only monospecific antivenoms are available.

***SYNDROME 1:** Local envenoming (swelling etc) with bleeding/clotting disturbances = Viperidae (all species)*

***SYNDROME 2:** Local envenoming (swelling etc) with bleeding/clotting disturbances, shock or acute kidney injury = Russell's viper; with conjunctival oedema (chemosis) and acute pituitary insufficiency = Russell's viper, Myanmar and South India with bilateral ptosis, external ophthalmoplegia, facial paralysis etc. and dark brown urine = Russell's viper, Sri Lanka and South India*

***SYNDROME 3:** Local envenoming (swelling etc.) with paralysis = cobra or king cobra*

***SYNDROME 4:** Paralysis with minimal or no local envenoming:
Bitten on land while sleeping on the ground with/without abdominal pain = krait*

Bitten in the sea, estuary and some freshwater lakes = sea snake

Bitten in Indonesia Maluku or West Papua with/without bleeding/clotting disturbance = Australasian elapid

***SYNDROME 5:** Paralysis with dark brown urine and acute kidney injury:
Bitten on land (with bleeding/clotting disturbance) = Russell's viper, Sri Lanka or South India*

Bitten on land while sleeping indoors = krait (B. niger, B. candidus, B. multicinctus), Bangladesh, Thailand

Bitten in the sea, estuary and some freshwater lakes (no bleeding/clotting disturbances) = sea snake

Long term complications: at the bite site - tissue loss, amputation, chronic ulceration (risk of malignant change), infection, osteomyelitis, arthritis, arthrodesis, contracture and hypertrophic or keloid scars cause permanent physical disability. Chronic kidney disease, chronic panhypopituitarism, chronic neurological deficits after strokes. Chronic psychological morbidity (depression, anxiety, impaired function, post-traumatic stress disorder, unexplained residual physical disability).

Cobra-spit ophthalmia: there is immediate intense pain, profuse watering with whitish discharge, congested conjunctivae and spasm and swelling of eyelids.

Victims of snakebite may suffer any or all of the following:

1. No physical effects other than the fang/tooth puncture. This is explained by bites by non-venomous snakes, animals other than snakes (e.g. lizards, fish, rodents, spiders see **Fig 53**), by being impaled on a thorn or other sharp object, or "dry bites" by venomous snakes in which no venom was injected. Patients who develop no or negligible local swelling and no systemic envenoming are identified by clinical evaluation. They can be managed at the most peripheral level of the health service without referral to higher centres (Harris et al., 2010).

Figures 53: Animal bite marks: (a) venomous European adder *(Vipera berus)*; (b) venomous Western Russell's viper *(Daboia russelii)* (fatal case); (c) non-venomous back-fanged rice paddy or plumbeous water snake *(Enhydris plumbea)*; (d) rat; (e) Brazilian wandering spider *(Phoneutria nigriventer)*; (f) catfish (Siluridae) (Copyright DA Warrell)

2. Local envenoming confined to the part of the body that has been bitten. These effects may be transient, resolving in hours or a few days; persistent for weeks; or debilitating, sometimes permanently, due to locally necrotic effects of venom and complicating infections.

3. Systemic envenoming involving organs and tissues distant from the part of the body that has been bitten. These effects may be transient, persistent, life threatening and debilitating, sometimes permanently.

4. Effects of anxiety prompted by the frightening experience of being bitten (real or imagined) and by exaggerated beliefs about the potency and speed of action of snake venoms. These symptoms can be misleading for medical personnel. They may persist causing psychological morbidity (Williams et al., 2011).

5. Effects of first-aid and other pre-hospital treatments that may cause misleading clinical features. These may be debilitating and rarely even life-threatening. (Harris et al., 2010)

5.1 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, and foreboding about the consequences of a real venomous bite. Anxious people may over breathe so that they develop pins and needles (paraesthesiae) of the extremities, stiffness or tetany of their hands and feet and dizziness. Others may develop vasovagal shock after the bite or suspected bite - faintness and collapse with profound

slowing of the heart. Others may become highly agitated and irrational and may develop a wide range of misleading symptoms. Blood pressure and pulse rate may increase and there may be sweating and trembling. Others may vomit and have diarrhoea.

Another source of symptoms and signs not caused by snake venom is first aid and traditional treatments (Harris et al., 2010). Constricting bands or tourniquets may cause pain, swelling and congestion that suggest local envenoming. Ingested herbal remedies may cause vomiting. Instillation of irritant plant juices into the eyes may cause conjunctivitis. Forcible insufflation of oils into the respiratory tract may lead to aspiration pneumonia, bronchospasm, ruptured ear drums and pneumothorax. Incisions, cauterisation, immersion in scalding liquid and heating over a fire can result in devastating injuries.

5.2 When venom has been injected
5.2.1 Early symptoms and signs
Following the immediate pain of mechanical penetration of the skin by the snake's fangs, and the fear associated with such a terrifying experience as being bitten by a snake, 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 bites in the upper limb). However, bites by kraits, sea snakes and Philippine cobras may be virtually painless and may cause negligible local swelling. Someone who is sleeping may not even wake up when bitten by a krait and there may be no detectable fang marks or signs of local envenoming.

5.2.2 Clinical patterns of envenoming by snakes in South East Asia

Symptoms and signs vary according to the species of snake responsible for the bite and the amount of venom injected. Sometimes the identity of the biting snake can be confirmed by examining the dead snake or an image of the snake sent by mobile 'phone; it may be strongly suspected from the patient's description or the circumstances of the bite or from knowledge of the clinical effects of the venom of that species. This information will enable the doctor to choose an appropriate antivenom, anticipate the likely complications and therefore take appropriate action. If the biting species is unknown, the patient should be observed closely to allow recognition of the emerging pattern of symptoms, signs and results of laboratory tests ("the clinical syndrome"), together with other evidence, which may suggest which species was responsible.

5.2.3 Local symptoms and signs in the bitten part

- fang marks **(Fig 54a)**
- local pain
- local bleeding **(Fig 54b)**
- bruising **(Fig 54c)**
- spreading local swelling **(Fig 55)**
- lymphangitis
- lymph node enlargement
- inflammation (swelling, redness, heat)
- blistering **(Fig 54c, 54d, 54e)**
- local infection, abscess formation **(Fig 56)**
- necrosis **(Fig 57)**

Figures 54: Local signs of envenoming: (a) Fang marks 2.5 cm apart inflicted by a large Russell's viper in Sri Lanka; (b) Persistent local bleeding from fang marks 40 minutes after a bite by a Malayan pit viper; (c) Swelling, blistering and bruising following a bite by a Malayan pit viper; (d) Blistering with early necrosis at the site of a monocellate cobra bite; (e) blistering and early tissue necrosis following a bite by an Indo-Chinese spitting cobra *(Naja siamensis)* in south Viet Nam. (Copyright DA Warrell)

Figure 55: Local swelling after a saw-scaled viper *(Echis ocellatus)* bite on the hand rapidly extending proximally (Copyright DA Warrell)

Figure 56: Local abscess at the site of a Western Russell's viper *(Daboia russelii)* bite in Sri Lanka (Copyright DA Warrell)

Figures 57: Local necrosis that required surgical debridement: (a) after Malayan pit viper *(Calloselasma rhodostoma)* bite in Thailand; (b) after spectacled cobra *(Naja naja)* bite in Sri Lanka (Copyright DA Warrell)

5.2.4 Generalized (systemic) symptoms and signs

General

Fear, anxiety, nausea, vomiting, malaise, abdominal pain, weakness, drowsiness, prostration.

Cardiovascular (Viperidae)

Visual disturbances, dizziness, faintness, collapse, shock, hypotension, cardiac arrhythmias, myocardial damage (reduced ejection fraction).

Generalized increase in capillary permeability ("capillary leak syndrome") (Russell's vipers: D. siamensis in Myanmar (Myint-Lwin et al., 1985) and D. russelii in India; Facial and conjunctival oedema (chemosis) **(Fig 58)**, bilateral parotid enlargement **(Fig 59 a, b)** (Chakraborty and Bhattachcharjee, 2010; Deepak et al., 2013), pleural and pericardial effusions, pulmonary oedema, massive albuminuria, haemoconcentration.

Figure 58 Bilateral conjunctival oedema (chemosis) after bite of Eastern Russel's viper *(Daboia siamensis)* in Myanmar (Copyright DA Warrell)

Bleeding and clotting disorders (Viperidae)

- traumatic bleeding from recent wounds (including prolonged bleeding from the fang marks (**Fig 54b**, venipunctures etc) and from old partly-healed wounds - spontaneous systemic bleeding - from gums **(Fig 60a)**, epistaxis, bleeding into the tears, intracranial haemorrhage (meningism from subarachnoid haemorrhage - **Fig 60b**, lateralising signs and/or coma from cerebral haemorrhage – **Fig 61**), haemoptysis **(Fig 62)**, haematemesis), rectal bleeding or melaena, haematuria, vaginal bleeding, bleeding into the mucosae (eg conjunctivae – **Fig 63**), skin (petechiae, purpura, discoid haemorrhages – **Fig 64** and ecchymoses.

Figure 59 a, b: Bilateral parotid gland enlargement ("viper's head" appearance) after bite of Western Russel's viper *(Daboia russelii)* in Kerala, India (Copyright Dr Joseph K Joseph)

Figures 60: Spontaneous systemic bleeding: (a) from gingival sulci in a patient bitten by a Malayan pit viper; (b) neck stiffness (meningism) from sub-arachnoid haemorrhage after a saw-scaled viper bite (Copyright DA Warrell)
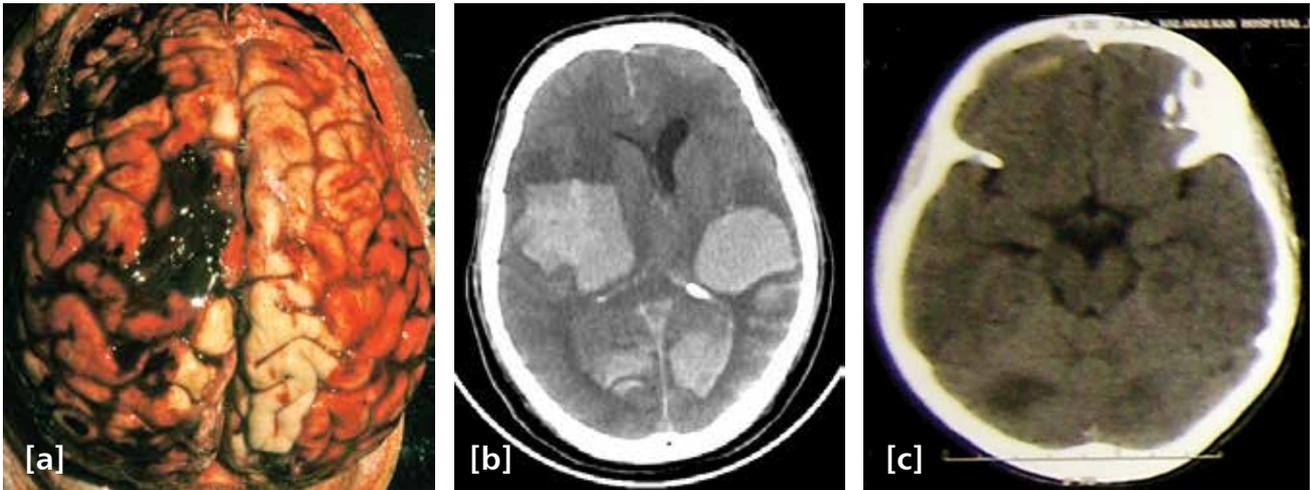
Figures 61: Strokes after Russell's viper bites: (a) fatal cerebral haemorrhage in Myanmar (Copyright Dr U Hla Mon); (b) intra cerebral haemorrhages in Maharashtra, India; (c) ischaemic/thrombotic stroke in Maharashtra, India (b, c, Copyright Dr Suvarna Patil)

Figure 62: Haemoptysis from a tuberculous lung cavity in a patient bitten by a Malayan pit viper (Copyright DA Warrell)

Figure 63: Subconjunctival haemorrhages in a patient bitten by a Burmese Russell's viper (Copyright DA Warrell)

Figure 64: Cutaneous signs: (a) lymphangitic lines extending towards regional lymph nodes (b) Cutaneous discoid haemorrhages in a patient bitten by a Malayan pit viper in Viet Nam (Copyright DA Warrell)

Cerebral arterial thrombosis (Russell's vipers *Daboia russelii* and *D. siamensis*)

Thrombotic strokes, confirmed by angiography or imaging, are increasingly recognized after envenoming by *D. russelii* in India **(Fig 61c)**, Sri Lanka (Gawarammana et al., 2009) and Taiwan.

Neurological (Elapidae, Viperidae eg Russell's viper *D. russelii*, *Gloydius* species)

Drowsiness, paraesthesiae, abnormalities of taste and smell, "heavy" eyelids, ptosis **(Fig 65a,b)**, external ophthalmoplegia **(Fig 66)**,

[a] [b]

Figures 65a,b: Bilateral ptosis: (a) in a patient bitten by a common krait in Sri Lanka; (b) in a patient bitten by a Russell's viper in Sri Lankan (Copyright DA Warrell)

Figure 66: External ophthalmoplegia in a patient bitten by a Russell's viper in Sri Lanka. The patient is attempting to look to his right. The eyes must be held open becauseof the bilateral ptosis (Copyright DA Warrell)

paralysis of facial muscles and other muscles innervated by the cranial nerves, nasal voice or aphonia, regurgitation through the nose, difficulty in swallowing secretions, respiratory and generalized flaccid paralysis.

Skeletal muscle breakdown (sea snakes, some krait species – Bungarus

niger and B. candidus, western Russell's viper Daboia russelii)

Generalized pain, stiffness and tenderness of muscles, pain on passive stretching **(Fig 71b)** trismus, myoglobinuria **(Fig 67, 71c)**, hyperkalaemia, cardiac arrest, acute kidney injury.

Figure 67: Patient bitten by a Russell's viper in Sri Lanka. She began to pass dark brown urine containing myoglobin and haemoglobin 8 hours after the bite. (Copyright DA Warrell)

Renal (Viperidae, sea snakes)
Loin (lower back) pain (Tin-Nu-Swe et al. 1993), haematuria, haemoglobinuria, myoglobinuria, oliguria/anuria, symptoms and signs of acute kidney injury/ uraemia (acidotic breathing, hiccups, nausea, pleuritic chest pain etc., see below).

Endocrine (acute pituitary/adrenal insufficiency from infarction of the anterior pituitary – **(Fig 68 a,b)** (Russell's viper in Myanmar and several parts of India) (Eapen at al., 1976; Tun-Pe et al., 1987; Bandyopadhyay et al 2012; Chatterjee et al., 2008; Golay et al., 2014; Murthy et al., 2002)
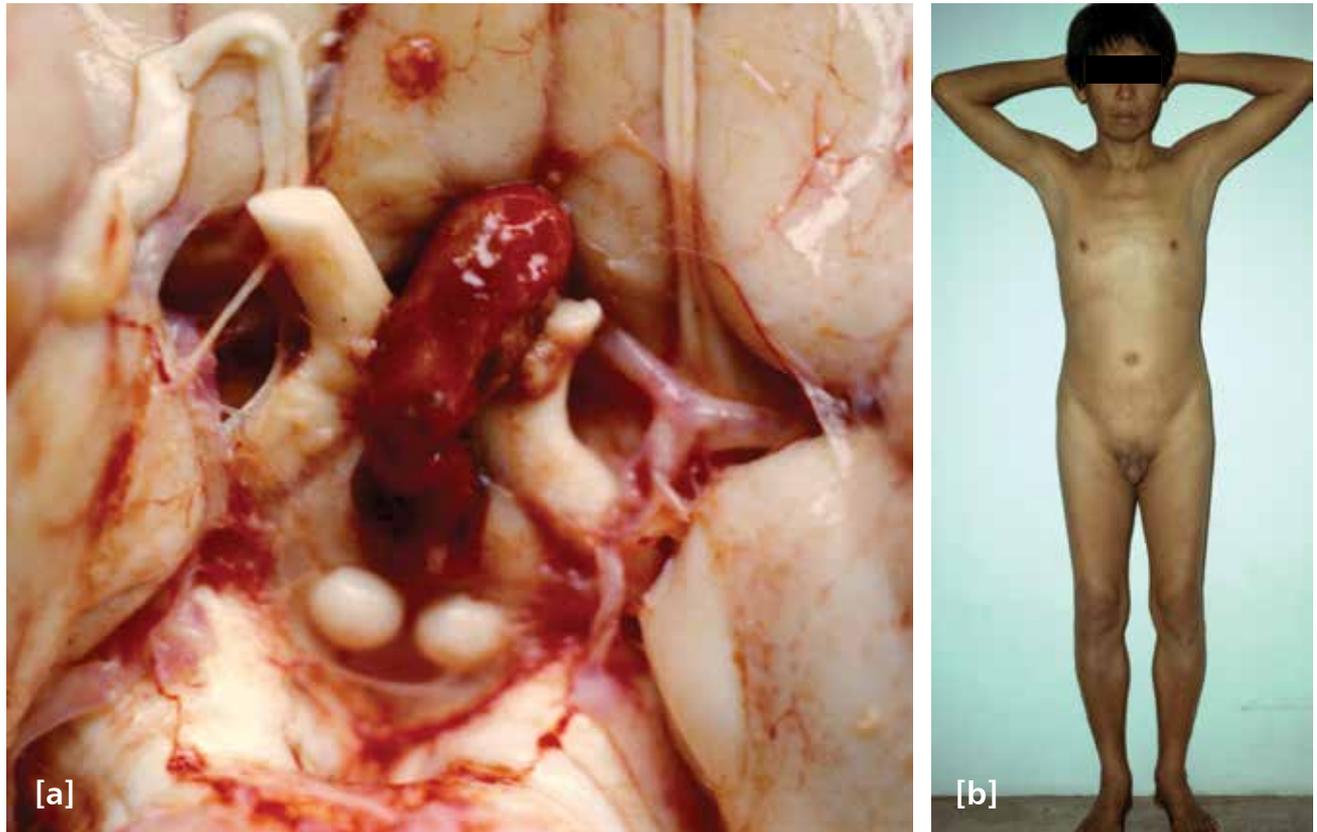
Figures 68: Haemorrhagic infarction of the anterior pituitary resulting in Sheehan's-like syndrome (pan-hypopituitarism) after Russell's viper bite in Myanmar: (a) appearances at the base of the brain at autopsy in a patient who died acutely after the bite (Copyright Dr U Hla Mon); (b) Patient presenting with symptoms and signs of panhypopituitarism three years after severe envenoming by Russell's viper. There is loss of secondary sexual hair and testicular atrophy (Copyright DA Warrell)

Acute phase: shock, hypoglycaemia Chronic phase (months to years after the bite): weakness, loss of secondary sexual hair, loss of libido, amenorrhoea, testicular atrophy, hypothyroidism etc **(Fig 68b).**

Hyponatraemia has been observed in victims of krait bites in the area of Hanoi and around Ho Chi Minh City in Viet Nam *(Bungarus* nr. *multicinctus/candidus)* (Hung and Höjer 2009; Kiem-Xuan-Trinh et al., 2010; Höjer et al., 2010), implying natriuretic hormone like activity in the venom.

5.3 Clinical syndromes of snakebite in South-East Asia

Limitations of syndromic approach:
The more carefully the clinical effects of snakebites are studied, the more it is realised that the range of activities of a particular venom is very wide. For example, some elapid venoms, such as those of Asian cobras, can cause severe local envenoming **(Fig 54d, 54e, 57b, 66)**, formerly thought to be an effect only of viper venoms. In Sri Lanka and India, Russell's viper venom causes paralytic signs (ptosis etc.) **(Figs 65b, 66, 67)**, suggesting elapid neurotoxicity, and muscle pains and dark brown urine **(Fig 67)**, suggesting sea-snake rhabdomyolysis. Envenoming by the greater black krait (B. niger) can cause generalized rhabdomyolysis leading to acute kidney injury (Faiz et al., 2010). Although there may be considerable overlap of clinical features caused by venoms of different species of snake, a "syndromic approach" may still be useful, especially when the snake has not been identified and only monospecific antivenoms are available (see Annexes 1 and 2) (Pathmeswaran et al, 2006; Ariaratnam et al., 2009).

SYNDROME 1: Local envenoming (swelling etc) with bleeding/clotting disturbances = *Viperidae* (all species)

SYNDROME 2: Local envenoming (swelling etc) with bleeding/clotting disturbances, shock or acute kidney injury = **Russell's viper** with conjunctival oedema (chemosis) and acute pituitary insufficiency = **Russell's viper, Myanmar and South India** with ptosis, external ophthalmoplegia, facial paralysis etc. and dark brown urine = **Russell's viper, Sri Lanka and South India (?Myanmar)**

SYNDROME 3: Local envenoming (swelling etc) with paralysis = **cobra or king cobra**

SYNDROME 4: Paralysis with minimal or no local envenoming:
Bitten on land while sleeping on the ground with/without abdominal pain = **krait**

Bitten in the sea, estuary and some freshwater lakes = **sea snake**

Bitten in Indonesia Maluku or West Papua with/without bleeding/clotting disturbance = **Australasian elapid**

SYNDROME 5: Paralysis with dark brown urine and acute kidney injury:

Bitten on land (with bleeding/clotting disturbance) **= Russell's viper, Sri Lanka or South India**

Bitten on land while sleeping indoors = **krait *(B. niger, B. candidus, B. multicinctus)*, Bangladesh, Thailand**

Bitten in the sea, estuary and some freshwater lakes (no bleeding/clotting disturbances) = **sea-snake**

5.4 Long term complications (sequelae) of snakebite

At the site of the bite, loss of tissue may result from sloughing or surgical débridement of necrotic areas or amputation: chronic ulceration, infection, osteomyelitis or arthritis may persist causing severe physical disability **(Fig 70a)**. Malignant transformation may occur in skin ulcers after a number of years (Marjolin's ulcer) **(Fig 70b)**.

Chronic kidney disease (renal failure) may occur after bilateral cortical necrosis (Russell's viper and hump-nosed pit viper bites) (Ariaratnam et al., 2008b); and

[a]
[b]

Figures 70: Chronic physical handicap resulting from necrotic envenoming by Malayan pit vipers: (a) Deformity and dysfunction after a snakebite and subsequent necrosis of the calf; (b) Squamous cell carcinoma arising at the site of a chronic skin ulcer with osteomyelitis 8 years after the bite (Copyright DA Warrell)

chronic panhypopituitarism or diabetes insipidus after Russell's viper *(Daboia russelii* and *D. siamensis)* bites in India (Golay et al., 2014) and Sri Lanka and, most commonly, in Myanmar, **(Fig 68b)**. Chronic neurological deficit is seen in patients who survive intracranial haemorrhages and thromboses (Viperidae).

Abnormalities of electrophysiological tests can persist for over 12 months following elapid bites in Sri Lanka (Bell et al, 2010).

Delayed psychological morbidity has been reported one to four years after snakebite envenoming in Sri Lanka. Depression and anxiety, impaired functioning, post-traumatic stress disorder and unexplained residual physical disability were reported (Williams et al, 2011). Chronic musculoskeletal disabilities have been reported following snake envenoming in Sri Lanka. The disabilities involved mostly the lower limbs. They ranged from swelling, muscle wasting, stiff joints, reduced muscle power, impaired balance, fixed deformities, chronic non-healing

ulcer, and persisting lump to amputations. (Jayawardene et al., submitted for publication). Unexplained residual symptoms have also been reported following snakebite in Tamil Nadu, India (Vaiyapuri et al, 2013).

5.5 Symptoms and signs of sea-snake envenoming
(Reid, 1979; Warrell, 1994)
Envenoming by sea snakes (Hydrophiinae) and sea kraits (Laticaudinae): the bite is usually painless and may not be noticed by the wader or swimmer. Fangs and other teeth may be left in the wound.

[c]

[a]

[b]
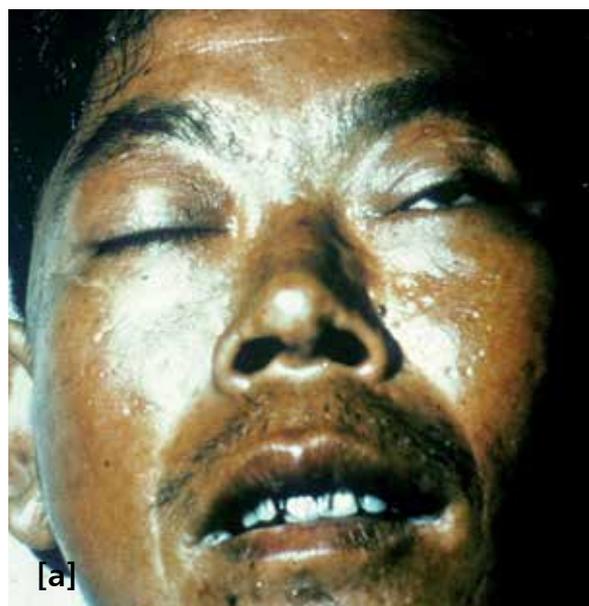
Figures 71: Sea-snake bite in North-west Malaysia: (a) Ptosis, facial paralysis and trismus; (b) Generalised myalgia making passive movement of the limbs extremely painful; (c) myoglobinuria (Copyright the late H Alistair Reid)

> *If the "spat" venom enters the eyes, there is immediate and persistent intense burning, stinging pain, followed by profuse watering of the eyes with production of whitish discharge, congested conjunctivae, spasm and swelling of the eyelids, photophobia, clouding of vision and temporary blindness.*

conscious until the respiratory muscles are sufficiently affected to cause respiratory failure. Myoglobinaemia and myoglobinuria develop 3–8 hours after the bite **(Fig 71c)**. These are suspected when the serum/plasma appears brownish and the urine dark reddish brown ('Coca-Cola-coloured'). Bedside 'sticks' tests will appear positive for haemoglobin/blood in urine containing myoglobin. Myoglobin and potassium released from damaged skeletal muscles may contribute to acute kidney injury, while hyperkalaemia developing within 6–12 hours of the bite may precipitate cardiac arrest.

There is minimal or no local swelling and involvement of local lymph nodes is unusual. Generalized rhabdomyolysis is the dominant effect of envenoming by these snakes although patients without this feature have been described. Early symptoms include headache, a thick feeling of the tongue, thirst, sweating and vomiting. Generalized aching, stiffness and tenderness of the muscles becomes noticeable between 30 minutes and 3½ hours after the bite. Trismus is common **(Fig 71a)**. Passive stretching of the muscles is painful **(Fig 71b)**. Later, there is progressive flaccid paralysis starting with ptosis, as in other neurotoxic envenomings. The patient remains

5.6 Symptoms and signs of cobra-spit ophthalmia
(eye injuries from spitting cobras) (Fig 72)

If the "spat" venom enters the eyes, there is immediate and persistent intense burning, stinging pain, followed by profuse watering of the eyes with production of whitish discharge, congested conjunctivae, spasm and swelling of the eyelids, photophobia, clouding of vision and temporary blindness. Corneal ulceration, permanent corneal scarring and secondary endophthalmitis are recognized complications of African spitting cobra venom but have not been described in Asia.

Figure 72: Bilateral conjunctivitis in a patient who had venom spat into both eyes by an Indo-Chinese spitting cobra *(Naja siamensis)* (Copyright DA Warrell)

Management of snakebites in South-East Asia

Management of snakebites in South-East Asia

Essentials:

First-aid should be carried out immediately after the bite, by the victim or others present. Most traditional methods are useless and harmful. To prevent deaths from respiratory paralysis or shock before victims reach medical care, delay venom spread with pressure-pad or pressure-bandage plus immobilization, accelerate transport to hospital (improve ambulance services), and train accompanying medical workers in airway management, assisted ventilation and resuscitation. The snake is valuable evidence, but should not be pursued, killed or handled. Close-up mobile 'phone images ' are useful.

Recommended first-aid: reassurance, immobilization of the whole patient, especially their bitten limb, accelerated transport to medical care (summoned by emergency telephone helpline) ideally in recovery position. Unless neurotoxic elapid bite can be excluded, apply pressure-pad (simpler, more practicable than pressure-bandage immobilization). Never use, recommend or condone tight (arterial) tourniquets.

Medical treatment in dispensary or hospital Rapid clinical assessment accompanies urgent resuscitation of shocked or

asphyxiated patients. Clear airway, give oxygen, establish intravenous access, monitor vital signs. Beware of removing tight tourniquets before antivenom and resuscitation facilities are available.

Key questions: "Where (in which part of your body) were you bitten? Point to the place"; "When were you bitten and what were you doing then?"; "Where is the snake that bit you?" or "What did it look like; did anyone take a picture?"; "How are you feeling now?"

Examination of the bitten part: extent of tenderness/swelling, lymph nodes draining bitten limb, early signs of necrosis (blistering, demarcated altered pigmentation, putrefaction odour. General: blood pressure (postural drop indicates hypovolaemia), gingival sulci, nose, skin and mucosae for evidence of bleeding, chemosis, abdominal tenderness, loin pain and tenderness, meningism, lateralising neurological signs (asymmetrical pupils), impaired consciousness, bilateral ptosis, diplopia, external ophthalmoplegia, mouth opening/ closing, trismus, tongue protrusion, facial muscles, gag reflex neck flexors "broken neck sign", swallowing, "paradoxical respiration", fasciculations or myokymia,

measure ventilatory capacity. If adequately ventilated, totally paralysed patient are fully conscious and can communicate by flexing a digit. Conventional tests of brain death misleading. Generalised tender, painful muscles and dark brown urine suggest rhabdomyolysis. Pregnant women: suspect antepartum or postpartum haemorrhage, vaginal bleeding, premature labour, fetal distress, intra-uterine fetal death, abortion/stillbirth.

Species diagnosis: expert identification of dead snake or a mobile 'phone photo image is useful. Otherwise, infer species from the patient's description and circumstances of bite (e.g. nocturnal bite while sleeping on ground suggests krait) and clinical syndrome.

Investigations/laboratory tests: 20 minute whole blood clotting test (20WBCT) is a simple, informative bedside test requiring only a new, clean, dry, ordinary glass tube, bottle, vial or syringe. Positive (non-clotting) result indicates severe consumption coagulopathy and need for immediate antivenom treatment. False positive (non-clotting) 20WBCT results from use of plastic, polystyrene or polypropylene rather than ordinary glass, or glass cleaned with detergent, soap or washing fluid that destroy surface-activation of blood coagulation. If new glass tubes not available, re-use ordinary glass vessels (e.g. antibiotic bottles), washed with "normal 0.9% saline" for intravenous infusion, without detergent or other cleaning agent, dried in hot air.

Other more sensitive laboratory tests of blood coagulation: International Normalized Ratio (INR) based on prothrombin time (PT) (> or =1.2 is abnormal), activated partial thromboplastin time (aPPT), fibrin(ogen) related antigens (fibrin degradation products -FDP) or D-dimer. Point-of-care (bedside) devices for

measuring INR and D-dimer unreliable in snakebite victims.

Other laboratory tests: haemoglobin concentration/haematocrit, thrombocytopenia, neutrophil leucocytosis, fragmented red cells ("helmet cell", schistocytes) signifying microangiopathic haemolysis. Observe spontaneously sedimented plasma for haemoglobinaemia/ myoglobinaemia.

Biochemical abnormalities: plasma creatinine, urea/blood urea nitrogen and potassium concentrations raised in acute kidney injury (Russell's viper, hump-nosed pit-viper, sea-snake envenoming). Elevated aminotransferases and muscle enzymes (creatine kinase, aldolase etc.) indicate local and generalized muscle damage (sea snakes, some kraits, some Australasian Elapidae and Russell's viper bites). Hyponatraemia associated with krait bites.

Urine examination: dipsticks test for blood, haemoglobin or myoglobin and proteinuria. Microscopy to detect erythrocytes and red cell casts, indicating glomerular bleeding, eosinophilia suggesting acute interstitial nephritis.

Other investigations: chest radiography for detecting pulmonary oedema, haemorrhages, infarcts, pleural effusions, secondary bronchopneumonia; ultrasound for assessing local envenoming, deep vein thrombosis, pleural and pericardial effusion and bleeding; echocardiography for myocardial dysfunction; CT and MRI imaging for intracranial and spinal haemorrhages and infarcts and osteomyelitis at the bite site; ECG for arrhythmias, myocardial damage, evidence of hyperkalaemia.

Antivenom treatment
Antivenom (= antivenin, anti-snakebite serum, ASV etc.) is the only specific

antidote to snake venom. A most important decision in managing snakebite victims is whether or not they need antivenom. It is immunoglobulin [usually pepsin-refined F(ab')2 fragments of whole IgG] purified from plasma of horses or sheep hyperimmunised with venoms of one (to make mono-specific antivenom) or more (to make poly-specific antivenom) snake species, medically the most important species in a particular geographical area. Paraspecific neutralization of venoms of closely related species is possible but not certain. Indian "polyvalent anti-snake venom serum" (ASV) is raised against venoms of their "big four" species: spectacled cobra (N. naja); common krait (B. caeruleus), Russell's viper (D. russelii), saw-scaled viper (E. carinatus), but other species, now recognized as being important, are not covered. Thai Red Cross Society manufactures "neuro polyvalent snake antivenin" covering 4 elapids and "haemato polyvalent snake antivenin" covering 3 vipers.

Design, quantity, quality, stability, safety and dosage guidelines of antivenoms require review and improvement.

Antivenom treatment is indicated if/when patients with proven/suspected snakebite develop one or more of the following signs. Systemic envenoming: haemostatic abnormalities [spontaneous systemic bleeding, coagulopathy (+ve non-clotting 20WBCT, INR >1.2, or prothrombin time >4-5 seconds longer than control), or thrombocytopenia; neurotoxicity (bilateral ptosis, external ophthalmoplegia, paralysis etc.); cardiovascular abnormalities (hypotension, shock, cardiac arrhythmia, abnormal ECG); Acute kidney injury (oliguria/anuria, rising blood creatinine/urea); haemoglobin-/myoglobin-uria (dark brown/black urine, +ve urine dipsticks, other evidence of intravascular

haemolysis/generalized rhabdomyolysis); supporting laboratory evidence.
Local envenoming: local swelling involving more than half bitten limb (in absence of tourniquet) within 48 hr of the bite; swelling after bites on digits; rapid extension of swelling beyond wrist/ankle within few hours of bites on hand/foot); enlarged tender lymph node draining bitten limb

Antivenom should be given only when benefits exceeds risks. Since it is expensive and in limited supply, it must not be used indiscriminately. It should be given as soon as it is indicated and as long as anti-haemostatic abnormalities persist, even two weeks after the bite. It is unlikely to prevent/limit local tissue damage unless given within a few hours of the bite.

Antivenom reactions: many patients develop early (within a few hours) or late (after 5 days or more) reactions. Depending on type of antivenom and dose, the incidence may be as high as 81% (43% severe) of early anaphylactic or pyrogenic reactions or as low as 3.5%. IgE-mediated Type I hypersensitivity after previous exposure to equine serum is uncommon.

Early anaphylactic reactions (1 - 180 minutes after starting antivenom) can have all classic features of anaphylaxis from urticaria to life-threatening shock, bronchospasm and angio-oedema. Most are attributable to complement activation by IgG aggregates/residual Fc fragments,

or stimulation of mast cells/basophils by antivenom proteins.

Pyrogenic (endotoxin) reactions (within 1-2 hours) involve rigors, fever (risk of febrile convulsions in children), vasodilatation, hypotension and a fall in blood pressure. Attributable to pyrogen contamination during manufacture.

Late (serum sickness-type) reactions (1-12, mean 7, days after treatment) involve fever, nausea, vomiting, diarrhoea, itching, recurrent urticaria, arthralgia, myalgia, lymphadenopathy, periarticular swellings, mononeuritis multiplex, proteinuria, immune complex nephritis, rarely encephalopathy.

Prediction: skin and conjunctival "hypersensitivity" tests, often recommended in "package inserts" predict acquired IgE-mediated Type I hypersensitivity to horse/sheep proteins, but not large majority of early (anaphylactic) or late (serum sickness type) antivenom reactions. Their use is strongly discouraged.

Prevention:

A powerful, well-designed study in Sri Lanka showed that adrenaline (0.25 ml/ mg of 0.1% solution subcutaneously) given before antivenom was started reduced severe reactions by 43% (95% CI 25–67) at 1 h and by 38% (95% CI 26–49) up to and including 48 h after antivenom administration; hydrocortisone (200 mg intravenously) and promethazine (25 mg intravenously) were ineffective. Hydrocortisone negated benefit of adrenaline. Dilution and slow infusion (10-120 minutes) does not alter risk of reactions.

At the earliest sign of early anaphylactic antivenom reaction, temporarily suspend antivenom administration and give

intramuscular injection of 0.1% adrenaline, initial adult dose 0.5 ml/mg (0.01 mg/kg body weight for children). Since severe, life-threatening anaphylaxis can evolve rapidly, adrenaline must be available at the bed-side and should be given at the first sign of anaphylaxis (e.g. when itching, tachycardia, restlessness develop and a few spots of urticaria appear). Repeat adrenaline every 5-10 minutes if reaction persists or worsens. Adrenaline safe in pregnancy. In case of asthmatic symptoms, given salbutamol bronchodilator. After adrenaline, give intravenous antihistamine anti-H1 blocker (e.g. chlorphenamine maleate, adults 10 mg, children 0.2 mg/ kg intravenously) and hydrocortisone (adults 100 mg, children 2 mg/kg body weight). Anaphylactic shock unresponsive to adrenaline is treated by laying patient supine, legs elevated, and giving intravenous volume replacement (0.9% saline, adults 1-2 litres rapidly). Consider intravenous adrenaline infusion (adults 1mg/1.0 ml of 0.1% solution in 250 ml IV fluid) infused at 15–60 drops/min using micro-dropper burette chamber, or dopamine. Unresponsive bronchospasm or angioedema is treated with optimal nebulised/inhaled and/or parenteral bronchodilator and oxygen.

Pyrogenic reactions are treated by physical cooling (undressing, tepid sponging, fanning) and giving antipyretic paracetamol. Intravenous fluids should be given to correct hypovolaemia. Patients with features of anaphylaxis should be given adrenaline.

After recovery from early reactions, cautiously resume and complete administration of the dose of antivenom.

Late (serum sickness) reactions respond to 5-day course of oral antihistamine or, failing that, 5-day course of prednisolone.

Supply, selection, storage and shelf-life of antivenom

Polyvalent (polyspecific) antivenoms are preferred in many countries because of problems with specific diagnosis. Antivenom should be given only if its stated range of specificity and paraspecific neutralization includes the species known or suspected to have been responsible for the bite. Lyophilised antivenoms (shelf life about 5 years) are stored <25ºC, liquid antivenoms (shelf life 2-3 years) at 2-8 ºC. Ideally, antivenoms should be used before stated expiry dates, antivenoms retain useful activity for months or even years after these dates. In patients with severe envenoming, recently expired antivenoms may be considered if there is no alternative.

Intravenous administration is mandatory, either by slow "push" injection (maximum 2ml/minute) or by intravenous infusion, diluted in 5 ml of isotonic fluid/kg body weight, over 30-60 minutes. Intramuscularly administered antivenom is poorly bioavailable. This route should be considered only in the absence of anyone capable of giving an intravenous injection.

Initial dose of antivenom:
Guidance on average initial dose of a particular antivenom, appropriate for envenoming of different severities, in patients bitten by different species based on clinical trials is rarely available. Usually, dosages quoted on manufacturers' package inserts are based on laboratory mouse LD_{50}s and ED_{50}s which are unreliable clinically. In practice, choice of initial dose is usually empirical. Regimens based on a higher initial (loading) dose are more logical than low doses repeated over several days.

Antivenom failure (ineffectiveness) may be due to batch-to-batch variations in potency.

Geographical intra-species variation, in venom composition and antigenicity, explains why antivenoms raised against venom of a species (e.g. Russell's viper) from one area (e.g. Tamil Nadu, India) may not be effective in patients envenomed by the same species elsewhere in its geographical range (e.g. Kerala, Maharashtra). Regional polyspecific antivenoms may not cover all medically important snakes (e.g. N. kaouthia, H. hypnale, T. (Craspedocephalus) malabaricus, T (T.) erythrurus in parts of India).

Response to antivenom includes rapid decrease in general malaise (?placebo effect), cessation of spontaneous systemic bleeding (in 15-30 minutes), restoration of blood coagulability (in 3-9 hours), normalisation of blood pressure in shocked patients (in 30-60 minutes) and sinus rhythm, reversal of post-synaptic type neurotoxicity (after cobra bite) (after 30 minutes), cessation of active haemolysis and rhabdomyolysis (within a few hours).

After an initial response to antivenom, signs of systemic envenoming may recur within 24-48 hours. Improved perfusion of the bite site following correction of shock/ hypovolaemia increases venom absorption from bite site "depot" and redistribution of venom from tissues to vascular space at a time when therapeutic antivenom has been eliminated.

After the first dose of antivenom, the initial dose should be repeated 6 hours later if blood remains incoagulable, or 1 hour later if spontaneous systemic bleeding continues, or neurotoxic or cardiovascular signs persist or deteriorate. However, further doses of antivenom have no proven value in paralysed patients who are being ventilated.

When no appropriate antivenom is available, patients must be treated

if patient is unresponsive, summon assistanceby 'phone, open and maintain airway using "head tilt - chin lift" or "jaw thrust" manoeuvres to improve air flow by dislodging tongue and reopening upper airway.

conservatively. Respiratory paralysis: try anticholinesterases, but without delaying assisted ventilation. Haemostatic abnormalities: rest in bed to avoid trauma, transfuse cryoprecipitate, fresh frozen plasma, fresh whole blood and platelets. Shock, myocardial damage: correct hypovolaemia and consider vasopressor drugs. In hypotension with bradycardia, try atropine. Acute kidney injury: conservative treatment or renal replacement therapy. Rhabdomyolysis: correct hypovolaemia with intravenous fluid, acidosis with sodium bicarbonate. Severe local envenoming: surgical intervention, prophylactic broad spectrum antimibiotics.

Supportive/ancillary treatment
Neurotoxic envenoming
Indications for intubation: imminent respiratory arrest (respiratory distress, breathing absent/inadequate); neck muscle weakness with shallow respiration or paradoxical breathing; secretions pooling in pharynx with loss of gag/ cough reflexes; upper airway obstruction with stridor (secondary to anaphylaxis angioedema); oxygen saturation <90% (equivalent to Pa02 <60 mmHg) despite high flow oxygen; respiratory acidosis (hypoxia PaO2 < 60 mm Hg with PaCO2 > 45 mm Hg)

Insert cuffed endotracheal tube using laryngoscope under sedation,or laryngeal mask airway or i-gel supraglottic airway.

For acute airway obstruction (e.g. angioedema) perform cricothyroidotomy.

Resuscitation: if patient is unresponsive, summon assistanceby 'phone, open and maintain airway using "head tilt - chin lift" or "jaw thrust" manoeuvres to improve air flow by dislodging tongue and reopening upper airway. Remove foreign material from upper airway (suction or forceps, not finger) and insert oropharyngeal (Guedel) airway. Administer oxygen by any available means and assess breathing. If breathing is adequate, lay victim in recovery position (important because of venom-induced vomiting, bleeding and hypersalivation with loss of airway-protective reflexes), but check breathing every 2 minutes.

If breathing is inadequate or not discernible, respiratory rate low, respirations shallow, patient taking agonal (gasping) breaths, central cyanosis, finger oximeter oxygen saturation <90%, end-tidal PCO_2 high or increasing - assisted ventilation is required.

Techniques:
If no health facilities are immediately available - Expired Air Resuscitation

In health care centre - Non-invasive ventilation using bag-mask/bag-mask-valve ventilation

In hospital - Invasive Ventilation (intubation and mechanical ventilation) for Type I respiratory failure (primary failure of oxygenation as in pulmonary oedema in Russell's viper envenoming) and Type II respiratory failure (primary ventilatory failure due to respiratory muscle paralysis or obstruction as in elapid envenoming).

Indications for invasive ventilation: patients who, despite receiving oxygen by mask or nasal catheters remain tachpnoeic (respiratory rate > 25/min), have

paradoxical respirations and deteriorating ventilatory capacity, hypoxia, respiratory acidosis. Sedate them with fentanyl and midazolam, or morphine and lorazepam. Ensure adequate hydration, nutrition, physiotherapy, regular turning to prevent pressure areas and lung collapse, eye care and safe weaning from ventilation.

Trial of anticholinesterase:
after making baseline observations, give atropine sulphate intravenously followed by intramuscular neostigmine (or, ideally, slow intravenous injection of short-acting edrophonium chloride – Tensilon, but rarely available), and observe over next 10-60 minutes for disappearance of ptosis or improved ventilatory capacity. Treat patients who respond convincingly with repeated neostigmine and atropine.

Hypotension and shock
Primary causes are anaphylaxis, vasodilatation, cardiotoxicity, hypovolaemia; secondary causes are antivenom reactions, respiratory failure, acute pituitary adrenal insufficiency, septicaemia

Measure postural change in blood pressure or passive leg raising test to determine fluid responsiveness. Control fluid therapy using jugular/central venous pressure, respiratory rate, detection of crepitations. Selective vasoconstrictor such as dopamine may be used.

Acute pituitary/adrenal insufficiency may occur in victims of Russell's viper bites (Myanmar, India, Sri Lanka). Hydrocortisone is life-saving in these cases.

Oliguria and acute kidney injury (AKI)
Impending AKI signalled by abrupt reduction in kidney function over 48 hours: decreasing/no urine output, increased/increasing serum creatinine concentration, clinical "uraemia syndrome"

(nausea, vomiting, acidotic breathing, hiccups, fetor, drowsiness, confusion, coma, flapping tremor, muscle twitching, convulsions, pericardial friction rub, signs of fluid overload). Patients with any of these features should be monitored for other clinical signs of "uraemic syndrome", pulse rate, postural blood pressure, height of jugular venous pulse, respiratory rate, temperature, auscultation of lung bases for crepitations, fluid balance chart and/or daily weight.

Most patients with AKI become oliguric (urine output < 400 ml/day or < 30 ml (children < 0.5ml/kg bodyweight /hour). Conservative management may tide the patient over, avoiding the need for renal replacement therapy (dialysis).

In patients with intravascular volume depletion: *establish intravenous access, give cautious fluid challenge (adult 250-500 ml of isotonic saline over one hour). Stop challenge immediately if pulmonary oedema develops. If the urine output does not improve, perform furosemide stress/ challenge test, if that fails to increase urine output, switch to conservative management.*

Conservative management of AKI: no further diuretics, restrict fluid intake to previous day's output plus "insensible losses" (500-1000 ml/day) and refer to renal unit. Diet bland, high calorie, normal protein, low potassium, low in salt.

Measure serum/plasma urea, creatinine and electrolytes daily until renal failure is resolving. Examine ECG for evidence of hyperkalaemia, for which emergency treatments include calcium gluconate, β2 agonist aerosol inhaler, 50% dextrose with insulin and sodium bicarbonate, followed by a low potassium diet. Severe acidosis is corrected with sodium bicarbonate.

Renal replacement therapy/dialysis
Patient with clinical uraemia (encephalopathy, pericarditis etc.), fluid overload not responding to diuretics, hyperkalaemia or hyperkalaemic ECG changes, symptomatic acidosis, raised plasma/serum creatinine and/or urea should be transferred to a health facility where they can receive renal replacement therapy.

In patients with AKI associated with thrombotic microangiopathy, there is no evidence for plasmapheresis using cryosupernatant. In patients with myoglobinuria or haemoglobinuria, correct hypovolaemia, maintain urine output 200-300 ml/hour, correct severe acidosis with bicarbonate, promote alkalinise diuresis, continuing until CK level <5000 U.

Diuretic phase of AKI: some patients develop persistent polyuria of 5-10 litres/24 hours and may become volume and electrolyte depleted.

Chronic kidney disease: oliguria and dialysis-dependence for more than 4 weeks demands referral to nephrologist to consider kidney biopsy.

Haemostatic disturbances: usually corrected by antivenom, but recurrent coagulopathy is possible. Exceptionally, in patients already treated with antivenom but who have persistent severe bleeding or require urgent surgery, restoration of coagulability can be accelerated with blood products.

Treatment of the bitten part:
Nurse painful, swollen limb in the most comfortable position, avoiding excessively elevation. Leave blisters, aspirate abscesses and culture pus. Necrotic tissue demands early surgical débridement and split-skin grafting. Primary and secondary infections involve aerobic and anaerobic bacteria from the snake's oral flora, patient's skin and asterile incisions. Tetanus toxoid booster and prompt antibiotic treatment of necrotic wounds is recommended.

Compartmental syndromes are often misdiagnosed and fasciotomies performed unnecessarily. Since classical signs of compartment syndrome are difficult to assess in snake-bitten limbs, direct measurement of intracompartmental pressure is mandatory and fasciotomy must not be attempted before haemostatic disturbances have been corrected by antivenom.

Rehabilitation: conventional physiotherapy accelerates functional recovery of the bitten limb, but is often forgotten.

Discharge assessment: discussion, encouragement, follow-up, warning about late serum sickness-type reactions and advice about reducing risk of future snakebites are important.

Management of cobra spit ophthalmia: first aid is irrigation of affected eyes and other mucous membranes with liberal quantities of water; medical treatment involves analgesia, exclusion of corneal abrasions and application of prophylactic topical antibiotics.

Management of snakebites at different levels of the health service: all levels of the health service can contribute to the management of patients with suspected snakebite. In rural areas, where snakebites are most common, transfer to a hospital may not be feasible, and so a lower level of health facility must cope with these medical emergencies. Training of doctors, nurses, dispensers, health assistants and paramedics in

diagnosis (including snake identification), early management and indications for and practicalities of administering antivenom is essential.

Snakebite treatment in developing countries is challenging, creating many management problems. It is, therefore, of utmost importance to train doctors and other health- care workers in the effective care of snakebite patients.

6.1 Stages of management
The following steps or stages are often involved:

> ### Management of snakebite
> - First-aid treatment
> - Transport to hospital
> - Rapid clinical assessment and resuscitation
> - Detailed clinical assessment and species diagnosis
> - Investigations/laboratory tests
> - Antivenom treatment
> - Observing the response to antivenom
> - Deciding whether further dose(s) of antivenom are needed
> - Supportive/ancillary treatment
> - Treatment of the bitten part
> - Rehabilitation
> - Treatment of chronic complications
> - Advising how to avoid future bites

6.2 First-aid treatment
6.2.1 Principles of first-aid
First-aid treatment is carried out immediately or very soon after the bite, before the patient reaches a dispensary or hospital. It can be performed by the snakebite victim himself/herself or by anyone else who is present and able.

Unfortunately, most of the traditional, popular, available and affordable first aid methods have proved to be useless or even frankly dangerous. These methods include: making local incisions or pricks/ punctures ("tattooing") at the site of the bite or in the bitten limb, attempts to suck the venom out of the wound, use of (black) snake stones, tying tight bands (tourniquets) around the limb, electric shock, topical instillation or application of chemicals, herbs or ice packs. Local people may have great confidence in traditional (herbal) treatments, but they must not be allowed to delay medical treatment or to do harm.

> ### Aims of first aid
> - reassure the snakebite victim
> - attempt to delay systemic absorption of venom
> - preserve life and prevent complications before the patient can receive medical care at a dispensary or hospital
> - control distressing or dangerous early symptoms of envenoming
> - arrange the transport of the patient to a place where they can receive medical care
>
> **ABOVE ALL, AIM TO DO NO HARM!**

6.2.2 The danger of respiratory paralysis and shock
The greatest fear is that a snakebite victim might develop fatal respiratory paralysis or shock before reaching a place where they may be resuscitated (Looareesuwan et al., 1988). This risk may be reduced by speeding up transport to hospital, by improving free ambulance services (Gimkala et al., 2016) or by recruiting village-based motor cyclist volunteers who transport the victim propped

Figure 73: Evacuation of a snakebite victim showing early signs of paralysis by a village-based motorcycle volunteer in the Terai region of Nepal. The victim is supported between the driver and a pillion passenger (Copyright Dr Sanjib Sharma) [CAUTION - If this method of transport has to be employed, because of local conditions and the terrain, ideally helmets should be worn and the legs of the passengers protected from exhaust burns]

upright between the driver in front and a supporting pillion passenger behind. This has proved effective in villages in the Nepal Terai (Sharma et al., 2013) **(Figure 73)**. Medical workers can be trained in airway management and assisted ventilation (see below). The special danger of rapidly developing paralytic envenoming after bites by some elapid snakes has prompted the use of pressure-bandage immobilization (Sutherland et al., 1979) and pressure-pad immobilization (Anker 1982; Tun-Pe et al.,1995b)(ANNEX 4). Pressure bandage immobilization requires equipment (long elasticated bandages and splints) (Canale et al., 2009; Currie et al., 2008) and skill.

As far as the snake is concerned - *do not attempt to kill it as this may be dangerous.*However, if the snake has already been killed, it should be taken to the dispensary or hospital with the patient in case it can be identified. However, *do not handle the snake with your bare*

hands as even a severed head can bite! Several close-up mobile 'phone images of the snake should be taken if possible to allow expert identification.

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

6.2.3 Recommended first-aid methods

- Reassure the victim who may be very anxious. Reassurance will drive away their fear and excitement, slow the patient's heart rate and reduce the spread of venom. Grounds for reassurance include the possibility of a "dry bite" even if the snake was venomous, the usually slow evolution of severe envenoming allowing time for treatment, and the effectiveness of modern medical management of snakebite.

- Immobilize the whole of the patient's body by laying him/her down in a comfortable and safe position, ideally in the recovery position (lying prone on the left side in case vomiting threatens to result in aspiration), and immobilize the bitten limb with a splint or sling. Any movement or muscular contraction, even undressing or walking, will increase absorption and spread of venom by squeezing veins and lymphatics.

- Unless the possibility of an elapid bite can confidently be excluded, apply pressure-pad immobilization (See ANNEX 4), or, if the necessary equipment and skills are available, pressure-bandage immobilization. In Myanmar, the pressure-pad method has proved effective in reducing spread of venom in victims of Russell's viper bite (Tun Pe et al., 1995b). Pressure-bandage immobilization has not become widely used in this Region,

Figure 74: Gangrenous limb caused by a tight tourniquet after a bite by Malayan pit viper (Copyright DA Warrell)

because provision of the necessary equipment (long, wide elasticated bandages), training and skills required to apply it safely and reliably have proved impossible to achieve. The pressure-pad immobilization method is preferred and **recommended** as being simpler and more practicable (O).

- 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.

CAUTION Delay the release of tight bands, bandages and ligatures: if the patient has already applied these very popular methods of first-aid, they should not be released until the patient is under medical care in hospital, medical staff and resuscitation facilities are available and antivenom treatment has been started (Watt et al., 1988) *see Caution below*.

Tight (arterial) tourniquets must never be recommended or condoned!
Traditional tight (arterial) tourniquets. If applied tightly around the upper part of the limb, these bands, bandages or ligatures are extremely painful as the limb becomes ischaemic and are very dangerous if left in place for long periods. **Many gangrenous limbs have resulted! (Fig 74)**

6.3 Transport to hospital
Emergency Helpline Numbers
Linkage with an emergency helpline number (e.g. in India 108 see http://www.emri.in/) can speed up the transport of a patient to a higher referral centre when emergency treatment is required. This will decrease delays in accessing emergency care and reduce mortality. Information about helpline numbers could be widely disseminated.

The patient must be transported to a place where they can receive medical care (dispensary or hospital) as quickly, but as safely and comfortably as possible. Any movement, but especially movement of the bitten limb, must be reduced to an absolute minimum to avoid increasing the systemic absorption of venom. Any muscular contraction will increase spread of venom from the site of the bite in veins and lymphatics. Where a conventional motor vehicle ambulance is not available or feasible, stretcher, bicycle, motorbike (Patel and Ekkiswata, 2010) - by recruiting village-based motorbike owners/cyclists (Sharma et al., 2013) **(Fig 73)**, cart, horse, train or boat may have to be considered, or the patient can be carried (e.g. using the "fireman's lift" method). If possible, patients should be placed in the recovery position during transit, in case they vomit.

6.4 Treatment in the dispensary or hospital
(Warrell 1990; 1995)

> ### Medical management of envenomed patients in dispensary or hospital
>
> - Rapid primary clinical assessment and resuscitation
>
> - Detailed clinical history, physical examination and species diagnosis
>
> - Simple test of blood coagulability [20-minute-whole-blood-clotting-test (20WBCT)]
>
> - Antivenom: indications, initial and repeated dosage, response, reactions
>
> - Treatment of organ and system failures
>
> - Treatment of the bitten limb
>
> - Rehabilitation, restoration of function
>
> - Advice at discharge from hospital and follow-up
>
> - Preventive health education towards reducing risk of future bites

6.4.1 Rapid primary clinical assessment and resuscitation
Snakebite is a medical emergency: history, symptoms and signs must be obtained rapidly so that appropriate, urgent and life-saving treatment can be given

Cardiopulmonary resuscitation may be needed, including administration of oxygen and establishment of intravenous access.

> ### Rapid primary clinical assessment and resuscitation: ABCDE approach
>
> **A**irway
>
> **B**reathing (respiratory movements)
>
> **C**irculation (arterial pulse)
>
> **D**isability of the nervous system (level of consciousness)
>
> **E**xposure and environmental control (protect from cold, risk of drowning etc)

Airway patency, respiratory movements, arterial pulse and level of consciousness must be checked immediately. Record the vital signs.

The Glasgow Coma Scale cannot be used to assess the level of consciousness of patients paralysed by neurotoxic venoms (see below).

Clinical situations in which snakebite victims might require urgent resuscitation:

a) *Profound hypotension and shock:* resulting from direct cardiovascular effects of the venom or secondary effects, such as hypovolaemia, release of inflammatory vasoactive mediators, haemorrhagic shock or rarely primary anaphylaxis induced by the venom itself.

b) *Terminal respiratory failure:* from progressive neurotoxic envenoming that has led to paralysis of the respiratory muscles; or simple airway obstruction.

c) *Respiratory distress:* from generalized increase in capillary permeability (Russell's viper bite victims)

d) **Sudden deterioration:** or rapid development of severe systemic envenoming after releasing a tight tourniquet or compression bandage *(see Caution above)*.

e) **Cardiac arrest:** precipitated by hyperkalaemia resulting from skeletal muscle breakdown (rhabdomyolysis) after bites by sea snakes, certain kraits and Russell's vipers.

f) **Late results of severe envenoming:** in someone arriving days/weeks after the bite: with severe bleeding/blood clotting disturbances, acute kidney injury or septicaemia complicating local necrosis.

6.4.2 Detailed clinical assessment and species diagnosis

6.4.2.1 History
A precise history of the circumstances of the bite and the progression of local and systemic symptoms and signs is very important.

Four useful initial questions:
1. *"Where (in what part of your body) were you bitten? Point to the place"* Observe any local signs – fang marks, swelling, bruising, persistent bleeding, pre-hospital traditional treatment.

2. *"When were you bitten and what were you doing when were you bitten?"* If the bite was very recent, there may not have been time for signs of envenoming to   develop. If the patient was bitten at night while asleep, a krait was probably implicated; if in a paddy field, a cobra or Russell's viper; if while tending fruit trees, a green pit viper; if while swimming or wading in water a cobra (fresh water) or sea snake (sea or estuary).

3. *"Where is the snake that bit you?"* or *"What did it look like; did anyone*

A common early symptom of systemic envenoming is vomiting and, after bites by some species, fainting and collapsing (sometimes causing injury) with transient unconsciousness and features of anaphylaxis (angioedema etc.)

take a picture?" If the snake has been killed and brought, or an adequate photo image is available (e.g. taken by mobile 'phone at the scene of the bite), its correct identification can be very helpful. If it is obviously a harmless species (or not a snake at all!), the patient can be quickly reassured and discharged from hospital. If it was killed and left at home, send someone to fetch it, in whatever condition!
4. *"How are you feeling now?"*

    Have any symptoms of envenoming developed?

A common early symptom of systemic envenoming is vomiting and, after bites by some species, fainting and collapsing (sometimes causing injury) with transient unconsciousness and features of anaphylaxis (angioedema etc.). Patients who become defibrinogenated or thrombocytopenic may begin to bleed from old, partially-healed wounds as well as bleeding persistently from the fang marks. The patient should be asked how much urine they have passed since the bite and whether it was a normal colour or very dark (implying haemoglobin/myoglobin – uria). Patients who complain of sleepiness, drooping eyelids or blurred or double vision may have neurotoxic envenoming. An important early symptom of sea snake envenoming that may develop as soon as 30 minutes after the bite is generalized

pain, tenderness and stiffness of muscles and trismus.

6.4.2.2 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 and squeeze gently while watching the patient's expression), should be recorded. Lymph nodes draining the limb should be palpated and overlying ecchymoses and lymphangitic lines noted. A bitten limb may be tensely oedematous, cold, immobile, painful on passive movement and with impalpable arterial pulses. These appearances may suggest intravascular thrombosis, which is exceptionally rare after snakebite, or a compartmental syndrome, which is uncommon. If possible, intracompartmental pressure should be measured (see Annex 5) and the blood flow and patency of arteries and veins assessed (e.g. by doppler ultrasound). Early signs of necrosis may include blistering, demarcated darkening (easily confused with bruising) **(Fig 54 d, e, Fig 69)** 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 hypovolaemia – see 14 Management of hypotension and shock) and heart rate. Examine the skin and mucous membranes for evidence of petechiae, purpura, discoid haemorrhages **(Fig 64b)** and, ecchymoses, the conjunctivae, for haemorrhages **(Fig 63)** and chemosis **(Fig 58)**, and the optic fundi for retinal haemorrhages. Examine the gingival sulci thoroughly, using a torch and spatula/tongue depressor, as these may show the earliest evidence of spontaneous systemic bleeding **(Fig 60a)**, a very valuable sign. Examine the nose for epistaxis. Abdominal tenderness may suggest gastrointestinal or retroperitoneal bleeding. Loin (low back) pain and tenderness suggest acute renal ischaemia (Russell's viper bites). Subarachnoid haemorrhage is suggested by neck stiffness (meningism) **(Fig 60b)**. Intracranial haemorrhage is suggested by lateralising neurological signs, asymmetrical pupils, convulsions or impaired consciousness (in the absence of respiratory or circulatory failure).

5.4.2.3 Neurotoxic envenoming: Bulbar and respiratory paralysis

To exclude early neurotoxic envenoming, ask the patient to look up and observe whether the upper lids retract fully **(Fig 75)**. Ask about diplopia and test eye movements for evidence of early external ophthalmoplegia **(Fig 66)**. Check the size and reaction of the pupils. Ask the patient to open their mouth wide and protrude their tongue; early restriction in mouth opening may indicate trismus (sea snake envenoming) **(Fig 71a)** or, more often, paralysis of pterygoid muscles **(Fig 76)**.

Check other muscles innervated by the cranial nerves (facial muscles, tongue, gag reflex etc.).

The muscles flexing the neck may be paralysed, giving the "broken neck sign" **(Fig 77)**.

Figure 75: Examination for ptosis in a patient with neurotoxic envenoming by a Papuan taipan. This is usually the earliest sign of neurotoxic envenoming (Copyright DA Warrell)

Figure 77: Broken neck sign in a child envenomed by a krait in Sri Lanka (Copyright DA Warrell)

Figure 76: Examination for ability to open the mouth and protrude the tongue in a patient with neurotoxic envenoming from the Malayan krait (Copyright DA Warrell)

Can the patient swallow or are secretions accumulating in the pharynx, an early sign of bulbar paralysis? Ask the patient to take deep breaths in and out. "Paradoxical respiration" (abdomen expands rather than the chest on attempted inspiration) indicates that the diaphragm is still contracting but that the intercostal muscles and accessory muscles of inspiration are

Figure 78: Generalized flaccid paralysis in a patient envenomed by a common krait in Sri Lanka. The patient was fully conscious and was able to communicate by flexing his index fingers (Copyright DA Warrell)

profound generalized flaccid paralysis from neurotoxic envenoming are fully conscious **(Fig 78)**.

Lifting their paralysed upper eyelids allows them to see their surroundings which they find very reassuring. If asked, they may still be able to flex a finger or toe, allowing simple communication. However, because their eyes are closed and they do not move or speak, they are commonly assumed to be unconscious or even dead. Conventional tests of brain death can prove misleading (Dayal et al., 2014) and there are media reports of a child with snakebite paralysis who was about to be placed on a funeral pyre before she was seen to be breathing and of snakebite victims being rescued when they were about to be buried alive.

Test the tone and power of limb muscles and the superficial and deep tendon reflexes. Look for lateralising signs suggesting intracranial haemorrhage or thrombosis. Observe involuntary movements such as fasciculations/ myokymia (as in anticholinesterase overdose or organo-phosphate poisoning) and writhing choreo-athetotic movements suggesting hypoglycaemia (Russell's viper envenoming).

paralysed. Where possible, serial objective measurements of ventilatory capacity are very useful. Use a peak flow metre, spirometer (to measure FEV_1 and FVC) or ask the patient to blow into the tube of a sphygmomanometer (mercury or aneroid) to record the maximum expiratory pressure (mmHg) or use the single-breath counting test (SBC). SBC measures how far the patient can count at two numbers per second in a normal speaking voice after taking a maximal inhalation (Ali et al., 2011). A finger oximeter will detect decreasing arterial oxygen saturation. Remember that, provided their lungs are adequately ventilated, patients with

Do not assume that snake-bitten patients are unconscious or even irreversibly "brain dead" just because their eyes are closed, they are unresponsive to painful stimuli, are areflexic, or have fixed dilated pupils. They may merely be paralysed! They may be severely paralysed and lack motor responses or spontaneous eye movements mimicking coma (locked-in syndrome). Check pulse, heart sounds and, if possible, ECG.

6.4.2.4 Generalized rhabdomyolysis

In victims of envenoming by sea snakes, some species of kraits *(B. niger* and *B. candidus)*, some Australasian elapids and Russell's vipers in Sri Lanka and South India, muscles, especially of the neck, trunk and proximal part of the limbs, may become tender and painful on active or passive movement **(Fig 71b)** and later may become paralysed. In sea snakebite envenoming, there is pseudotrismus that can be overcome by sustained pressure on the lower jaw. Myoglobinuria may be evident 3 hours after the bite **(Figs 67, 71c).**

6.4.2.5 Examination of pregnant women

Potential complications of envenoming in pregnancy include antepartum and postpartum hemorrhage indicated by vaginal bleeding, premature labour, abortion/stillbirth, fetal distress or intra-uterine fetal death. If possible, uterine contractions and fetal heart rate should be monitored continuously. Fetal distress may be signalled by fetal bradycardia, tachycardia, or late deceleration after each uterine contraction. If there is vaginal bleeding or the need for imminent surgery, correction of antihaemostatic abnormalities after antivenom treatment should be accelerated using blood products. Lactating women should be encouraged to continue breastfeeding.

6.5 Species diagnosis

If the dead snake has been brought, it can be identified, but this requires skill and even experienced medical personnel may mistake harmless mimics for venomous snake, or they may confuse different venomous species (Viravan et al., 1992; Ariaratnam et al., 2009). As a result, the patient may be given antivenom unnecessarily, as in the case of hump-nosed pit viper *(Hypnale hypnale)* bites mistaken for saw-scaled viper *(Echis*

carinatus) bites in SW India (Joseph et al., 2007); or mistaken for Russell's viper *(Daboia russelii)* bites in Sri Lanka, since available polyvalent antivenoms do not cover the venom of this species. An image of the dead snake may be taken and then easily sent by mobile 'phone, "What's App", or internet to a local, national or international snake expert or Poisons Information Centre for definitive identification. Otherwise, the species responsible must be inferred indirectly from the patient's description of the snake, circumstances of the bite (e.g. nocturnal bites by kraits in people sleeping on the ground, Ariaratnam et al., 2008), and the clinical syndrome of symptoms and signs (see above and Annexes 1 and 2). This was particularly important in countries where only monospecific antivenoms are available.

6.6 Investigations/ laboratory tests
6.6.1 20 minute whole blood clotting test
(20WBCT) (Warrell et a., 1977; Sano-Martins et al., 1994) (Fig 79)
This very useful and informative bedside test requires very little skill and only one piece of

Figure 79: 20 minute whole blood clotting test in a patient still bleeding from incisions made at the site of the bite. The blood is icoagulable indicating venom-induced consumption coagulopathy (Copyright DA Warrell)

apparatus - a new, clean, dry, ordinary glass vessel (tube, bottle or syringe).

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20 minute whole blood clotting test (20WBCT)

- Place 2 mls of freshly sampled venous blood in a small, new, dry, glass vessel
- Leave undisturbed for 20 minutes at ambient temperature
- Tip the vessel once
- If the blood is still liquid (unclotted) and runs out, the patient has hypofibrinogenaemia ("incoagulable blood") as a result of venom-induced consumption coagulopathy
- In the South-East Asia Region, incoagulable blood is diagnostic of a viper bite and rules out an elapid bite
- ***Warning! If the vessel used for the test is not made of ordinary glass, or if it has been cleaned with detergent, its wall may not stimulate clotting of the blood sample (surface activation of factor XII – Hageman factor) and test will be invalid***
- If there is any doubt, repeat the test in duplicate, including a healthy "control" (blood from a healthy person such as a relative)

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Problems with the 20WBCT

False positive results: a "false positive" (i.e. non-clotting) 20WBCT in a patient who is not envenomed and has normal blood coagulation, results from the use of a tube, bottle, syringe or other vessel that is made of plastic, polystyrene, polypropylene rather than ordinary glass, or a glass vessel that has been cleaned with detergent, soap or washing fluid or is wet or contaminated, or in the case of some glass syringes, has a lubricant that is anticoagulant. In

these cases, surface activation of blood coagulation by the glass surface, mediated by Hageman Factor XII is lacking or has been destroyed by cleaning with the result that blood coagulation is not activated and the blood will not clot.

A major difficulty is that many hospitals/dispensaries in countries where snakebites-are common, cannot afford to provide a new, unwashed, un-recycled bottle, tube, syringe or other vessel for each test and ordinary glass tubes/vessels may be difficult to purchase in this age of plastic. However, the commonly used recycled glass antibiotic bottles can be made suitable and reliable, provided that they are cleaned by washing with "normal 0.9% saline" for intravenous infusion, without any added detergent of other cleansing agent, followed by hot air drying.

Variants of the 20WBCT, such as the 30 minute WBCT, "2,3,5 syringe test" used in Myanmar, or the capillary tube test have not been standardised or validated and are susceptible to the same risks of false positivity outlined above.

False negative results: a "false negative" (i.e. clotting) 20WBCT may occur in patients with milder degrees of coagulopathy. The 20WBCT is less sensitive to mild depletion of fibrinogen and other clotting factors, in the early stages of evolving snake venom induced DIC and consumption coagulopathy, than laboratory tests such as prothrombin time (PT), activated partial thromboplastin time (aPPT), and fibrinogen assay. The 20WBCT becomes positive (i.e. non-clotting) at plasma fibrinogen concentrations below 0.5g/L (Sano-Martins et al., 1994). A study of 20WBCT in victims of taipan bites *(Oxyuranus scutellatus)* in Papua New Guinea found that a positive 20WBCT (i.e. non-clotting) was associated with a median PT of 120.0s (IQR 24.4-200s),

median aPTT of 132 sec (IQR=69.1-180s) and median fibrinogen concentration of 0.01 g/L (IQR=0.01-0.18 g/L). A positive (i.e. non-clotting) 20WBCT had a positive predictive value of 89.7%, negative predictive value of 93.5%, sensitivity of 92.9% and specificity of 90.6% for fibrinogen concentrations of <0.5 g/L. (Paiva et al., 2015). However, a study in Sri Lanka that is open to many criticisms found that in some patients bitten by Russell's vipers, whose 20WBCTs were negative (i.e. clotting) on admission to hospital, blood samples taken up to one hour later, frozen and flown to Australia for testing, showed prolonged prothrombin times [International Normalized Ratio (INR) >1.5 see below]. This was not a comparison of 20WBCT and INR in blood sample taken at the same time. In every case, the INR sample was taken later than the 20WBCT sample, by which time the process of venom-induced DIC and consumption coagulopathy in the envenomed patient would have evolved. The authors considered that the use of the 20WBCT was associated with an unacceptable level of false negative (clotting) results and that it consequently delayed antivenom treatment. However, if blood clots in the 20WBCT, the sample must contain sufficient clotting factors, albeit at reduced levels, to make this possible, indicating that haemostasis is maintained. However, no evidence was adduced that this false negative result was in any way deleterious to the patients whose antivenom treatment was delayed until their 20WBCTs became positive (i.e. non-clotting) some hours later (Isbister et al., 2013). The authors admitted that prothrombin times could not be performed in Sri Lankan hospitals and, unfortunately, they were unable to suggest any practicable alternative to the 20WBCT for the many provincial and rural hospitals in tropical developing countries where snakebites are common.

Every effort should be made to eliminate false positive (non-clotting) results by ensuring that ordinary glass is used, that recycled glass vessels are not cleaned with detergents or other cleansing fluids and that a normal control blood is used for comparison in cases where the 20WBCT result is inconsistent with the patient's clinical condition.

Recommendation: in the absence of an alternative simple bed-side test of blood coagulability available in hospitals in the developing world, the 20WBCT should continue to be used. However, every effort should be made to eliminate false positive (non-clotting) results by ensuring that ordinary glass is used, that recycled glass vessels are not cleaned with detergents or other cleansing fluids and that a normal control blood is used for comparison in cases where the 20WBCT result is inconsistent with the patient's clinical condition. Accepting that the 20WBCT may remain negative (clotting) in patients with evolving venom-induced DIC, the test should be repeated frequently and antivenom treatment should not be delayed if there is other evidence of anti-haemostatic disturbances (e.g. spontaneous systemic bleeding distant from the bite site)

6.6.2 Other tests of blood coagulation

More sensitive laboratory tests that are rapid and relatively simple to perform are plasma prothrombin time (PT) or activated partial thromboplastin time (aPPT) and measurement of fibrin(ogen) related antigens, also known as fibrin degradation products (FDP) or fibrin split products (FSP), by agglutination of sensitized latex particles or of D-dimer (cross-linked fibrin fragments) by assays using monoclonal antibodies that detect an epitope that is present in the factor XIIIa–crosslinked fragment D domain of fibrin. The International Normalized Ratio (INR) is the patient's PT divided by the laboratory control PT (normal range 0.8 - 1.2). An abnormal INR result, indicating coagulopathy, is 1.2 or above. Point of care (bed-side) devices for measuring INR and D-dimer are expensive and are unreliable in snakebite victims (Cubitt et al., 2013). Measurement of plasma concentrations of fibrinogen and other individual clotting factors are more demanding in time and laboratory skills.

Thrombo-elastography (TEG) and thromboelastometry (TEM, ROTEG, ROTEM) have been suggested as a simple bed-side method for assessing coagulopathy in snakebite victims but the equipment is expensive. Analysis of the TEG tracing provides measures of time to initiation of clotting, speed of clot formation and clot strength that reflect coagulation factor activity, fibrinolysis and platelet function. In a study of envenomed children in South Africa, TEG predicted severe bleeding diathesis in 50% of patients with 94% sensitivity (Hadley et al., 1999). It has also been used in envenomed dogs (Armentano et al., 2014).

6.6.3 Other laboratory tests
Haemoglobin concentration/
haematocrit: a transient increase indicates haemoconcentration resulting from a generalized increase in capillary permeability (e.g. in Russell's viper bite).

More often, there is a decrease reflecting blood loss or, in the case of Indian, Thai and Sri Lankan Russell's viper bite, intravascular haemolysis.

Platelet count: this may be decreased in victims of envenoming by vipers and Australasian elapids.

White blood cell count: an early neutrophil leucocytosis is evidence of systemic envenoming by any species. Lymphopenia has been described in patients envenomed by Australasian Elapidae.

Blood film: fragmented red cells ("helmet cell", schistocytes) are seen when there is microangiopathic haemolysis or thrombotic microangiopathy (TMA). Haemolytic uraemic syndrome (HUS) consists of persistent, profound thrombocytopenia, microangiopathic haemolytic anaemia (fragmented red cells, "helmet cells", or schistocytes) and acute kidney injury. It is associated with envenoming by Russell's vipers, hump-nosed pit vipers and Australian Elapidae. The pathophysiology of TMA is unknown, but in other diseases, such as thrombotic thrombocytopenic purpura (TPP), it is thought to be due to deficiency of the metalloproteinase ADAMTS 13 which cleaves von Willebrand multimers. These multimers initiate platelet activation and formation of microthrombi which is the key factor in the development of acute kidney injury. In an Australian tiger snake *(Notechis scutatus)* bite victim with TMA, ADAMTS 13 levels were normal before and after plasmapheresis with cryosupernatant (Ho et al., 2010).

Plasma/serum in blood samples
allowed to sediment spontaneously (without centrifugation) may be stained pinkish or brownish if there is gross haemoglobinaemia or myoglobinaemia.

Biochemical abnormalities: plasma creatinine, urea/blood urea nitrogen and potassium concentrations are raised in the acute kidney injury of Russell's viper, hump-nosed pit-viper and sea-snake envenoming. Aminotransferases and muscle enzymes (creatine kinase, aldolase etc.) will be elevated if there is severe local damage or, particularly, if there is generalized muscle damage (sea-snakes, some kraits, some Australasian Elapidae and Sri Lankan, Indian, Bangladeshi and Myanmar Russell's viper bites). Mild hepatic dysfunction is reflected in slight increases in other serum enzymes. Bilirubin is elevated following massive extravasation of blood. Early hyperkalaemia may be seen following extensive rhabdomyolysis in sea snakebites. Bicarbonate will be low in metabolic acidosis (e.g. acute kidney injury). Hyponatraemia is reported in victims of krait bites in northern Viet Nam *(Bungarus near candidus)*.

Arterial blood gases and pH may show evidence of respiratory failure (neurotoxic envenoming) and acidaemia (respiratory or metabolic acidosis).

> ***Warning: arterial puncture is contraindicated in patients with haemostatic abnormalities (Viperidae and some Australasian Elapidae)***

Desaturation: arterial oxygen saturation can be assessed non-invasively in patients with respiratory failure or shock using a finger pulse oximeter. Remember that an oxygen saturation below 90% is equivalent

to an arterial PO_2 of less than 60 mmHg (8.8 kPa).

Urine examination: the urine should be tested by dipsticks for blood or haemoglobin or myoglobin. Standard dipsticks do not distinguish blood, haemoglobin and myoglobin. Haemoglobin and myoglobin can be separated by immunoassays but there is no easy or reliable test. Microscopy will confirm whether there are erythrocytes in the urine.

Red cell casts indicate glomerular bleeding. Massive proteinuria is an early sign of the generalized increase in capillary permeability in Russell's viper envenoming and an early indicator of acute kidney injury. Urine eosinophilia suggests acute interstitial nephritis, but this can be confirmed only by renal biopsy (Priyamvada et al., 2016).

6.6.4 Other investigations
Radiography: chest radiography is useful for detecting pulmonary oedema (e.g. after bites by *Vipera* and *Daboia* species), pulmonary haemorrhages and infarcts, pleural effusions, and secondary bronchopneumonia.

Ultrasound: ultrasonography was found to be useful for assessing local envenoming, including deep vein thrombosis in a case of Russell's viper bite in Pondicherry, India, and for detecting pleural and pericardial effusion and bleeding into serous cavities.

Echocardiography has proved useful in detecting reduced left ventricular ejection fraction in hypotensive and shocked patients envenomed by Russell's vipers in Sri Lanka..

Imaging: CT and MRI imaging is increasingly available in the Region. It has detected haemorrhages and ischaemic

infarcts in the brain (subarachnoid, subdural, cerebral, cerebellar, brainstem) **(Figs 61b, 61c, 52d), spinal cord,** peritoneum and elsewhere in Russell's viper victims in India, Sri Lanka and Myanmar. Cerebral imaging has shown pituitary shrinkage in cases of chronic panhypopituitarism and unexplained haemorrhagic and demyelinating leucoencephalopathies after Russell's viper bites in India. Imaging can show oedema and haemorrhage in fascial compartment muscles and the degree of osteomyletis and soft tissue changes in chronic snakebite ulcers that have undergone malignant change to squamous cell carcinomas (Marjolin's ulcers).

Electrocardiography: ECG abnormalities reported in snakebite victims include tachyarrhythmias, sinus bradycardia, ST-T wave changes, varying degrees of atrioventricular block, and evidence of hyperkalaemia. Shock may induce myocardial ischaemia or infarction in patients with diseased coronary arteries.

6.7 Antivenom treatment

Antivenom is the only specific antidote to snake venom. A most important decision in the management of a snakebite victim is whether or not to give antivenom.

6.7.1 What is antivenom?
(WHO 2010)
Antivenom treatment for cobra bites was introduced by Albert Calmette at the Institut Pasteur in Saigon, Viet Nam 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 immunised 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.

For example, the Indian antivenom manufacturers' "polyvalent anti-snake venom serum" is raised in horses, using the venoms of the four most important venomous snakes in India (Indian cobra, *Naja naja*; Indian krait, *Bungarus caeruleus*; Russell's viper, *Daboia russelii*; saw-scaled viper, *Echis carinatus*), although the validity of the concept of "the big four" is increasingly challenged by the discovery that other species are also important in certain regions [e.g. *Echis carinatus sochureki* in Rajasthan (Kochar et al., 2007); *H. hypnale* in SW India (Joseph et al., 2007); *Trimeresurus (Craspedocephalus) malabaricus* in southern India; *Trimeresurus (Peltopelor) macrolepis* (ref) in hilly regions of Tamil Nadu and Kerala; *Trimeresurus (T.) erythrurus* in Assam and Sikkim; *Naja kaouthia* in North east India; *Bungarus sindanus* in W and NW India (Pillai et al., 2012); *B. walli* and possibly *B. niger* in NE India (Faiz et al., 2010)] (Whitaker and Martin 2014; Whitaker 2015). Antibodies raised against the venom of one species may have cross-neutralizing activity against other venoms, usually from closely related species. This is known as paraspecific activity. For example, the manufacturers of Haffkine polyvalent anti-snake venom

serum claim that this antivenom also neutralizes venoms of two *Trimeresurus* species.

The Thai Red Cross Society now manufactures two polyvalent antivenoms to cover the venoms of neurotoxic Elapidae *(Naja kaouthia, O. hannah, Bungarus candidus, B. fasciatus)* and haematotoxic Viperidae *(Daboia russelii, Calloselasma rhodostoma, Trimeresurus (T.) albolabris)*.

In Indonesia, Biofarma produces a polyvalent antivenom to cover venoms of neurotoxic *Naja sputatix, Bungarus fasciatus* (that rarely, if ever, bites humans) and *Calloselasma rhodostoma*, but, unaccountably, ignores important species such as *Bungarus candidus, Daboia siamensis, Trimeresurus* species and all the Eastern Indonesian Australasian Elapidae.

There is an urgent need to improve the design (species cover), quantity, and quality of antivenoms produced in South-East Asia Region countries, in the interests of reducing snakebite mortality and morbidity.

6.7.2 Indications for antivenom treatment (see also Annexes 1 and 2)

> *Antivenom should be given only to patients in whom its benefits are considered likely to exceed its risks. Since antivenom is relatively costly and often in limited supply, it should not be used indiscriminately. The risk of reactions should always be taken into consideration.*

Indications for antivenom

Antivenom treatment is recommended if and when a patient with proven or suspected snakebite develops one or more of the following signs:

There is an urgent need to improve the design (species cover), quantity, and quality of antivenoms produced in South-East Asia Region countries, in the interests of reducing snakebite mortality and morbidity.

Systemic envenoming

- *Haemostatic abnormalities:* spontaneous systemic bleeding distant from the bite site *(clinical)*, coagulopathy [+ve (non-clotting) 20WBCT or other laboratory tests such as INR >1.2 or patient's prothrombin time >4-5 seconds longer than laboratory control value] or thrombocytopenia [<100 x 10^9/ litre, or <100 000/cu mm, or (India) < 1.0 lakh per microlitre of blood)] *(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 *(laboratory)*

- *Haemoglobin-/myoglobin-uria:* dark brown urine *(clinical)*, urine dipsticks, other evidence of intravascular haemolysis or generalized rhabdomyolysis (generalized muscle aches, pains, tenderness, pain on passive stretching (hyperkalaemia) *(clinical, laboratory)*

- Supporting laboratory evidence of systemic envenoming (see above) *Local envenoming*

- Local swelling involving more than half of the bitten limb (in the absence of a tourniquet) within 48 hr 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 bites on the hands or feet)

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

6.7.3 Inappropriate use of antivenom

In some parts of the world, a small standard dose of antivenom is given routinely to any patient claiming to have been bitten by a snake, irrespective of symptoms or signs of envenoming. Sometimes the local community are so frightened of snakebite that they compel the doctor to give antivenom against medical judgement. Even doctors themselves may administer antivenom to patients envenomed by snakes against which the antivenom is known to be ineffective (Seneviratne et al, 2000).

Inappropriate use of antivenom should be strongly discouraged as they expose patients who may not need treatment to the risks of antivenom reactions; they also waste valuable and scarce stocks of antivenom.

6.7.4 How long after the bite can antivenom be expected to be effective?

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 given within the first few hours after the bite (Warrell et al., 1976; Tilbury 1982).

6.7.5 Antivenom reactions

A substantial proportion of patients develop reactions, either early (within a few hours) or late (5 days or more) after being given antivenom. In Sri Lanka, Indian polyvalent antivenoms incur reactions in as many as 81% of recipients and severe reactions in as many as 43% (Ariaratnam et al. 2001, de Silva et al, 2016). In India, these antivenoms cause reactions in 5.6 to 56% of recipients, 10-15% of which are moderate to severe (Srimannarayana et al., 2004; Deshpande et al., 2013; Cherian et al., 2013; Menon et al., 2016a). Other antivenoms have much lower reported reaction rates. In Thailand, among 254 patients receiving Thai Red Cross (TRC) antivenoms during 1997–2006, early reactions occurred in 9 (3.5%) including 3 (1.2%) with hypotension. Most patients were being treated for *Trimeresurus* (84%) and *Naja* (13%) bites, in whom the incidence of reactions was 2.3% and 12.5% respectively, reflecting the difference in dose (3 and 10 vials respectively) (Thiansookon and Rojnukarin, 2008). In Australia, use of CSL antivenoms incurred early anaphylactic reactions in 25% and severe raections in 5% of recipients (Isbister et al., 2008). The risk of antivenom reactions is dose-related, except in rare cases in which there has been sensitisation (IgE-mediated Type I hypersensitivity) by previous exposure to animal serum, for example to equine antivenom, tetanus-immune globulin or rabies-immune globulin.

Figures 80: Early anaphylactic reaction to antivenom: (a, b) urticaria and pruritus of the trunk and face; (c) life-threatening angioedema of face tongue, gums, throat, neck and upper airway (Copyright DA Warrell)

1. ***Early anaphylactic reactions:*** usually within minutes and up to 180 minutes after starting antivenom, the patient begins to itch (often over the scalp) and develops urticaria **(Fig 80 a,b)**, dry cough, fever, nausea, vomiting, abdominal colic, diarrhoea and tachycardia. A minority of these patients may develop severe life-threatening anaphylaxis: hypotension, bronchospasm and angio-oedema **(Fig 80c)**.

   Fatal reactions have probably been under-reported as death after snakebite 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 Ihypersensitivity 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.

2. ***Pyrogenic (endotoxin) reactions:*** usually 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.

3. ***Late (serum sickness type) reactions:*** develop 1-12 (mean 7) days after treatment. Clinical features include fever, nausea, vomiting, diarrhoea, itching, recurrent urticaria, arthralgia, myalgia, lymphadenopathy, periarticular swellings, mononeuritis multiplex, proteinuria with immune complex nephritis and rarely encephalopathy. Patients who suffer

Adrenaline (epinephrine) is the most effective treatment for anaphylactic reactions, by reducing bronchospasm and capillary permeability.

early reactions that are treated with antihistamines and corticosteroid are less likely to develop late reactions.

6.7.5.1 Prediction of antivenom reactions

Skin and conjunctival "hypersensitivity" tests can only detect IgE mediated Type I hypersensitivity to horse or sheep proteins. However, the large majority of early (anaphylactic) or late (serum sickness type) antivenom reactions result from direct dose-related complement activation rather than from non-dose-related IgE-mediated hypersensitivity, and so these tests are not predictive. Since they may delay treatment and can in themselves be sensitising, these tests should not be used.

6.7.5.2 Contraindications to antivenom: Prophylaxis of high risk patients

There is no absolute contraindication to antivenom treatment, but patients who have reacted to horse (equine) or sheep (ovine) serum in the past (for example after treatment with equine anti-tetanus serum, equine anti-rabies serum or equine or ovine antivenom) and those with a strong history of 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. Subcutaneous epinephrine

(adrenaline) *adult dose 0.25mg of 0.1% solution is given just before antivenom treatment is started (see below), followed by an intravenous anti-H_1 antihistamines such as chlorphenamine. In asthmatic patients, prophylactic use of an inhaled adrenergic β_2 agonist such as salbutamol may prevent bronchospasm.

6.7.5.3 Prevention of antivenom reactions

One of only two systematic reviews carried out in the field of snakebite treatment (Nuchpraryoon and Garner, 2000) concluded that routine prophylactic adrenaline for antivenom known to have high adverse event rates seemed sensible, based on only one trial (Premawardhena et al., 1999) and that antihistamine appeared to be of no obvious benefit, again based on one trial (Fan et al., 1999). Since then, more definitive data have been published.

1. Prophylactic drugs (adrenaline, antihistamine anti-H1 blockers, corticosteroids)

Adrenaline (epinephrine) is the most effective treatment for anaphylactic reactions, by reducing bronchospasm and capillary permeability. However, the risks of adrenaline make it less attractive for prophylaxis (Rusznak and Peebles, 2002). Premawardhena et al. (1999) used premedication with subcutaneous adrenaline in 105 snakebite victims and found a reduction from 43% to 11% (p=0.04) in the incidence of acute adverse reactions compared to placebo. No adverse reactions to the adrenaline were observed in this study. However, a subsequent fatality (Dassanayake et al., 2002) raised concerns about intracranial bleeding (a known complication of systemic envenoming following bites by vipers and Australian elapid snakes), hypertension and arrhythmias if adrenaline prophylaxis

were to be used routinely especially in children, pregnant women and in patients with heart disease who had been excluded from the trial. Gawarammana et al. (2004) tested parallel pre-antivenom infusion of placebo, hydrocortisone alone, or hydrocortisone plus chlorphenamine in 52 patients. Reactions were reduced from approximately 80% in the first two groups to 52% in the premedicated group though the results did not achieve statistical significance and the study was underpowered. A randomized placebo-controlled trial of 101 patients in Brazil by Fan et al. (1999) showed that premedication with intramuscular promethazine had no significant effect on the high rate (68%) of anaphylactic reactions to antivenom. A review of 10 years of experience with various premedication regimens in Papua New Guinea (Williams et al., 2007) further illustrates the heterogeneity and lack of standardization of snakebite victim care in developing countries where most venomous snakebites occur but suggested efficacy of some prophylactic regimes, as did the study of Caron et al., 2009 in Ecuador.

A large and well-designed study was carried out in Sri Lanka. In total, 1,007 patients were randomized, using a 2 x 2 x 2 factorial design, in a double-blind, placebo-controlled trial of adrenaline (0.25 ml of a 0.1% solution subcutaneously), promethazine (25 mg intravenously), and hydrocortisone (200 mg intravenously), each alone and in all possible combinations. The interventions, or matching placebo, were given immediately before infusion of antivenom. Patients were monitored for mild, moderate, or severe adverse reactions for at least 96 h. (de Silva et al., 2011). Compared with placebo, adrenaline significantly reduced severe

reactions to antivenom by 43% (95% CI 25–67) at 1 h and by 38% (95% CI 26–49) up to and including 48 h after antivenom administration; hydrocortisone and promethazine did not. Adding hydrocortisone negated the benefit of adrenaline. The plasma half-life of adrenaline is about 2-3 minutes. However, when given by subcutaneous or intramuscular injection, local vasoconstriction may delay absorption so that the effects may last longer than the half-life suggests.

2. Speed and dilution of intravenous antivenom administration

The in vitro anti-complementary activity of several commercial antivenoms led Sutherland (1977) and others to advocate dilution and slow infusion of antivenom (Reid, 1980; WHO, 1981). However, in a small randomized study, Malasit et al. (1986) found no difference in rate or severity of reactions in patients given diluted antivenom over 30 minutes compared to those in whom intravenous push injection over 10 minutes was used. In Ecuador, Caron et al., 2009 found a strikingly lower incidence of reactions in a group of patients premedicated with intravenous hydrocortisone and diphenhydramine and given antivenom by infusion over 60 minutes compared to a group of historical controls who had been given no prophylaxis and in whom antivenom had been injected intravenously over 10 minutes. In Sri Lanka, 104 patients were randomly allocated to receive antivenom by intravenous infusion over 20 minutes and 94 by infusion over 2 hours. There was no difference in the incidence of early severe anaphylactic reactions in the two groups (32% vs. 35%; difference 3%; 95% CI: -10% to +17%; p = 0.65). The frequency of mild/moderate reactions was also similar (Isbister et al., 2012).

> **Recommendation: based on the results of a powerful and well-designed trial in Sri Lanka, routine use of prophylactic adrenaline is recommended before antivenom treatment, except in those older patients in whom there is evidence or suspicion of underlying cerebrovascular disease and when the particular antivenom in use has a proven low incidence of reactions (<5%). The adult dose of epinephrine (adrenaline) is 0.25ml of 0.1% solution (0.25 mg) by sub-cutaneous injection (children 0.005 ml/kg body weight of 0.1% solution) (T).**
>
> **Use of histamine anti-H1 and anti-H2 blockers, corticosteroid, and the rate of intravenous infusion of antivenom (between 10 and 120 minutes), do not affect the incidence or severity of early antivenom reactions (T,O).**

6.7.5.4 Treatment of antivenom reactions

Early anaphylactic antivenom reactions: Epinephrine (adrenaline) is given intramuscularly (ideally into the upper lateral thigh) in an initial dose of 0.5 mg for adults, 0.01 mg/kg body weight for children. Because severe, life-threatening anaphylaxis can evolve so rapidly, epinephrine (adrenaline) should be given at the very first sign of a reaction, even when only a few spots of urticaria have appeared or at the start of itching, tachycardia or restlessness. The dose can be repeated every 5-10 minutes if the reaction persists or the symptoms become worse. Adrenaline has proved safe in pregnant women, whereas anaphylaxis can induce abortion.

Additional treatment: After epinephrine (adrenaline), patients ith bronchospasm should be given an inhaled short-acting β_2 agonist bronchodilator such as salbutamol or terbutaline ideally by oxygen-driven nebuliser) and an antihistamine anti-H$_1$ blocker can be given, such as chlorphenamine maleate (adults 10 mg, children 0.2 mg/kg by intravenous injection over a few minutes). Intravenous hydrocortisone (adults 100 mg, children 2 mg/kg body weight) can be given, but it is unlikely to act for several hours. Corticosteroids do not reduce the risk of recurrence (biphasic) anaphylaxis (Grunau et al., 2015).

Anaphylaxis unresponsive to intramuscular epinephrine (adrenaline): a few patients may not respond to single or repeated doses of intramuscular epinephrine (adrenaline).

Patients who remain shocked and hypotensive should be laid supine with their legs elevated and given intravenous volume replacement with 0.9% saline (1-2 litres rapidly in an adult). Intravenous epinephrine (adrenaline) infusion should be considered [adult dose 1mg (1.0 ml) of 0.1% solution in 250 ml 5% dextrose or 0.9% saline - i.e. 4 μ (micro) g/ml concentration) - infused at 1–4 μ (micro) g/minute (15–60 drops/min usin a microdropper burette chamber), increasing to maximum 10 μ (micro) g/min] and, in patients who remain hypotensive, a vasopressor agent such as dopamine [dose 400mg in 500ml 5% dextrose or 0.9% saline infused at 2–5 μ (micro) g/kg/min].

Patients who remain dyspnoeic, with bronchospasm or angioedema, should be propped up at 45 degrees and given supplemental oxygen by any available route together with optimal nebulised/inhaled and/or parenteral bronchodilator (β_2 agonist) (Kemp and Kemp 2014).

Pyrogenic reactions: the patient must be cooled physically (remove clothing, tepid sponging with fanning) and given an antipyretic (e.g. paracetamol by mouth or suppository). Intravenous fluids should be given to correct hypovolaemia. Patients who also exhibit features of anaphylaxis should be given adrenaline as well (see above).

> **At the earliest sign of a reaction:**
>
> • **Antivenom administration must be temporarily suspended**
> • **Epinephrine (adrenaline) (0.1% solution, 1 in 1 000, 1 mg/ml) given by intramuscular injection is the effective treatment for early anaphylactic antivenom reactions**

Completion of administration of antivenom dose:
After the patient has recovered from the early anaphylactic or pyrogenic reaction, the indications for antivenom therapy should be critically re-examined. If antivenom is still indicated, intravenous administration should be cautiously resumed until the total dose has been given.

Treatment of late (serum sickness) reactions: Late (serum sickness) reactions may respond to a 5-day course of oral antihistamine. Patients who fail to respond within 24-48 hours should be given a 5-day course of prednisolone.

Doses: Chlorphenamine: adults 2 mg six hourly, children 0.25 mg/kg /day in divided doses.

Prednisolone: adults 5 mg six hourly, children 0.7 mg/kg/day in divided doses for 5-7 Days

6.7.6 Supply, selection, storage and shelf-life of antivenom

Supply: it is important to determine how much antivenom remains unused at the end of each year in different parts of the country, to allow the calculation of antivenom requirements, and the efficient deployment of adequate stocks of this scarce resource to areas where it is most needed. Adequate buffer stocks are mandatory in areas where natural disasters, such as the annual floods in Bangladesh, cause epidemics of snakebite. These provisions will reduce preventable deaths. Adequate training of medical personnel in the rational use of antivenom is important to reduce mortality and morbidity and minimise wastage.

Selection: Polyvalent (polyspecific) antivenoms are preferred in many countries because of the difficulty in identifying species responsible for bites. They can be just as effective as monovalent (monospecific) ones. An antivenom should be given only if its stated range of specificity and paraspecific neutralization includes the species known or suspected to have been responsible for the bite. If the biting species is known, the ideal treatment may be with a monovalent (monospecific) antivenom, as this may be less expensive and may involve administration of a lower dose of antivenom protein than with a polyvalent (polyspecific) antivenom. However, immunisation of a horse or sheep with venoms of several related species of snakes (e.g. Viperidae) may produce an enhanced antibody response to common antigens, making the resulting polyvalent antivenom more rather than less potent than a monovalent antivenom (Raweerith and Ratanabanangkoon, 2005; WHO, 2010).

Storage and shelf-life: to retain their full potency within the limits of stated expiry dates, lyophilised antivenoms (shelf life about 5 years) should be stored at below 25ºC and liquid antivenoms (shelf life 2-3 years) should be stored at 2-8 ºC and not frozen. Ideally, antivenoms should be used before the stated expiry dates but, provided that they have been properly stored, they can be expected to retain useful activity for months or even years after these dates (WHO, 1981; O'Leary et al., 2009). TRC antivenoms retain their potency after 5 years even when stored temperatures of 25-50 °C (Prof Sumana Komvilai, personal communication).

In patients with severe envenoming, recently expired antivenoms may be used if there is no alternative. However, liquid antivenoms that have become opaque or which contain visible particles should not be used as precipitation of protein indicates loss of activity and an increased risk of reactions.

6.7.7 Administration of antivenom

- *Epinephrine (adrenaline) should always be available at the bed-side, ideally drawn up in readiness, before antivenom is administered.*

- *Antivenom should be given by the intravenous (iv) route whenever possible, either by slow iv "push" injection (maximum 2 ml/minute) or by iv infusion diluted in about 5 ml of isotonic fluid per kg body weight over about 30-60 minutes.*

Freeze-dried (lyophilised) antivenoms are reconstituted, usually with 10 ml of sterile water for injection per ampoule. If the freeze-dried protein is difficult to dissolve, it may have been denatured by a faulty freeze-drying technique during manufacture (WHO, 2010).

Two methods of administration are recommended:

1. *Intravenous "push" injection:* reconstituted freeze-dried antivenom or neat liquid antivenom is given by slow intravenous injection (not more than 2 ml/minute). This method has the advantage that the doctor, nurse, or dispenser giving the antivenom must remain with the patient during the time when some early reactions may develop. It is also economical, saving the use of intravenous fluids, giving sets, cannulae etc.

2. *Intravenous infusion:* reconstituted freeze-dried or neat liquid antivenom is diluted in about 5 ml of isotonic fluid per kg body weight (i.e. about 250 ml of isotonic saline or 5% dextrose in the case of an adult patient) and is infused at a constant rate over a period of about 30-60 minutes.

Patients must be closely observed for at least one hour after starting intravenous antivenom administration, so that early anaphylactic antivenom reactions can be detected and treated early with epinephrine (adrenaline).

Local administration of antivenom at the site of the bite is not recommended! Although this route may seem rational, it should not be used as it is

extremely painful, may increase intracompartmental pressure and proved to be much less effective than by the intravenous route (O).

Intramuscular injection of antivenom:
Antivenoms are large molecules, [F(ab')$_2$ fragments or sometimes whole IgG] which, after intramuscular injection, are absorbed slowly via lymphatics. Bioavailability is poor, especially after intragluteal injection, and blood levels of antivenom never reach those achieved rapidly by intravenous administration **(Fig 81)** Theakston RDG, Warrell DA unpublished). Other disadvantages are the pain of injection of large volumes of antivenom and the risk of haematoma formation in patients with haemostatic abnormalities.

The only situations in which intramuscular administration might be considered is in the absence of anyone capable of giving an intravenous injection:

1. at a peripheral first aid station, before a patient with obvious envenoming is put in an ambulance for a journey to hospital that may last several hours (Win-Aung et al., 1996);
2. on an expedition exploring a remote area very far from medical care;
3. when intravenous access has proved impossible.

Although the risk of antivenom reactions is less with intramuscular than intravenous administration, epinephrine (adrenaline) must be readily available

Antivenom must never be given by the intramuscular route if it could be given intravenously.

1 VIAL FAB ANTIVENOM I.V.I. COMPARED WITH 1 VIAL I.M.I. (9 PATIENTS VIA EACH ROUTE)
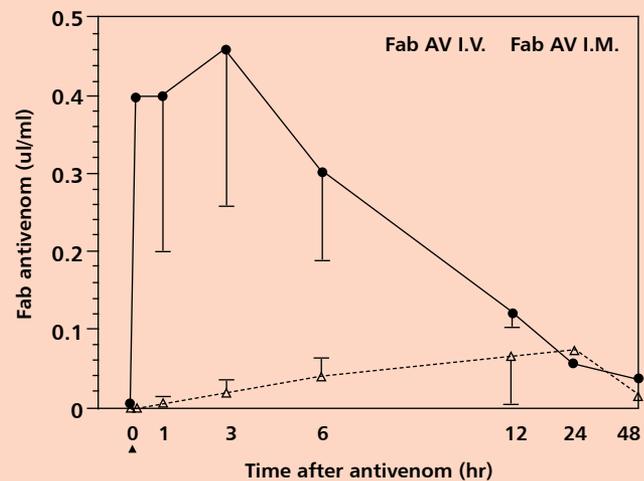
Figure 81: Comparison of intravenous and intramuscular administration of an Fab fragment antivenom. Antivenom administered intramuscularly appeared slowly in the bloodstream (dashed line) compared to that given by the intravenous route (solid line). (RDG Theakston and DA Warrell unpublished data).

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.

Under these exceptional circumstances, the dose of antivenom should be divided between a number of sites in the upper anterolateral region of both thighs. A maximum of 5-10 ml should be given at each site by deep intramuscular injection followed by massage to aid absorption. Local bleeding and haematoma formation is a problem in patients with incoagulable blood. Finding enough muscle mass to contain such large volumes of antivenom is particularly difficult in children.

6.7.8 Dosage of antivenom
(Table 1 and Annex 3)
Initial dose of antivenom

A fundamental piece of information for those treating envenomed patients is the average initial dose of a particular antivenom appropriate for different levels of clinical severity in patients bitten by different species. Unfortunately, these data, based on clinical trials, are rarely available. In any case, since the neutralizing power of antivenoms varies from batch to batch, and between different antivenoms, the results of a clinical trial may soon become obsolete if the manufacturers change the strength of their antivenom. This happened in Myanmar in the 1990s, when the national producer arbitrarily halved the strength of their antivenom. As a result, medical personnel must usually rely on manufacturers' recommendations stated in the package insert. These are usually based on laboratory assays in which venom and antivenom are incubated in vitro before being injected into the test animals, usually mice. The recommended dose is usually the amount of antivenom required to neutralize the average venom yield when captive snakes are milked of their venom, but, quite apart from many theoretical objections to this protocol, the maximum venom yield may be seriously underestimated (Tun Pe and Khin Aung Cho, 1986). In practice, the choice of an initial dose of antivenom is usually empirical. Some antivenom dosage regimens recommended in national management guidelines seem illogical, based on what is known of the pharmacokinetics and pharmacodynamics of venom-antivenom interactions.

Nepal: the Nepalese national guidelines recommend prolonged and repeated dosage of antivenom. An initial dose of 2 vials of antivenom given by IV

"push" injection, is followed by infusion of 4 vials over 4 hours, and, as long as signs of envenoming persist, 4 vials over 4 hours every 4 hours for a further 12 hours, followed by 2 vials over 4 hours, repeated until recovery. Following this regimen, cumulative doses may reach 140 vials (1000 ml) in patients with neurotoxic envenoming by kraits (Magar et al., 2013). A recent study in Nepal compared the effectiveness and safety of this regimen with a single higher initial dose of 10 vials given over 1 hour in patients with neurotoxic envenoming. There was no statistically significant difference between the two regimens in the proportion of patients reaching the primary endpoint (48.7% in the low initial dose arm versus 38.5% in the high initial dose arm, p=0.264). Likewise, there was no difference in the incidence of antivenom reactions (53.8% of patients given the high dose compared to 52.6% given the low initial dose). Among the 51 patients in whom the snake species could be identified, 29 had been bitten by cobras (*Naja* spp) and 22 by kraits (*Bungarus* spp.). Patients bitten by kraits were more severely envenomed and recovered less often (40.9% versus 96.5%, p<0.001) and more slowly (mean recovery time 18 hours versus 5 hours, p<0.001) than did patients bitten by cobras. These findings suggested that there was no difference in effectiveness and safety between initially low and high doses of antivenom for neurotoxic snakebite in southern Nepal, and that systemic envenoming due to krait bites was less responsive to antivenom than that following cobra bites (Alirol E, Sharma SK et al., in press). Since the high single initial dose was non-inferior to the low initial dose (but much higher total dose), the former is preferred on grounds of cost and convenience.

India: there have been many publications on treatment of snakebite with national

polyvalent antivenoms, but there is little reliable evidence to guide initial dosage. Manufacturers' recommendations are based on the amount of venom (mg) neutralized by 1 ml of antivenom. The Indian national snakebite protocol (Directorate General of Health Services, 2009) and previous editions of WHO guidelines recommend immediate administration of 5 vials, and a recent consensus 4-6 vials (Menon et al., 2916b) in the case of *Echis carinatus*; and 10 vials for patients envenomed by the other species, with repeated dosing if the patient fails to improve, to a maximum of 20 vials. There are no adequately designed dose finding studies that selected snakebites by identified species, controlled for clinical severity, were randomised and employed defined clinical end points including measurement of antigaenemia (Warrell, 2011). In clinical practice, the dose of antivenom used is very variable. In government hospitals where antivenom is freely available, higher doses of antivenom are prescribed, often exceeding 20 vials. Other non-profit rural hospitals use a low dose regimen of less than 10 vials in view of the high cost and scarcity of antivenom. Several randomised controlled trials from such hospitals claimed to demonstrate that lower doses were equally effective in victims of predominantly haemotoxic snakebites in South India in (Thomas and Jacob, 1985; Tariang et al., 1999; Paul et al., 2004; Srimannarayana et al., 2004; Cherian et al., 2013). However, these studies, without exception, had severe limitations in patient slection and case definition, snake species identification, design, end-points and power, rendering their results uninterpretable.

Thailand: in 1984, a small randomised controlled trial was carried out in patients with systemic *C. rhodostoma* envenoming, comparing three antivenoms that were then available. An initial dose of 5 vials

> *In clinical practice, the dose of antivenom used is very variable. In government hospitals where antivenom is freely available, higher doses of antivenom are prescribed, often exceeding 20 vials.*

was effective in permanently restoring blood coagulability. Subsequently, in 2003-4, a retrospective study of 225 *C. rhodostoma* victims suggested that 4-9 vials of Thai Red Cross (TRC) Malayan Pit Viper antivenin was effective in correcting coagulopathy and systemic symptoms but appeared to do little to counteract local tissue necrosis (Wongtongkam et al., 2005). In a small observational study, an average dose of 165 (+/- 59.3) ml of TRC Russell's Viper antivenin corrected blood incoagulability in a group of 38 patients envenomed by *D. siamensis*. The authors recommended that 60 ml of this antivenom should be administered at 6-hour intervals until blood coagulability was restored (Karnchanachetanee et al., 1994). In the case of cobra *(Naja kaouthia)* bite victims with respiratory paralysis, envenoming, treated between 1981 and 1991, a single dose of 100 ml of TRC Cobra antivenin reduced time on a respirator from approximately 40 h if no antivenin or an inadequate dose was used to 10h (Pochanagool et al., 1997). Increasing the dose did not lead to added benefits. In victims of *Trimeresurus (T.) albolabris* or *T.(T.) macrops,* 50 ml of TRC Green Pit Viper antivenin rapidly corrected coagulopathy (Hutton et al., 1990). A large retrospective review of patients envenomed by these species found that TRC Green Pit Viper antivenin given on average 21 hours after the bite for the treatment of severe coagulopathy did not affect the risk of their developing local necrosis (Chotenimitkhun and Rojnuckarin,

2008). A randomized, double-blind, placebo-controlled trial of TRC Green Pit Viper antivenin in patients bitten by these *Trimeresurus* species who had marked limb swelling, but no severe coagulopathy suggested that antivenom accelerated resolution of local swelling, although not to a clinically useful degree (Rojnukarin et al., 2006).

Reasons for antivenom ineffectiveness

There is an urgent need for well-designed and adequately-powered national clinical dose-finding studies to establish initial doses of antivenom for patients with different severities of envenoming by the major medically important species in the Region. These should focus on bites by reliably-identified species, should be randomised, comparing two doses of the same antivenom or two different antivenoms, should have objective end-points to assess effectiveness and safety, and should, ideally, be blinded to exclude bias.

There have been anecdotal and unpublished reports of clinical ineffectiveness of individual batches of antivenom. The variable efficacy may be due to lower antibody titre, reduced antibody binding specificities and lack of antibodies to low molecular weight proteins. Studies have shown batch to batch variability in effectiveness of Indian antivenoms, manifested by increased complications and mortality with particular batches (Zachariah A, personal communication; Zacharaiah, 2015). Possible explanations include

geographical intra-species venom variation, lack of adequate neutralizing antibodies against key toxic venom proteins, inability of the antibodies to neutralize toxins that are tissue bound or to reverse the pathological consequences of tissue injury. Envenoming by the larger northern sub-species of saw-scaled viper *(Echis carinatus sochureki)* requires larger antivenom doses (Kochar et al., 2007) and envenoming by Russell's vipers in Kerala and Maharashtra require higher antivenom doses (Warrell et al., 2013). Biochemical studies have shown variations in venom composition in different parts of India for *Naja naja* (Mukherjee and Maity., 1998; Shashidharamurthy and Kemparaju, 2007) and *Daboia russelii* (Jayanthi and Gowda, 1988; Prasad et al., 1999). Antivenom raised against venom from one geographical location may not be as effective against envenoming in other geographical locations. In India, most of the venom used for antivenom manufacture is obtained from the Irula cooperative in Mammallapuram (Warrell et al., 2013). A recent comparison of two commercially available antivenoms showed that one had a higher protein content, and antibody binding and neutralizing capacity for *Echis carinatus* and *Daboia russellii* venom. Indian polyvalent antivenoms are raised against venoms of the classic "big four" species and may not neutralize venoms of other medically important snakes, such as monocellate cobra *(N. kaouthia)* in the North-East and any of the Indian pit-vipers, notably the hump-nosed pit-viper *(Hypnale hypnale)* and Malabar pit-viper *(Trimeresurus (Craspedocephalus) malabaricus)* of the south-west coast.

Suggested initial doses of some of the available antivenoms are given in Table 1 (by species of snake), based on clinical experience; and in Annex 3 (by country),based on manufacturers' recommendations.

Table 1: Guide to initial dosage of some antivenoms for treating bites by medically-important snakes in the South-East Asia Region, based on clinical experience, rather than manufacturers' recommendations (E)

Latin name	English Name	Manufacturer, antivenom	Approximate average initial dose
Acanthophis species	death adder	CSL[1] Death Adder or Polyvalent Antivenom	1-3 vials
Bungarus caeruleus	common krait	Indian manufacturers[2] polyvalent	100 ml
Bungarus candidus	Malayan krait	TRC[3] Malayan Krait Antivenin Mono OR TRC[3] Neuro Polyvalent	50-100 ml 100 ml
Bungarus fasciatus	banded krait	TRC[3] Malayan Krait Antivenin OR TRC[3] Neuro Polyvalent	50-100 ml 100 ml
Bungarus multicinctus	Chinese krait	Shanghai Vaccine & Serum Institute NIPM Taipei Naja-Bungarus antivenin	5 vials 5 vials
Calloselasma (Agkistrodon) rhodostoma	Malayan pit viper	TRC[3] Malayan Pit Viper Antivenin Monovalent OR TRC[3] Hemato Polyvalent	30-50 ml 30-30 ml
Daboia russelii	Western Russell's viper	Indian manufacturers[2] polyvalent	100 ml
Daboia siamensis	Eastern Russell's viper	Myanmar Pharmaceutical Factory TRC[3] Russell's Viper Antivenin Monovalent OR TRC[3] Hemato Polyvalent	80 ml 30-50 m 30 ml
Echis carinatus India Gloydius (Agkistrodon) brevicaudus	saw-scaled viper Chinese Mamushi	Indian manufacturers[4] polyvalent Shanghai Vaccine & Serum Institute Mamushi antivenom	50 ml 1 vial
Hydrophiinae	sea snakes	CSL[1]Sea Snake Antivenom	1-10 vials
Micropechis ikaheka	New Guinean small-eyed snake	CSL[1] Polyvalent Antivenom	2 vials
Naja kaouthia	monocellate Thai cobra	TRC[3] Cobra Antivenin Mono OR TRC[3] Neuro Polyvalent	100 ml 100 ml
Naja naja, N oxiana	Indian cobras	Indian manufacturers[2] polyvalent	50 ml
Ophiophagus hannah	king cobra	TRC[3] King Cobra Antivenin Mono OR TRC[3] Neuro Polyvalent	100 ml 100 ml
Oxyuranus scutellatus	Australian/Papuan taipans	CSL[1] Taipan or Polvalent Antivenom	1-6+ vials
Pseudonaja species	Australian brown snakes	CSL[1] Brown Snake or Polyvalent Antivenom\	1-2 vials
Pseudechis species	Australian black snakes	CSL[1] Black Snake Antivenom	1-3 vials
Rhabdophis tigrinus, R. subminiatus	Japanese yamakagashi, SE Asian red-necked keelback	Japanese Snake Institute, Nitta-gun Yamakagashi antivenom	1-2 vials
Trimeresurus (T.) albolabris T. (T.) macrops etc.	Green pit-vipers	TRC[3] Green Pit Viper Antivenin OR TRC[3] Hemato Polyvalent	30-50 ml 30-50 ml

[1] CSL, Parkville, Australia http://www.toxinology.com/fusebox.cfm?staticaction=generic_static_files/avp-csl-01.html
[2] Indian Manufacturers: Bharat Serums & Vaccines, Mumbai https://www.bharatserums.com/; Central Research Institute, Kasauli http://www.nti.org/learn/facilities/145/ ; Haffkine Biopharma, Mumbai; Serum Institute of India, Pune http://www.seruminstitute.com/content/products/product_list.htm ; Vins Bioproducts, Hyderabad: Premium Serums and Vaccines, Narayangaon http://www.premiumserums.com/
[3] Thai Red Cross, Queen Saovabha Memorial Institute, Bangkok, Thailand http://www.snake-antivenin.com/

Observation of the response to antivenom: If an adequate dose of an appropriate antivenom has been administered, the following responses may be seen.

a) **General:** the patient feels better. Nausea, headache and generalized aches and pains may disappear very quickly. This may be partly attributable to a placebo effect.

b) **Spontaneous systemic bleeding** (e.g. from the gums) usually stops within 15-30 minutes.

c) **Blood coagulability** (as measured by 20WBCT) is usually restored in 3-9 hours. Bleeding from new and partly healed wounds usually stops much sooner than this.

d) **In shocked patients,** blood pressure may increase within the first 30-60 minutes and arrhythmias such as sinus bradycardia may resolve.

e) **Neurotoxic envenoming** of the post-synaptic type (cobra bites) may begin to improve as early as 30 minutes after antivenom (Faiz et al., cobra bites in press), but *may* take several hours. Envenoming by presynaptic toxins (kraits and sea snakes) will not respond in this way.

f) **Active haemolysis and rhabdomyolysis** may cease within a few hours and urine colour returns to normal.

6.7.9 Recurrence of systemic envenoming

In patients envenomed by vipers, after an initial response to antivenom (cessation of bleeding, restoration of blood coagulability), signs of systemic envenoming may recur within 24-48 hours.

This is attributable to:

1. continuing absorption of venom from the "depot" at the site of the bite, perhaps promoted by improved blood supply following correction of shock, hypovolaemia etc., after elimination of antivenom (range of elimination half-lives: IgG 45 hours; F(ab')$_2$ 80-100 hours; Fab 12-18 hours) (Ho et al., 1986; Ho et al., 1990)

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

Recurrent neurotoxic envenoming after treatment of cobra bite has also been described.

5.7.10 Criteria for repeating the initial dose of antivenom

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. There is no evidence to guide the exact timing for repeating the dose of antivenom for paralysis or shock, but it seems reasonable to repeat the initial dose after 1 hour if the patient's condition is deteriorating. Full supportive treatment must be considered. Repeating doses of antivenom after the patient is paralysed and being ventilated has no proven value, increases the risk of reactions, is expensive and wastes a valuable resource.

6.8 Conservative treatment when no antivenom is available

This will be the situation in many parts of the Region, where supplies of antivenom run out or where the bite is known to have been inflicted by a species against whose venom there is no available specific antivenom.

The following conservative measures are suggested:

Neurotoxic envenoming with respiratory paralysis: assisted ventilation. This has proved effective, and has been followed by complete recovery, even after being maintained for

periods of more than one month. Manual ventilation (anaesthetic bag) by relays of doctors, medical students, relatives and nurses has been effective where no mechanical ventilator was available. Anticholinesterases should always be tried (see below).

Haemostatic abnormalities - strict bed rest to avoid even minor trauma including intramuscular injections; transfusion of clotting factors and platelets; ideally, fresh frozen plasma (FFP) or cryoprecipitate with platelet concentrates or, if these are not available, fresh whole blood. The indications for these blood components are the same as those for antivenom administration for bleeding tendency, but it is important to recognize that, in the presence of un-neutralized circulating venom procoagulant toxins, administered clotting factors will be rapidly consumed, with the potential danger of formation of microthrombi.

Shock, myocardial damage: hypovolaemia should be corrected with colloid/crystalloids, controlled by observation of the central venous pressure. Ancillary pressor drugs (dopamine or epinephrine-adrenaline) may also be needed. Patients with hypotension associated with bradycardia should be treated with atropine.

Acute kidney injury: conservative treatment or dialysis (see below).

Dark brown urine (myoglobinuria or haemoglobinuria): correct hypovolaemia with intravenous fluid, correct acidosis with a slow intravenous infusion of 50-100 mmol of sodium bicarbonate.

Severe local envenoming: local necrosis, intracompartmental syndromes and even thrombosis of major vessels is more likely in patients who cannot

be treated with antivenom. Surgical intervention may be needed but the risks of surgery in a patient with consumption coagulopathy, thrombocytopenia and enhanced fibrinolysis must be balanced against the life threatening complications of local envenoming. Prophylactic broad spectrum antimicrobial treatment is justified (see below).

6.9 Supportive/ancillary treatment

Antivenom treatment can be expected to neutralize free circulating venom, prevent progression of envenoming and allow recovery. However, these processes 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.

6.9.1 Treatment of neurotoxic envenoming

Antivenom treatment alone cannot be relied upon to save the life of a patient with bulbar and respiratory paralysis.

Death may result from aspiration, airway obstruction or respiratory failure. A clear airway must be maintained. Once there is loss of gag reflex and pooling of secretions in the pharynx, failure of the cough reflex or respiratory distress, a cuffed endotracheal, laryngeal mask airway or i-gel supraglottic airway should be inserted. If this is impossible for any reason, or the need for prolonged ventilation is anticipated, a tracheostomy should be performed and a snugly-fitting or cuffed tracheostomy tube inserted **(Caution – in patients with uncorrected coagulopathy, more**

antivenom and fresh-frozen plasma or clotting factors will be needed to control bleeding after this procedure.)

In urgent situations where acute airway obstruction has developed and where the patient cannot be intubated, cricothyroidotomy will establish an airway faster than tracheostomy.

Although artificial ventilation was first suggested for neurotoxic envenoming 140 years ago, patients continue to die of asphyxiation because some doctors believe that antivenom alone is sufficient treatment.

6.9.2 Practical guide to airway management and respiratory support

The following guidelines have been produced specifically to aid health care workers in the acute management of snakebite patients. However, it is important to recognize that the techniques described below are applicable to the care of all critically ill patients.

The techniques discussed below are not complicated. However, expert instruction is desirable, ideally from a fully trained doctor, nurse, first-aid worker or other health professional, with experience in resuscitation, airway management, use of the necessary equipment, intubation and assisted ventilation. These techniques must be practised frequently, under supervision, using a manikin (dummy/model – see **Fig 82a**) or, but only where appropriate and culturally acceptable, a dead body in the mortuary, to acquire essential understanding of the anatomy of the upper airway and the techniques themselves, and to maintain an adequate baseline level of skill **(Fig 82b)**.
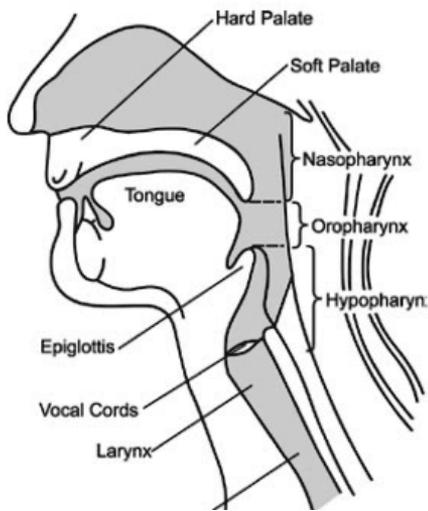
Figure 82b: Anatomy of the upper airway

Resuscitation

This follows the general principles of life support given below:

DRABCDE
D - DANGER
R - RESPONSE
A - AIRWAY
B – BREATHING
C - CIRCULATION
D - DISABILITY
E – EXPOSE THE PATIENT
(Only DRAB are discussed here)

D - DANGER - Scene safety: The rescuer should ensure that there is no risk of exposure to danger of a further snakebite to the victim, to themselves, or to other helpers by observing standard precautions possible under the circumstances (e.g. removing the victim from undergrowth and, in the case of sea snakebite, removal from the water to avoid drowning) and ensuring that any snake brought to hospital with the patient, for identification, will not bite another person.

R - RESPONSE -The rescuer checks responsiveness of the victim (e.g. vocal - "Are you all right?", with gentle shaking).

Importance of training (Fig 82a)

Figure 82: Treatment of neurotoxic envenoming: (a) Training health workers in techniques of endrotracheal intubation and airway management in Papua New Guinea (Copyright DJ Williams)

If there is no response, or limited response, summon assistance. Call out for help, send someone for medical assistance, or make a very quick telephone call.

Making an emergency call

If the victim does not respond:
1. In a field situation: emergency medical services (EMS) are activated by calling the local emergency number (either by a second rescuer or by the first rescuer him/herself). The response team (ambulance) is asked to bring the necessary resuscitation equipment (also termed "code cart" or "code blue cart" in some hospitals/clinics), including an automated external defibrillator (AED).

2. In a health centre: emergency cart and defibrillator are summoned. Once the EMS/emergency cart has been summoned, the rescuer starts airway management

A – AIRWAY PROTECTION AND MANAGEMENT
Basic Airway Management (BAM)
Opening and maintaining the airway:
The airway can be opened using the "head tilt - chin lift" manoeuvre **(Fig 82c)**, bringing the patient's head into the "sniffing" position. If there is any suspicion of cervical spine trauma, jaw thrust should be used rather than this procedure.
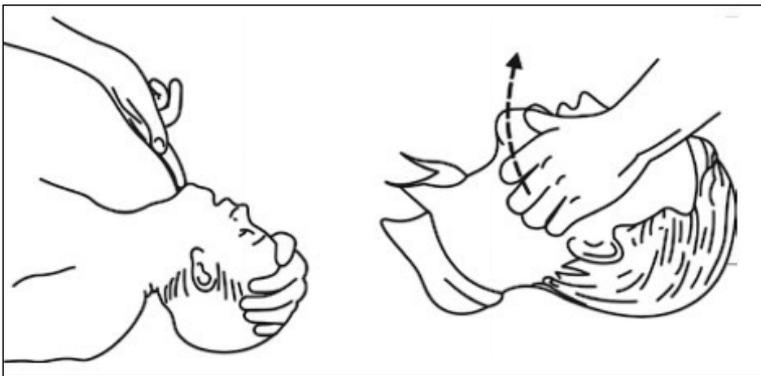
Figure 82c: Head-tilt, chin-lift (left) and jaw-thrust manoeuvres (right)

If this does not improve air flow, the "jaw thrust" manoeuvre **(Fig 82c)** should be performed as the tongue may have fallen or been sucked backwards, obstructing the oropharynx. "Jaw thrust" helps to lift the tongue forward, and is often effective in improving air flow as lifting the patient's chin and extending their neck serves to dislodge the tongue and reopen the upper airway.

Next look inside the victim's mouth. There may be blood, vomit or excessive oral secretions contributing to airway obstruction and putting the patient at risk of aspirating (inhaling) this material into their lungs. Remove any foreign material by suction, using a suitable suction catheter, such as a Yankeur suction

catheter (attempts should not be longer than 10 seconds) or by using forceps. Use of a gloved finger is discouraged as this may push the material or object further down the airway and may put the rescuer at risk of being bitten.

Finally, insert an oropharyngeal (Guedel) airway (OPA), measured to suit the patient (from the corner of the mouth to the angle of the jaw), being sure to avoid causing trauma to the lips and mouth, especially if there is evidence of bleeding or the if the patient has been bitten by a snake which causes bleeding abnormalities. While nasopharyngeal airway (NPA) devices are better tolerated by semi-conscious patients, who may still have a gag reflex, or in those who have trismus, they are more likely to cause nasal bleeding, and so are not preferred.

If an OPA device cannot be inserted because of trismus (rigidity of the chewing muscles, preventing opening of the mouth), the patient may have one of the following life-threatening conditions, which must be urgently treated:

- Severe hypoxia;
- Hypoglycaemia;
- Seizure;
- Active rhabdomyolysis affecting the masseter muscles (e.g. in sea-snakebite envenoming)
- Or they may, in fact, be awake and simply resisting you.

Advanced Airway Management (AAM)
AAM is defined as the use of more advanced techniques in airway management. It may be used in the following circumstances:

- To maintain (keep open) the airway over long periods;

- To protect the airway (prevent the inhalation/pulmonary aspiration of saliva, vomit or blood):

- To ventilate a paralysed patient (such as after a bite by a snake with neurotoxic venom);

- To allow high concentrations of oxygen (up to 100%) to be delivered;

- To remove, and control the concentration of, carbon dioxide in the blood.
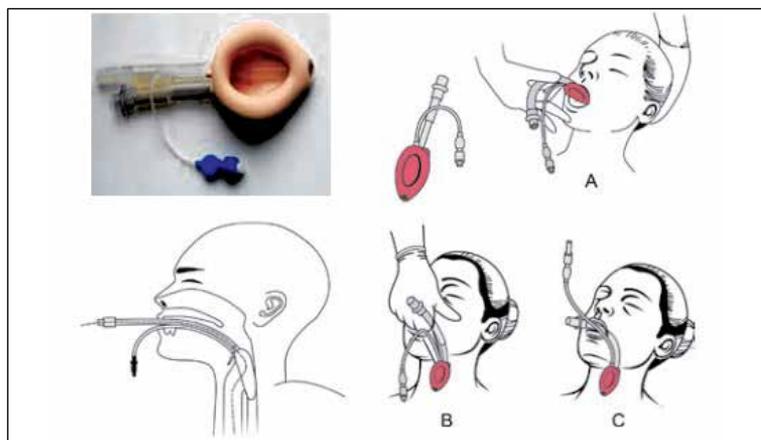
Figure 82d: "Supraglottic (above the larynx) devices" Laryngeal mask airway, introduction and position

Indications for intubation [insertion of endotracheal tube (ETT) or other airway]:

a. *Imminent respiratory arrest (breathing is absent or inadequate)*
b. *Neck muscle weakness with shallow respiration or paradoxical breathing*
c. *Upper airway obstruction with stridor (secondary to anaphylaxis)*
d. *Oxygen saturation <90% (equivalent to Pa0$_2$ <60 mmHg) despite high flow oxygen*
e. *Blood gas measurement showing respiratory acidosis (hypoxia PaO$_2$ < 60 mm Hg with PaCO$_2$ > 45 mm Hg)*

The devices used for this type of airway management are divided into 2 categories:

Supraglottic (above the larynx) devices (Fig 82d)
Laryngeal mask airways. Many models with different features benefits and disadvantages are now available, depending on the country in which you work, but they may not be freely available in peripheral hospitals. They do not require special equipment to insert them, and even medically untrained people can be taught to insert them successfully after minimal (as little as one hour's) tuition, making them potentially ideal in a low-skill setting. However, they not provide good protection of the airway as, potentially, fluids can still leak past them into the patient's lungs. They do not permit high ventilation/airway pressures, and require a gastric tube to reduce the risk of gastric insufflation (distension with gas) and the risk of gastro-oesophageal reflux.

i-gel supraglottic airway. i-gel airways are made of a thermoplastic elastomer, which is soft, gel-like and transparent. They are designed to create a non-inflatable anatomical seal of the pharyngeal, laryngeal and perilaryngeal structures. Insert with the i-gel cuff outlet facing towards the patient's chin with head extended and neck flexed in the "sniffing" position (see above). Glide the device downwards and backwards along the hard palate with a continuous but gentle push until a definitive resistance is felt. At this point the tip of the airway should be located into the upper oesophageal opening and the cuff should be located against the laryngeal

(Fig 82e) i-gel supraglottic airway
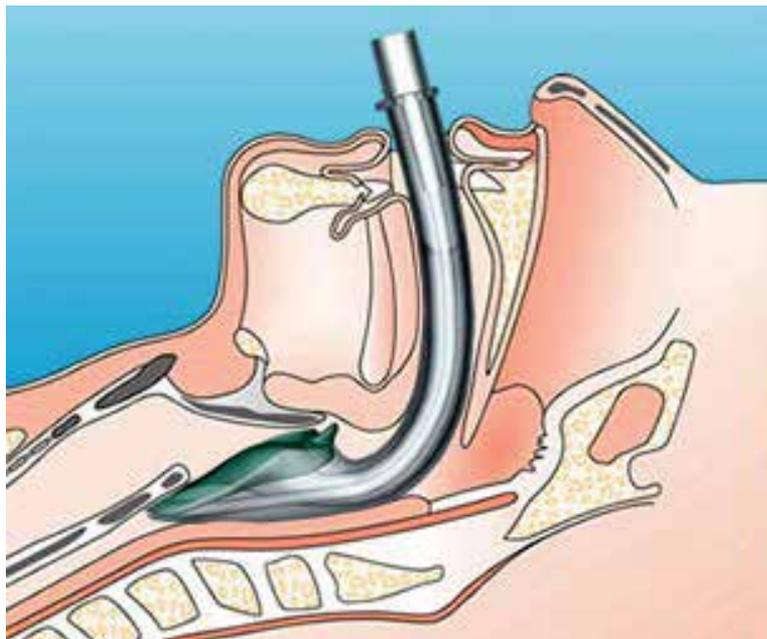
Figure 82e: Treatment of neurotoxic envenoming i-gel supraglottic airway

framework. The incisors should be resting on the integral bite-block.

Infraglottic (extending below the larynx) devices:

The most familiar, and by far the most readily available, is the endotracheal tube (ETT), typically a cuffed tube for adults and an uncuffed tube for children, though the use of cuffed (low pressure, high volume) tubes for children is becoming more acceptable.

These do provide protection of the lower airway (the lungs) against contamination by fluids and also permit higher ventilation pressures and the highest inspired oxygen concentrations.

However, they require a laryngoscope of some sort to permit visualization of the laryngeal structures, and even the most basic of these are not available in small health centres.

To insert these devices safely and quickly (to reduce the period of no ventilation,

and hence the risk of hypoxia) experience is required.

Induction/intubation drugs should be used, though these may not be available or the staff may not be experienced in their safe use.

Discussion of the actual techniques involved is beyond the scope of this document. However, essentially an endotracheal tube is inserted under laryngoscopic vision between the vocal cords so that its tip lies in the mid trachea **(Fig 82f)**.

An endotracheal tube is inserted under laryngoscopic vision between the vocal cords so that its tip lies in the mid trachea. Intubation is more invasive than supra-glottic devices and needs laryngoscopy and more skill to perform.

Surgical airway devices (tracheostomy)

These are discouraged and are rarely necessary because:

Patients rarely require ventilation beyond a week, once the correct type and dose of antivenom has been given; Many patient venom-induced bleeding disorders and will bleed excessively from any such

Figure 82f: Insertion of an endotracheal tube

intervention. Therefore, "tracheostomy" is a term that should be removed from snakebite management protocols.

B – BREATHING – Assessing breathing: Place your ear near the victim's mouth and nose, keeping your gaze towards the victim's chest. Look for chest to rise and fall, listen for air escaping during exhalation, feel for the flow of air against your cheek. Take at least 5 seconds but no more than 10 seconds to make this assessment.

If oxygen is available, it should be administered by any available means (nasal prongs/catheters, mask, bag-valve-mask etc.) between each suctioning attempt (which should not be prolonged). [Arterial Peripheral oxygen saturation (SpO2) should be monitored by digital oximeter, if available.]

Positioning the patient to protect airway patency (Dangers of vomiting and aspiration)

If breathing is present and adequate (with or without airway opening manoeuvres), put the victim in the recovery position **(Fig 82g)** and keep checking for breathing every 2 minutes. This position and a chin-up tilt can be maintained using pillows, sand bags or an assistant, often the patient's relative. The recovery position is especially important in envenomed patients because vomiting is such a common early symptom, oral bleeding is common if there is a bleeding disorder, there may be hypersalivation and, since patients with neurotoxicity cannot cough or swallow, they are at increased risk of inhaling any of these secretions and fluids. However, when the patient is placed in the correct recovery position, these fluids will drain harmlessly from their mouth. The recovery position will also help to stop the tongue from falling back and blocking the airway.

If breathing stops at any time, lay the victim supine, go through the airway opening manoeuvres again, and then provide breathing artificially, if required.

If breathing is absent or inadequate, such as if:
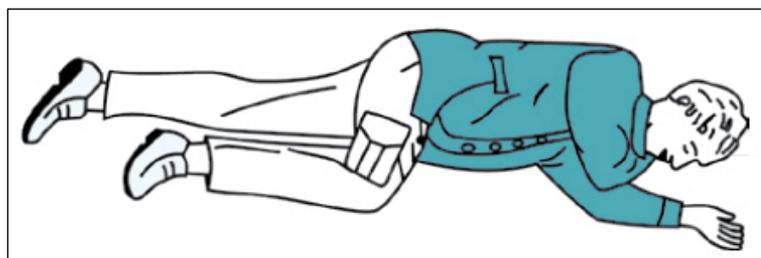
Figure 82g: The recovery position

- No breathing is discernible within 10 seconds (or 5 seconds in a child, 2 seconds in a baby);

- The respiratory rate is low (a general idea of normal ranges of age-related respiratory rates and other basic physiological parameters is required of all health care workers, or this information should be readily available to them);

- The depth of respiration is inadequate (shallow) (the tidal volume is low);

- The patient is taking agonal (gasping) breaths;

- The patient is cyanosed centrally (blue lips, ears, or tongue) (this might not be visible if the patient is very anaemic, such as from malnutrition, chronic malaria or chronic gastrointestinal parasite infestation), or

- The measured blood peripheral oxygen saturation is low (a poor trace, and so a potentially low reading, may be obtained if the patient has cold peripheries or a low blood pressure -shock);

> *If chest movement is inadequate, a correctly-sized OPA should be inserted. This will usually assist with air flow in and out of the lungs. If there is no bleeding disorder, a NPA (or 2) may be used instead of, or in addition to, an OPA.*

- The end-tidal CO2, by whichever method is being used, is high, or climbing;

ASSISTED VENTILATION IS REQUIRED!
How this is delivered will depend on:

- The clinical circumstances, i.e. whether the patient is in the bush, in an small health centre or in a hospital;
- The skills of the rescuer;
- The availability of assistants;
- Equipment available.

Methods for providing assisted ventilation
Expired Air Resuscitation (EAR) (no health facilities immediately available):

Deliver 2 initial "rescue breaths" as follows **(Fig 82h)**: close the patient's nose with one hand and pull the jaw down with the other, and place your mouth over the

Figure 82h: Technique of giving "rescue breaths"

patient's mouth and deliver a breath over a second, enough to see the chest rise, and allowing 4 seconds for exhalation before giving a second breath. In the case of a small child the mouth and nose may be covered by the rescuer's mouth.

Assisted ventilation by this means will provide a maximum of approximately only 16% inspired oxygen concentration (FIO$_2$ 0.16).

The risk of communicable disease transmission to the rescuer is low, but can be diminished further by the use of:

- A special EAR face shield, manufactured for this purpose;
- A mask of the type used with Bag-Valve-Mask (devices);
- A piece of cloth thin enough to allow for the free passage of air.

If the patient does not begin to breathe, or to breathe more effectively, at this point, the decision will need to be made about how long to continue this method of assisted ventilation.

This will depend on:

- The clinical circumstances, e.g. the likely diagnosis, the age of the patient (the rescuer might reasonably persist for longer if the patient is a small child), or the distance from medical assistance or from more advanced health care facilities;

- The presence of effective cardiac activity; as determined by the presence of a carotid pulse (palpate on both sides before determining that this is absent), more advanced tests such as auscultation of audible heart sounds, or visible cardiac contraction on ultrasound; are supportive tests which may be available.

The presence of electrical activity, as determined using a cardiac monitor of some kind, with no demonstrable cardiac output or pulse (so-called "pulse-less electrical activity") usually carries a very poor prognosis, though there is a list of potentially reversible conditions which may cause this. This topic is not covered in these guidelines, but should be covered in any advanced life support course material.

Non-invasive ventilation:

Bag-mask/Bag-mask-valve ventilation: In a health-care centre, a commonly used method for providing initial respiratory assistance is with a bag-mask/Bag-Valve-Mask (BVM) (resuscitator bag) **(Fig 82i)** Even the simplest health-care centre should have these, with different sizes required for different ages of patients, and the staff should be well versed in how to check that the device is functioning correctly and know how to use it correctly and safely.

The rescuer positions him/herself at the victim's head end. Holding the bag with one hand, he/she places the mask on the victim's face with the apex of the mask on the bridge of the nose and its base on the groove over the chin. With the other hand, he/she seals the mask around the victim's nose and mouth, tilts (extends) the victim's head, lifts the jaw forward and gives breaths at approximately the normal respiratory rate for the patient by squeezing/pressing the bag, looking for visible chest rise. Any chest movement is usually adequate, especially in children.

If chest movement is inadequate, a correctly-sized OPA should be inserted. This will usually assist with air flow in and out of the lungs. If there is no bleeding disorder, a NPA (or 2) may be used instead of, or in addition to, an OPA.

Bag-mask breathing suffices for short-

Figure 82i: bag-mask/Bag-Valve-Mask (BVM) (resuscitator bag)

term respiratory support but if there is no breathing or inadequate breathing that needs longer term support, the airway needs to be secured more definitively and even the bag may have to be replaced with a ventilator. However, many snakebite patients around the developing world have been kept alive for days, or week, using simply an OPA and a BVM, or with an ETT and a BVM, using relatives to squeeze the bag, though this is far from ideal.

Invasive Ventilation:

Indications for intubation and mechanical ventilation are Type I respiratory failure (primary failure of oxygenation as in pulmonary oedema in Russell's viper envenoming) and Type II respiratory failure (primary ventilatory failure due to respiratory muscle paralysis or obstruction as in elapid envenoming). Suggestive clinical features in patients receiving oxygen by mask or nasal catheters include tachpnoea (respiratory rate > 25/min) or paradoxical respirations (abdomen moves out on inspiration) and deteriorating ventilatory capacity (see above); hypoxia (central cyanosis, SpO2 < 90%, arterial PO_2 < 50 mm Hg, < 6.7 kPa); and respiratory acidosis (arterial PCO_2 > 50 mm Hg, < 6.7 kPa, arterial pH <7.36). Supraglottic or infraglottic devices are used to open the airway and assist with both the supply of oxygen to the lungs and removal of carbon dioxide from the lungs. Generally, and where possible,

endotracheal intubation (insertion of an ETT) should be performed and the patient placed on a ventilator, attended constantly by a suitably qualified nurse, with a suitably qualified doctor always on call to provide additional assistance, if required. Tube blockages are a frequent cause of morbidity and mortality. They are prevented by regular suctioning, humidification and training of staff to recognize the symptoms of a blocked tube.

Sedation for patients being mechanically ventilated: fentanyl 2-40 microg/hour and midazolam 2-4 mg/hour OR (to avoid acute kidney injury) morphine 1-5 mg/hour with lorazepam 1-2 mg/hour.

Adequacy of respiratory assistance can be assessed by reversal of clinical signs of inadequate respiration and stabilization of SpO_2 and end-tidal CO_2 (where available) and improvement in the victim's level of consciousness if respiratory failure was the sole cause of his/her unresponsiveness. However, assessing the level of consciousness of a patient with neurotoxic envenoming can be difficult because of their often generalized flaccid paralysis, such that the normal method of ascertaining the level of consciousness (the Glasgow Coma Scale – GCS) is irrelevant since the patient is unable to open their eyes, unable to speak and often unable to obey commands. They are, contrary to common belief, awake, able to hear everything which is said around them. They should be sedated during the period of their ventilation.

Other important aspects of the care of a ventilated patient include:

- Adequate hydration, monitoring of renal function and of fluid balance;

- Nutrition (in addition to the minimal nutrition contained in normal IV fluids);

- Physiotherapy (including chest physiotherapy, regular turning to prevent pressure areas and lung collapse, and maintenance of the range of motion of paralysed, immobile joints and muscles, as well as limbs where significant cytotoxicity and tissue damage has occurred).

- Eye care (synthetic tears and closure of the eyelids to prevent drying and damage to corneas in patients on ventilators).

- Safe and effective weaning from ventilation.

Always be careful to minimize trauma to the airway of a snakebite patient; this includes the insertion of basic airway devices, advanced airway devices and gastric tubes. Orogastric tubes are much preferred over nasogastric ones – the latter often lead to bleeding which is difficult to deal with in the patient who has a coagulopathy, and may even lead inexperienced staff to give more antivenom or blood products when these are not necessary.

Such care also applies to the insertion of intravenous catheters and urinary (urethral) catheters. Central venous lines may be inserted, if required and possible, but the insertion site will depend on the presence or absence of a bleeding disorder. Intra-arterial lines may be useful in many respects, but, again, are discouraged in the presence of a bleeding disorder.

6.9.3 Trial of anticholinesterase
Anticholinesterase drugs have a variable, but potentially very useful effect in patients with neurotoxic envenoming, especially those bitten by cobras (Banerji et al., 1972; Watt et al., 1986; Watt et al., 1989; Faiz et al., cobra in press), but not usually in those envenomed by kraits (Anil

et al., 2010). However, recent claims that intra-nasal neostigmine might provide a universal first-aid method for snakebite victims have achieved a high media profile but are unsubstantiated, misleading and fanciful (Lewin et al., 2013; Lewin et al., 2014).

> *A trial of anticholinesterase (e.g. "Tensilon test") should be performed in every patient with neurotoxic envenoming, as it would be in any patient with suspected myasthenia gravis. However, this should not delay antivenom treatment or endotracheal intubation. Patients must be observed closely as they may deteriorate while the trial of anticholinesterase is being carried out*

Procedure

1. Baseline observations or measurements are made against which to assess the effectiveness of the anticholinesterase.

2. Atropine sulphate (0.6 mg for adults; 50 μg/kg for children) or glycopyrronium is given by intravenous injection followed by neostigmine bromide or methylsulphate (Prostigmin) (or distigmine, pyridostigmine, ambenomium etc. in appropriate doses) by intramuscular injection 0.02 mg/kg for adults, 0.04 mg/kg for children. Short acting edrophonium chloride (Tensilon) is ideal for this test but is rarely available in the Region. It is given by slow intravenous injection in an adult dose of 10 mg, or 0.25 mg/kg for children.

3. The patient is observed over the next 30-60 minutes (neostigmine) or

Figures 83: Anti-cholinesterase: (a) Before and (b) after intravenous atropine followed by intravenous edrophonium chloride in a patient envenomed by a Malayan krait *(Bungarus candidus)* (Copyright DA Warrell)

10-20 minutes (edrophonium) for signs of improved neuromuscular transmission. Ptosis may disappear **(Fig 83)** and ventilatory capacity (peak flow, FEV-1 or maximum expiratory pressure) may improve.

4. Patients who respond convincingly can be maintained on neostigmine methylsulphate, 0.5-2.5 mg every 1-3 hours up to 10 mg/24 hours maximum for adults or 0.01-0.04 mg/kg every 2-4 hours for children by intramuscular, intravenous or subcutaneous injection together with atropine to block muscarinic side effects. Patients able to swallow tablets may be maintained on atropine 0.6 mg twice each day, neostigmine 15 mg four times each day or pyridostigmine 60 mg four times each day.

> *Anticholinesterase (e.g. "Tensilon") test*
> - *Baseline observations*
> - *Give atropine intravenously*
> - *Give anticholinesterase drug (e.g. neostigmine intramuscularly)*
> - *Observe effect*
> - *If positive, institute regular atropine and neostigmine*
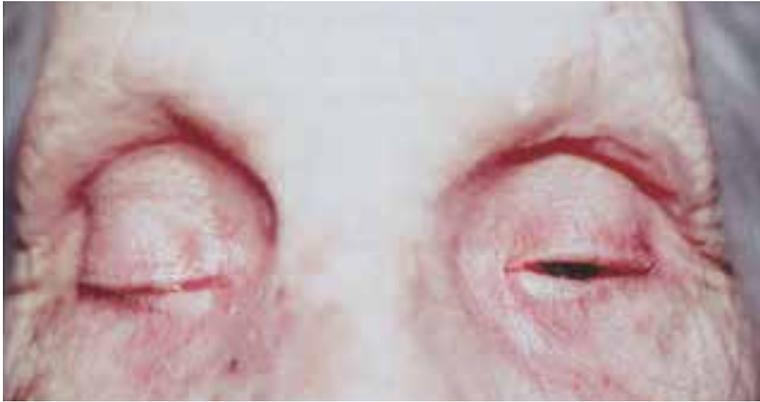
Figure 84: Ice test recovery of ptosis in the left eye after applying an ice pad that inhibits intrinsic cholinesterase in a patient with post-synaptic blockade of neuro-muscular transmission. (Delaney Y, Khooshabeh R, Benjamin L (2002). Acute severe ocular myasthenia in a 92-year-old woman. Eye (Lond);16(3):323-4).

The "ice pack test" as a possible alternative to the Tensilon test

(Golnik et al., 1999).

In patients with myasthenia gravis who have ptosis, cooling of the ptotoc (drooping) eyelid results in improvement in ptosis, due to inhibition of intrinsic cholinesterase (Golnik et al., 1999). This quick and simple test might obviate the need for the Tensilon test in predicting the effectiveness of anticholinesterase (neostigmine) treatment. However, it has not yet been evaluated in patients with neurotoxic envenoming. This study must be done!

Suggested method: in a patient with bilateral ptosis from neurotoxic snake-bite, the distance between the upper and lower lid margins of both eyes (palpebral fissures) is measured using a mm ruler. Digital pressure is applied to the frontalis muscle to avoid its influencing upper eyelid retraction. An ice-filled plastic glove or frozen ice pack is then gently applied to one eyelid for 2 minutes, after which the palpebral fissures of both eyes are immediately re-measured. A more-than-2mm difference in palpebral fissure between the cooled and control eyelids might be considered a positive result **(Fig 84)**.

6.9.4 Treatment of Hypotension and shock

This is usually the result of hypovolaemia [from loss of circulating volume into the swollen limb, as a result of generalized increase in capillary permeability (e.g. Russell's viper envenoming in Myanmar) or internal/external haemorrhage], venom-induced vasodilatation or direct myocardial effects with or without arrhythmias.

Postural (orthostatic) blood pressure measurement: hypovolaemia is best detected by measuring blood pressure with the patient lying supine, and repeating the measurement when the patient is propped up, ideally in a fully sitting position but, depending on their condition, at 45 degrees if 90 degrees is not tolerated **(Fig 85)**. A clinically significant fall in blood pressure during this procedure (orthostatic hypotension) is a fall in systolic blood pressure of 20 mm Hg or diastolic blood pressure of 10 mm Hg or more.

Passive leg raising test (fig. 85c): another way of assessing fluid responsiveness is to sit the patient in a 45 degrees head-up semi-recumbent position. Lower their upper body to the horizontal and passively raise their legs at 45 degrees

Figures 85 a, b: measurement of postural change in blood pressure as evidence of hypovolaemia: (a) supine; (b) sitting up (Copyright DA Warrell)

transfer of blood from the legs and abdominal compartments

= test for fluid responsiveness

Passive leg raising

Passive leg raising. The passive leg raising test consists in measuring the hemodynamic effects of a leg elevation up to 45°. A simple way to perform the postural maneuver is to transfer the patient from the semirecumbent posture to the passive leg raising position by using the automatic motion of the bed.

Figure 85. c: Passive leg raising test to guide fluid therapy
(see Marik et al., 2011)

up, increasing circulating volume by about 150-300 ml. The maximal effect of this "auto-infusion" occurs at 30-90 seconds, measured by clinical features of improved cardiac output (e.g. increase in pulse pressure and decrease in heart rate) (Boulain et al., 2002; Marik et al., 2014).

Treatment with crystalloids should be controlled by observation of the fluid status (jugular venous pressure, respiratory rates and crepitations, see Annex 6). Excessive volume replacement may cause pulmonary oedema when plasma extravasated in the bitten limb and elsewhere is reabsorbed into the circulation.

In patients with evidence of a generalized increase in capillary permeability, a selective vasoconstrictor such as dopamine

may be given by intravenous infusion, preferably into a central vein (starting dose 2.5-5 μ (micro) g/kg/minute).

> *Snakebite: causes of hypotension and shock*
> 1° Anaphylaxis
>   Vasodilatation
>   Cardiotoxicity
>   Hypovolaemia
> 2° Antivenom reaction
>   Respiratory failure
>   Acute pituitary adrenal insufficiency
>   Septicaemia

In victims of Russell's viper bites in Myanmar, India and Sri Lanka, acute pituitary adrenal insufficiency resulting

from haemorrhagic infarction of the anterior pituitary may contribute to shock, while neurological manifestations of hypoclycaemia, such as impaired consciousness, extensor posturing and other involuntary movements, may be presenting signs that respond to a test dose of intravenous 50% dextrose injection (Warrell, 2009) (Tun-Pe et al., 1987) (Fig 52a). Hydrocortisone, fluid and electrolyte replacement may needed acutely in these patients. In chronic cases, addition of thyroxin, oestrogen or testosterone may be needed (Antonypillai et al., 2011; Jeevagan et al., 2013).

6.9.5 Treatment of oliguria and acute kidney injury
(Sitprija and Boonpucknavig 1979; Chugh 1989)

> *Detection of acute kidney injury*
>
> - *Abrupt (within 48h) reduction in kidney function (Acute Kidney Injury Network criteria) Decreasing or no urine output (<0.5 mL/kg/h for more than 6 h) Increase in serum creatinine concentration [serum creatinine ≥26.5 µmol/L (≥0.3 mg/dL)] or increasing by ≥150 - 200% (x 1.5 - 2) compared to baseline [?urea]*
>
> - *Clinical "uraemia syndrome": nausea, vomiting, acidotic ("Kussmaul") breathing hiccups, fetor, drowsiness, confusion, coma, flapping tremor, muscle twitching, convulsions pericardial friction rub, signs of fluid overload*

In patients with any of the above features, the following should be monitored

- other signs of "uraemia syndrome"
- pulse rate
- blood pressure, lying and sitting, to detect postural hypotension (see 14 Treatment of hypotension and shock)
- respiratory rate
- temperature
- height of jugular venous pulse
- auscultation of lung bases for crepitations
- fluid balance chart and/or daily weight

6.9.5.1 Oliguric phase of renal failure
Most, but not all, patients with acute renal failure are oliguric, defined as a urine output of less than 400 ml/day or less than **30** ml/hour (children less than 0.5ml/kg bodyweight /hour). Conservative management may tide the patient over, avoiding the need for renal replacement therapy (dialysis).

If the patient has intravascular volume depletion, indicated by supine or postural hypotension, or empty neck veins, proceed as follows:

1. Establish intravenous access

2. Give a cautious fluid challenge: an adult patient can be given 250-500 ml of isotonic saline over one hour or, until the jugular venous pressure/ central venous pressure has risen to 8-10 cm above the sternal angle (with the patient propped up at 45°). The patient must be closely observed while this is being done. The fluid challenge must be stopped immediately if pulmonary oedema develops. If the urine output does not improve it is reasonable to perform a furosemide stress/challenge test (see below for details).

Note – in some patients it can be difficult to determine the height of the central venous pressure by clinical examination. Direct measurement of central venous (superior vena caval) pressure through a long catheter, preferably inserted at the antecubital fossa (see Annex 6), can be helpful in this circumstance. The catheter is connected to a saline manometer, the 0 point of which must be placed at the same level as the right atrium (that is, at the sternal angle when the patient is propped up at 45°). This measurement is reliable only if the level varies freely with respiration and the zero point is correctly positioned.

In a patient who is obviously volume-depleted, resuscitation should start immediately, and not be delayed until a central venous line has been inserted.

3. Insert a urethral catheter (full sterile precautions!) but in male patients, try using a condom catheter first.

4. Furosemide (frusemide) stress/challenge: once the patient has been given adequate fluid replacement 1-1.5 mg/kg of furosemide is injected slowly (4-5 mg/minute) intravenously and urine output is monitored for 2 h. A urine output of < 200 ml in hour (100 ml/hour) predicts progression of renal failure (Chawla et al., 2013). In this case, the patient is likely to progress to acute kidney injury and requires conservative management. Results of a small study done in Myanmar, showed a statistically significant lower requirement for renal replacement therapy (acute peritoneal dialysis) in patients given furosemide infusion compared to those given placebo (Kyaw San Lwin, personal communication, 2012).

5. Conservative management for acute kidney injury: if the urine output does not improve, despite these challenges, no further diuretics should be given and fluid intake should be restricted to a total of the previous day's output plus "insensible losses" (500-1000 ml/day). If possible, the patient should be referred to a renal unit. The diet should be bland, high in calories (1800/day), normal in protein (0.8-1 g/day), low in potassium (avoid fruit, fruit juices, energy drinks and potassium-containing drugs) and low in salt. Infections will cause tissue breakdown and increase urea levels. They should be prevented or treated promptly with non-nephrotoxic antibiotics (i.e. avoid aminoglycosides such as gentamicin).

6. Biochemical monitoring: In patients with acute kidney injury it is recommended that serum/plasma urea, creatinine and electrolytes be monitored daily if possible, until renal failure is resolving. Serum potassium, urea, creatinine and, if possible, pH, bicarbonate, calcium and phosphate should be measured. If this is not possible the electrocardiogram (ECG) should be examined for evidence of hyperkalaemia, especially following bites by sea snakes, or Sri Lankan, Indian, Bangladeshi or Myanmar Russell's vipers or if the patient is passing dark brown urine, suggestive of rhabdomyolysis or intravascular haemolysis.

7. Detection and management of hyperkalaemia (UK Renal Association, 2014)

•   ECG evidence of hyperkalaemia: tall peaked T waves, prolonged P-R interval, absent P waves, wide QRS complexes. Emergency treatments, which will control hyperkalaemia for 3-6 hours

only, should be given if serum potassium >6.5 mmol/l or ECG changes

- Calcium Gluconate 10%: 0.5 ml/kg 10 ml slow intravenous injection over 2-5 minutes if haemodynamically unstable, or over 15-20min if stable (onset of action 3 minutes). Check for normalisation of ECG. Repeat if necessary.

- β2 agonist aerosol by inhaler (e.g. salbutamol nebulisation 5mg q 1-2h - onset of action 30 minutes - up to 10-20 mg.

- Give 50 ml of 50% dextrose with 10 units of soluble insulin intravenously (onset of action 15 minutes)

- Sodium Bicarbonate 8.4% 1 ml/kg IV slow over 5 minutes

  Followed by a low potassium diet.

8. Management of severe acidosis
   If the patient is hypotensive and profoundly acidotic (deep sighing "Kussmaul" respirations, very low plasma bicarbonate concentration or very low pH - <7.10),Sodium bicarbonate should be given. Based on volume of distribution of bicarbonate which is 40% of body weight, bicarbonate deficit can be calculated. Usually 2-3 ampoules (40 ml. of 8.4% sodium bicarbonate equivalent to 1 mmol/ml) in 5% dextrose water, or half of the calculated deficit can be replaced in 3-4 hours. Severe acidosis in snakebite is usually associated with acute renal failure. Volume expansion by sodium bicarbonate can cause fluid overload. Therefore, if there is no clinical improvement dialysis is required. Caution: Intravenous bicarbonate may precipitate profound hypocalcaemia and fitting, especially in patients with rhabdomyolysis.

9. Renal replacement therapy Dialysis **(Fig 86)**

Figures 86: Dialysis for treatment of acute kidney injury: (a) Peritoneal dialysis in a township hospital in Myanmar; (b) Haemodialysis in a district hospital in India (Copyright DA Warrell)

Transfer the patient who has developed the following indications to a health facility where they can receive renal replacement therapy.

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Indications for dialysis

a) *clinical uraemia (encephalopathy, pericarditis etc.)*
b) *fluid overload not responding to diuretics*
c) *plasma potassium concentration > 7 mmol/l (or hyperkalaemic ECG changes)*
d) *symptomatic acidosis*
e) *blood biochemistry - one or more of the following*
   Creatinine > 4 mg/ dl (354 micromol/l)
   Urea > 130 mg/ dl (46 mmol/l)
Caution: biochemical criteria alone is not sufficient to start dialysis

</div>

The choice between peritoneal dialysis and haemodialysis depends on availability. Haemodialysis is referred for management of hyperkalaemia, fluid overload and hypercatabolic patients. Each dialysis session should be decided based on daily clinical assessment (fluid status, urine output and biochemical data). In patients who are hypotensive, slow efficiency daily dialysis (SLEDD) or continuous renal replacement therapy (CRRT [dialysis over 24 hours]) is preferred. However, these are available only in well-equipped ICUs. In patients with acute kidney injury, dialysis may be required for up to 3 weeks. After that time, the kidney should be biopsied to establish the diagnosis and indicate prognosis.

6.9.5.2 Bleeding/ blood clotting disturbances in patients with acute kidney injury

Most patients with acute kidney injury associated with snakebite will have been envenomed by Viperidae, notably *Daboia, Hypnale* and *Trimeresurus* species. The only major exception is sea snakebites. Viper-bite victims may have venom-induced bleeding and blood coagulation disturbances although in most *Daboia* cases these will have been corrected by antivenom before acute kidney injury has developed. However, patients who still have active bleeding/clotting disturbances require fresh frozen plasma and platelet infusions to cover insertion of dialysis catheters and dialysis.

In patients with snakebite related thrombotic microangiopathy with acute kidney injury, the role of plasmapheresis using cryosupernatant (by analogy with thrombotic thrombocytopenic purpura/ haemolytic uraemic syndrome) is not clear and has no sound theoretical basis.

6.9.5.3 Prevention of renal damage in patients with myoglobinuria or haemoglobinuria

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To minimise the risk of renal damage from excreted myoglobin and/or haemoglobin:
• *correct hypovolaemia (see above) and maintain urine output of 200-300 ml/hour.*
• *correct severe acidosis with bicarbonate*
• *promote alkalinise diuresis (urine pH > 6.5)*
• *continue these measures until there is evidence that of rhabdomyolysis is decreasing (CK level <5000 U).*

</div>

6.9.5.4 Diuretic phase of renal failure

Some patients will develop polyuria that is as important and as life-threatening as the oliguric phase. Urine output increases to 5-10 litres/24 hours following the period of anuria. The patient may become volume depleted so that salt and water must be carefully replaced.

Hypokalaemia may develop, in which case a diet rich in potassium (fruit and fruit juices) is recommended.

6.9.5.5 Renal recovery phase

The diuretic phase may last for months after Russell's viper bite.

6.9.5.6 Persisting renal dysfunction

In Myanmar, persistent tubular degenerative changes were observed in Russell's viper bite victims who showed continuing albuminuria, hypertension and nocturia for up to 11 months after the bite, despite apparent recovery in renal function. In India, 20-25% of patients referred to renal units with acute kidney injury following Russell's viper bite suffered oliguria for more than 4 weeks suggesting the possibility of bilateral renal cortical necrosis and the need for referral to a nephrologist. Patients with patchy cortical necrosis show delayed and partial recovery of renal function but those with diffuse cortical necrosis require regular maintenance dialysis and eventual renal transplantation.

6.10 Haemostatic disturbances

Bleeding and clotting disturbances usually respond satisfactorily to treatment with specific antivenom, but the dose may need to be repeated several times, at six hourly intervals, before blood coagulability (assessed by the 20WBCT) is finally and permanently restored.

In exceptional circumstances, such as persistent severe bleeding or imminent urgent surgery, once specific antivenom has been given to neutralize venom procoagulants and other antihaemostatic toxins, restoration of coagulability and platelet function can be accelerated by giving fresh frozen plasma, cryoprecipitate (fibrinogen, factor VIII), fresh whole blood or platelet concentrates.

> *Heparin is ineffective against venom-induced thrombin and may cause bleeding on its own account. It should never be used in cases of snakebite*.

Antifibrinolytic agents are not effective and should not be used in victims of snakebite.

6.10.1 Dangers of venipuncture in patients with haemostatic abnormalities

In patients with incoagulable blood, any injection (subcutaneous, intramuscular) and, particularly venipuncture, carries a risk of persistent bleeding and haematoma formation.

Arterial puncture is contraindicated in such patients.

Repeated venipuncture can be avoided by using an indwelling cannula and three-way tap system. When blood coagulability has been restored, the dead space should be filled with heparinised saline, but **beware!** If this is not flushed out before blood sampling, misleading results will be obtained in clotting tests, including the 20WBCT.

In patients with coagulopathy, sites of venous access and placement of intravenous cannulae or catheters should be chosen where haemostasis by external pressure is most likely to be effective, eg the antecubital fossa. If possible, avoid

jugular, subclavian and femoral vein puncture. A pressure pad must be applied at the site of any venipuncture.

6.11 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 ischaemia.

6.11.1 Wound management

Blisters/bullae/"blebs" may be large and tense but they should not be de-roofed and require aspiration only if they threaten to rupture. Abscesses should be aspirated with a needle and the pus cultured (see below infection). Once frank skin necrosis is detected (demarcated, hypo/hyperpigmented areas with an odour of putrefaction), surgical débridement is indicated to remove the risk of anaerobic sepsis. During debridement, all unhealthy tissue should be excised till viable tissue margins are achieved. However, bruised muscle may appear dead but should not be excised as muscle fibres may regenerate. Amputation may be indicated in case of gangrene of toes or limbs.

6.11.2 Bacterial infections

The oral flora of wild snakes includes aerobic and anaerobic bacteria, especially the faecal gram-negative rods as their prey may defecate while being ingested. Oral and venom cultures from American snakes yielded Enterobacteriaceae including *Morganella* spp., *Escherichia coli*, Group D streptococci, *Aeromonas* spp., and anaerobes such as *Clostridium* spp.

In Asia, local bite wound infections may be due to single or multiple bacteria including gram-positive aerobes *(Staph. aureus*, coagulase-negative *Staphylococcus*

and *Enterococcus)*, aerobic gram-negative bacterial *(E. coli, Klebsiella, Pseudomonas, Enterobacter, Morganella morganii)*, anaerobic bacteria *(Peptostreptococcus* and *Bacteroides fragilis)* (Theakston et al., 1990; Chena et al., 2011; Garg et al., 2009). Infection at the time of the bite with organisms from the snake's venom and buccal cavity is a problem with some species such as the Malayan pit viper *(Calloselasma rhodostoma)* and severe and fatal tetanus has been reported. However, prophylactic antibiotics were not effective in a controlled study in Brazil (Jorge et al., 2004). Interference with the wound (incisions made with an unsterilised razor blade/knife etc.) creates a risk of secondary bacterial infection and justifies the use of immediate broad spectrum antibiotics (e.g. gentamicin with benzyl penicillin, amoxycillin or a cephalosporin plus a single dose only of gentamicin – to avoid the risk of kidney injury- plus metronidazole) and tetanus prophylaxis. Other possible antibiotics include amoxycillin/caluvulenic acid, piperacillin/tazobactam, ciprofloxacin and third generation cephalosporin (Mao et al., 2016). Mao YC, Liu PY, Hung DZ, Lai WC, Huang ST, Hung YM, Yang CC. Bacteriology of Naja atra Snakebite Wound and Its Implications for Antibiotic Therapy. Am J Trop Med Hyg. 2016 May 4;94(5):1129-35Later infections in patients treated in hospital include nosocomial pneumonias and urinary tract infections.

6.11.3 Compartmental syndromes and fasciotomy

(Fig 83) (Matsen 1980; Mars and Hadley 1998; Mars et al., 1991)

The appearance of an immobile, tensely-swollen, cold and apparently pulseless snake-bitten limb may suggest to surgeons the possibility of increased intracompartmental pressure, especially if the digital pulp spaces or the anterior tibial compartment are involved. Swelling

Figure 87: Results of unnecessary fasciotomies in snakebite victims in Thailand: (a) profuse bleeding in a patient with mild local envenoming but severe coagulopathy following bites by green pit vipers *(Trimeresurus T. albolabris)*; (b) Residual skin loss and exposure of tendons following fasciotomy for mild local envenoming in a patient bitten by a green pit viper *(Trimeresurus T. albolabris)* (Copyright the late Sornchai Looareesuwan); (c) Persistent bleeding for 10 days, resulting in haemorrhagic shock despite transfusion of 20 unites of blood, in a victim of Malayan pit viper bite in whom fasciotomy was performed before adequate antivenom treatment had been given to correct the coagulopathy (Copyright DA Warrell)

of envenomed muscle within such tight fascial compartments could result in an increase in tissue pressure above the venous pressure, resulting in ischaemia. However, the classical signs of an intracompartmental pressure syndrome may be difficult to assess in snakebite victims and many unnecessary, dangerous and debilitating fasciotomies are performed, especially where surgeons rather than physicians have the primary responsibility for managing snakebite cases (**Fig 87**). Fasciotomy is generally falling out of favour for the treatment of snake-bitten limbs (Cumpston, 2011).

> **Clinical features of a compartmental syndrome**
> - Disproportionately severe pain
> - Weakness of intracompartmental muscles
> - Pain on passive stretching of intracompartmental muscles
> - Hypoaesthesia of areas of skin supplied by nerves running through the compartment
> - Obvious tenseness of the compartment on palpation

Detection of arterial pulses by palpation or doppler ultrasound probes, does not exclude intracompartmental ischaemia. The most reliable test is to measure intracompartmental pressure directly through a cannula introduced into the compartment and connected to a pressure transducer or manometer (Annex 5). In orthopaedic practice, intracompartmental pressures exceeding 40 mmHg (less in children) may carry a risk of ischaemic

necrosis (eg Volkmann's ischaemia or anterior tibial compartment syndrome). However, envenomed muscle may not be saved by fasciotomy. Animal studies have suggested that muscle sufficiently envenomed and swollen to cause intracompartmental syndromes, may already be irreversibly damaged by the direct effects of the venom (Garfin et al., 1984). In any case, fasciotomy should not be contemplated until haemostatic abnormalities have been corrected, otherwise the patient may bleed to death (Fig 66c).

Among 105 cases of rattle snakebites in USA in which fasciotomy was either just discussed or actually carried out, the 28 patients given surgery showed no advantage in morbidity, but spent on average 2 extra days in hospital (Darracq et al., 2015).

In green pit viper bite (genus *Trimeresurus*) victims, antivenom not only reversed coagulopathy, but also reducing severe limb oedema (Rojnuckarin et al., 2006). However, corticosteroids are not effective in ameliorating local effects of envenoming and, since they carry the risk of side-effects, they should not be used (Reid et al., 1963; Nuchprayoon et al., 2008).

Early treatment with antivenom remains the best way of preventing irreversible muscle damage.

Criteria for fasciotomy in snake-bitten limbs
haemostatic abnormalities have been corrected (antivenom with or without clotting factors)
- clinical evidence of an intracompartmental syndrome
- intracompartmental pressure >40 mmHg (in adults)

6.12 Rehabilitation
In patients with severe local envenoming, the limb should be maintained in a functional position. For example, in the leg, equinus deformity of the ankle should be prevented by application of a back slab and avoiding the pressure of heavy bed clothes.

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, arthrodeses, contractures, tissue loss, especially dermonecrosis and chronic ulceration requiring skin grafting, and gangrene requiring débridement 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 rehabilitating activities. Conventional physiotherapy may accelerate functional rec overy of the bitten limb.

6.13 Discharge assessment
Before the patient leaves hospital, discuss the following topics with them and their accompanying family members.

- Implications of having had a snakebite: most patients can be assured of a full recovery in time.

- Rehabilitation exercises: encourage them to continue until normal function is restored to the bitten limb.

- Follow-up appointment: encourage the patient to return after an interval of 1-2 weeks to check on their progress and to allow further reassurance.

- Late serum sickness-type reactions:

Consists of urgent irrigating the affected eyes and other mucous membranes with liberal quantities of water, saline, Ringer's lactate, milk or any other available bland liquid.

warn them of the symptoms and reassure them that this complication of antivenom can be treated.

- Reducing the risk of further bites: provide advice, ideally in the form of a leaflet, explaining the principles of snakebite prevention (see Section 1 above), to be shared with their families and neighbours.

6.14 Management of cobra spit ophthalmia
(Chu et al., 2010)

First aid: consists of urgent irrigating the affected eyes and other mucous membranes with liberal quantities of water, saline, Ringer's lactate, milk or any other available bland liquid (even urine has been used). No medicines, oils or traditional ointments should be put in the eye(s) and there should be no delay in going to hospital. The spitting cobra should not be pursued or killed as this may result in further multiple spits.

Medical treatment consists of:

1. Further urgent decontamination is achieved by copious irrigation

2. Pain is intense. Topical vasoconstrictors with weak mydriatic activity [e.g. instillation of 0.5% epinephrine (adrenaline) drops] relieve pain and inflammation. However, topical local anaesthetics (eg 0.4% oxybuprocaine hydrochloride ("Novesin"), 4% lidocaine hydrochloride or tetracaine hydrochloride ("Decicaine") are more

effective but, by rendering the eye temporarily insensitive, may allow trauma to the cornea. They should be applied only once and the eye must be protected until sensation returns. By overcoming blepharospasm, these drugs may allow more efficient irrigation.

3. Corneal abrasions must be excluded by fluorescein staining and/or slit lamp examination

4. Endophthalmitis or blinding corneal opacities must be prevented by application of prophylactic topical antibiotics (eg tetracycline, chloramphenicol, 0.5% framycetin "Soframycin", ciprofloxacin, penicillin-streptomycin ointment, polymixin B sulphate, gatifloxacin, and moxifloxacin).

5. Posterior synechiae, ciliary spasm and discomfort can be prevented with topical cycloplegics (e.g. 2% atropine, scopolamine or homatropine). However, beware, these mydriatics may precipitate acute glaucoma.

6. Allergic kerato-conjunctivitis may develop in those previously sensitised by spitting or other habitual exposure to snake venoms. It is treated with antihistamines.

Instillation of diluted antivenom causes irritation and is of no benefit since any residual venom in the conjunctival sac is removed by liberal irrigation.

Topical corticosteroids are contraindicated because of the risk of *Herpes simplex* keratitis.

Some ophthalmologists recommend the use of a dressing pad to close the eye.

6.15 Management of snakebites at different levels of the health service

(refer to sections above for details of treatments etc.)

All levels of the health service can contribute to the management of patients with suspected snakebite. Since the treatment of severe envenoming is a medical emergency that may require a range of medical skills, equipment, antivenom and other medicines, referral should be to the highest level of care that is readily available. However, in the rural areas where snakebites are most frequent, transfer to a hospital may not be feasible within the reasonable time frame of a few hours. In that case, a lower level of health facility must cope with the emergency as suggested below. Ideally, a specialist team and a defined area or ward should be allocated for the management of snakebite victims. **Training of doctors, nurses, dispensers, health assistants and paramedics in all the skills required for diagnosis (including snake identification) and early management of snakebite patients (including indications for and practicalities of administering antivenom) is essential at every level.**

A. At community or village level

1. *Assess:* check history of snakebite and look for obvious evidence of a bite (fang puncture marks, swelling of the bitten part).

2. *Reassure*

3. *First-aid:* immobilize the whole patient as far as possible by laying him/her down in a relaxed but safe position (e.g. recovery position), immobilize the bitten limb with a splint and apply pressure-pad.

4. *Transport:* Arrange (by emergency contact number) transport of the patient to medical care as quickly, safely and passively as possible by vehicle, boat, bicycle, motorbike, stretcher etc. Ideally the patient should lie in the recovery position (prone, on the left side) with his/her airway protected to minimise the risk of shock and inhalation of vomit.

5. *Snake:* if the snake responsible has already been caught or killed take it (safely in a bag or container) with the patient or take images on a mobile 'phone , but ensure safety by avoiding direct contact.

6. *Traditional treatment:* discourage time-wasting and potentially dangerous traditional treatments such as tight ligatures (tourniquets), incisions, suction and application of herbs, ice, chemicals, "snakestones" etc.

B. At the Rural Clinic, Dispensary, Health Post, or Primary Health Centre

1. **Assess for signs of local and systemic envenoming:** carry out a simple medical assessment including history and simple physical examination – local swelling, painful tender enlarged local lymph glands, persistent bleeding from the bite wound, blood pressure, pulse rate, bleeding (gums, nose, vomit, stool or urine), level of consciousness, drooping eyelids (ptosis) and other signs of paralysis. Monitor these signs hourly.

2. **Check:** 20 minute whole blood clotting test (20WBCT), urine examination (appearance, sticks testing for blood etc.). Identify the snake or a photo of it (if brought).

3. **Analgesia:** give analgesia by mouth if required: paracetamol (acetaminophen) (adult dose 500 mg to 1 g maximum 4 g in 24 hours; children 10-15 mg/

kg maximum 100mg/kg/day) or codeine phosphate (adult dose 30-60 mg maximum 240 mg in 24 hours; children more than 2 years old, 0.5 mg/kg, maximum 2 mg/kg/day) can be given every 4-6 hours by mouth as required (not aspirin or non-steroidal anti-inflammatory drugs which can cause bleeding).

4. **Antivenom:** if the patient fulfils criteria for antivenom treatment and if the necessary skills, equipment, antivenom, adrenaline and other necessary drugs are available, give antivenom. These skills include ability to diagnose local and systemic envenoming, set up intravenous infusion or intravenous injection, identify the early signs of anaphylaxis and treat it with intramuscular adrenaline. Reasess for repeated dose(s) of antivenom. If no antivenom is available, transfer to a hospital.

5. **If the patient is shocked/ hypotensive:** give cautious intravenous fluid challenge (adult 250-500 ml of 0.9% saline) to correct hypovolaemic shock.

6. **If the patient has evidence of respiratory paralysis:** give oxygen by mask, consider atropine and neostigmine, and transfer to hospital. It is assumed that assisted ventilation other than by a tight-fitting face mask connected to an anaesthetic (Ambu) bag will not be possible at this level.

7. If the patient is oliguric: initiate conservative management.

8. The bite wound: if necrotic, tampered with (incisions etc.) or obviously septic, give antibiotics and tetanus prophylaxis.

9. Assess the need and feasibility of transporting the patient to a higher level of the health service (see A above) especially in case of:

a. Substantial bleeding, 20WBCT still positive (non-clotting) 6 hours after initial antivenom dose
b. Progressive paralysis (muscle weakness) or respiratory difficulty
c. Reduced urine output
d. Anaphylaxis –unresponsive to adrenaline
e. Shock/hypotension- unresponsive to fluids
f. Severe local necrosis or signs suggestive of compartment syndrome

10. Discourage the use of ineffective and potentially harmful drugs (e.g. corticosteroids, antihistamines, and heparin).

C. At the District Hospital
Proceed as in B above plus:

1. Assessment: carry out a more detailed clinical and laboratory assessment including biochemical and haematological measurements, ECG or radiography, as indicated.

2. Antivenom: if no antivenom is available, transfer to a hospital that has antivenom or treat conservatively; this may require transfusion of blood or fresh frozen plasma (see above).

3. Analgesia: (see B above) and, if required, consider stronger parenteral opioid drugs as required all with great caution (e.g. subcutaneous, intramuscular or even intravenous pethidine, initial adult dose 50-100 mg; children 1-1.5 mg/kg; or morphine, initial adult dose 5-10 mg; children 0.03-0.05 mg/kg,).

4. If the patient has evidence of local necrosis (gangrene): give tetanus toxoid booster, antibiotics and do surgical débridement of dead tissue.

5. If the patient has evidence of bulbar or respiratory paralysis: insert endotracheal tube, laryngeal mask airway or i-gel aiway. If there is evidence of respiratory failure, assist ventilation manually by anaesthetic (Ambu) bag or mechanical ventilator.

6. If the patient has evidence of acute kidney injury: treat with peritoneal dialysis. If this is not available, transfer to a specialized hospital.

7. If the patient is bleeding severely or is already seriously anaemic: cross-match and transfuse.

8. Rehabilitation: encourage exercising of bitten limb.

D. At the Referral (Specialized) Hospital
Proceed as in B and C above plus:

1. More advanced surgical management of local necrosis (e.g. split skin grafting).

2. More advanced investigations including bacterial cultures and imaging (CT scans) as indicated.

3. If the patient has evidence of acute renal failure peritoneal or haemodialysis or haemofiltration.

4. Implement rehabilitation by physiotherapists.

Conclusions: Strengthening of health system in managing snakebite

To reduce complications and deathsfrom snakebites, health systems need to be improved at various levels. The government must develop a policy for snakebite, making it a notifiable disease, developing a snakebite programme that includes standard treatment guidelines, training of health personnel and ensures an adequate supply, distribution and storage of good quality antivenom. Strengthening of public health systems

Figure 88 Health system strengthening

GOVERNMENT

Snakebite policy
1. Making snakebite reportable
2. Developing a snakebite programme
3. Standard treatment guidelines
4. Ensuring production and supply of adequate quantity and quality of antivenom
5. Training of health personnel at all levels
6. Research

HEALTH SYSTEM

TERTIARY REFERRAL HOSPITAL
Infrastructure- dialysis and ICU, surgical set up, coagulation lab
Personnel- physician, surgeon, nephrologist, anaesthetist

DISTRICT HOSPITAL
Infrastructure- blood bank, ICU, surgical set up
Personnel- physician, surgeon

PRIMARY HEALTH CENTRE
Infrastructure- basic emergency care and resuscitation, airway and Ambu bag, antivenom administration
Personnel- doctor, nurse

VILLAGE
Infrastructure- ambulance Transport
Personnel- health aid, health worker, paramedic

Strengthening of health system
1. Training of all levels of health system
2. Ensuring infrastructure at each level
3. Antivenom availability
4. Epidemiological monitoring of snak-bite, deaths, complications and antivenom reactions
5. Community education

requires an appropriate infrastructure of facilities and drugs at each level, training of personnel, epidemiological monitoring and community education.

6.16 Summary of current evidence for treatment of snakebite envenoming

Currently proposed treatment and their likely benefit

1. Antivenom:
Benefits: recommended for treatment of bleeding/blood clotting disturbances, shock/hypotension, post-synaptic neurotoxicity (cobras, death adders, rhabdomyolysis (sea snakes). Optimal initial dosage largely unknown

Risks: early anaphylactic and pyrogenic reactions, late serum sickness-like reactions

2. Adrenaline (epinephrine)
Benefits: recommended for prevention and treatment of early antivenom reactions

Risks: cerebral haemorrhage in elderly patients with underlying cerebrovascular disease

3. Blood clotting factors
Benefits: recommended to speed up restoration of normal haemostasis in patients already treated with antivenom and for conservative treatment of bleeding/blood clotting disturbances, when antivenom is not available

Risks: fatalities reported (reactions and possibly thromboses)

4. Antihistamines (H1 blockers) and corticosteroids
Benefits: late serum sickness-type reactions

5. Antibiotics
Benefits: treating secondary and primary bite wound infections, prophylaxis in necrotic wounds or those that have been tampered with using non-sterile instruments

6. Renal replacement therapy and assisted ventilation:
Benefits: life-saving in patients with acute kidney injury and respiratory failure

7. Anticolinesterase (neostigmine) with atropine
Benefits: can rapidly improve neuro muscular transmission in some patients with post-synaptic neurotoxicity (cobras, Australasian death adders)

Risks: muscarinic side-effects, cholinergic crisis

8. Traditional first-aid methods
(incisions, tourniquets, suction, tattooing, topical herbal remedies, black "snake-stone", electric shocks etc.)

Risks: harmful and useless – should never be used

9. First-aid pressure pad immobilization, rapid transport to medical care
Benefits: reduces venom spread and risk of early death

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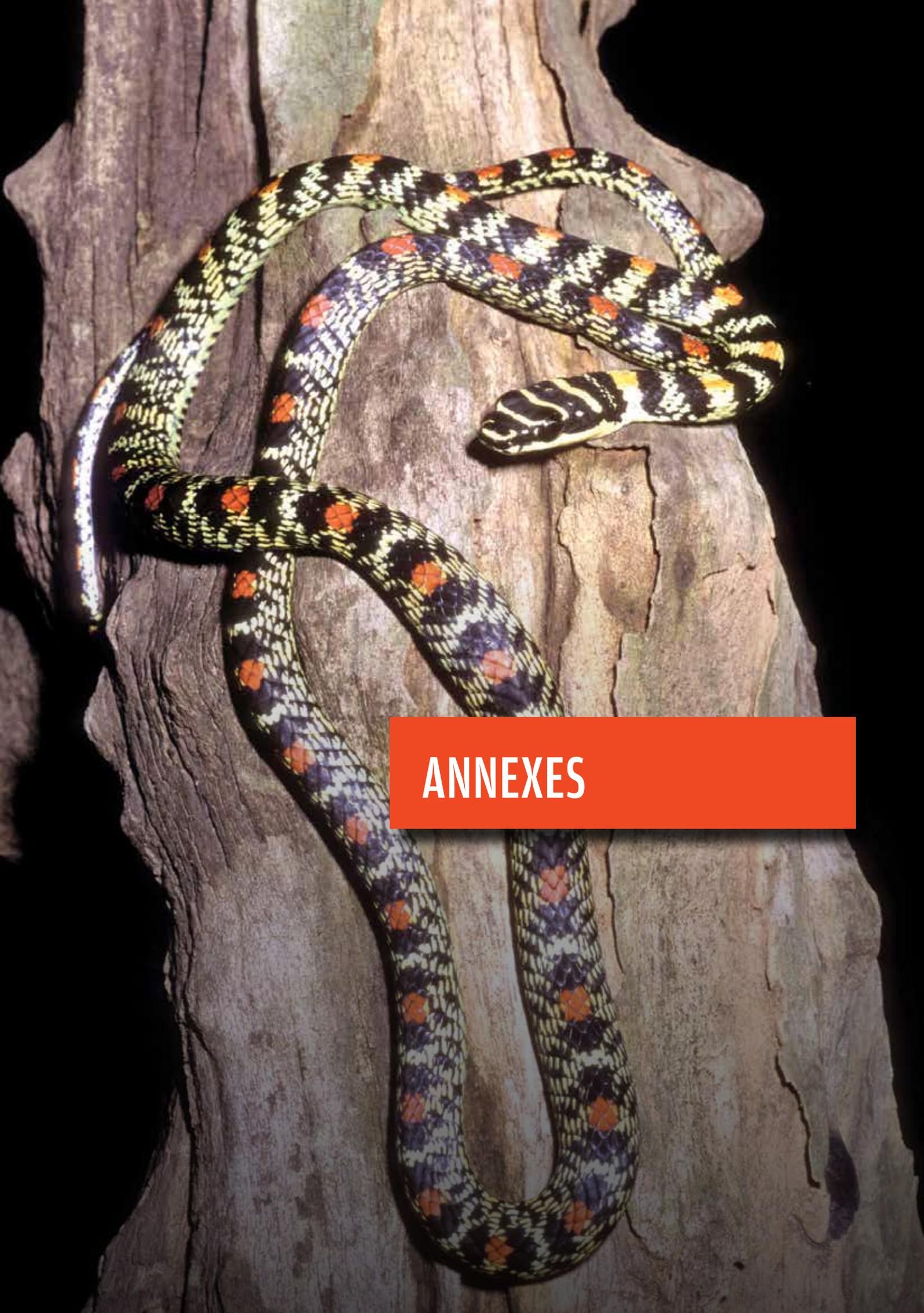
ANNEXES

Algorithm: Diagnosis of snakebite cases based on clinical data as a basis for antivenom treatment

Algorithms should be created based on local data so that they can be relevant for local use. The example below is intended for use in Sri Lanka (Ariaratnam et al., 2009).
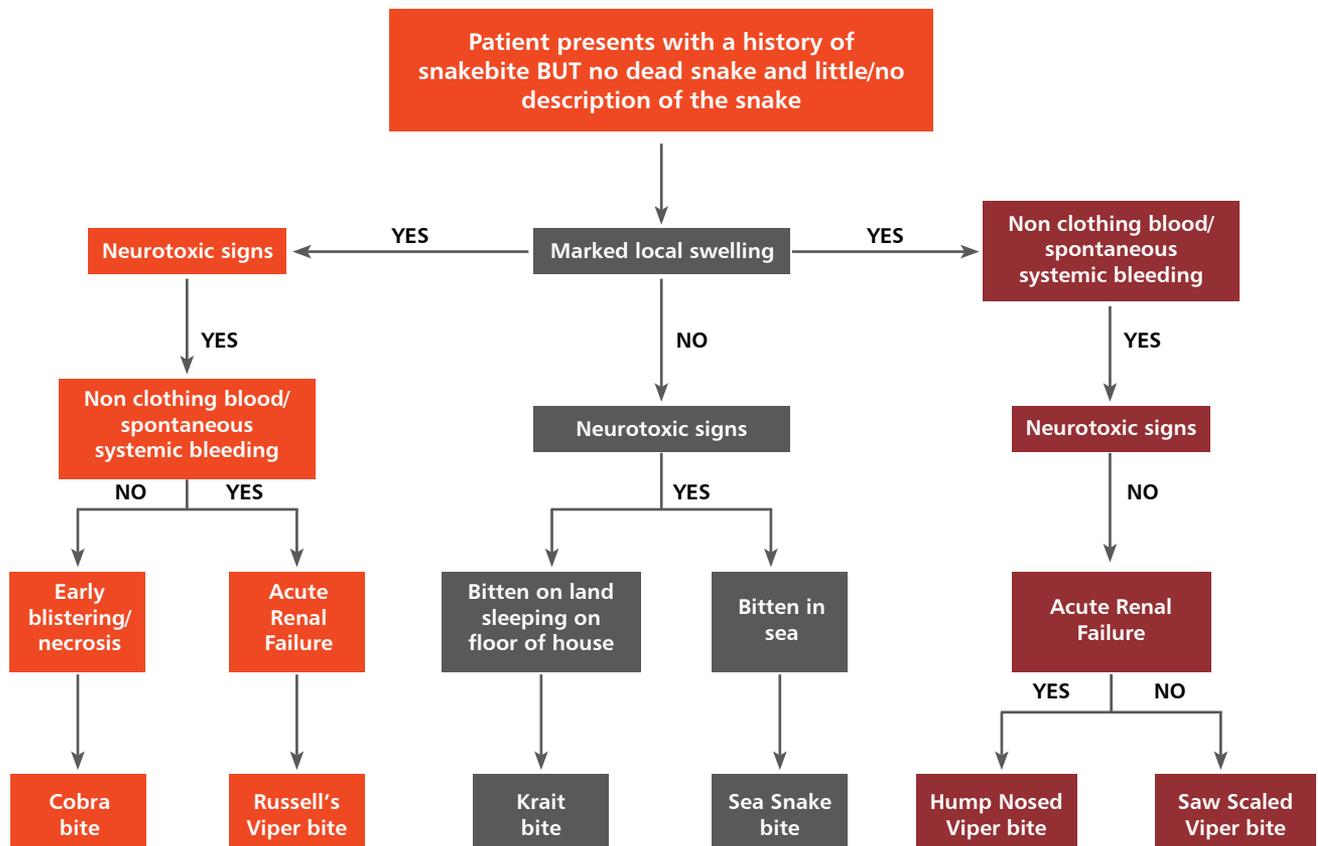
Figure 89a. Algorithm for diagnosis of the snake responsible for a bite in Sri Lanka (Ariaratnam et al., 2009)

Algorithm: Differentiating major Asian snake species by clinical syndrome

These should be created based on local data so that they can be relevant for local use. The example below is intended for use in Sri Lanka (Ariaratnam et al., 2009).

VIPERIDAE

Daboia russelii

Echis carinatus

Trimeresurus trigonocephalus

Hypnale hypnale
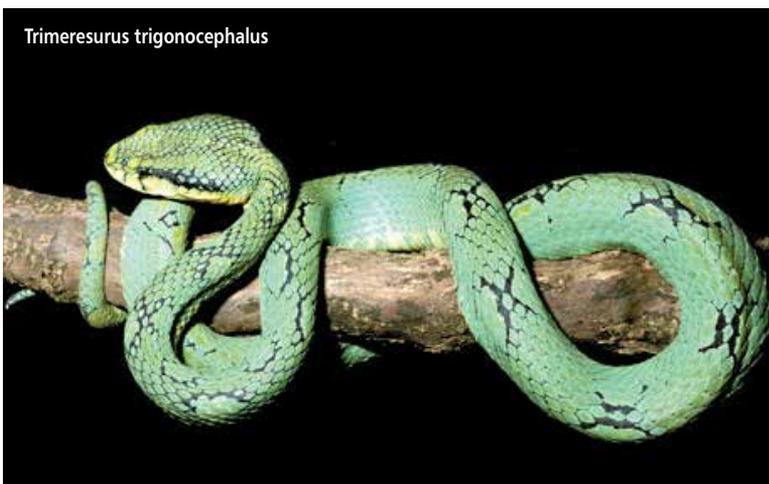
ELAPIDAE

ELAPIDAE

Figure 89b: Syndromic approach to snakebite management in Sri Lanka: venomous snakes of Sri Lanka (Ariaratnam et al., 2009)

Clinical spectrum of syndromes of snakebites, Sri Lanka

Species	No.	Local effects (%)	Coagulopathy (%)	Neurotoxicity (%)	Renal toxicity (%)	Myotoxicity (%)
Russell's viper	319	96	76	59	19	24
Hump-nosed viper	302	91	39	-	10	-
Common krait	88	9	-	95	-	-
Cobra	45	91	-	80	-	-

Sensitivity and specificity of clinical syndromes as a screening test in identifying snakebites, Sri Lanka

Snake	Sensitivity (%)	Specificity (%)
Russell's viper	14	100
Cobra	78	96
Common krait	66	100
Hump-nosed viper	10	97

Antivenoms for treatment of bites by South-East Asian snakes

Antivenoms for treatment of bites by South-East Asian snakes (listed by country of manufacture). Recommended doses are those quoted by the manufacturers. For recommended initial doses of some of these antivenoms, according to the species of snake responsible for envenoming, based on clinical experience, are given in Table 1

A. Australia

Bio CSL Commonwealth Serum
Laboratories
45 Poplar Rd
Parkville, Victoria 3052, Australia
Phone: +61 3 9389 1911
Fax: +61 3 9389 1434
customerservice@csl.com.au
Phone: +61 39389 1204
Black snake (Pseudechis spp.), brown
snake (Pseudonaja spp.), death adder
(Acanthophis spp.), polyvalent, sea snake
antivenoms.
Recommended initial dose: 1-3 vials

B. China

Shanghai Institute of Biological Products,
Ministry of Health, 1262 Yan An Road (W),
Shanghai 200052, China
Tel + 8621-62803189;
Fax +8621-62801807.
Contact: Ms Minzhi Lu, Manager,
International Affairs & Trade Department
(Tel +8621-62805234)
(liquid antivenoms, 10-15 ml/ampoule)

"Agkistrodon" acutus antivenin (purified)
(= *Deinagkistrodon acutus*, found in North
Viet Nam).
Recommended initial dose: 8000 IU (= 4
ampoules)

"Agkistrodon halys" (= *Gloydius
brevicaudus*) antivenin (purified) (said to be
active against venoms of *Protobothrops/
Trimeresurus mucrosquamatus* and
Viridovipera/Trimeresurus stejnegeri).
Recommended initial dose: 6000 IU
(= 1 ampoule)

Bungarus multicinctus antivenin (purified)
(said to be effective against the venom of
Ophiophagus hannah).
Recommended initial dose; for bites by
both species 10 000 IU (= 1.25 ampoules)

"Naja naja" antivenom (purified)
(= *Naja atra*).
Recommended initial dose: 2000 IU
(= 2 ampoules)

C. India

Polyvalent antivenoms raised in equines against venoms of *Bungarus caeruleus, Naja naja, Daboia russelii, Echis carinatus* collected in Mamallapuram, Tamil Nadu but more recently also from other areas (to be confirmed). Antivenoms are lyophilised (reconstituted to 10ml per vial) or liquid.

Recommended initial dosage for all these antivenoms is:
Bungarus caeruleus: 10-20 vials
Naja naja: 10-20 vials
Daboia/Vipera russelli: 10 vials
Echis carinatus: 5 vials (10 vials for *E. c. sochureki* in N and NW India)

Note: venoms of other species (including hump-nosed pit-viper *Hypnale hypnale* – SW India and Sri Lanka, and all other pit-vipers) are not covered by Indian polyvalent antivenoms, nor are venoms by *Naja, Daboia* or *Echis* species, sea snakes or other species occurring outside India.

Annual production estimates of number of 10 ml vials of polyvalent antivenom ("ASV") (2015-16) are given in parentheses.

Public sector

1. Central Research Institute, Kasauli 173204 Kasauli (H.P.)
   Tel:+91-1-792-72114
   Fax:+91-1-792-72049
   (reduced/stopped production)]

2. Haffkine Institute
   Haffkine Bio-Pharmaceutical Acharya Donde Marg,
   Parel -400012 Mumbai
   Tel:+91-22-412-9320,
   Fax:+91-22-416-8578
   (production 2015-16: 400 000 vials)
   (supplying Maharashtra State)

3. Bengal Chemicals and Pharmaceuticals Ltd,
   6 Ganesh Chunder Avenue 700013 Kolkota
   Tel: +91-33-2237-1525
   Fax:+91-33-2225-7697
   (currently stopped production)

4. King Institute, Chennai (in 2016, announced resumption of production after a 15 year break)

Private sector

1. Serum Institute of India
   212/2, Hadapsar
   Off Soli Poonawalla Road 411028 Pune
   Tel:+91-20-26993900
   Fax:+91-20-26993921
   (reduced/stopped production)

2. VINS Bioproducts Ltd
   806,Essjay House,
   Road Nr 3, Banjara Hills 500034
   Hyderabad Tel:+91-40-23354550,
   Fax:+91-40-23350410 Cobra Antivenin, Russell's Antivenin, Anti snake Venom Polyvalent
   (production 2015-16: 1 000 000 vials)

3. Biological E. (Evans) Limited 18/1 and 3, Azamabad 500020 Hyderabad
   Tel:+91-40-30213999,
   Fax:+91-40-27615309
   E-mail info@biologicale.co.in
   (production 2015-16: 500 000 vials of liquid antivenom only)

4. Bharat Serum and Vaccine
   Plot No. K-27, Anand Nagar, Additional M.I.D.C. Ambernath (East)
   Tel:+91-251-2621 645,
   Fax:+91-251-2621 089
   Snake Venom Antiserum I.P.
   (production 2015-16: 800,00)

5. Mediclone Biotech Pvt. Ltd., 36/37 Millenium House, M.K.Srinivasan Nagar Main road, Perungudi, Chennai
Tel +91-44-24963845
Fax +91-44-24963846
(production 2015-16: 40 000 vials)
(reducing production)

6. Premium Serum and Vaccines Narayangaon
406, B Wing, Highway Rose Co-op. Housing Society,
92 Dixit Road Extensions,
Vile Parle (East), Mumbai 400057, Maharashtra,
Farm and manufacturing facility
S.No 354-1,354-2A/1 At and post Narayangaon, near Champagne India, Tal- Junnar, Dist- Pune-410504, Maharashtra,
E-mail sales@premiumserums.com
premiumserums@gmail.com
website: www.premiumserums.com
Polyvalent Snake Venom Antiserum both in Lyophilized or liquid form
(production 2015-16: 600 000 vials)
Venom sources Maharashtra and Uttar Pradesh in addition to Irula Society in Tamilnadu.

D. Indonesia
PT Bio Farma (persero)
Jl Pasteur no 28 Bandung - 40161
Tel. +62 22033375
Fax +62 222041306
Website: www.biofarma.co.id
Email : mail@biofarma.co.id
Recommended initial dose: 2 x 5 ml vials (maximum 80-100 ml)
Liquid antivenom

Biosave (polyvalent Anti-Snake Venom Sera, Equine) "serum anti bisa ular polivalen (kuda)" *Naja sputatrix-cobra, Bungarus fasciatus* - banded krait, *Agkistrodon rhodostoma* – Malayan pit viper

E. Iran
State Serum & Vaccine Institute,
Razi Hessarek, bP 656, Teheran
(liquid antivenoms, 10 ml/ampoule)
(Tel +98 2221 2005)
Polyvalent snake antivenom (equine)
(said to neutralize the venoms of two South-East
Asian species - *Naja oxiana* and *Echis carinatus* (probably *E sochureki*), *Vipera lebetina* (= *Macrovipera lebetina*) and *Pseudocerastes persicus*
Recommended initial dose: ?

F. Japan
Japan Snake Institute
Nihon Hebizoku Gakujutsu Kenkyujo
3318 Yunoiri Yabuzuka
Yabuzukahonmachi Nittagun
Gunmaken 379-2301
Tel 0277 785193 Fax 0277 785520
Snake-c@sunfield.ne.jp
www.sunfield.ne.jp/~snake-c/

Yamakagashi *(Rhabdophis tigrinus)* antivenom (also effective against red-necked keelback *R. subminiatus* venom)

G. Myanmar (Burma)
Myanmar Pharmaceutical Factory, Insein, Yangon (production capacity 100 000 vials/year)
(lyophilized and liquid equine F(ab')$_2$ antivenoms, 10 ml/ampoule)
Viper antivenom *(V. russelli = Daboia siamensis)*
Cobra antivenom *(N. kaouthia)*
Recommended initial dose: 8 vials for *D. siamensis*, 4 vials for *N. kaouthia*
A new ovine *D. siamensis* antivenom is now in production (Dr Aung Zaw, personal communication).

H. Pakistan
National Institute of Health,
Biological Production Division, Islamabad
Tel +9251- 240946;
Fax +9251-20797; Telex 5811-NAIB-PK

(no recent information available)
Dr. Birjees Mazher Kazi, Executive Director
National Institute of Health, Islamabad
Tel: (051) 9255117
Fax: (051) 9255099, 9255125
Email: edoffice@isb.apollo.
net.pk webmaster@nih.org.pk
Contact: Shahid Akhtar
(liquid and lyophilized antivenoms,
10 ml/ampoule)
Polyvalent anti-snake venom serum
(B. caeruleus, E. carinatus, N. naja,
V. lebetina (=Macrovipera lebetina),
V. russelli (= Daboia russelii)
Recommended initial dose: 5 vials for *Echis carinatus,* 10 vials for other species.

J. Taiwan
National Institute of Preventive Medicine,
161 Kun-Yang Street, Nan-Kang,
Taipei, ROC 11513
Tel +8862-7859215;
Fax +8862-7853944.
Contact: Dr Gong-Ren Wang, Director
(lyophilised antivenoms, 10 ml/ampoule)
Bungarus multicinctus and *N atra* bivalent antivenom
Trimeresurus mucrosquamatus
(= Protobothrops mucrosquamatus) and
Trimeresurus grammineus (= Viridovipera stejnegeri) bivalent antivenom
Recommended initial dose: 5 vials
Agkistrodon acutus (= Deinagkistrodon acutus) antivenom
Recommended initial dose: ?

K. Sri Lanka
A new polyspecific, freeze-dried whole IgG antivenom, manufactured by caprylic acid precipitation, has been developed through a collaboration between Instituto Clodomiro Picado (University of Costa Rica), Animal Venom Research International (AVRI), USA, and University of Peradeniya. The antivenom has been raised against venoms from Sri Lankan

D. russelii, E. carinatus, H. hypnale, and *N. naja*. It showed satisfactory preclinical potency and will be subjected to clinical trials in Sri Lanka. Antivenom against *B. caeruleus* is also being developed, to provide cover against all five medically important snakes.

L. Thailand
The Thai Red Cross Society (production capacity 75 000 – 82 000 vials/year)
Queen Saovabha Memorial Institute,
1871 Rama VI Road, Bangkok 10330
Tel +662-2520161-4;
Fax +662-2540212;
Telex 82535 THRESCO TH)
(freeze-dried monovalent antivenoms, 10 ml/ampoule)

1. Cobra antivenom *(Naja kaouthia)*: recommended dose 100 ml*
2. King cobra antivenin *(Ophiophagus hannah)*: 50 ml*
4. Russell's viper antivenin *(Daboia siamensis)*: 30 ml*
5. Malayan pit viper antivenin *(Calloselasma rhodostoma)*: 30 ml*
6. Green pit viper antivenin *(Cryptelytrops – Trimeresurus albolabris)*: 30 ml*
7. Malayan Krait Antivenin *(Bungarus candidus)*: 50 ml*

(freeze-dried polyvalent antivenoms, 10 ml/ampoule)
Neuro polyvalent (raised against 1-3 and 7): 20 ml* for all species

Haemato polyvalent (raised against 4-6): 20 ml* for all species

*Recommended doses according to approved registration dossiers from Thai FDA (Professor Sumana Khomvilai, personal communcation 21-07-2016). These differ from suggested initial doses quoted in Table 1, based on clinical experience.

Pressure-immobilization and pressure

Pressure-immobilization methods
Bites by cobras, king cobras, kraits, Australasian elapids or sea snakes may lead, on rare occasions, to the rapid development of life-threatening respiratory paralysis. This paralysis might be delayed by slowing down the absorption of venom from the site of the bite. The following techniques are currently recommended:

Pressure-pad plus immobilization
(Anker et al., 1982; Tun-Pe et al., 1995) **(Fig 90)**

A rubber and/or folded material pad approximately 5 cm square and 2-3 cm thick is placed directly over the bite site anywhere on the body and bound in place with a non-elastic bandage at a pressure of at least 70 mmHg.

Pressure-bandage plus immobilization
Sutherland et al., 1979 ; Sutherland and Tibballs, 2001) **(Fig 91)**.

Ideally, an elasticated bandage, approximately 10 – 15 cm wide and at least

- pad of rubber or cloth approx. 6 x 6 x 3 cm applied directly over bite site
- secured tightly with inelastic bandage at approx 70 mmHg pressure

Figure 90: Pressure-pad immobilization method (Copyright Dr David J Williams)

4.5 metres long should be used (Canale et al., 2009). If that it not available, any long strips of material can be used. The bandage is bound firmly around the entire bitten limb, starting distally around the fingers or toes and moving proximally, to include a rigid splint. The bandage is bound firmly (at a pressure of 50-70 mmHg), but not so tightly that the peripheral pulse (radial, posterior tibial, dorsalis pedis) is occluded or that the patient develops severe (ischaemic) pain in the limb.
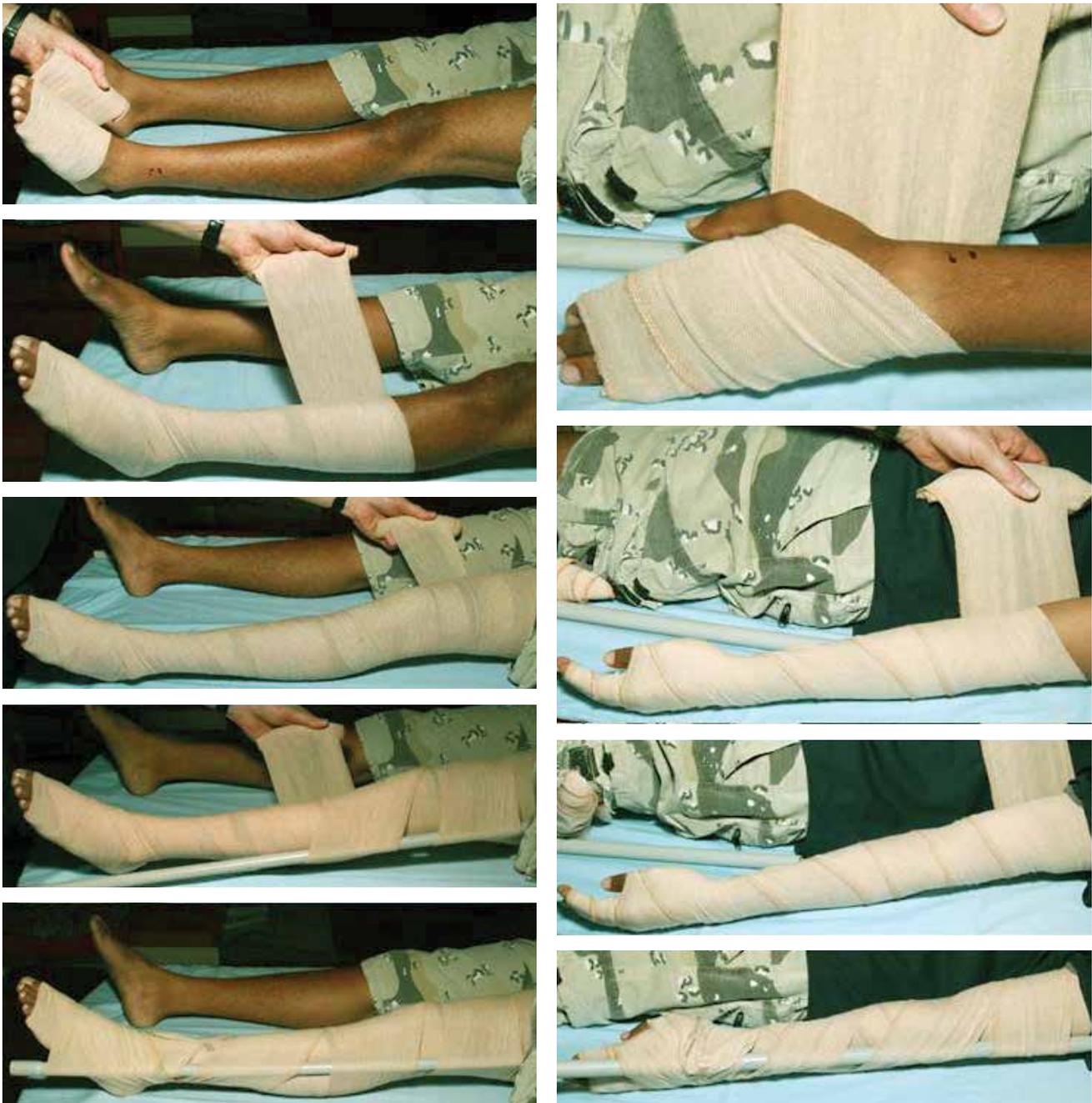
Sutherland's Pressure bandage -immobilisation: Elastic (not crepe) bandages 10 cm wide x 3.5 - 4.5 m long
Figure 91: Pressure-bandage immobilization: left – lower limb; right - upper limb (Copyright Dr David J Williams)

GUIDELINES FOR THE
MANAGEMENT OF SNAKEBITES

Measurement of central venous pressure

In seriously ill patients with shock or renal failure in whom clinical assessment of the jugular venous pressure is difficult or considered inaccurate, a central venous catheter should be inserted percutaneously. In those with no haemostatic problems, a catheter may be inserted into the jugular or subclavian vein provided adequate facilities for a sterile procedure and subsequent nursing are available. However, patients who have been bitten by vipers may have obvious haemostatic problems or may develop coagulopathy. In these cases, the antecubital approach is by far the safest as haemostasis can be achieved by local pressure. A long catheter (at least 50-70 cm for an adult) is required **(Fig 92a)**. The catheter is connected via a three-way tap and pressure tubing to a manometer. The whole system is filled with sterile isotonic saline. Before readings can be taken, the zero on the manometer must be aligned as accurately as possible with the horizontal plane of the left atrium. A simple spiritlevel (eg a 20 ml glass ampoule with bubble, taped to a ruler) can be used to locate the manometer zero at the same height as an appropriate chest-wall landmark, such as the midaxillary line, in the supine patient **(Fig 92b)** or the sternal angle in a patient sitting up at 45º. There should be strict attention to asepsis. Infection and thrombosis are potential complications; especially if the catheter remains in place for a long time.

Figures 92: Central venous pressure monitoring in patients with shock: (a) 70 cm long catheter inserted into an antecubital vein (Seldinger percutaneous guidewire technique) and advanced until its tip was in the superior vena cava. An extension tube connects with a simple saline manometer whose zero point is at the level of the mid-axillary line; (b) Adjusting the zero point of the central venous pressure manometer to the midaxillary line, using a home-made ruler-plus-glass-ampoule "spirit level" (Copyright DA Warrell)

6 ANNEX

Measurement of intracompartmental pressure

Measurement of intracompartmental pressure in tensely swollen snake-bitten limbs

To confirm a clinical suspicion of intracompartmental syndrome the pressure inside the particular compartment should be measured directly (Matsen 1980; Mars and Hadley 1998; Mars et al., 1991).

The threshold pressure required to initiate the flow of liquid into the fascial compartment is a measure of the tissue pressure inside that compartment. With full sterile precautions and after infiltrating local anaesthetic, a 21 or 22 gauge cannula, approximately 3-4 cm long, is inserted into the compartment through or around an introducing 20 or 21 gauge needle. The cannula is connected through narrow pressure tubing to a syringe or low speed infusion pump. Through a three-way tap, the system is connected, through a side arm to a blood pressure transducer or saline or mercury manometer (**Fig 93a**). The system is filled with sterile isotonic saline. If a syringe-type infusion pump and arterial blood pressure transducer with monitor is used, the pressure can be measured continuously at a very slow rate of infusion (eg 0.7 ml/day). If a saline or mercury manometer is used, a much higher rate of infusion is required to initiate flow into the compartment. These systems are not suitable for continuous intracompartmental pressure monitoring. Alternatively, the simple but expensive Stryker pressure monitor can be used **(Fig 93b)**.

Whatever system is employed, the zero point in the pressure measuring device must be aligned to the level at which the cannula enters the fascial compartment.
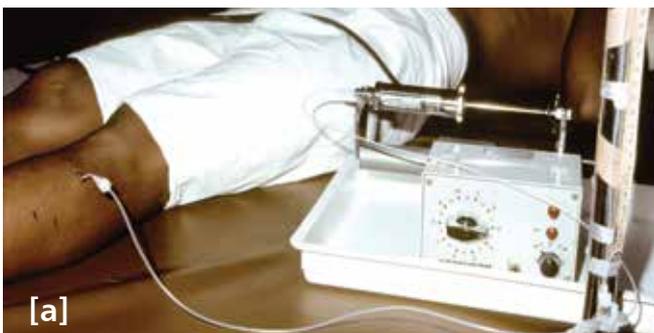
Figures 93: Measurement of intracompartmental pressure to exclude compartment syndrome in a snakebite victim: (a) infusion pump, saline manometer system in use for measuring the tissue pressure inside the anterior tibial compartment; (b) Stryker pressure monitor in use for measurement of intracompartmental pressure (Copyright DA Warrell)

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Snakebites are well-known medical emergencies in many parts of the world, especially in rural areas. Agricultural workers and children are the most affected. The incidence of snakebite mortality is particularly high in South-East Asia. Rational use of snake anti-venom can substantially reduce mortality and morbidity due to snakebites. These guidelines are a revised and updated version of Regional Guidelines for the Management of snakebites published by the WHO Regional Office in South-East Asia in 2011. These guidelines aim to promote the rational management of snakebite cases in various health facilities where trained health functionaries and quality snake anti-venom are available.