MINISTRY OF HEALTH MALAYSIA
MOH/P/PAK/341.17(GU)

GUIDELINE

MANAGEMENT OF SNAKEBITE

GUIDELINE:

MANAGEMENT OF SNAKEBITE

CONTENT

FOREWORD

Datuk Dr Noor Hisham Abdullah
Director General of Health Malaysia

Envenomation from snakebite remains a major cause of morbidity and mortality in Southeast Asia, Rapid urbanization in Malaysia has led to snake envenomation to continue to become a threat not just for rural and jungle areas, but also for city dwellers.

Cases of envenomation due to snakebite continue to be seen in our hospitals. Many of the species of snakes seen in Malaysia are unique to our region. This poses a problem to doctors managing victims of envenomation as many relevant textbooks are authored by physicians managing envenomation seen in Europe or North America.

The recent World Health Organisation guidelines on management of snakebite for South-East Asia has propelled patient care forward and highlighted to the international community the sheer burden of disease caused by envenomation in our region. Unfortunately, snakebite is still not included in the World Health Organisation's list of neglected tropical diseases.

Recent efforts by doctors, pharmacists and scientists with a keen interest in snakes and management of envenomation in Malaysia have significantly helped to improve management of snake envenomation in our country. The Remote Envenomation Consultation Services has assisted several doctors by providing 24-hour consultation services nationwide for management of envenomation due to snakebite.

This guideline will prove useful to health care workers managing patients suffering from snake envenomation. I would like to thank and congratulate the committee for their concerted efforts in producing this work.

FOREWORD

Datuk Dr Jeyaindran Tan Sri Sinnadurai
Deputy Director General Health Malaysia

The management of snakebite in Malaysia has improved in the past few years, thanks to work done by scientists, physicians, emergency physicians and pharmacists with a keen interest in toxinology. Recognizing that at times, we were using inappropriate antivenom for our region, they shared their knowledge on the local snake species and advised our doctors and pharmacists on the appropriate antivenom required. A revised guideline for management of snakebite emphasizing the medically important snake species thus became a necessity.

The World Health Organization's guidelines on snake bite management in South-east Asia mentions all countries in the region, except for Malaysia and Singapore. Due to the unique geographical classification used by the organization, Malaysia is not included in the guidelines. Nevertheless, our country shares many of the types of snakes encountered in our neighbouring countries. Creating our own guidelines for our physicians reference is necessary to improve patient care.

These guidelines will provide our Malaysian doctors the information they require to help them manage victims of snake envenomation comprehensively and accurately. I would like to thank and congratulate all those involved in preparing these guidelines for their hard work and efforts.

FOREWORD

Dato' Dr Hj. Azman Bin Hj Abu Bakar
Director Medical Development Division

Envenomation due to snakebite is a well-known cause of morbidity and mortality worldwide. Each continent and region faces its own unique species of snakes and corresponding envenomation syndrome.

The World Health Organisation's guideline on management of snakebite in South-east Asia was published in 2010. The guidelines addressed the unique spectrum of snakes and envenomation syndromes seen in our region. Understanding and identifying the snake species commonly seen in our country is crucial to improving and optimising patient management and care.

The hard work and effort by doctors, pharmacists and zoologists in identifying the different snake species seen in our country are commendable and has facilitated in sourcing for the appropriate antivenom.

Mapping the geographical location of these select snake species is still a work in progress. Once completed, it will prove invaluable to doctors when deciding on antivenom therapy to be administered. This guideline is one step further towards improving patient care and management for victims of snakebite envenomation. Congratulations and well done to all involved in preparing this important work.

FOREWORD

Dr. Sabariah Faizah Jamaluddin
Head of National Emergency Medicine
And Trauma Services

The management of envenomation due to snakebite in our country has always been a challenge. Previous guidelines and reference textbooks were not tailored to our local snake species. Signs and symptoms seen after envenomation were often misinterpreted and as a result, we were unable to optimise patient care.

The publication of the World Health Organisation's guidelines on snakebite management in South-east Asia as well as work done by our own Malaysian doctors, pharmacists and zoologists has helped us to better understand management of envenomation in our country. Shared experience from doctors managing these cases on a day-to-day basis helped us increase our knowledge and skills.

I applaud the multidisciplinary team from MOH and Universities comprising among others, emergency physicians, physicians, orthopaedic surgeons, paediatricians, pharmacists and pharmacologists who have worked hard towards creating a cohesive document that could easily be understood by all levels of health care workers. This guideline would prove to be important and crucial to help refine and improve the management of snakebite envenomation in Malaysia.

Further to these guidelines the Remote Envenomation Consultation Services (RECS) continues to provide 24 hour consultation services in regards to management of snakebite envenomation. As we continue to learn more about the different snake species seen in our country as well as the unique clinical picture produced by each snake's venom we will continue to update these guidelines as necessary. I would like to congratulate all those involved in preparing this excellent work.

GLOSSARY OF ABBREVIATIONS

aPTT	Activated Partial Thromboplastin Time
HPAV	Haemato Polyvalent Snake Antivenom
INR	International Normalized Ratio
MOH	Ministry of Health
MST	Malaysian Society on Toxinology
NFFC	Non Front Fanged Colubridae
NPAV	Neuro Polyvalent Antivenom
PSP	Pain Score Progression
PT	Protrombin Time
RECS	Remote Envenomation Consultation Services
RPP	Rate of Proximal Swelling Progression
VTRL	Venom and Toxin Research Laboratory
WBCT	Whole Blood Clotting Test
WFI	Water for Injection
WHO	World Health Organization

CHAPTER 1 :
INTRODUCTION

INTRODUCTION

Bites by venomous snakes can cause local and/or systemic envenomation that can result in a life-threatening medical emergency. Snakebite envenomation remains prevalent in many tropical and subtropical countries; unfortunately the true epidemiology and the global burden measure of snakebite envenomation remain unknown and speculative due to the lack of reliable information on its incidence, morbidity and mortality [1], [2]. It is estimated that worldwide the problem has resulted in at least 20,000 deaths yearly, although the figure may be close to 100,000 per year [3]. Thus far in Malaysia, literature on snakebite epidemiology is scarce: the three most recent epidemiological studies (published in 2004, 2006, 2011). [4],[5],[6] were limited to three individual hospitals, but flawed with doubtful primary data especially on the identification and documentation of the snake species involved. For instance, species were unidentified in more than 50% of cases, while some species responsible for inflicting bites were collectively identified as "viper". Snakebite envenomation has not been formally made a notifiable disease in the country; nonetheless the overall number of snakebites in the country (based on case registry) is available from the Malaysian Health Informatics Center. Taken for the years 2010 to 2014, a total of 15798 snakebite cases had been reported in the country (**Table 1**). The number of deaths over the same period totaled 16, averaging 3 to 4 deaths per year. The states with the highest number of snakebite cases were Kedah and Perak, presumably associated with agricultural activities. Unfortunately, data showing number of cases that did not present to a health care facility is not available.

Prior to year 2015, snakebite envenomation was obscurely listed under the "Other Categories" of the Neglected Tropical Diseases by WHO, lacking systematic attention and official global support programme. In fact, the persistent underestimation of snakebite morbidity and mortality has made it the most neglected condition among many other diseases in the tropics [7]. In 2015, this critical health problem was removed from the WHO list of Neglected Tropical Diseases. Regional toxinologists have been taking up proactive approaches to tackle the various challenges associated with snakebite envenomation, including the need for proper assessment of antivenom to ensure the supply of an affordable and efficacious antivenom product [8] and the appropriate recommendation of antivenom use in clinical management. In Malaysia, it should be noted

that the management of snakebite envenomation and the scientific research on antivenom have improved tremendously in recent years, attributable to the effort by several emergency physicians and scientists who show special interests in toxinology [9],[10]. Notably, the emergency physicians, under RECS (Remote Envenomation Consultation Services), provide phone consultations (on 24/7 basis) to guide doctors in diagnosis and treating snakebite envenomation all over Malaysia; while a group of toxin researchers from the Venom and Toxin Research Laboratory (VTRL), University of Malaya have also actively engaged in the characterization of venom toxins and neutralization profiles of antivenom against our regional snake venoms. Together, the management for snakebite can be optimized through application of evidence-based medical practice. Of note, various educational and research activities have been conducted by both groups of clinical and laboratory toxinologists; many of the events are organized under the flag of the Malaysian Society on Toxinology (MST).

This Guideline elaborates on the important aspects of snakebite clinical management, particularly on the recognition of the species involved and the clinical syndrome caused by envenoming as well as the appropriate investigation and treatment. Medically important species found in Malaysia and the predominant clinical features of envenoming are described to facilitate species diagnosis and syndrome recognition, which constitute the most basic information to determine the treatment approach. The pharmacology of venom and antivenom is also discussed, and correlated with the choice of antivenom used in Malaysia. It should be acknowledged that the promotion of the use of appropriate antivenom has led to a better care and improved treatment outcome in the patients. Until 2012, nearly all Malaysian hospitals stocked antivenoms procured from India (for instance, the VINS product), which are manufactured specifically for “the Big Four” (derived from the four most commonly encountered species in envenomation) in India and do not cover the snake species in the Malaysian setting. The appropriate antivenom, which is elaborated in details in this guideline, has been actively promoted starting in 2012 to present in Malaysia. The effectiveness of the antivenom used has been supported by research findings and clinical observation.

Preventive measures and proper treatment including the use of appropriate

antivenom will lead to a significant reduction in morbidity and mortality of snakebite envenomation. Malaysia should now move toward compulsory notification for all snakebite.

Table 1. Data from the Health Informatics Center - Number of snakebite cases by state from 2010-2014

State	2010		2011		2012		2013		2014	
	Dis-charged	Death	Dis-charged	Death	Dis-Charged	Death	Dis-charged	Death	Dis-Charged	Death
Johor	250	0	307	0	216	0	248	0	262	1
Kedah	849	2	836	0	590	0	422	0	577	0
Kelantan	281	0	303	1	262	1	260	0	241	0
Melaka	54	0	35	0	13	0	9	0	18	0
Negeri Sem-bilan	110	0	122	0	93	1	107	0	91	0
Pahang	235	0	246	1	182	0	178	0	208	0
Pulau Pinang	224	0	194	0	72	0	195	0	201	0
Perak	588	1	576	0	307	2	382	1	460	0
Perlis	172	0	170	0	152	0	161	0	108	0
Selangor	180	0	252	0	236	0	270	0	280	0
Terengganu	226	0	196	0	186	0	262	1	207	0
Sabah	174	0	157	0	120	1	123	0	163	0
Sarawak	269	1	260	1	174	1	202	0	167	0
WP Kuala Lumpur	39	0	26	0	7	0	13	0	15	0
WP Labuan	1	0	3	0	2	0	1	0	0	0
WP Putra-jaya	6	0	5	0	0	0	1	0	8	0
Total	**3,658**	**4**	**3,688**	**3**	**2,612**	**6**	**2,834**	**2**	**3,006**	**1**

CHAPTER 2 :

SNAKE OF MEDICAL IMPORTANCE IN MALAYSIA

2. SNAKES OF MEDICAL IMPORTANCE IN MALAYSIA

2.1 CLASSIFICATION

There are several families of snakes in Malaysia that are equipped with venom. All members of the family of Elapidae and Viperidae and a few in the family Natricidae are potentially dangerous to humans when bitten.

2.1.1 Elapidae: This family includes cobras, king cobra, kraits, coral snakes, sea snakes and their allies. Elapidae are relatively long, thin, with large smooth symmetrical scales (plates) on the top (dorsum) of the head. They have relatively short fixed front fangs. There is no loreal scale between the pre-ocular and nasal scales. Some, notably cobras, raise the front part of their body off the ground and spread and flatten the neck to form a hood. One cobra, *Naja sumatrana* can spray its venom for one metre or more towards the eyes of perceived enemies. Most sea snakes have flattened paddle-like tails and their ventral scales are greatly reduced in size or absent.

2.1.2 Viperidae comprises two subfamilies, true viper or Old World vipers(Viperinae) and pit vipers (Crotalinae). They have relatively long fangs which are normally folded against the upper jaw and are erected during a bite. The Crotalinae have a special sense organ, the loreal pit organ, to detect their warm-blooded prey. This is situated between the nostril and the eye. Pit vipers are from the Crotalinae subfamily. The toxinology of venoms from Crotalinae snakes is significantly different from that of venoms from Viperinae snakes.

2.1.3 Natricidae. Most of keelback snakes do not cause significant harm to human. One species of medically important Natricidae has been identified in Malaysia, the red-necked keelback (*Rhabdophis subminiatus),* which has the potential to cause significant coagulopathy. Several other species of the genus occur in Malaysia, and their medical significance is so far unknown.

2.2 SPECIES IDENTIFICATION

There is no simple rule for identifying venomous snake. Some harmless snakes are morphologically similar to venomous snakes. **Table 7** compares several snakes equipped with venom and the snakes that mimic them. These snakes can be recognized by their morphological features such as size, shape, colour, markings and behaviour. For example, the defensive behaviour of *Naja* species is well known; they rear up, spread a hood, hiss and may make repeated strikes towards the aggressor. Colouration may vary significantly. However, some patterns, like the alternating black and yellow circumferential bands of the banded krait are distinctive for certain species.

Identification of a severed, crushed or decapitated snake can be extremely challenging. Accurate identification is still possible by an experienced specialist. Verification of snake identification is best to be performed by experts in the field.

Description of the snake that bites the victim solely using local names can be inaccurate and misleading. Proper identification of the snake is possible only by examining the snake if it was killed or restrained and brought to the hospital. Care should be taken when examining the snake, and attempts to capture it a strongly discouraged because this may place others at serious risk of envenomation. Nonetheless, it may be illegal to kill a snake, as many species are protected by law. An option for identification is using good quality pictures of the snake that bit the patient, perhaps using a smartphone.

When getting help for snake identification using photos, several photos taken from several angles will be helpful for a reliable identification:

1. **Dorsal view**: take a picture from above
2. **Ventral view**: take a picture from below (turn the snake over)
3. Close-up of the head from above and the sides.

Get an experienced physician or clinical toxinologist familiar with snake species to verify. You may preserve dead specimens in an airtight container of 10% formaldehyde or 70 % alcohol.

When the snake or its picture is not available, the snake species deemed responsible for the envenoming should be considered using available photographs of venomous snakes. For example, one may use the Image Gallery of Snakes of Medical Importance in Malaysia produced by the Malaysian Society of Toxinology. Show the patient all the available images in the gallery and ask the patient to select the snake with similar features to the one that bit him/her. It is advisable not to use random picture search from the internet or sources not relevant for Malaysia.

Caution: Accurate snake species identification is important and may be difficult due to morphological variations between sexes and ontological progression, even within the same species. Therefore it is important to consult an expert for species identification and verification.

Table 2: Malaysian medically important snakes based on geographical location

Venomous snakes of Peninsular Malaysia (Elapidae)					
Snake	**Scientific name**	**Common name**	**Local name**	**Local effect**	**Systemic effect**
Cobra	*Naja kaouthia*	Monocled cobra	Ular senduk	Pain, swelling, tissue damage	Paralysis
	Naja sumatrana	Equatorial spitting cobra	Ular senduk sembur	Pain, swelling Local necrosis with or without paralysis Venom opthalmia	Local necrosis with or without paralysis Cardiac dysrythmia
King Cobra	*Ophiophagus hannah*	King cobra	Ular tedung selar	Pain, swelling, tissue damage	Paralysis
Krait	*Bungarus candidus*	Malayan krait		None or Minimal	
	Bungarus fasciatus	Banded krait	Ular katang tebu	None or Minimal	
	Bungarus flaviceps	Red-headed krait	Ular katang kepala merah	None or Minimal	
Coral (Coral snakes are landsnakes)	*Calliophis intestinalis*	Banded coral snake		Mild to moderate	Potential paralysis (limited case reports)
	Calliophis bivirgatus	Malayan blue coral snake		Mild to moderate	
	Calliophis maculiceps	Spotted coral snake		Unknown	
Sea snake			Ular laut	Minimal	Rhabdomyolysis causing renal failure & hyperkalaemia Paralysis

Table 3 : Malaysian medically important snakes based on geographical location

Venomous pit viper snakes of Peninsular Malaysia (Crotalinae)					
Genus	**Scientific name**	**Common name**	**Local name**	**Local effect**	**Systemic effect**
Calloselasma	*Calloselasma rhodostoma*	Malayan pit viper	Ular kapak bodoh	Pain, Swelling, Bruising, Blistering, Necrosis, Bleeding	Consumptive coagulopathy Thombocy-topenia
Ovophis	*Ovophis convictus*	Mountain pit viper	Ular kapak gunung	Pain, Swelling, Bruising, Bleeding	
Trimeresurus (***Trimeresurus*** **complex species)**	*Trimeresurus (Cryptelytrops) purpureomaculatus*	Mangrove pit viper	Ular kapak bakau	Pain, Swelling, Bruising, Bleeding	Consumptive coagulopathy Thrombocy-topenia
	Trimeresurus (Popeia) fucata	Thai peninsula pit viper			
	Trimeresurus (Popeia) buniana	Tioman island pit viper	Ular kapak Tioman		
	Trimeresurus (Popeia) nebularis	Cameron pit viper	Ular kapak Cameron		
	Trimeresurus (Parias) hageni	Hagen's green pit viper			
	Trimeresurus (Parias) sumatranus	Sumatran pit viper			
	Trimeresurus wiroti	Leaf nose palm pit viper			
Tropidolaemus	*Tropidolaemus wagleri*	Wagler's pit viper, Temple pit viper	Ular kapak tokong	Pain, swelling	Does not cause coagulopathy

Table 4 : Malaysian medically important snakes based on geographical location

Venomous snakes of Sabah & Sarawak (Elapidae)					
Snake	Scientific name	Common name	Local name	Local effect	Systemic effect
Cobra	*Naja sumatrana*	Equatorial spitting cobra	Ular senduk	Pain, swelling Local necrosis with or without paralysis Venom ophthalmia	Local necrosis with or without paralysis Cardiac dysrythmia
	Ophiophagus hannah	King cobra	Ular tedung selar	Pain, swelling, tissue damage	Paralysis
Krait	*Bungarus fasciatus*	Banded krait	Ular katang tebu	None or Minimal	Paralysis
	Bungarus flaviceps	Red-headed krait	Ular katang kepala merah	None or Minimal	Paralysis
Coral	*Calliophis intestinalis*	Banded coral		Mild	Potential paralysis & myolysis (limited case reports)
	Calliophis bivirgatus	Malayan blue coral		Mild	
	Calliophis maculiceps	Spotted coral		Unknown	
Sea snake	Hydrophiinae family	Sea snake		Minimal	Rhabdomyolysis causing renal failure & hyperkalaemia Paralysis

Table 5: Malaysian medically important snakes based on geographical location

Venomous pit viper snakes of Sabah & Sarawak (Crotalinae)					
Genus	Scientific name	Common name	Local name	Local effect	Systemic effect
Ovophis	*(Garthius) chaseni*	Kinabalu brown pit viper		Pain, Swelling, Bruising, Bleeding Necrosis	Consumptive coagulopathy Thombocy-topenia
Trimeresu-rus (*Trimeresurus* complex species)	*Trimeresurus (Popeia) sabahi*	Sabah green pit viper			
	Trimeresurus (Parias) malcomi	Kinabalu green pit viper			
	Trimeresurus (Parias) suma-tranus	Sumatran pit viper			
	Trimeresurus borneensis	Bornean palm pit viper			
	Trimeresurus venustus	Beautiful pit viper			
Tropi-dolaemus	*Tropidolaemus subannulatus*	Bornean keeled pit viper		Pain, swelling	Does not cause coagulopathy

Table 6 : Malaysian medically important snakes based on geographical location

Common Non Venomous Snakes in Malaysia (Non-front fanged)			
Genus	Scientific name	Common name	Notes
Malayopython	*Malayopython reticulatus*	Reticulated Python	
Lyocodon	*Lycodon capucinus*	Common House Snake	
Boiga	*Boiga dendrophila*	Gold-ringed Cat Snake Ular cincin emas/tiong emas/ punti	Mimics *B. fasciatus*
	Boiga cynodon	Dog-toothed Cat Snake	
Chrysopelea	*Chrysopelea ornata*	Golden Tree Snake	
	Chrysopelea paradisi	Paradise Tree Snake	
Ahaetulla	*Ahaetulla prasina*	Oriental Whip Snake	
Den-dralaphis	*Dendrelaphis caudolineatus*	Striped Bronzeback	
Gonyosoma	*Gonyosoma oxycephalum*	Red-tailed Racer	Mimics Green pit viper
Homalopsis	*Homalopsis buccata*	Puff-faced Water Snake	
Enhydris	*Enhydris plumbea*	Yellow bellied water snake	
Ptyas	*Ptyas carinata*	Keeled Rat Snake	When threatened or confronted it exhibits behaviour reminis-cent of a cobra because it rears up
Coelog-nathus	*Coelognathus radiatus*	Rat snake Ular tedung tikus	

IMAGE GALLERY OF MEDICALLY IMPORTANT LANDSNAKES IN MALAYSIA

***Naja kaouthia* , Monocled cobra** (Photos copyrighted to Ahmad Khaldun Ismail and Taksa Vasaruchapong)		
		
	Presence of a white ring when seen from the back	Leucitus monocled Cobra

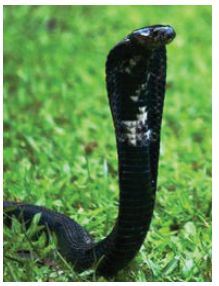
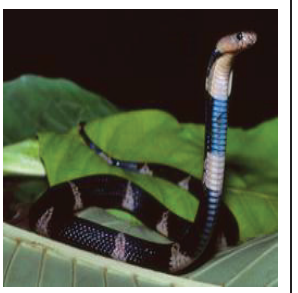
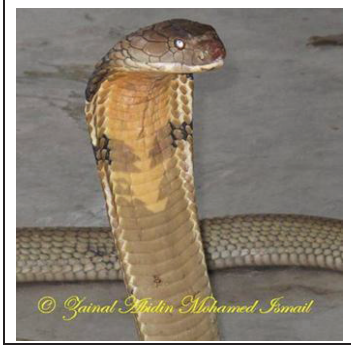
***Naja sumatrana* , Equatorial spitting cobra** (Photos copyrighted to Ahmad Khaldun Ismail, Taksa Vasaruchapong and Indraneil Das)			
			
	A golden phase *N. sumatrana*	The hood is not visible when the snake is not threatened / dead	Juvenile *N. sumatrana*

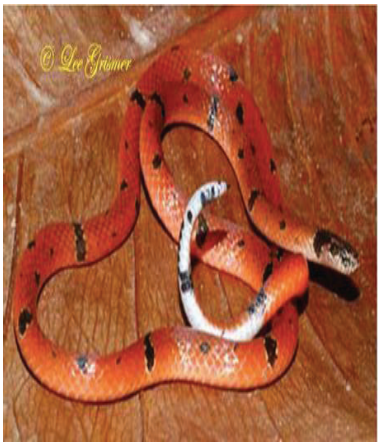
IMAGE GALLERY OF MEDICALLY IMPORTANT LANDSNAKES IN MALAYSIA

***Ophiophagus hannah*, King cobra**
(Photos copyrighted to Zainalabidin Mohamed@Ismail, Ahmad Khaldun Ismail and Taksa Vasaruchapong)



Bungarus candidus Malayan krait (Photo copyrighted to Taksa Vasaruchapong)	***Bungarus fasciatus*** Banded krait (Photo copyrighted to Taksa Vasaruchapong)	***Bungarus flaviceps*** Red-headed krait (Photo copyrighted to Jeet Sukumarn)
		

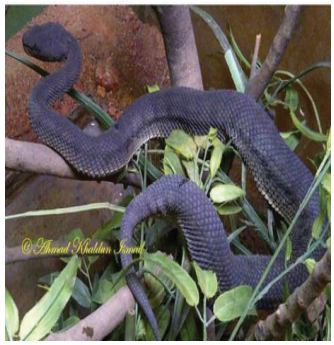
IMAGE GALLERY OF MEDICALLY IMPORTANT LANDSNAKES IN MALAYSIA

Calliophis maculiceps Spotted coral (Photo copyrighted to Lee Grismer)	***Calliophis intestinalis*** Banded coral (Photos copyrighted to Ahmad Khaldun Ismail)	***Calliophis bivirgatus*** Malayan blue coral (Photo copyrighted to Ahmad Khaldun Ismail)
	 	
	Banded pattern of the ventral part	

Calloselasma rhodostoma Malayan pit viper (Photo copyrighted to Ahmad Khaldun Ismail)	***Ovophis convictus*** Mountain pit viper (Photo copyrighted to Ahmad Khaldun Ismail)	***Garthius chaseni*** Kinabalu brown mountain pit viper (Photo copyrighted to Indraneil Das)
		

IMAGE GALLERY OF MEDICALLY IMPORTANT LANDSNAKES IN MALAYSIA

Crytelytrops purpureomaculatus
Mangrove pit viper
(Photos copyrighted to Ahmad Khaldun Ismail and Indraneil Das)

Popeia fucata
Thai peninsula pit viper
(Photos copyrighted to Indraneil Das, Teo Eng Wah and Akrachai Aksornnaem)


Male	Female

IMAGE GALLERY OF MEDICALLY IMPORTANT LANDSNAKES IN MALAYSIA

Popeia nebularis Cameron pit viper (Photo copyrighted to Ahmad Khaldun Ismail)	***Popeia buniana*** Tioman island pit viper (Photo copyrighted to Frank Tillack)	***Popeia sabahi*** Sabah green pit viper (Photo copyrighted to Indraneil Das)
		

Parias hageni Hagen's pit viper (Photos copyrighted to Taksa Vasaruchapong and Ahmad Khaldun Ismail)	
	

IMAGE GALLERY OF MEDICALLY IMPORTANT LANDSNAKES IN MALAYSIA

Parias sumatranus Sumatran pit viper (Photos copyrighted to Mohd Khairul Anwar Adan and Jeet Sukumaran)		***Parias malcomi*** Kinabalu green pit viper (Photo copyrighted to Steven Wong)
		

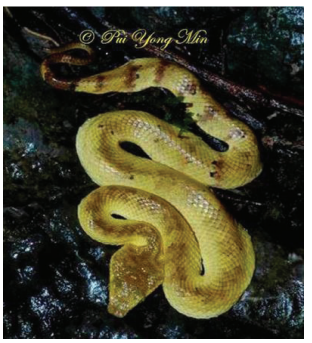
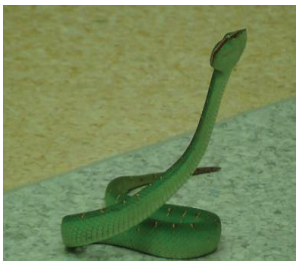
Trimeresurus wiroti Leaf nose palm pit viper (Photo copyrighted to Indraneil Das)	*Trimeresurus borneensis* Bornean palm pit viper (Photos copyrighted to Pui Yong Nin and Muhamad Na'im Abd Razak)	
		

IMAGE GALLERY OF MEDICALLY IMPORTANT LANDSNAKES IN MALAYSIA

Tropidolaemus wagleri Wagler's pit viper/Temple pit viper (Photos copyrighted to Ahmad Khaldun Ismail)		
		
Male	Female	Size difference between male and female

Tropidolaemus subannulatus Bornean keeled pit viper (Photos copyrighted to Indraneil Das)	
	
Male	Female

IMAGE GALLERY OF MEDICALLY IMPORTANT LANDSNAKES IN MALAYSIA

Phyton reticulatus **Reticulated phyton** **(Photo copyrighted to Ahmad Khaldun Ismail)**	*Phyton brongersmai* **Brongersma's short phyton** **(Photo copyrighted to Indraneil Das)**	*Phyton breitensteini* **Bornean short/blood phyton** **(Photo copyrighted to Indraneil Das)**
		

Rhabdophis subminiatus **Red-neck keelback** **(Photo copyrighted to Taksa Vasaruchapong)**


Table 7 : Non-dangerous snakes mimicking potentially dangerous snakes

Non-dangerous snakes mimicking potentially dangerous snakes

Potentially Dangerous	Non-dangerous
	 **Special note** : *B. dendrophila* can cause significant local envenoming effect by inoculating its Duvernoy"s gland contents using its uniquely grooved large rear fangs when biting.
Banded krait *(Bungarus fasciatus)* (Photo copyrighted to Taksa Vasaruchapong)	Gold-ringed cat snake *(Boiga dendrophila)* (Photo copyrighted to Ahmad Khaldun Ismail)
		
Malayan krait *(Bungarus candidus)* (Photo copyrighted to Ahmad Khaldun Ismail)	Juvenile equatorial spitting cobra *(Naja sumatrana)* (Photo copyrighted to Indraneil Das)	Banded wolf snake (*Lycodon subcintus*) (Photo copyrighted to Ahmad Khaldun Ismail)
		
Red-headed krait *(Bungarus flavicep)* (Photo copyrighted to Jeet Sukumaran)	Malayan blue coral *(Calliophis bivirgatus)* (Photo copyrighted to Indraneil Das)	Pink-headed reed snake *(Calamaria schlegeli)* (Photo copyrighted to Peter Lee Shiuh Hwa)

Non-dangerous snakes mimicking potentially dangerous snakes

Potentially Dangerous		Non-dangerous
		
Thai peninsula pit viper *(Popeia fucata)* (Photo copyrighted to Akrachai Aksornneam)	Cameron pit viper *(Popeia nebularis)* (Photo copyrighted to Ahmad Khaldun Ismail)	Red-tailed green ratsnake *(Gonyosoma oxycephalum)* (Photo copyrighted to Ahmad Khaldun Ismail)

CHAPTER 3 :

SNAKE VENOM

CHAPTER 3: SNAKE VENOM

Snake venoms are complex toxic secretions produced by highly specialised venom glands, and are comprised of proteins and peptides (> 90% of the venom dry weight) that can cause deleterious effects when injected through modified teeth (e.g. with lumen; hollow „fangs") located on the anterior maxilla into the tissue of a recipient organism [11]. By definition, venom is therefore distinct from poison, and the pathology arises from the introduction of such biological secretion into the body is called envenoming, not poisoning. Venom proteins and peptides are mostly pharmacologically active compounds; termed "toxins", they are responsible for the various toxic effects observed in envenomation cases.

Venoms evolved multiple times and largely represent a refined trophic adaptive trait of the advanced snakes. Molecular adaptation accompanied with protein neofunctionalisation has led to the emergence of toxins of a wide variety to suit specific niches [12],[13],[14]. When injected, snake venom toxins often act synergistically to interfere with normal physiology, especially the neurological or hemostatic functions of the prey or human following defensive bites. Biochemically, these toxic proteins can be classified into non-enzymatic toxins (e.g., three-finger toxins, platelet aggregation factors, serine protease inhibitors, C-type lectins and lectin-like proteins (collectively called snaclecs), natriuretic peptides, nerve growth factors), or enzymatic toxins (e.g. phospholipases A_2, metalloproteinases, phosphodiesterases, acetylcholinesterases, L-amino acid oxidases, serine proteinases).

In general, dominance of major proteins in venoms often follows broad taxonomic trends; however, venoms can and do vary substantially in their molecular compositions between species or even within a species. Recent studies revealed marked variability in snake venoms across many lineages, including several species in this region, such as the monocled cobra where locale-specific differences were recognized at genetic, proteomic and functional levels as well as in their imunoneutralization profiles [15],[16]. Snake variation can result in discrepancies of clinical syndrome (due to varied toxin composition) and therapeutic response to antivenom (due to varied antigenicity of toxins). The latter has

deep medical ramification as it underlies the principle that antivenom effectiveness is usually species-specific, and correct identification of species is vital to ensure a successful therapeutic outcome.

Clinically, the presentation of an envenomed patient is often complex because of the pathophysiological responses to the actions of different toxins in a venom. The toxic effects of snake venom have often been conveniently classified as neurotoxic, hemotoxic, cytotoxic, nephrotoxic, myotoxic, etc., based on the predominant clinical effect of a venom. It should be noted that organ- or system-based descriptions as such tend to oversimplify the complexity of venom effects and does not represent the holistic interaction of various toxins on different tissues. Nonetheless, these descriptions indicate the prominent clinical syndrome caused by a particular type of snake. Thus, they have a practical "prognostic" value in clinical management in anticipation of the likely pathological complication from the bite of a certain species and the need for emergency measures such as intubation, renal replacement therapy or hemodynamic correction.

Images and description of medically important Malaysian snakes are given in this work. Elapid snakes, such as cobras, kraits and sea snakes generally produce flaccid paralysis and respiratory failure, while the crotaline snakes, including the Malayan pit viper and Cameron Highland pit viper produce venom-induced consumptive coagulopathy and hemorrhagic syndrome. Elapid venoms mainly contain proteins/peptides of low to moderate molecular mass (< 15 kDa), with one key toxin group called the three-finger toxins (6-8 kDa), which include various neurotoxins and cytotoxins/cardiotoxins. The pit vipers have have venoms that often contain proteins with higher molecular masses (e.g. >15 kDa), many of which are enzymes, such as procoagulant serine proteases, hemorrhagic metalloproteases, cytotoxic L-amino acid oxidases. [17]. Phospholipases A_2 present usually in substantial amount in both the elapid and viperid venoms. Envenoming caused by elapid bites usually develops rapidly and death can ensue within hours due to respiratory failure; whereas that of pit viper bites tends to develop more insidious and manifest as hemorrhage and coagulopathy. Sea snake envenoming, on the other hand, produces myotoxicity accompanied by acute kidney injury (due to rhabdomyolysis) in humans [18]. Bites by sea snakes and kraits, unlike cobras, king cobra and pit vipers, are

generally painless and the bites may go unnoticed as the envenoming effect develops. Envenoming from bites by many species of cobras, as well as pit vipers often cause severe tissue necrosis that generally contraindicates the use of pressure bandage immobilization. Certain species from the family Colubridae and Natricidae, generally regarded as mildly venomous pose less threats but can cause potentially serious local envenoming effects. A summary of important species and their venom effects is provided in **Table 8**.

Table 8: Major constituents and toxic effects of the venoms of some medically important snakes in Malaysia

Family	Important com-Ponent	Envenoming effect		References
		Local	Systemic	
Viperidae				
Calloselasma rhodostoma *Cryptelytrops pur-pureomaculatus* *Popeia* sp. *Parias* sp.	L-amino acid oxidase Phospholipase A_2 Thrombin-like serine proteases C-type lectins Metalloproteinase	Pain, hemorrhages, cytotoxicity and necrosis	Hypofibrinogenemia, platelet dysfunction, thrombocytopenia, consumptive coagulopathy	[19],[10],[20].
Tropidolaemus wagleri	Phospholipases A_2, low molecular mass toxins/wa- glerins	Edema, erythema, mild bleeding, pain (all well-docu-mented bites so far only feature mild-moderate local effects)	Rarely serious in humans	
Elapidae				
Naja sumatrana *Naja kaouthia*	Three-finger toxins (neurotoxins, cytotoxins – abundant in *N. sumatrana* and Malaysian *N. kaouthia*), Phos- pholipase A_2	Pain, cytotoxicity, tissue necrosis Venom ophthalmia in *N. sumatrana* venom spitting	Post-synaptic neuromuscular paralysis Questionable cardiac abnormality	[9],[21].[22], [23],[24],[25]
Ophiophagus hannah	Three-finger toxin (mainly neurotoxins) L-amino acid oxidases Phospholipase A_2	Pain, cytotoxicity, tissue necrosis	Post-synaptic neuromuscular paralysis	
Bungarus sp.	Three-finger toxins (mainly neurotoxins), Neurotoxic phos-pholipase A_2	Minimal (painless bite)	Pre- and post-synaptic neuro-muscular paralysis	

CHAPTER 4:

CLINICAL ASSESSMENT

AND DIAGNOSIS

4. CLINICAL ASSESSMENT AND DIAGNOSIS

4.1 HISTORY

A detailed history of the event surrounding envenomation is important for an accurate diagnosis. Snakes have different habitats and geographical distribution. Arboreial snakes are good climbers while certain species lack this ability. History regarding the snake's behaviour and location will give important clues in indentifying the possible snake species.

Table 9 : Obtain targeted history

History		Information
When	Date and time of bite	Precise time of incident to monitor the progression of the signs and symptoms
Where	Geolocation of the incident	Knowledge on geolocation of Malaysian indigenous snake in the region may give clue to possible of snake species involved and the most appropriate antivenom to use if indicated.
How	Detailed event of the bite	What the patient is doing before the bite Was the snake situated on the ground/floor or on a tree Any particular behaviour of the snake (e.g., hooding, "spitting") Number of bites/strikes & duration of the bite What happen to the snake - escaped, captured or killed. Description of the snake Picture(s) of the snake if available
Where	Part of body bitten	Bite at the hand may indicate the patient was bitten while trying to hold the snake.
What	What was done to the bitten limb /area	Manipulation or treatment given for example tourniquet , cutting the wound and suction or application of traditional medicine
What	Treatment given at Primary health facility	Medication given or procedures done.

History		Information
What	Anaphylaxis risk	Determine allergies, and any history of snake bite or antivenom administration and history of anaphylaxis. History of exposure to snakes (e.g., snake handlers, snake catchers)

4.2 CLINICAL FEATURES

Symptoms and signs vary according to the species responsible for the bite, size/ age and the amount of venom injected. If the biting species is unknown, patient should be observed closely for at least 24 hours to allow recognition of the emerging pattern of symptoms, signs and results of laboratory tests. Together with history, this may help in identification of the snake species responsible.

4.2.1 General:

Nausea, vomiting, malaise, abdominal pain, weakness, drowsiness, prostration. These symptoms are nonspecific.

4.2.2 Cardiovascular:

Visual disturbances, dizziness, fainting or light-headedness, collapse, shock, hypotension, cardiac arrhythmias and pulmonary oedema. These symptoms are nonspecific.

4.2.3 Bleeding and clotting disorders:

Prolonged bleeding from the bitten site, site of venepuncture, conjunctiva, oral cavity, petechial rashes or bleeding from occult sites. Bleeding from occult sites include gastrointestinal, urinary and intracranial bleeding, i.e., haematuria; antepartum haemorrhage in pregnant women. The onset of coagulopathy may be delayed.

4.2.4 Neurological:

Patients present with a descending type of paralysis. The early sign is ptosis. Other signs are external opthalmoplegia, paralysis of facial muscles and other muscles innervated by cranial nerves. The patient may have a nasal voice, aphonia or dysphagia, regurgitation through the nose, difficulty in swallowing secretions leading to respiratory and generalised flaccid paralysis.

4.2.4.1 Examining for ptosis (weakness of the upper eyelids):

i. Hold your finger or a pen in front of the patient.

ii. Instruct the patient to follow the movement with his/ her eyes without moving the head.

iii. Slowly move your finger/pen upwards.

iv. If ptosis is present, the upper eyelids upward movement is reduced or absent.

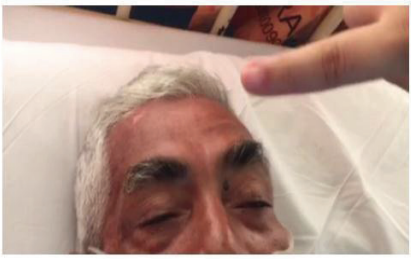
4.2.4.2 Examining for external opthalmoplegia (weakness of extraocular eye muscles):

i. Hold your finger or a pen in front of the patient.

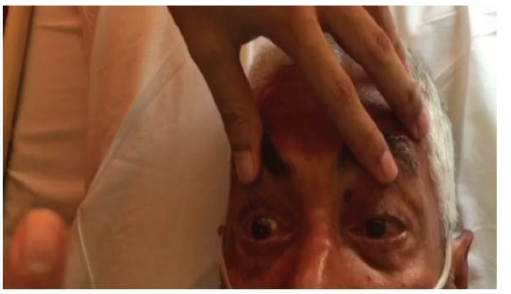
ii. Instruct the patient to follow the movement of your finger/pen without moving their head.

iii. Observe eye movement.

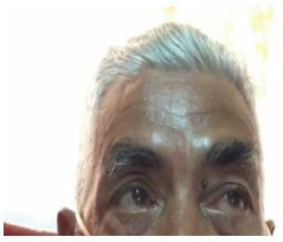
iv. If external opthalmoplegia is present, the affected eye(s) is unable to follow and move in certain direction. The patient may also have diplopia.



Ptosis. The concious patient is trying to look up



Poor extraocular muscle movement (External opthalmoplegia). The upper eyelids were manually elevated due to ptosis.



After *Naja kaouthia* antivenom given, ptosis and external opthalmoplegia resolved

4.2.5 Musculoskeletal and Renal:

Generalised severe myalgia, stiffness, tenderness, dark coloured urine, and oliguria/anuria.

4.3 EXAMINATION

Thoroughly examine the patient for local, general and systemic envenoming signs. Serial clinical assessment is more informative to guide management.

Table 10 : Serial clinical assessment

Resuscitation	Assess for airway and breathing problem due to paralyzing neurotoxic effect. Assess local wound and control bleeding as necessary.
General examination	Assess vital signs - Blood Pressure, Pulse rate, Respiratory rate, SPO2, Pain score, Temperature
Bite site examination	Look for **puncture** wound (fang / teeth mark(s) although these are not always evident, and also may not present with identifiable tooth marks), **swelling**, **inflammation**, **bruising** (early sign of dermonecrosis), **blistering.** Initiate RPP measurement (refer Chapter 7 - Monitoring). **DO NOT** mark the wound with permanent marker. Use removable small micropore tape for labelling. Take serial good quality pictures to monitor progress.
Draining lymph node	Palpate for tenderness or enlargement (serial assessment).
Systemic signs	Assess for: 1. General – early nonspecific features (e.g. nausea, vomiting) 2. Neurotoxic effect 3. Coagulopathy due to haematotoxic effect 4. Rhabdomyolysis Refer to Chapter 7: Monitoring

4.4 BITE SITE EXAMINATION

4.4.1 Local symptoms and signs in the bitten part:

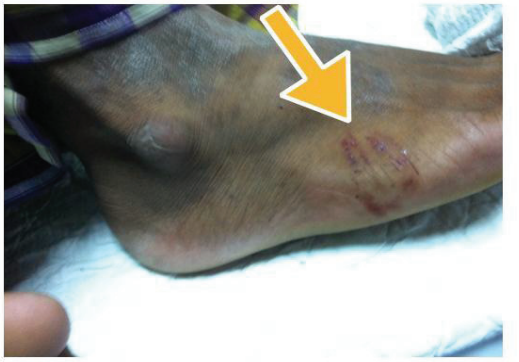
Bruising, swelling, pain, bleeding, blistering or local necrosis may be seen. Draining lymph nodes may be painful and support a diagnosis of either moderate to severe local or systemic envenoming. For krait bites there may be no local signs or early symptoms, but seriously envenomed patients may suddenly develop progressive descending paralysis.

4.4.2 Examination of the bitten part:

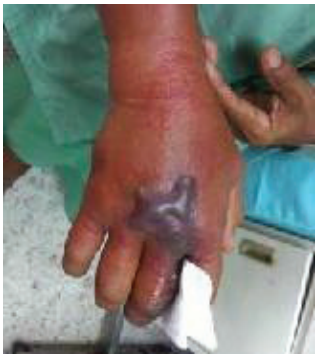
Bite mark, the number of puncture wounds or lacerations, the width of the puncture wound, number of rows of teeth marks seen on the skin should be documented.

Bite marks by non-front fanged snakes:

Wound inflicted by python bite



Wound inflicted by a Non-front fanged Boiga dendrophila snake.
Note the multiple puncture mark from upper and lower jaw

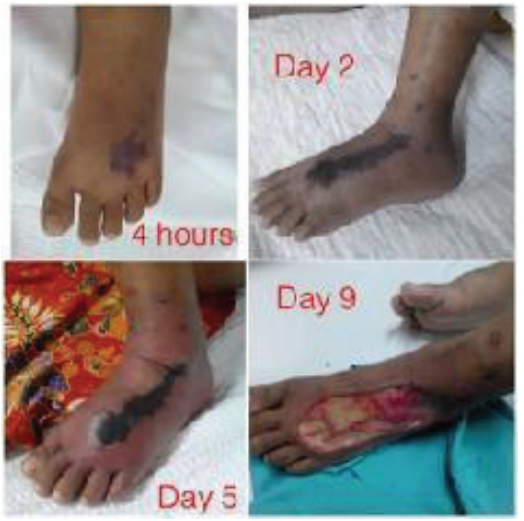


Blister that formed following *a Naja kaouthia* bite.

Progression of local tissue injury following a Malayan pit viper envenoming. This patient completed a total of 3 vials *Calloselasma rhodostoma* antivenom by 2.5 hours post bite

Calloselasma rhodostoma bite with local envenomation effect shown in timeline.

Dermonecrosis (local tissue necrosis):



Unidentified snake bite:
The wound progression shows typical dermonecrosis due to cytotoxic venom components that are present in venoms of some spp.

4.5 INVESTIGATIONS

4.5.1 Coagulation profile: APTT/PT and INR. Fibrinogen level and D-dimer can be sent if available. Coagulation profile should be repeated 6 hourly for suspected pit viper cases.

4.5.2 Full blood count: Platelet count may be decreased in victims of envenoming by vipers. Serial FBC will reveal a drop in hemoglobin if there is significant bleeding.

4.5.3 Renal profile: Serum creatinine is necessary to rule out renal failure. Also to detect electrolyte imbalance in patients with repeated vomiting. Early hyperkalemia may be seen following extensive rhabdomyolysis in sea snake bites.

4.5.4 Creatine kinase: For early detection of rhabdomyolysis. Serial monitoring to monitor trend.

4.5.5 Urinalysis: To assess for myoglobinuria, hematuria and proteinuria.

4.5.6 Liver function test: Mild hepatic dysfunction is reflected in slight increases in serum enzymes after severe local muscle damage.

4.5.7 ECG: To detect arrhythmia especially in envenoming involving *Naja* species bite.

4.5.8 ABG: To monitor and assess respiratory function. To detect metabolic acidosis in renal failure. Arterial puncture is **contraindicated** in patients with suspected coagulopathy (viperidae).

Tests should be repeated as indicated.

Patients with a non-venomous snakebite identified by an expert with no clinical signs and symptoms of envenoming, may not require any blood investigation.

4.5.9 20 minute whole blood clotting test (20WBCT):

i. When laboratory test for coagulation profile is not available, consider doing 20WBCT. It is a quick bed side test for an unidentified bite or when a pit viper bite is suspected. Although some low powered investigations have raised questions about the sensitivity/specificity of this assay under some conditions, the test has been useful in a variety of clinical settings lacking laboratory instrumentation.

ii. Place 2mls of freshly sampled venous blood in a small, new or heat cleaned, dry GLASS test tube.

iii. Leave undisturbed for 20 minutes at ambient temperature, then tip the tube once. If the blood has not clotted the patient may have coagulopathy.

iv. The test may be repeated as necessary.

v. 20WBCT result alone should not be used as determinant for antivenom treatment. It should be interpreted with the patient's clinical condition and reaffirmed with coagulation profile results once available.

Table 11: Laboratory Investigations during the first 48 hours post snakebite

	Elapid	Pit viper	Sea snake	Unidentified
FBC	Daily	6 hourly	Daily	6 hourly
Coagulation profile	Baseline	6 hourly	Baseline	6 hourly
Creatinine kinase	6 hourly	6 hourly	4 to 6 hourly	6 hourly
Renal function test	Baseline	Baseline	6 hourly	Baseline
Liver function test	Baseline	Baseline. Serial if deranged	Baseline	Baseline. Serial if deranged
Urine FEME	-	-	Serial	-
D-dimer & fibrinogen level	-	If coagulopathy present	-	If coagulopathy present

4.6 DETERMINING THE MOST LIKELY TYPE OF SNAKE / VENOM INVOLVED

4.6.1 Geographic location

Several snakes are widespread in the country, while others have a more limited range and may be further restricted to specific altitudes. It is also helpful for identification by noting the exact locality where a snake is found. Identifying the geographical distribution of these medically significant snakes will determine the need for appropriate antivenom for that state or region [2]. The list of medically significant snakes for Malaysia is in the **Chapter 2**.

4.6.2 Clinical and laboratory features

Table 12 : Important signs of envenomation from Malaysian snakes

Signs	Cobra	Krait	Coral	Pit viper	Sea snake
Severe pain at bite site	+	-	-	+	-
Progressive swelling	+	-	-	+	-
Tissue necrosis	+	-	-	- /+	-
Blister	+	-	-	+	-
Neurotoxic effect					

Table 12 : Important signs of envenomation from Malaysian snakes

Ptosis *(ask patient to look down and look up and observe the upper eyelids retracting fully or lagging)*	+	+	+	-	+
External opthalmoplegia (paralysis of eye muscles)	+	+	+	-	+
Dilated pupils	+	+	+	-	+
Cranial nerve palsy	+	+	+	-	+
Broken neck sign *(Paralysis of neck flexor muscles)*	+	+	+	-	+
Swallowing difficulty *(bulbar paralysis)*	+	+	+	-	+
Speaking difficulty	+	+	+	-	+
Paradoxical respiration	+	+	+	-	+
Poor respiratory effort	+	+	+	-	+
Haematotoxic effect					
Spontenous bleeding from wound, gum, nose, skin, haemoptysis, hematemesis, haematuria etc.	-	-	-	+	-
Rhabdomyolysis					
Generalised muscle pain & tenderness	-	-	+	-	+
Trismus	-	-	-	-	+
Myoglobinuria	-	-	-	-	+
Acute kidney injury	-	-	-	-	+

4.6.3 Snake Identification

Refer to **Chapter 2**.

4.7 DIAGNOSIS

Diagnosis is based on the history, clinical features and investigation results obtained. The list of possible diagnosis is below:

Table 13 : List of possible diagnosis

Diagnosis	Criteria
Unidentified injury	The exact cause of injury is unknown
Unidentified animal bite	The patient was sure it was an animal bite but did not see the causative animal.
Unidentified snakebite	The patient was sure it was a snake that bit him/her. Specific snake species name should only be stated in the diagnosis if positive identification of the snake species is made from sighting of the snake (alive / dead or good quality picture) by an expert. If the patient can only give a verbal description of the snake the diagnosis should be stated as an unidentified snakebite.
Identified Snakebite	Visual confirmation of the species. e.g. *Naja kaouthia* snakebite
Venom opthalmia	Venom sprayed (commonly by the equatorial spitting cobra, *Naja sumatrana*) enters the patient"s eyes.

The clinical features of the patient should also be included in the diagnosis if local or systemic envenoming is present. Examples of a complete diagnosis:

- *Naja sumatrana* snakebite with local envenoming
- Malayan pit viper *(Calloselasma rhodostoma)* snakebite with local and haematotoxic envenoming (severe coagulopathy)
- Unidentified snakebite with systemic neurotoxic envenoming (possible *Naja* species bite)

The diagnosis is dynamic and may change depending on the progress of the patient.

4.8 DISPOSITION

4.8.1 Indication for observation and admission:

i. Snakebite with local and/or systemic envenomation

ii. Venomous snake bite

iii. Unidentified snakebite

iv. Unidentified animal bite

4.8.2 Following a **non-venomous** snakebite, patient can be safely discharged if:

i. The snake can be positively identified as a non-venomous species by a trained expert.

ii. The clinical condition of the patient correlates with the expected effect of a bite from the identified snake species.

iii. The bite did not cause any significant tissue injury such as lacerations or persistent bleeding that may need further treatment.

Most bites by non-venomous snakes, such as by a non-front-fanged colubridae (NFFC) species is not associated with envenomation because it only causes mechanical injury which can be treated symptomatically. However, two Malaysian species from the Colubridae/Natricidae familes can cause significant tissue injury (*Boiga* sp.) and coagulopathy (*Rhabdophis subminiatus).*

CHAPTER 5 :

MONITORING

5. MONITORING : SERIAL CLINICAL ASSESSMENT

Serial assessment of the patient's clinical progression should be performed for the first 48 hours of presentation and charted into the snakebite chart (refer **Appendix 1**). In severely envenomed patients, hourly clinical assessment of these parameters is required. These serial assessments are useful to objectively monitor the progression of envenomation before and after antivenom therapy.

Depending on the snake species that bit the patient, the following are important **clinical parameters** to be serially monitored.

5.1 Neurotoxic envenoming effect:

- **5.1.1** Paradoxical respiration
- **5.1.2** Ptosis
- **5.1.3** Fixed dilated pupils, absence of light reflex
- **5.1.4** External ophthalmoplegia
- **5.1.5** Paralysis of neck flexor muscles (Broken neck sign)
- **5.1.6** Difficulty in swallowing (bulbar paralysis)
- **5.1.7** Cranial nerve palsy
- **5.1.8** Regurgitation
- **5.1.9** Aphonia

5.2 Haematotoxic envenoming effect:

- **5.2.1** Evidence of bleeding (e.g. skin, mucous membrane, conjunctiva, gums and nose)
- **5.2.2** Coagulopathy - reducing platelet count, prolonged PT, aPTT & INR

5.3 Rhabdomyolysis:

- **5.3.1** Generalised muscle pain and tenderness
- **5.3.2** Myoglobinuria
- **5.3.3** Markedly elevated creatinine kinase level
- **5.3.4** Acute renal failure
- **5.3.5** Hyperkalaemia

5.4 Monitoring Local envenoming (local tissue injury / dermonecrosis):

5.4.1 The following parameters should be monitored:

5.4.1.1 Rate of Proximal Progression (RPP)

5.4.1.2 Pain Score Progression (PSP)

5.4.1.3 Lymph nodes draining the bitten site (for enlargement and tenderness)

5.4.1.4 Progression of local tissue injury such as early necrosis, blisters, bullae, redness or bruising. Consider taking serial pictures of the bitten area.

5.4.2 Cobra and pit viper venom contains various enzymes that are capable of causing severe tissue injury and necrosis.

5.4.3 Enzymes such as snake venom metalloproteases and phospholipases A2 can cause direct and/or indirect damage to vascular endothelium, red blood cells, leucocytes, platelets, peripheral nerves, skeletal muscle and leads to the release of inflammatory mediators.

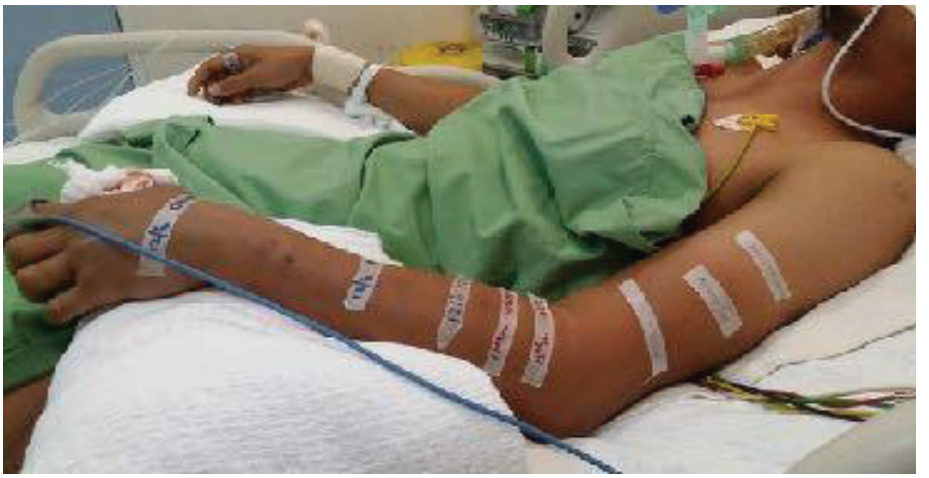
5.4.4 The enzyme, hyaluronidase, probably promotes the spread of venom through tissue. Increased vascular permeability causes oedema, blistering and necrosis at the site of bite.

5.4.5 Knowing the above mentioned effects of some well-known medically significant venom components is important to understand the pathophysiology of **pain** and **progressive edema** that occurs in venomous snakebite.

5.4.6 Swelling often progresses proximally from the bite site (e.g., when bitten on the finger, the swelling will progress from the hand towards forearm and later, the arm).

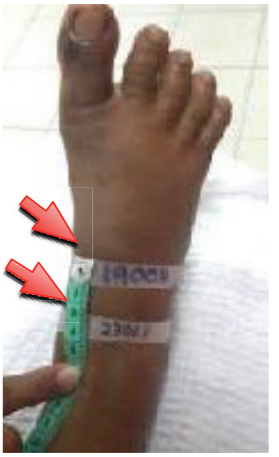
5.4.7 Ultrasound can be used to more accurately determine the extent of tissue edema. It is seen on ultrasound as „cobblestone sign".

5.4.8 By monitoring the serial **Pain Score Progression (PSP)** and the **Rate of Proximal swelling Progression (RPP)** (measured in centimetre per hour), we can monitor the progression and assess the severity of local envenoming.



Swelling progresses proximally after the left thumb was bitten by a king cobra

5.4.8.1 Measuring the Rate of Proximal Progression (RPP):



Measuring the RPP

- The distal border of the 1900H label to the distal border of the 2300H label is the oedema progression proximally for this time interval.
- The distance is 2.5cm in 4hours
- The RPP is 0.6cm/H.

Note: The labels should be removed after measurement is taken. Keep two of the most recent labels only.

5.4.8.2 Measuring limb circumference (girth measurement):

Measuring the limb circumference/girth at a fixed site is not recommend in snakebite patients. The pathophysiology of swelling and pain due to snake venom is different from a swollen limb due to traumatic compartment syndrome. Envenomation causes the swelling to progress proximally. Measuring the limb girth does not give additional information for patient clinical management.

1. A more informative parameter for reviewing progressive painful swelling

2. First: Determine the border of the micropore to be used to mark the proximal margin of the oedema e.g. distal border to distal border of the micropore markers (Figure 1)

3. Second: Palpate for the most proximal margin of the swelling and apply a small strip of micropore tape to the most proximal margin of the oedema

4. Label the current time and date on the micropore

5. Determine a fixed time interval to review the progression e.g. every 2 hours or 3 hours

6. Measure the distance between two micropore tape borders over the fixed time interval (Figure 2)

7. The RPP for that interval will be documented in **cm/hr**

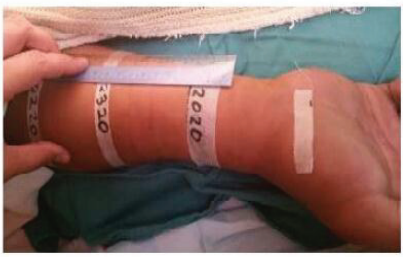


Figure 1.

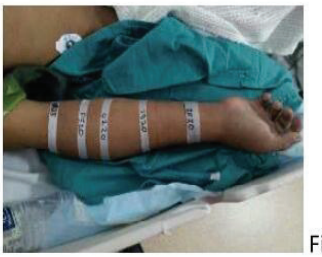


Figure 2.

5.4.8.3 Assessing the Pain Score Progression (PSP):

Moderate to severe pain is common in envenoming involving cobra and pit viper snakebite. Serial assessment of the pain score is beneficial to guide analgesia decision. Serial pain score assessment is also important to assess response to antivenom therapy.

Refer to **Appendix 2** for the Snakebite Monitoring charts

5.5 LABORATORY INVESTIGATION:

5.5.1 The important laboratory parameters to be serially monitored are :

5.5.1.1 Full blood count

5.5.1.2 Creatinine kinase

5.5.1.3 Coagulation profile (PT, aPTT & INR) for pit viper bite and unidentified snakebite.

5.5.2 Baseline investigations (consider serial test if clinically indicated) :

5.5.2.1 Renal function test (serially 6 hourly in sea snakebite)

5.5.2.2 Liver function test

5.6 RELEVANT TEST ONLY IN CERTAIN CASES WHEN INDICATED:

5.6.1 Urine FEME & urine for myoglobin for sea snake bite or unidentified marine animal bite

5.6.2 D-dimer and serum fibrinogen level if coagulopathy present to determine defibrination syndrome. (These test do not affect the decision on antivenom administration)

CHAPTER 6:

TREATMENT

6.TREATMENT

6.1 TRIAGE:

Triage patients with possible systemic and local envenomation to critical/red zone. Asymptomatic patients can be managed in the semi critical/yellow zone.

6.2 RAPID CLINICAL ASSESSMENT:

The goal of primary assessment is to identify any life threatening conditions. Resuscitation must be initiated immediately upon recognition.

A – Airway patency

B – Breathing effort (poor respiratory effort/bradypnoea)

C – Circulation (look for evidence of shock and bleeding)

D – Disability of nervous system (conscious level, muscle weakness)

E – Exposure and environmental control

6.3 RESUSCITATION

6.3.1 To optimise airway patency, perform “head tilt chin lift‟ manouver with adequate suctioning. Depending on patient‟s conscious state, position patient in the left lateral, supine or propped up position to ensure airway is maintained.

6.3.2 Administer oxygen with an appropriate-delivery-device as indicated.

6.3.3 Consider inserting an oropharyngeal airway to aid airway patency. Do not attempt this if gag reflex is still present.

6.3.4 Neurotoxic envenoming can lead to paralysis of the respiratory muscles and cause respiratory failure. Positive pressure ventilation via bag valve mask may be required and must be followed by definitive airway insertion when indicated.

6.3.5 Profound hypotension and shock can be due to direct cardiovascular effects of the venom or secondary effects, such as hypovolaemia, release of inflammatory vasoactive mediators and haemorrhagic shock. Profound hypotension can also rarely be caused by primary anaphylaxis induced by the venom itself. In skeletal muscle breakdown (rhabdomyolysis), hyperkalemia can also lead to cardiac arrest.

6.3.6 Cardiopulmonary resuscitation should be initiated if patient is in cardiac arrest. At least two large bore intravenous cannulas should be inserted with appropriate fluid resuscitation. Look for any source of external bleeding and apply appropriate method of bleeding control.

6.3.7 Cardiac monitor shall be attached to look for arrhythmias and management shall be according to advanced life support management.

6.3.8 Close serial monitoring of blood pressure, heart rate, respiratory rate, SpO2, pain score, PEFR (if applicable) every 5-15 minutes in acute stage is required. Temperature monitoring can be done four hourly. Use a snakebite chart as in appendix. Monitor urine output hourly. Note the colour changes of the urine in sea snake bites.

6.4 GENERAL MANAGEMENT

6.4.1 Immobilize the bitten limb and examine the bite site for swelling, bleeding and neurovascular compromise. Clinical findings suggesting progressive neurovascular compromise should be serially monitored with intracompartmental pressure measurements and/or bedside Doppler.

6.4.2 Position the affected limb in a neutral position or at the same level as the heart.

6.4.3 Prophylactic hydrocortisone and antihistamines are not recommended. Administer only if patient has signs of allergic reaction or anaphylaxis.

6.4.4 Intramuscular injections should be avoided in pit-viper snakebite victims due to risk of haematoma formation as patient has potential risk of coagulopathy. Oral or intravenous route is preferred.

6.4.5 Anti tetanus toxin should be administered as indicated. Please refer to the MOH guidelines for vaccination.

6.4.6 If there is venom exposure in the eye, perform eye irrigation with copious amounts of normal saline (5 to 10 litres). Refer to management of venom ophthalmia.

6.4.7 If the patient is in severe pain, envenomation has probably occurred. Patient can be given an analgesic but avoid the use of NSAIDS in pit-viper bite. Non-sedating analgesics which do not affect coagulation can be administered. Serial assessments of the pain score are important.

6.4.8 Administer anti venom if indicated. (**Chapter 7**)

6.4.9 Bleeding caused by hematotoxic snake bites may be life threatening. However, it must be stressed upon that blood products are not a substitute for antivenom. Giving blood products in these situations without concomitant administration of the appropriate antivenom will not correct coagulopathy. In cases where the antivenom is not readily available, blood products should be administered if the bleeding is life threatening until the appropriate antivenom is available.

6.5 SUPPORTIVE/ANCILLARY TREATMENT

6.5.1 Steroid and antihistamines:

6.5.1.1 Steroid and antihistamines should not be administered without clear indication. The sedative effect of certain antihistamines can make neurological assessment inaccurate or misleading.

6.5.1.2 Rarely, anaphylactic reaction can occur in individuals sensitised to snake products such as the snake's saliva and shedding. This may occur in snake handlers who are regularly exposed to snakes.

6.5.2 Analgesia:

6.5.2.1 For mild pain, paracetamol can be administered every 4-6 hours orally as required.

6.5.2.2 Aspirin or non-steroidal anti-inflammatory drugs should be avoided in patients who are at risk to developing coagulopathy.

6.5.2.3 For moderate to severe pain, intravenous opioids should be administered in titrated doses.

6.5.3 Antivenom:

6.5.3.1 Administer anti venom if indicated.(Chapter 7)

6.5.4 Anticholinesterases (adapted from WHO-SEA Snakebite Guideline 2016):

6.5.4.1 Anticholinesterase drugs have a variable, but potentially useful effect in patients with neurotoxic envenoming, especially those bitten by cobras but not kraits. Appropriate and adequate antivenom should take precedence to trial of anticholinesterase administration.

Procedure:

6.5.4.1.1 Baseline observations or measurements should be done to assess the effectiveness of the anticholinesterase.

6.5.4.1.2 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. inappropriate doses) by intramuscular injection of 0.02 mg/kg for adults, 0.04 mg/kg for children. Short acting edrophonium chloride (Tensilon) is ideal for this test if available. It is given by slow intravenous injection in an adult dose of 10 mg, or 0.25 mg/kg for children.

6.5.4.1.3 The patient should be observed over the next 30-60 minutes for neostigmine or 10-20 minutes for edrophonium. Monitor for signs of improved neuromuscular transmission such as disappearance of ptosis and improved ventilatory capacity (peak flow, FEV-1 or maximum expiratory pressure)

6.5.2.1.4 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 who are 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.

6.5.5 Antibiotics:

6.5.5.1 Antibiotics should be considered in snakebite with local tissue necrosis/dermonecrosis or extensive tissue injury/damage (e.g. bite by a python).

6.5.5.2 Selection of antibiotics should cover both aerobic and anaerobic organisms.

6.5.6 Tranexamic acid and Vitamin K:

6.5.6.1 Anti-fibrinolytic agents (e.g. tranexamic acid) and vitamin K are not effective in envenomation induced coagulopathy.

6.6 SPECIAL CONSIDERATIONS IN PREGNANCY, PEDIATRICS, ELDERLY AND PATIENTS WITH CO-MORBIDITIES

6.6.1 There is no contraindication for antivenom as it is the only known antidote for envenomation.

6.6.2 Dosage of antivenom is the same for all patients, regardless of age or co-morbidities.

6.6.3 Dilution of antivenom may be reduced (5-10 mls/kg of NS or D5%) when volume is a concern for paediatric patients or patients with underlying co-morbidities such as renal failure or cardiac failure.

6.6.4 Undiluted antivenom(reconstituted antivenom without dilution) may be given to reduce the volume of fluids administered.

6.7 SNAKEBITE BY A NON-INDIGENOUS SNAKE SPECIES

6.7.1 Hospitals in Malaysia only keep-in-stock antivenom capable of neutralising venom from local (indigenous) venomous species. A bite by an exotic snake species not indigenous to Malaysia will pose a challenge in providing appropriate antivenom to the victim if antivenom therapy is indicated. These snake species may be kept in zoos, pet stores and may be illegally acquired for personal interest.

6.7.2 Expert help should be acquired and appropriate antivenom may need to be sourced. Antivenom for these non-indigenous snake species may be acquired with assistance from the department of pharmaceutical services.

6.8 SEVERE COAGULOPATHY DUE TO RHABDOPHIS SUBMINIATUS BITE

6.8.1 *Rhabdophis subminitus*, the red-necked keelback bite is capable of causing severe coagulopathy. Specific antivenom for the above is the Anti-Yamakagashi antivenom. The antivenom has to be sourced from Japan.

A red-necked keelback, *Rhabdophis subminiatus*, a non-front-fanged colubroid. (Photos copyrighted to Taksa Vasaruchapong)

6.9 VENOM OPHTHALMIA

Venom ophthalmia is an acute reaction of the ocular surface tissues to venom sprayed into the eyes by *Naja sumatrana* (equatorial spitting cobra). Signs and symptoms include severe stinging pain and diminution of vision, excessive watering in eyes, severe blepharospasm and corneal erosions. Permanent vision loss is rare and systemic envenoming has not been documented in human patients.

Immediate treatment is to irrigate the affected eye with copious irrigation using normal saline or water or ringer's lactate or any bland fluid (such as milk) if water or saline is unavailable.

Any patient that presents with venom ophthalmia should also be thoroughly examined for any evidence of snake bite.

After decontamination of the affected eye, fluorescein stain may be used to exclude corneal abrasions. Topical analgesics like tetracaine drops or adrenaline 0.5% (ophthalmic solution) may be used to provide pain relief. However, prolonged use of topical analgesics is not recommended as the risk of bacterial infection in anesthetized damaged cornea. Topical cycloplegic drops such as atropine or scopalamine can be used to prevent ciliary spasm and discomfort. Topical antibiotics is recommended if corneal erosion cannot be excluded by fluorescein stain or slit lamp examination.

Topical steroids is contraindicated as it enhances calcium ion mobilisation which facilitates the corneal collagenase enzyme in venom resulting in corneal melting. Urgent opthalmology referral for slit lamp examination is vital.

Note: topical use of antivenom is not recommended.

CHAPTER 7 : ANTIVENOM THERAPY

7. ANTIVENOM THERAPY

7.1 INTRODUCTION

Antivenom is the definitive treatment for snake envenomation [2]. An effective antivenom when given appropriately is able to arrest or reverse envenoming effects in patients.

Antivenoms are biologics comprising immunoglobulin molecules or their fragments derived typically from the plasma of animals which have been immunised with venom(s) [28]. The product is called a monospecific (monovalent) antivenom when the animal is immunised against venom of a single species, or a polyspecific (polyvalent) antivenom when a mixture of venoms from different species is used as the immunogen. In some products, polyspecific antivenom can be a mixture of several monospecific antivenoms, formulated according to the need of clinical use. Antivenom works as an immunotherapy; it acts by binding to venom toxins (forming immunocomplexes), rendering the toxins inactive while enhancing their elimination from the body[29].

Current pharmaceutical technologies produce three main types of antivenoms: whole IgG molecules (approximately 150 kDa), $F(ab")_2$ fragments (approximately 100 kDa) and Fab fragments (approximately 50 kDa). The Fc fragment of IgG molecule is a suspected common cause for hypersensitivity; its removal produces $F(ab")_2$ or Fab, which is now the common antivenom preparation. The different forms of antivenom, nonetheless, vary in several important pharmacological properties such as the volume of distribution, elimination half-life, elimination route, number of paratopes and the size of immunocomplexes formed. These differences have important implications on the therapeutic value of an antivenom. For instance, Fab with a large volume of distribution is ideal for targeting most elapid toxins which are small and deep-tissue penetrating; however, its short elimination half-life can result in a half-life mismatch with toxins those of viperid venoms that exhibit relatively long half-life [30] . Failing to maintain an adequate level of antivenom in

the circulation as the antivenom is eliminated quicker than the circulating toxins gives rise to the phenomenon of recurrent envenomation (recurrence of signs and symptoms at later time after the initial effective treatment of envenomation) [31]. The optimization of the therapeutic outcome of antivenom relies on good understanding of the pharmacokinetic-pharmacodynamic relationships of antivenom, interpreted in the light of the toxicokinetics and mechanisms of a particular venom (more specifically, its toxins) being neutralized [32].

A practical issue associated with antivenom use is its availability and suitability for use in a country. In Malaysia where local antivenom production is not feasible, imported products are the only choice of antivenom for treating envenomation inflicted by local species However, these products require stringent and rigorous preclinical assessment to demonstrate the potential paraspecific protection that can be possibly conferred in humans. In this context, only a few foreign products have been shown effective when tested in *in vivo* animal model and supported by *in vitro* studies. Cross-neutralization as such is possible as venoms of closely-related species may share similar toxin antigens to which the antivenom binds. Malaysia depends greatly on antivenom supply from Thailand, notably products from the Thai Red Cross Society of the Queen Saovhaba Memorial Institute (QSMI), Bangkok, for the fact that many venomous snakes in Thailand are similar or closely related to those in Malaysia (at least some from the Peninsular Malaya) [9],[10]. Recent studies revealed that polyvalent antivenoms imported from India, raised against the Indian “Big Four” (*Naja naja*, *Bungarus caeruleus*, *Daboia russelii* and *Echis carinatus*), has weak or negligible protective effect against the venom toxicities of most Malaysian snakes, but promising cross-neutralization has been observed with the Thai antivenoms [21],[33],[19],[15]. The Thai antivenom products range from monovalent antivenoms against many venomous snakes in Thailand, to two polyvalent antivenoms produced based on a syndromic approach, i.e., Neuro Polyvalent Antivenom (NPAV) and Hemato Polyvalent Antivenom (HPAV). The QSMI antivenoms are equine $F(ab")_2$ refined through capric acid precipitation and pepsin digestion of the IgG. $F(ab")_2$ antivenoms carry two paratopes for stable immunocomplexation, and have been shown to have an intermediately long

elimination half-life of 3-4 days (approximately 50-70 hours): these are the pharmacokinetic properties that make $F(ab")_2$ favourable in many types of snake envenomation.

NPAV is raised against *N. kaouthia*, *O. hannah*, *B. candidus* and *B. fasciatus* venoms; while HPAV is raised against *C. rhodostoma*, *C. albolabris* and *D. siamensis*, all of Thai origin. These polyvalent antivenoms, usually indicated when the biting species is uncertain, show higher neutralizing capacity per vial unit in animal studies compared to their monovalent counterparts, presumably due to synergistic cross-neutralizing components in the polyvalent antivenom, and technical enrichment or concentration process during the manufacturing process. The monovalent antivenoms, nevertheless, are the first choice of antidote when the biting species is confirmed. The QSMI antivenoms recommended for treating Malaysian snake bites is listed in **Table 14.** In general, antivenoms for elapids and viperids are distinctly different in efficacy; among the elapids, satisfactory cross- neutralization is not well documented between the *Naja* cobra and king cobra, or between Malayan krait and banded krait. Among the pit vipers, satisfactory cross- neutralization does not occur between Malayan pit viper and other species from the *Trimeresurus* complex in Malaysia [19].

Against the sea snakes, especially the commonly encountered *Hydrophis schistosus* (till recently referred to as *Enhydrina schistosa*), the specific antidote is CSL sea snake antivenom (Australia, branded as Seqirus) which is raised against *Hydrophis schistosus* and *Notechis scutatus* venoms [15]. Cross-neutralization of sea snake venoms by Thai cobra antivenoms (*N. kaouthia* monovalent antivenom and NPAV) has been shown possible but weak in laboratory animals; such finding is merely indicative for the improvement of the spectrum of new antivenom in the future [25],[15]. There is currently no antivenom known to be effective against the venoms of the Asiatic coral snakes (*Calliophis* sp.) although weak neutralization by the Taiwan Neuro Polyvalent Antivenom (raised against *Naja atra* and *Bungarus multicinctus*) had been observed in rodents[23]. On the other hand, no

antivenoms (including HPAV) have been proven effective in neutralizing the venom of Wagler‟s pit viper (*Tropidolaemus wagleri*)[19]. Fortunately, envenomation by this species is generally regarded as non-lethal with a low level of venom toxicity for humans. Thus far, cross-neutralization of most *Trimeresurus* complex species by Thai Green Pit Viper Monovalent Antivenom (raised against *Cryptelytrops albolabris*) and HPAV is generally considered possible and effective due to the similar antigenicity of their major toxins.

The choice of antivenom is clear provided the diagnosis of envenoming species is correct, or the syndrome approach is rightly applied. The dosing regimen, however, requires optimal monitoring of syndrome progression and clinical judgment from case to case, while referring to the dosage recommendation (**Table 15**). It is noteworthy that in general the potency values of antivenom used against elapid venoms are low as compared to antivenom used against viperid/crotalid venoms, presumably due to the low immunogenicity of low molecular mass proteins that form the principal toxins in elapid venoms, especially for the cobras [21],[34],[35]. This is the basis for low neutralization capacity of elapid antivenoms and the need of a higher starting dose in confirmed envenoming cases by these species (up to 10 vials initial dose). The current research trend entails the investigation of toxin-specific neutralization, complemented by proteomic and antivenomic approaches for the production of highly potent and “broad-spectrum” antivenoms [24],[10],[15].

7.2 INDICATION FOR ANTIVENOM

Antivenom treatment should be given as soon as it is indicated. Antivenom treatment can reverse systemic envenoming even if it has persisted for weeks. Clinical evidence shows that local necrosis of the bite area can be prevented if antivenom is given within few hours after the bite.

Antivenom treatment is recommended if patient with proven or suspected snake bite develops one or more of the following signs:

7.2.1 Systemic envenoming

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

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

7.2.1.3 **Cardiovascular abnormalities**: hypotension, shock, cardiac arrhythmia (clinical), abnormal ECG

7.2.1.4 **Acute kidney injury (renal failure):** oliguria/anuria (clinical), rising blood creatinine/ urea (laboratory).

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

7.2.1.6 Supporting laboratory evidence of systemic envenoming.

7.2.2 Local envenoming

7.2.2.1 Local swelling involving more than half of the bitten limb (in the absence of a tourniquet) within 48 hours of the bite. Swelling after bites on the digits (toes and especially fingers).

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

7.2.2.3 Development of an enlarged tender lymph node draining the bitten

limb with other clinical signs of envenomation.

7.3 ANTIVENOM AVAILABLE IN MALAYSIA

The frequency and severity of snake envenoming determines the selection and stocking of antivenom in specific regional hospitals. The amount and type of antivenom stocked is based on the requirement of burden of snake bite for the individual hospital, therefore, antivenom stocks often differ in each hospital [36].

Consult the pharmacist in the hospital for availability of specific antivenom. At times, limited resources can be mobilized and shared via close communication between treating physicians, pharmacist and RECS consultants.

Table 14: Antivenoms available in Malaysian hospitals

Antivenom	Homologous venom used to raise antiserum	Neutralization capacity*
Hemato Polyvalent Snake Antivenom (QSMI Thai Red Cross)	*Malayan pit viper (*Calloselasma rhodostoma*) *Green Pit Viper *(Trimeresurus albolabris)* * Southeast Asian Russell"s viper *(Daboia siamensis)* not indigenous to Malaysia	*Neutralize 1.6 mg/ml of *Calloselasma rhodostoma* venom *Neutralize 0.7 mg/ml of *Trimeresurus albolabris* venom. *Neutralize 0.6 mg/ml of *Daboia siamensis* venom.
Neuro Polyvalent Snake Antivenom (QSMI Thai Red Cross)	*Monocled Cobra (*Naja kaouthia* *King Cobra (*Ophiophagus hannah)* *Banded Krait (*Bungarus fasciatus)* *Malayan Krait (*Bungarus candidus*)	*Neutralize 0.6 mg/ml of *Naja kaouthia* venom. *Neutralize 0.8 mg/ml of *Ophiophagus hannah* venom. *Neutralize 0.6 mg/ml of *Bungarus fasciatus* venom. *Neutralize 0.4 mg/ml of *Bungarus candidus* venom.

Cobra Antivenin (QSMI Thai Red Cross)	Monocle cobra (*Naja kaouthia)*	Neutralize 0.6 mg/ml of venom
King Cobra An- tivenin (QSMI Thai Red Cross)	King Cobra (*Ophiophagus hannah)*	Neutralize 0.8 mg/ml of venom
Green Pit Viper Antivenin (QSMI Thai Red Cross)	Green Pit Viper *(Trimeresurus albolabris)*	Neutralize 0.7 mg/ml of venom
Malayan Pit Viper Antivenin (QSMI Thai Red Cross)	Malayan pit viper (*Cal- loselasma rhodostoma)*	Neutralize 1.6 mg/ml of venom
Malayan Krait An tivenin (QSMI Thai Red Cross)	Malayan krait (*Bungarus candidus)*	Neutralize 0.4 mg/ml of venom
Banded Krait Antivenin (QSMI Thai Red Cross)	Banded krait (*Bungarus fasciatus)*	Neutralize 0.6 mg/ml of venom
Polyvalent Sea snake Antivenom (CSL,Australia)	Beaked sea snake *(Hydrophis schistosus)*	Contains 1000 unit of neu- tralizing capacity of the target venoms

Important Note :
*The Indian Polyvalent antivenom (that may still available in some hospitals) is NOT appropriate for treating snake envenomation in Malaysia. It may have weak neutralizing capacity against the venoms of Equatorial spitting cobra (*Naja sumatrana*) Monocle cobra (*Naja kaouthia*) King Cobra (*Ophiophagus hannah*) and Malayan Krait (*Bungarus candidus*), however its use is NOT recommended in Malaysia.

**Values as indicated on the product leaflet and may vary clinically. Refer to Table 15 and 16 for appropriate antivenom choice based on species, genus and corresponding dose of antivenom.

***The neutralization estimates are not clinically derived, but are obtained from mouse lethal potency experiments.

7.3.1 Antivenom administration

Choice of antivenom must be selected by a physician trained and familiar with management of snakebite in Malaysia. All antivenom is administered intravenously.

Adrenaline should be prepared in readiness to treat possible anaphylaxis, that may occur in response to antivenom. This must be prepared before the administration of antivenom (0.5 mg for adults and 0.01mg/kg body weight for children (0.1% solutions, 1 in 1,000 dilution,1mg/ml).

7.3.1.1 Recommended method of administration:

Intravenous infusion

i. Reconstitute freeze-dried antivenom with the solution supplied or 10ml water for injection (WFI). Gently swirl (never shake) to dissolve the freeze-dried antivenom.

ii. Reconstituted solution is further diluted with 5-10ml per kg body weight of NS/D5% for children or 250-500ml NS/D5% for adult.

iii. Antivenom mixture should be infused starting slow (1 to 2 ml/min) over 10-15 min then increased to a higher rate if no reaction to complete within a period of one hour or earlier.

Patient must be monitored during and for at least one hour AFTER completion of intravenous infusion. Serially chart vital signs and clinical progression.

7.4 DOSAGE OF ANTIVENOM

In practice, the choice of an initial dose of antivenom is usually empirical (based on clinical presentation) or based on manufacturer's recommendation. The same amount of antivenom will be required to neutralize a given injected amount of venom regardless of patient age differences. In some severe envenomations, some children may require a greater volume of antivenom because of a lower volume of distribution.

Appropriate antivenom choice based on species, genus and corresponding dose of antivenom is listed in **Table 15** and **Table 16.**

Table 15 : Appropriate snake antivenom for snake envenomation in Peninsular Malaysia

Snake	Common & Scientific name	1st Choice Antivenom	2nd Choice Antivenom	Initial dose of 1st choice antivenom
Cobra	Monocled cobra *(Naja kaouthia)*	QSMI Cobra Antivenin	QSMI Neuro Polyvalent Snake Antivenom	Local - 5-10 vials Systemic - 10 vials Subsequent dose 1-2 hr
	Equatorial spitting cobra *(Naja sumatrana)*	QSMI Cobra Antivenin (*Naja kaouthia*) **cross neutralizing effect*		Local - 5-10 vials Systemic - 10 vials Subsequent dose 1-2 hr
King Cobra	King cobra *(Ophiophagus hannah)*	QSMI King cobra antivenin		10 vials Subsequent dose 1-2 hr

Table 15 : Appropriate snake antivenom for snake envenomation in Peninsular Malaysia				
Snake	**Common & Scientific name**	**1st Choice Antivenom**	**2nd Choice Antivenom**	**Initial dose of 1st choice antivenom**
Krait	Malayan krait *(Bungarus candidus)*	QSMI Malayan krait antivenin		5 vials Subsequent dose 1-2 hr
	Banded krait *(Bungarus fasciatus)*	QSMI Banded krait antivenin		5 vials Subsequent dose 1-2 hr
	Red-headed krait *(Bungarus flaviceps)*	QSMI Neuro Polyvalent Snake Antivenom **cross neutralizing effect*	Nil	5 vials Subsequent dose 1-2 hr
Coral	Banded coral *(Calliophis intestinalis)*	**No antivenom available** (Consider anticholinesterase e.g. Neostigmine + atropine if neurotoxicity develops)		
	Malayan blue coral *(Calliophis bivirgatus)*			
	Spotted coral *(Calliophis maculiceps)*			
Sea snake	*Sea snakes* (eg: *Hydrophis schistosus, Laticauda colubrina)*	CSL Polyvalent Sea snake antivenom	Nil	1-3 vials Subsequent dose 1-2 hr
Pit Viper	Malayan pit viper *(Calloselasma rhodostoma)*	QSMI Malayan pit viper antivenin	QSMI Haemato Polyvalent Snake Antivenom	4 vials Subsequent dose 6 hr
	Wagler's pit viper, Temple pit viper *(Tropidolaemus wagleri)*	**No antivenom available** (Antivenom usually not indicated)		
	Leaf nose palm pit viper *(Trimeresurus wiroti)*			
	Sumatran pit viper *Trimeresurus (Parias) sumatranus*			
	Mountain pit viper *(Ovophis convictus)*			

Table 15 : Appropriate snake antivenom for snake envenomation in Peninsular Malaysia				
Snake	**Common & Scientific name**	**1st Choice Antivenom**	**2nd Choice Antivenom**	**Initial dose of 1st choice antivenom**
Pit Viper	Hagen's green pit viper *Trimeresurus (Parias) hageni*	QSMI Green pit viper antivenin	QSMI Haemato Polyvalent Snake Antivenom	3 vials Subsequent dose 6 hr
	White lipped green pit viper *Trimeresurus (Cryptelytrops) albolabris*			
	Mangrove pit viper *Trimeresurus (Cryptelytrops) purpureomaculatus*			
	Thai peninsula pit viper *Trimeresurus (Popeia) fucata*			
	Tioman island pit viper *Trimeresurus (Popeia) buniana*			
	Cameron pit viper *Trimeresurus (Popeia) nebularis*			
Natricid	Red-neck keelback *(Rhabdophis subminiatus*	Anti-yamakagashi antivenom (Japan)	Nil	
Note: *Subsequent doses are according to the clinical symptoms. *Monocle cobra (*Naja kaouthia*) antivenom has good cross neutralization with the Equatorial spitting cobra (*Naja sumatrana*) venom. *For other types of snake not listed above, consult expert for the choice of antivenom.				

Table 16 : Appropriate snake antivenom for snake envenomation in Sabah & Sarawak

Snake (Family)	Common & Scientific name	1st Choice Antivenom	2nd Choice Antivenom	Initial dose of 1st choice antivenom
Cobra (Elapid)	Equatorial spitting cobra *(Naja sumatrana)*	QSMI Cobra Antivenin (*Naja kaouthia)* **cross neutralizing effect*	QSMI Neuro Polyvalent Snake Antivenom	Local - 5-10 vials Systemic - 10 vials Subsequent dose 1-2 hr
King Cobra (Elapid)	King cobra *(Ophiophagus hannah)*	QSMI King cobra antivenin		10 vials Subsequent dose 1-2 hr
Krait (Elapid)	Banded krait *(Bungarus fasciatus)*	QSMI Banded krait antivenin		5 vials Subsequent dose 1-2 hr
	Red-headed krait *(Bungarus flaviceps)*	QSMI Neuro Polyvalent Snake Antivenom **cross neutralizing effect*	Nil	5 vials Subsequent dose 1-2 hr
Coral (Elapid)	Banded coral *(Calliophis intestinalis)*	**No antivenom available** (Consider anticholinesterase e.g. Neostigmine + atropine)		
	Malayan blue coral *(Calliophis bivirgatus)*			
	Spotted coral *(Calliophis maculiceps)*			
Sea snake (Elapid)	Sea snakes (eg: *Hydrophis schistosus, Laticauda colubrina)*	CSL Polyvalent Sea snake antivenom	Nil	1-3 vials Subsequent dose 1-2 hr
Pit Viper (Viperid)	Kinabalu brown pit viper *Garthius chaseni*	QSMI Green pit viper antivenin	QSMI Haemato Polyvalent Snake Antivenom	3 vials Subsequent dose 6 hr
	Tropidolaemus subannulatus	**No antivenom available** (Antivenom usually not indicated)		
	Sabah green pit viper *Trimeresurus (Popeia) sabahi*			

Table 16 : Appropriate snake antivenom for snake envenomation in Sabah & Sarawak

Snake (Family)	Common & Scientific name	1st Choice Antivenom	2nd Choice Antivenom	Initial dose of 1st choice antivenom
	Kinabalu green pit viper *Trimeresurus (Parias) malcomi*	QSMI Green pit viper antivenin	QSMI Haemato Polyvalent Snake Antivenom	3 vials Subsequent dose 6 hr
	Sumatran pit viper *Trimeresurus (Parias) sumatranus*			
	Bornean palm pit viper *TrimereFsurus borneensis*			
Colubrid	Red-neck keelback *Rhabdophis subminiatus*	Anti-yamakagashi antivenom (Japan)	Nil	

Note:
*Subsequent doses are according to the clinical signs and symptoms.
*Malayan pit viper (*Calloselasma rhodostoma*), Monocle cobra (*Naja kaouthia*) and Malayan krait (*Bungarus candidus*) are not indigenous to Borneo.
*For other types of snake not listed above, consult expert for the choice of antivenom.

7.5 OBSERVATION OF THE RESPONSE TO ANTIVENOM

If an adequate dose of appropriate antivenom has been administered, the following responses may be observed:

7.5.1 General: The patient feels better. Nausea, headache and generalised aches and pains may disappear quickly. This may be partly attributable to a placebo effect.

7.5.2 Spontaneous systemic bleeding (e.g., from the gums): This usually stops within 15-30 minutes.

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

7.5.4 In shocked patients: Blood pressure may increase within the first 30- 60 minutes and arrhythmias such as sinus bradycardia may resolve.

7.5.5 Neurotoxic envenoming of the post-synaptic type (cobra bites) may begin to improve as early as 30 minutes after antivenom, but usually takes several hours. Envenoming with presynaptic toxins (kraits and sea snakes) will not respond in this way. Provision of adequate doses of AV does not always sufficiently arrest or reverse neurotoxicity. These patients require urgent intubation and ventilation in order to prevent respiratory arrest.

7.5.6 Active haemolysis and rhabdomyolysis may cease within a few hours and the urine returns to its normal colour. Renal function will still require close monitoring for several days thereafter.

7.6 CRITERIA FOR REPEATING THE INITIAL DOSE OF ANTIVENOM

7.6.1 Persistence or recurrence of blood incoagulability 6 hours after completion of antivenom administration.

7.6.2 In patients who continue to bleed briskly, the dose of antivenom should be repeated within 1-2 hours.

7.6.3 In case of deteriorating neurotoxicity or cardiovascular signs, the initial dose of antivenom should be repeated after 1-2 hours, and full supportive treatment must be considered.

7.7 ANTIVENOM REACTIONS AND ITS TREATMENT

In the event of antivenom induced anaphylaxis, antivenom should be temporarily withheld, and then resumed at a slower rate once anaphylactic reaction has been treated and resolved.

Refer to **Table 17** below on the possible types of antivenom reaction and its management.

Table 17 : Types of Antivenom Reaction and Its Treatment

Type of reactions	Onset	Manifestations	Treatment
Early anaphylactic reaction	Within 2-180 minutes of starting antivenom	* Itching (often over the scalp) and develops urticaria, 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.	* Adrenaline should be given at the first sign of anaphylactic reaction. Adult: 0.5 mg IM Child: 0.01mg/kg body weight IM (1 in 1,000, 1mg/ml) * The dose can be repeated every 5-10 minutes or start IV infusion at 1 microgm/kg/min if the condition deteriorates. * If the patient is having coagulopathy IM injection should be avoided, proceed directly to IV infusion. **Additional treatment**: a. Antihistamine (anti-H1 and anti-H2 blocker) *Anti H1:Chlorpheniramine Adult: 10 mg IV Child: 0.2 mg/kg by IV over a few minutes. * Anti H2:Ranitidine Adult: 50 mg IV Child: 1 mg/kg by IV over a few minutes. b. IV Hydrocortisone Adult: 2-4mg /kg, Child: 2-4mg/kg, maximum 200mg Corticosteroid can prevent delayed and recurrent anaphylaxis. **In pyrogenic reactions** the patients must also be cooled physically and with antipyretics (e.g., paracetamol by oral or suppository) IV fluids given to correct hypovolemia
Pyrogenic reaction	May develop 1-2 hours after treatment	* Shaking chills (rigors), fever, vasodilatation and a fall in blood pressure. * Febrile convulsions may be precipitated in children.	

Late (serum sickness type) reaction	Develop 1-12 days (mean 7 days) after treatment	Fever, nausea, vomiting, diarrhoea, itching, recurrent urticaria, arthralgia, myalgia, lymphadenopathy, periarticular swellings, mononeuritis multiplex, proteinuria with immune complex nephritis and, rarely, encephalopathy.	* Late reactions may respond to a 5-day course of oral antihistamine Chlorpheniramine: Adult: 2 mg six hourly Child: 0.25 mg/kg/day in divided doses. * Patients who fail to respond in 24-48 hours should be given a 5-day course of Prednisolone: Adult: 30-60 mg/day in divided doses for 5-7 days Child: 0.7- 1mg/kg/day in divided doses for 5-7 days.

CHAPTER 8 :

TREATMENT OF THE BITTEN PART

8. TREATMENT OF THE BITTEN PART

Prior to a more comprehensive characterization of the pathophysiology of envenomation, local effects of envenomation were often incorrectly and prematurely assigned to compartment syndrome. In fact, compartment syndrome is rare after snakebite envenomation. Historically, fasciotomy was inappropriately performed on a large number of envenomed patients, and this incorrect intervention not only was ineffective in treating the envenomation, but also caused unnecessary and severe disability, as well as deformity in a large number of patients. It is now understood and consensus-supported that antivenom is the effective treatment of both local injury and systemic sequale.[37]

Compartment syndrome caused by snake envenomation differs in two important ways. First, snake envenomation causes superficial edema and increased subcutaneous tissue pressure that often mimics compartment syndrome.[38]

In addition, it has been shown when venom is injected into a muscle compartment, myonecrosis is related to the action of the venom, and only to a lesser extent to increase the compartment pressure.[39]

It has been found that antivenom reduces intracompartmental pressure and prevents myonecrosis in animal studies. [38]

In any case fasciotomy must not be contemplated until anti-venom therapy has been fully optimized and haemostatic abnormalities have been corrected.

Fasciotomy may result in haemorrhage, secondary infection, disfiguring scars, contractures, nerve damage, significantly lengthening the course of treatment and frequently associated with permanent loss of limb function.[39] To avoid unnecessary surgery, confirmation in the form of measured tissue pressure and serial clinical examination for signs and symptoms of compartment syndrome must be made.

The clinical signs and symptoms of compartment syndrome include [39]:-

1. Pain out of proportion to injury
2. Increased compartmental Pressure
3. Paresthesia and
4. Paralysis
5. Pulselessness or weak pulse

Because snake envenomation can often mimic compartment syndrome, the diagnosis of compartment syndrome should not be solely made based on “soft signs” as above.[38]

Tissue pressure measurement is the preferred method to establish or to disapprove the diagnosis of compartment syndrome and should be performed whenever available. [38] The tissue pressure should be measured objectively using saline manometers or newer specialised equipment.

In orthopaedic practice, intracompartmental pressures exceeding 40 mmHg (less in children) may carry a risk of ischemic necrosis (e.g. Volkman‟s ischemia or anterior tibial compartment syndrome). However envenomed muscle may not be saved by fasciotomy.

In anatomical locations where tissue pressure measurement cannot be performed (e.g digits, foot and hand) , the diagnosis of compartment syndrome should only be made when clear evidence of neurological dysfunction an/or vascular compromise are present through serial clinical examination and assessment of arterial blood flow by Doppler.[38]

Clinical vigilance is essential to this approach. Patients who fail to improve after anti venom administration may require operative intervention. [38] However the decision of surgical intervention should be made after a multidiciplinary expert consultation.

Necrotizing fasciitis has been effectively managed with broad spectrum antibiotics, antivenom and debridement.

Debridement of necrotic tissue late in the clinical course is appropriate and should follow generally accepted surgical principle. Washout might be beneficial in cases involving venom injection into a joint. [38]

Debridement of necrotic tissue can be done when there is a clear demarcation to reduce the extent of debridement.[38]

CHAPTER 9:

FOLLOW UP & REHABILITATION

9. FOLLOW UP AND REHABILITATION

9.1 FOLLOW UP AND FURTHER MANAGEMENT:

9.1.1 Patients who have not suffered any signs or symptoms of envenomation can be discharged home after a suitable observation period.

9.1.2 Patients who have suffered both local and systemic envenomation will require follow up at a suitable time.

9.1.2.1 Systemic envenomation:

9.2.2.1.1 Patients who have received antivenom therapy should be advised to return to hospital if signs and symptoms of antivenom related illness develop.

9.2.2.1.2 Depending on patients" clinical condition and status on discharge follow up may be required for reevaluation and repeat investigations ordered as necessary.

9.2.2.1.3. Lab testing 5-7 days post discharge in order to assess any recurrence after crotaline envenoming is required. Most of the recurrence is lab detected coagulopathy, but variable petechiae may develop, and uncommonly active bleeding, but there have been several serious instances of recurrence bleeding, and 1 well-documented fatality. The risk of significant recurrence is obvioulsy increased with more severe coagulopathic envenoming and with Fab

antivenom, but these have occurred after less serious envenoming treated with intact IgG or F(ab')2 antivenom.

9.1.2.2 Local envenomation:

9.1.2.2.1 Patients who have significant tissue necrosis with surgical intervention would usually require daily dressing and careful wound management to monitor the healing process as well as signs of infection.

9.1.2.2.2 Co-morbidities such as diabetes mellitus and immunodeficiencies can aggravate or prolong the healing process.

9.1.2.2.3 Referral to plastic surgery may be required to reconstruct soft tissue defects for cosmetic purposes. Correction of deformities and contractures to improve functionality should be performed by an orthopaedic surgeon.

9.1.2.2.4 Early referral to a physiotherapist or occupational therapist may be required as necessary by the managing surgeons and physicians. Treatment should be designed to facilitate to as great an extent as possible the return of the functional

9.2 REHABILITATION

Rehabilitation of the snakebite patient may be an arduous process depending on the injury sustained and circumstances leading to the bite. The physical and psychosocial components of rehabilitation should be addressed.

9.2.1 Physical rehabilitation:

Patients, who have suffered significant injury to their limbs with contractures not amenable to surgical correction, or those who have required amputation, will require intensive rehabilitation in order to achieve the greatest possible extent of functional capacity.

Persistent local sequelae of local envenoming may include stiffness and induration due to sclerosis of veins, lymphatic and tissue planes through which the venom has spread. This may lead to severe deformity and tissue loss especially dermonecrosis requiring skin grafting or gangrene requiring debridement and amputation.

The physiotherapist and occupational therapist play an important role in physical rehabilitation. Patients should be able to perform their daily necessary routine as well as return to work. This physical rehabilitation is vital to prevent the onset or worsening of psychosocial disorders.

The success or failure of physical and occupational therapy can directly impact the future work capacity and income (often constituting most or all of a given family‟s financial support) of rehabilitating patients with livelihoods based in farming or manual labor.

9.2.2 Psychosocial rehabilitation:

The circumstances leading to the snakebite can result in post-traumatic stress disorders which may prevent the patient from leading a normal life. Patients bitten at their workplace may be reluctant to return to work. Those bitten in their own homes may develop sleep disturbances.

Some patients who showed no signs or symptoms of envenomation may develop significant post- traumatic stress syndrome due to the frightening experience of being bitten and false beliefs about envenomation. Public education may lead to increased correct perceptions about snakes and the risks/prevention of snakebites. This could prevent misconceptions, and facilitate effective prevention of envenomation.

Family members and even communities may be affected when a member suffers a catastrophic event such as death or a traumatic loss of function following a snakebite. The patient may be the sole bread winner for the family and/or is an important contributor to the community especially in an agricultural setting. Counseling and financial support from social welfare and associations related to certain occupations should be made available to patients and extended to their families and communities to enable them to function as close as possible to normal.

Referral to a psychiatrist or counselor should be provided as indicated. A recent study by [41] in Sri Lanka showed a brief psychological intervention which included psychological first aid and psychoeducation plus cognitive behavioural therapy provided by a non-specialist doctor appeared to reduce psychiatric symptoms and disability after snakebite envenoming but not depression or post-traumatic stress disorder.

CHAPTER 10 :

APPENDIX

Snakebite Chart: Serial Clinical Assessment

GCS = Glascow coma scale, **BP**= Blood pressure, **PR**= Pulse rate, **RR**= Respiratory rate

SPO2 = Oxygen saturation, **RPP** = Rate of Proximal Progression of swelling

Date	Time	GCS (3-15)	BP (mmHg)	PR (bpm)	RR	SPO2	Pain Score (0-10)	RPP (cm/H)	Tender Lymph node (Y/N)

Serial blood results every 4 - 6 hours for the first 24 to 48 hours.
For Elapidae bite (cobra, krait & coral) no need for serial coagulation profile unless indicated.

Date	Time	WBC	Hb	Platelet	PT	aPTT	INR	CK

Snakebite Serial Assessment Monitoring Chart

Perform serial assessment of patient clinical condition
Perform at least hourly assessment for the first 12 hour.
Inform your doctor immediately if the patient develop any of the signs / symptoms
The chart below summarize commonly observed signs and symptoms due to snake envenomation.

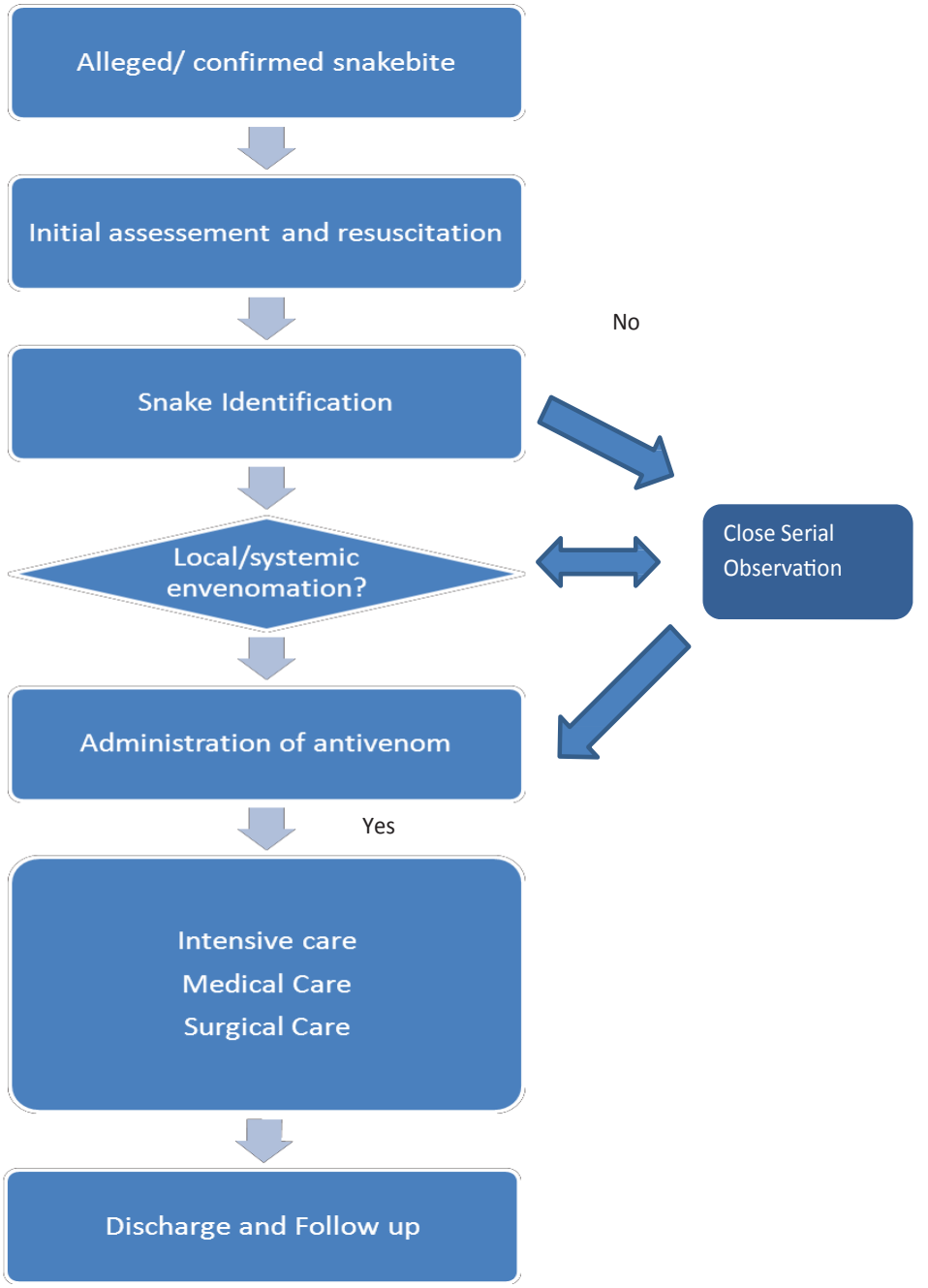
Mark (✓) if present. Mark (—) if absent .

Patient name:_____ RN: _____

Date							
Time							
General							
Drowsiness							
Vomiting							
Abdominal pain							
Local effect	Cobra and Pit viper						
Dermonecrosis (purplish bruise). Measure size if present							
Blister/ Bullae							
Neurotoxic effect	Elapids (Cobra, Krait, Coral and Sea snake)						
Ptosis *(ask patient to look up and observe the upper eyelids retracting fully or lagging)*							
External opthalmoplegia (*paralysis of eye muscles*)							
Dilated pupils							
Broken neck sign *(Paralysis of neck muscles)*							
Swallowing difficulty *(bulbar paralysis)*							
Speaking difficulty							

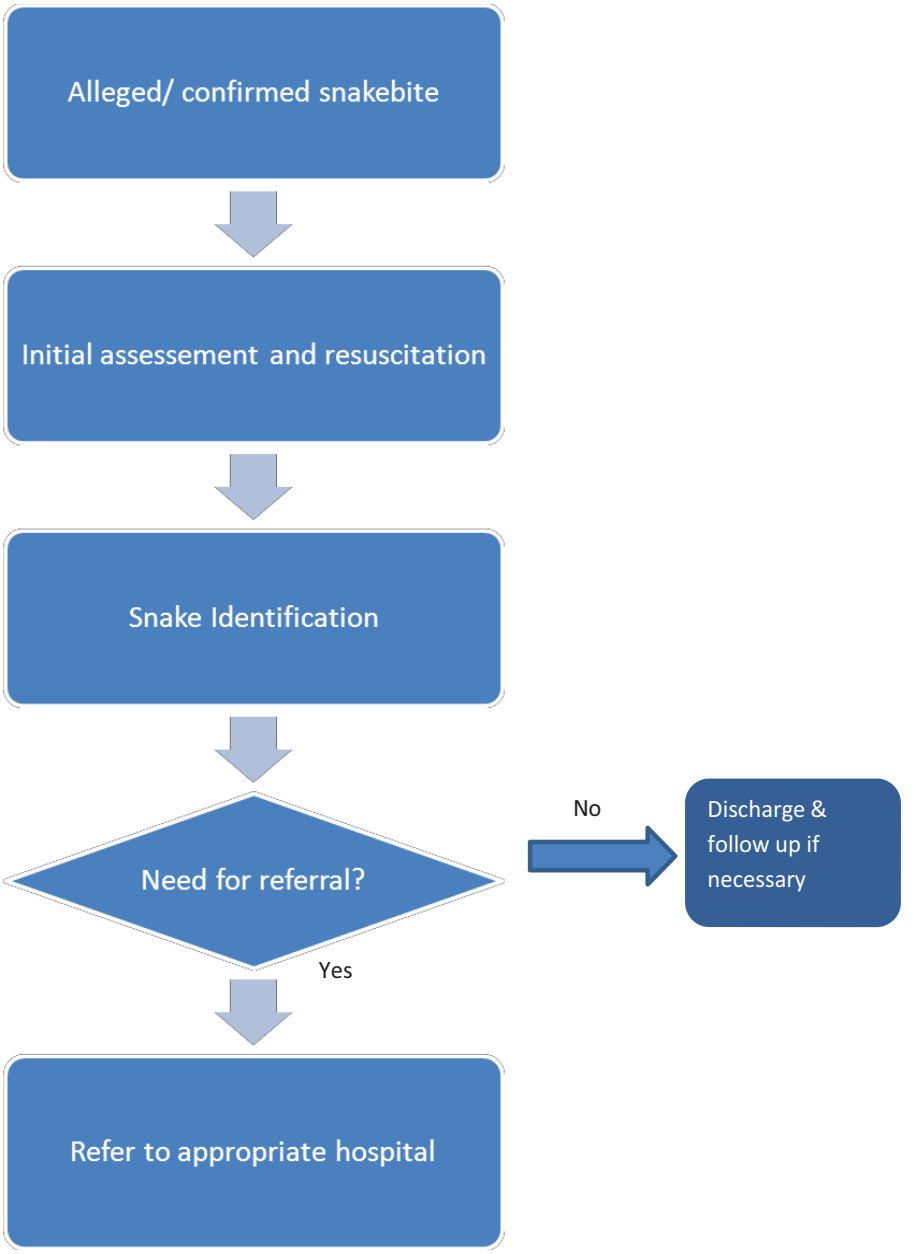
Poor respiratory effort / PEFR							
Haematotoxic effect	Pit viper						
Bleeding from bite site							
Other spontaneous bleeding (state site)							
Rhabdomyolysis	Sea snake and Coral snake						
Generalised muscle pain & muscle tenderness							
Dark urine (myogloninuria)							

FLOWCHART MANAGEMENT OF SNAKEBITE IN HOSPITAL



Specialist/Consultant can be consulted at any stage of management

FLOWCHART MANAGEMENT OF SNAKEBITE IN HEALTH CLINIC



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