Actions of snake venoms

Lecture 2: Snake Bite Management Course

Introduction

- Venoms are complex mixtures of bioactive toxins produced in highly evolved salivary glands
- Comprised of proteins, polypeptides and peptides
- Work by exerting toxic effects on a wide variety of different tissue systems in the body
- Many are among the most toxic substances known
- Understanding how the toxins in snake venoms exert their effects is critical to improving the care of snake bite patients

Biological role of snake venoms

- Venom is used primarily as a means of capturing and subduing prey animals
- It may also have a role in digestion as many venom components break down tissue
- The use of venom for defence is what brings snakes into conflict with human beings
- Amount of venom injected in a bite depends on the intended purpose, for example, defensive bites may result in injection of large amounts of venom

Venomous or poisonous?

- There are no “poisonous” snakes
- Poisons are passively acquired toxins produced by plants, animals and microbes; mainly for defence
- A poisonous animal has no system for delivering poison
- There is no ‘injection’ system for a poison
- Venoms are mixtures of toxins produced in specialized glands, that an animal uses a specific biting mechanism to deliver into its prey

General effects of snake venoms (1)

- Cytotoxins
  - A wide range of toxins are able to destroy cell tissue
  - Some increase membrane permeability leading to oedema and swelling
  - Cell membrane hydrolysis and proteolysis
- Haemorrhagins
  - Damage blood vessel walls resulting in haemorrhage
- Haemolysins
  - Damage blood cells, endothelial tissue and cell membranes

General effects of snake venoms (2)

- Procoagulants
  - Responsible for disruption of normal haemostasis by causing abnormal activation of blood factors
  - Factor depletion is rapid and results in consumption coagulopathy leading to incoagulable blood
  - Fatal haemorrhage can occur
- Platelet toxins
  - May either initiate aggregation or inhibit it
  - Contributes to bleeding disorder with thrombocytopenia common, especially after pit viper bites

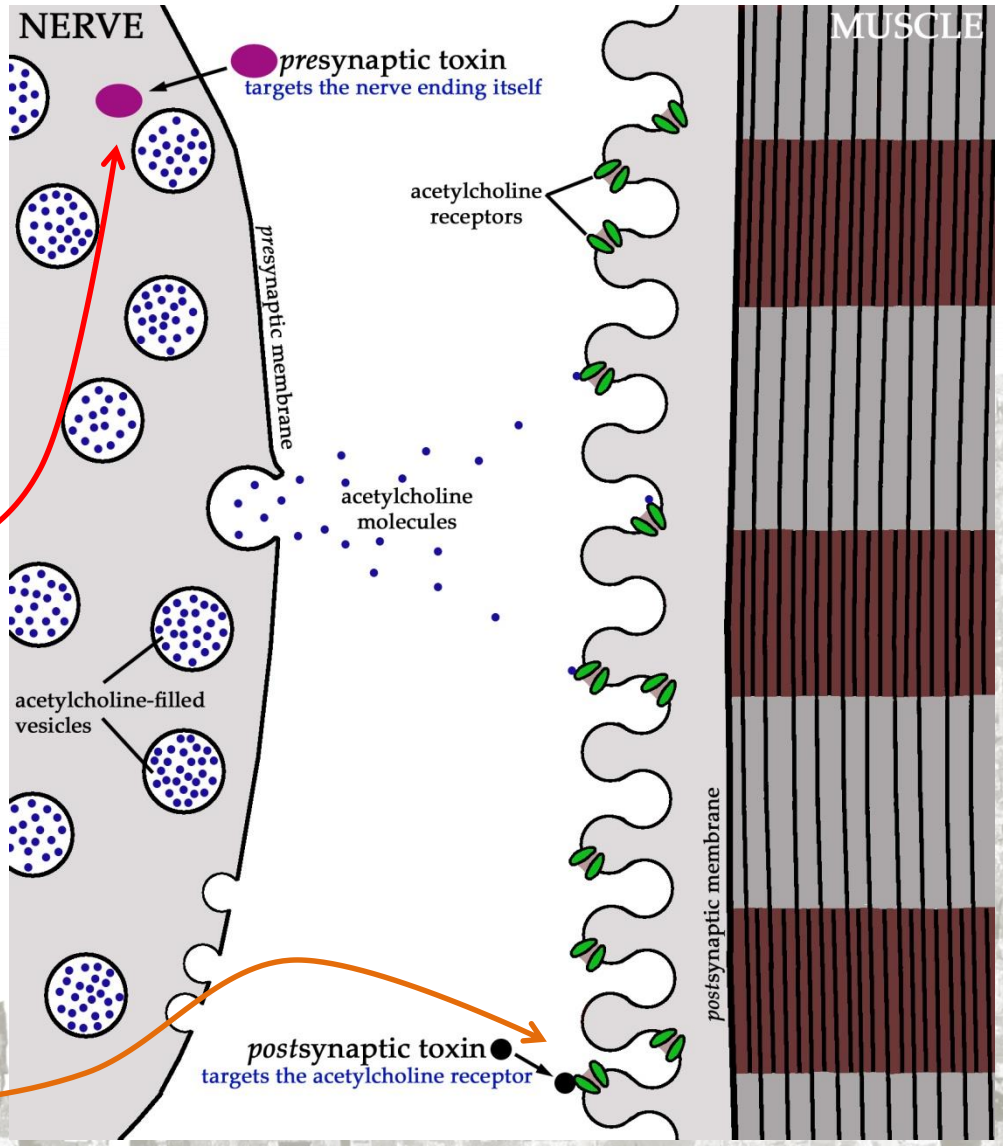
General effects of snake venoms (3)

- Neurotoxins
  - α-neurotoxins block acetylcholine binding to receptors in neuromuscular synaptic cleft
  - β-neurotoxins target nerve terminals and destroy them from inside after being internalised by endocytosis
  - Some species contain both types of toxins
  - Both cause paralysis by preventing the successful generation of action potentials
  - While paralysis due to α-neurotoxins can be reversed effectively with antivenom or anticholinesterases, the destructive effects of β-neurotoxins are not reversible

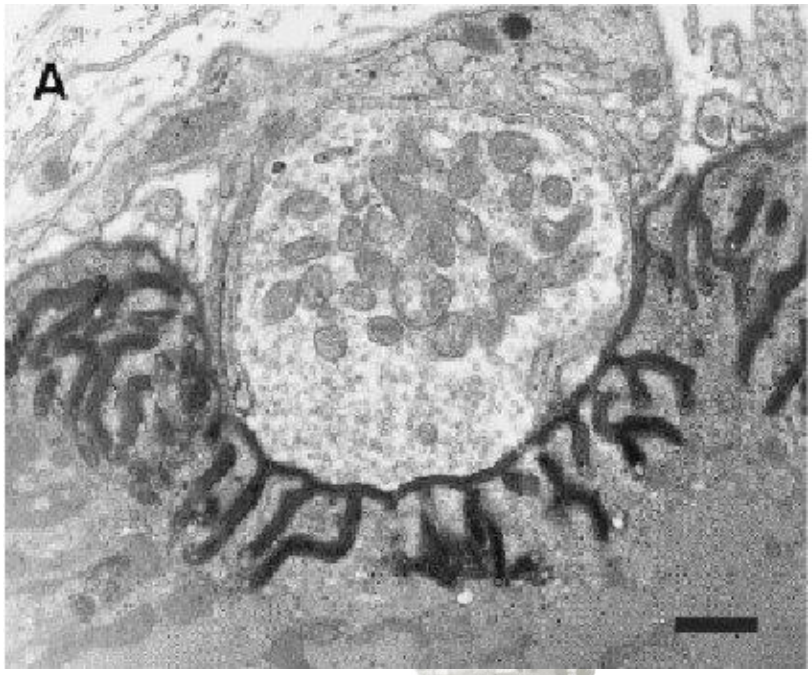
Target sites for neurotoxins

β-neurotoxins target binding sites on the axolemma of the nerve cell, and are taken up inside the cell by normal endocytosis. Once inside the cell they hydrolyse internal organelles, potentiate Ca^{2+} overload and cell death.

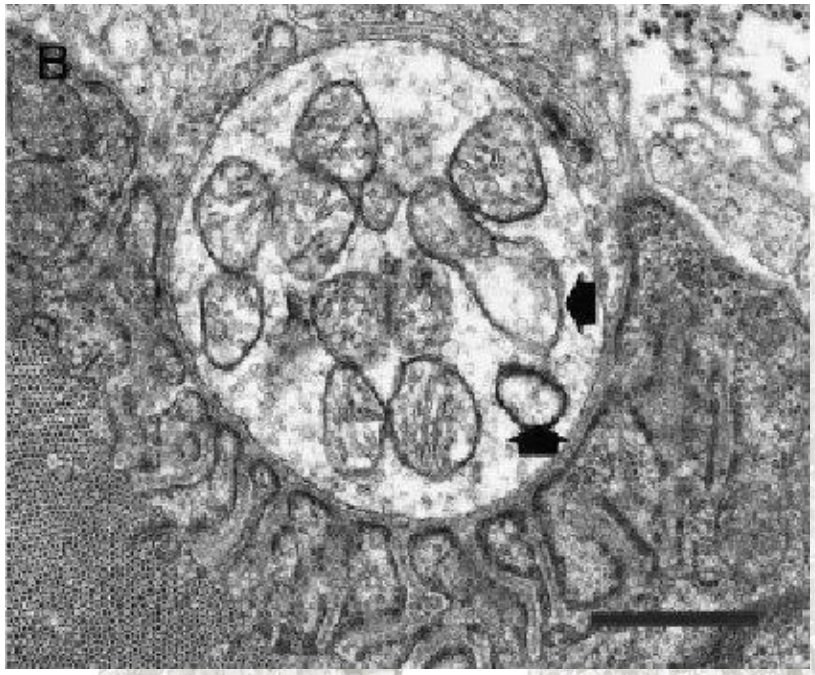
α-neurotoxins target the acetylcholine receptors embedded in phospholipid membranes of muscle cells and block action potential generation by competing for the same binding site as acetylcholine molecules.



Destructive activity of β-neurotoxins (1)



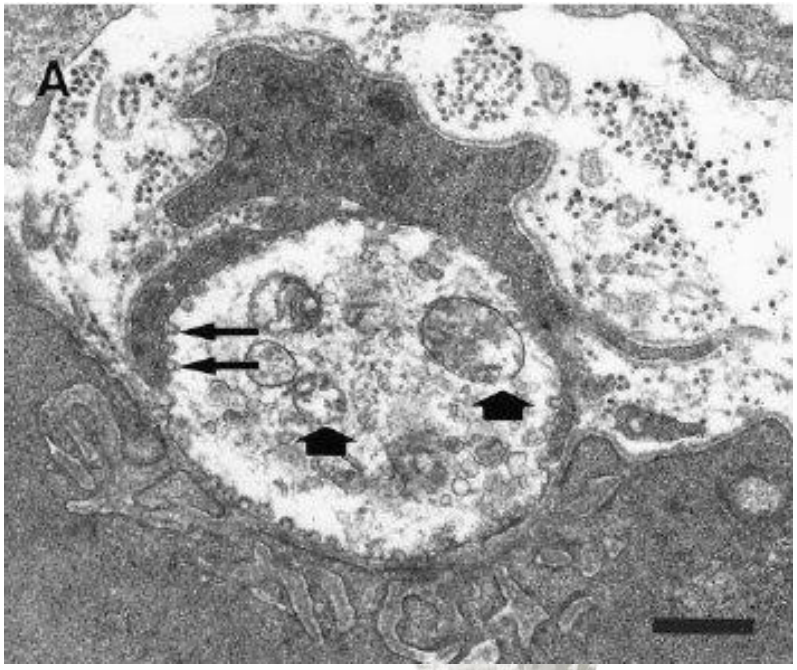
Normal neuromuscular junction in rat soleus muscle prior to subcutaneous injection with a β-neurotoxin (taipoxin)



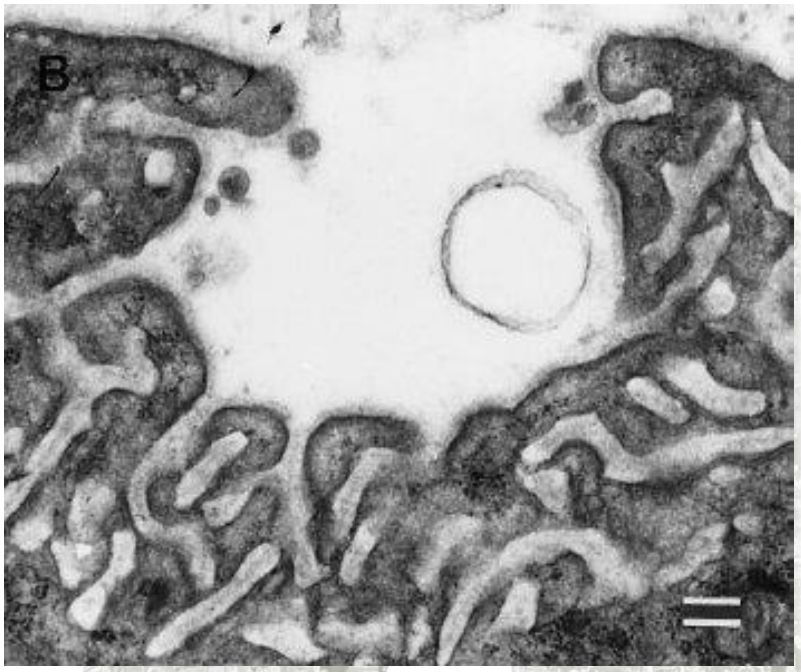
Rat soleus muscle NMJ one hour after s.c. injection with 2 µg of β-neurotoxin into the hind limb.

Arrows indicate depletion of synaptic vesicles and loss of cristae in damaged mitochondria

Destructive activity of β-neurotoxins (2)



NMJ in rat soleus muscle 24 hours after s.c. injection with β-neurotoxin.



NMJ in rat soleus muscle showing complete destruction of the nerve terminal.

Damaged mitochondria (heavy arrows) and clathrin-coated Ω-shaped indentations on inside of nerve terminal membrane (small arrows).

General effects of snake venoms (4)

- Myotoxins
  - Many β-neurotoxins are also potent myotoxins and destroy muscle through a similar mechanism to the one used to destroy nerve cells
  - Rhabdomyolysis can lead to indirect nephrotoxicity due to accumulation of cellular debris in kidney nephrules
  - Anuria and acute renal failure may result
- Nephrotoxins
  - The venom of Russell's vipers contains at least one toxin that can induce direct nephrotoxicity by causing renal tubular necrosis

Specific venom effects

- Each species produces a unique mixture of toxins with a range of different actions
- Variation in venom composition may even occur within the same species of snake
- Venom composition may also vary in an individual snake throughout its life, and sometimes even at different times of the year
- An understanding of what the venom of each type of snake can do, can sometimes help identification of the species responsible for a case of envenoming

Malayan pit viper

(Calloselasma rhodostoma)

- Contains haemorrhagins and several procoagulant toxins that destroy blood vessel walls or cause coagulopathy
- Platelet toxins can result in severe thrombocytopenia
- Cytotoxins, haemorrhagins and myotoxins contribute to severe local effects and shock
- Pain, swelling, oedema, blisters, bullae and ecchymoses, deep tissue necrosis and gangrene may occur
- Bleeding may be very severe

Indo-Chinese Russell's Viper

(Daboia siamensis)

- Venom contains activators of Factor X, Factor V and Factor IX
- Phospholipase A_2 toxins have neurotoxic, myotoxic, oedema-producing, indirectly haemolytic and cytotoxic actions
- A direct nephrotoxin contributes to acute renal failure
- Disintegrins and lectins inhibit platelet aggregation, and there are many minor components
- Bleeding and renal failure are two most important effects
- Fatal secondary shock common

White-lipped pit viper

(Cryptelytrops albolabris)

- Toxins that cause both platelet aggregation, and the inhibition of aggregation are present
- α-fibrinogenases activate both fibrinogen and plasminogen, and a trypsin-like serine protease also activates plasminogen
- PLA_2 cause local oedema
- Many bites cause no more than local pain, swelling and oedema
- Bleeding occurs in some patients and may be severe
- Local necrosis and shock can occur and fatalities are recorded

Other ‘green pit vipers’

(Cryptelytrops macrops and *Viridovipera vogeli)*

- Venoms contain similar toxins to those present in white-lipped pit viper venom but effects thought to be less severe
- Fibrinolysis & thrombocytopenia may lead to incoagulable blood
- Local pain, swelling and oedema are most common effects
- ‘Green pit viper’ bites rarely cause severe local injury and interventions such as fasciotomy should not be considered with definitive proof of compartment syndrome

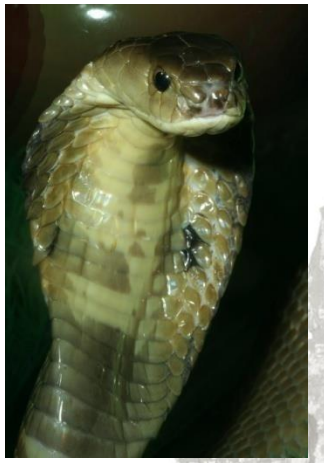
Monocellate cobra

(Naja kaouthia)

- Rich in postsynaptic neurotoxins, PLA_2, cardiotoxins, cobra venom factor, CRISP toxins, cytotoxins & platelet aggregation inhibitors
- α-cobrotoxin blocks nicotinic & muscarinic ACh receptors
- Kaouthiagin cleaves vWF and disrupts platelet aggregation
- Cardiotoxins activate tissue PLC, release Ca2+, cause haemolysis, muscle contracture, myolysis & cytolysis
- Subcutaneous necrosis occurs
- Paralysis occurs in up to 35%

Indo-Chinese spitting cobra

(Naja siamensis)



- Venom contains long- and short-chain postsynaptic α-neurotoxins
- Cytotoxic cardiotoxins, PLA2 with myotoxic and necrotic activity and metalloproteinase platelet activation inhibitors also present
- This snake will spit venom with little provocation and with great accuracy at the face and eyes.
- Ocular contact causes irritation, pain, conjunctivitis, excessive tear production and discharge
- Superficial corneal opacity with normal acuity has been reported

Malayan or blue krait

(Bungarus candidus)

- Effects are almost exclusively paralytic as the venom is rich in both postsynaptic α-neurotoxins and presynaptic β-neurotoxins
- The β-bungarotoxin homologues cause irreversible paralysis by destroying nerve terminals
- Neurotoxins target muscarinic and nicotinic receptors
- Response to antivenom and to anticholinesterases is often poor
- Good airway management and ventilation is absolutely essential if fatalities are to be avoided

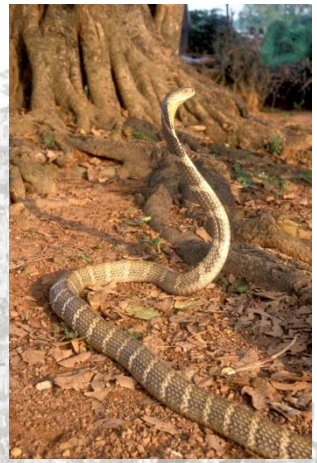
Banded krait & Red-headed krait

(Bungarus fasciatus and *Bungarus flaviceps)*

- Like the Malayan krait, both of these species produce potent neurotoxic venom containing both postsynaptic α-neurotoxins and presynaptic β-neurotoxins
- Although both are uncommon causes of snake bite, antivenom response may be poor, and in the absence of good airway and breathing support death is likely
- Krait bites have been reported to result in long-term residual parasympathetic neuropathy

King cobra

(Ophiophagus hannah)



- This snake has one of the highest venom yields of any species and may inject 3-4 mL when biting
- Venom is rich in postsynaptic neurotoxins, including a unique β_1/β_2-adrenergic receptor blocker, β-cardiotoxin
- Cytotoxins, platelet aggregation inhibitors and a fibrinogenolytic toxin are also present.
- Bites can result in severe local swelling, occasional necrosis and severe neurotoxicity.
- Death may result

Marine seasnakes

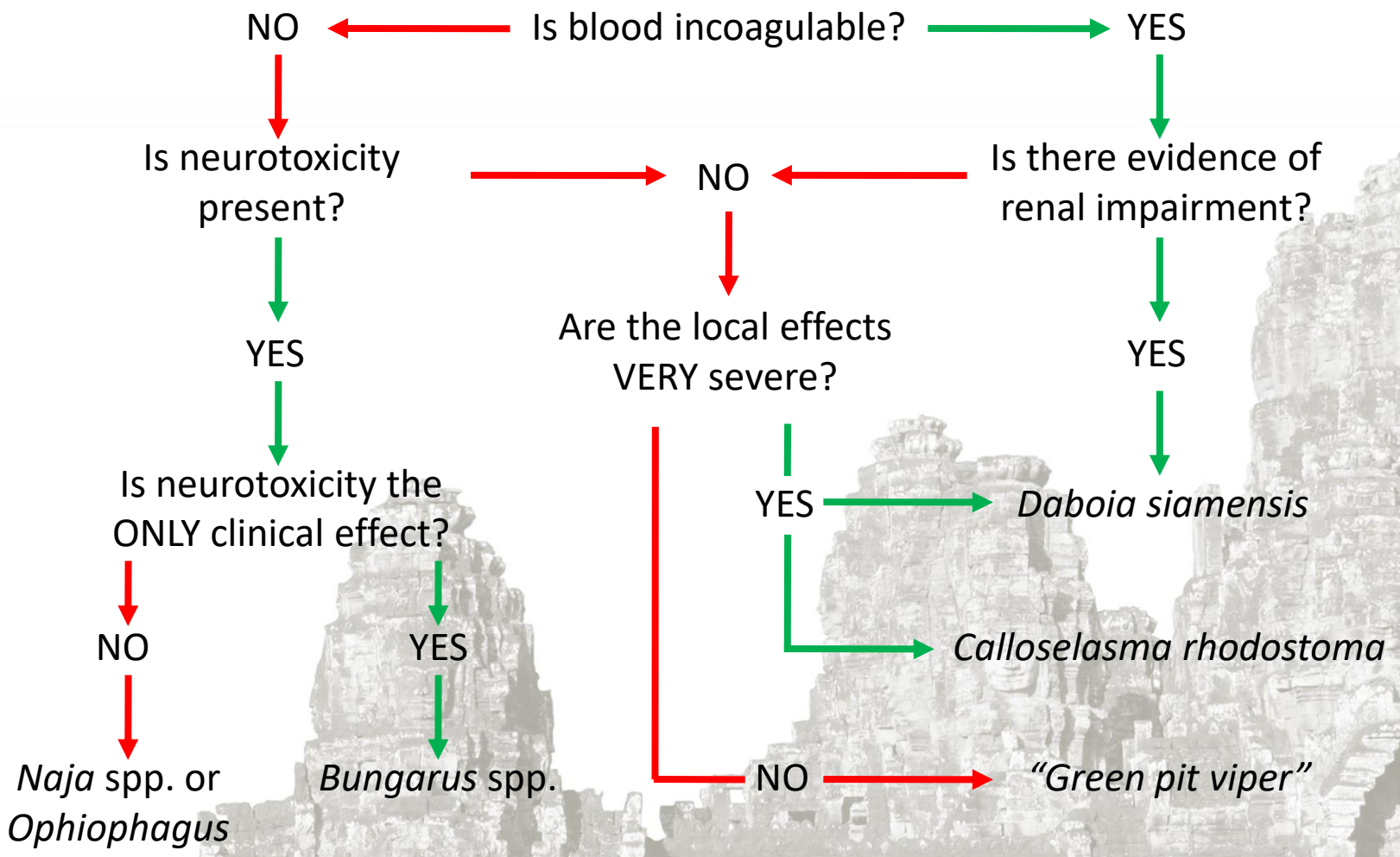
(Several species from different genera)

Beaked sea snake (*Enhydrina schistosa*)

Spine-bellied sea snake (*Lapemis hardwickei*)

- Some species such as the beaked sea snake have very potent neurotoxic venom that is also myotoxic
- Paralysis and rhabdomyolysis are the major clinical effects
- Mortality rates can be very high, often due to paralysis and renal failure
- Fisherman are especially at risk as the snakes are caught in their nets.

Presumptive identification



Summary (1)

- Venoms are diverse mixtures of different types of toxins that vary between species
- Incoagulable blood is an indication of pit viper envenoming
- Very severe local tissue destruction may be caused by *Calloselasma rhodostoma* or *Daboia siamensis*
- *Daboia siamensis* bites may result in acute renal failure
- Bites by ‘green pit vipers’ tend to cause less severe local tissue injury

Summary (2)

- Bites by true cobras (*Naja*) and king cobras cause local tissue injury that rarely penetrates below the subcutaneous tissue bed
- Bites by kraits (Bungarus) only cause paralysis, but the response to antivenom may be poor
- King cobra envenoming should be suspected if the snake was more than 2.5 metres long and the bites involves local injury and neurotoxicity
- The Indo-Chinese spitting cobra can cause damage to the eyes if venom is spat into them.