Bite Me!
An Overview of Australian Snakebite Envenomation

MORPHOLOGY OF A VENOMOUS SNAKE

- nostril
- venom canal
- fang
- tooth
- glottis
- forked tongue
- eye
- head
- poison gland
- neck
- scale

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Introduction

- Australia has a lot of dangerous creatures
- A lot of these are venomous
- A lot of these venomous creatures are snakes
- A lot of these venomous snakes look a bit similar
- A lot of these similar looking, venomous snakes have potentially lethal bites and different treatments
- A lot of this makes managing them all a bit tricky
Contents of Presentation

- Epidemiology of snake bite in WA
- Snake Classification
- Composition of Snake Venom
- Physiology of NMJ and Coagulation Cascade
- Action and clinical picture of envenomation from different snake species
- Practical management of snake bite
- Venom detection and anti-venoms
- Summary
Spiders: 54%
- 5-10,000 bites/year
- Mostly Red Back spider bites (<20% requiring specific treatment)
- Funnel Web spider bites (<50/yr)
- Necrotic Arachnadism (<100/yr)
- Paralysis Ticks (very common but paralysis very few)

Insects: 38%
- Ants, bees, wasps

Marine: 4%
- Box Jellyfish (<50/yr)
- Blue-ringed Octopus (10/yr)
- Venomous fish stings (Stonefish <10/yr)
Snake Bite Information

- Australian Poisons Centre:
  - 1,000 – 3,000 cases per year = 3%
  - Up to 200 requiring anti-venom
  - Not a notifiable disease
  - *Sutherland SK & Leonard RL. MJA 1995;163:616-618*

- World Health Organisation Data:
  - Global mortality 50-100,000 *hospital* deaths / year
  - Significant chronic disability in survivors
    - Physical handicap (necrosis, amputations)
    - Systemic disease
Size of the Problem

- Despite advances in the past 20 years with first-aid, venom detection, supportive care and the use of anti-venom, the number of snakebite fatalities appears to have risen
  - *White J. Emergency Med 2000;12:204-6*
- Between 1982 – 1992, 1.8 deaths per year
  - *Sutherland SK. MJA 1992;157:734-739.*
- Between 1992-1994, 3.7 deaths per year
  - *Sutherland SK, Leonard RL. MJA 1995;163:616-8*
Epidemiology of Snake Bite in Perth

- Admissions for suspected snake bite to the Perth adult teaching hospitals, 1979 to 1988
- 99 definite bites, 193 cases total
  - 53 envenomations (3 in snake handlers)
  - 30 equivocal envenomations
  - Dugite commonest snake bite (often coagulopathy only)
  - Tiger and Gwardar common
- 36% of snake genus identified by venom detection kits
  - All brown or tiger snake genus
- At least 5 fatalities in last 10 years
Epidemiology of Snake Bite in Perth

- **Use of Anti-venom:**
  - **RPH:**
    - 46 patients received anti-venom
    - 34 patients definitely envenomed
  - **SCGH:**
    - 15 patients received anti-venom
    - 13 patients definitely envenomed
  - **FH:**
    - 11 patients received anti-venom
    - 11 patients definitely envenomed
Snake Classification

- Kingdom: Animalia
- Phylum: Chordata
- Subphylum: Vertebrata
- Class: Reptilia
- Order: Squamata
- Suborder: Serpentes
Serpent Superfamilies

- **Henophidia:**
  - Boas, pythons and relatives

- **Typhlopoidea:**
  - Blind snakes

- **Xenophidia:**
  - Colubridae (back fanged)
  - Elapidae (front fanged)
  - Hydrophiidae

- **Australian Species**
  - 86 species of elapids
  - 33 species of hydrophiidae sea snakes
  - 2 species of acrochordidae sea snakes
  - 11 species of colubridae
  - 15 species of boas
  - 31 insectivorous blind snakes
  - **178 in total**
Australian Snakes

- 25% of world land snakes = venomous
- 70% of Australian land snakes = venomous

- 200 species of elapids, worldwide
  - 86 of these are specific to Australia
  - 20 of these are deadly
  - 12+ are potentially dangerous
Elapid Land Snakes of Australia

- Brown snakes
- Black snakes
- Tiger snakes
- Taipans
- Death adders

All ‘orrible
Snake Venom

- Venom is a substance which is capable of producing toxic reactions when introduced into another animal

- Purpose:
  - Incapacitates prey
  - Aids digestion of prey
  - Deterrent to predators

- 50% snake bites are dry bites (no venom injected)
Snake Venom Toxicity

- **Standard measure =** \( \text{LD}_{50} \) in mice
  - Various routes of administration
  - Number / weights of test animals
  - Venom binding to lab glassware
  - Milking may not produce *in vivo* venom composition
  - Quantity of venom important

- **Australia has dubious distinction of holding most dangerous snakes in the world (18/25):**
  - Inland Taipan LD50 = 0.025mg/Kg (250,000 mice, 100 men)
  - Common Brown snake = 0.053mg/Kg
  - Taipan = 0.099mg/Kg
Composition of Snake Venom

- **Enzymes:**
  - Phospholipases
  - Phosphodiesterases
  - Amino acid oxidases
  - Acetylcholinesterase
  - Proteolytic enzymes
  - Arginine esterases
  - Nucleosidases
  - Hyaluronidase

- **Peptides**
  - Neurotoxins
  - Cytotoxins
  - Myotoxins
  - Cardiotoxins
  - Disintegrins
Snake Venom Toxicity

- Local effects
- Systemic effects:
  - Neurotoxicity
    - Pre- and post-synaptic
  - Haemotoxicity
  - Myotoxicity
  - Nephrotoxicity
  - (Cardiotoxicity)
Neuromuscular Junction: Summary

- Interchange between somatic nerve ending and muscular end-plate
- Nerve synthesises Acetylcholine and stores it within vesicles
- Nerve stimulation causes vesicle migration to nerve surface, rupture and ACh release into cleft
- ACh receptors open post-junctional voltage gated Na$^+$ channels
- Na$^+$ influx initiates skeletal muscle contraction
- ACh detaches from receptor and is destroyed by acetyl cholinesterase
NMJ Morphology

- Motor neurones (group α fibres) run from ventral horn of spinal cord (monosynaptic)
- Branches repeatedly on muscle approach = motor unit
- Myelin sheath lost and replaced by Schwann cell cover
- Nerve separated from muscle by 20nm junctional cleft
- Nerve and muscle held in tight alignment by basal lamina
- Muscle layer corrugated into primary and secondary clefts
- ACh receptors on cleft shoulders (5 million per junction)
- Na+ channels exist deep within the clefts
**NMJ: Nerve Action Potential**

- Nerve action potential begins with sodium propagation down axon = *saltatory conduction*
- This depolarising voltage opens Ca$^{2+}$ channels
- Ca$^{2+}$ influx into cell causes ACh release into synaptic space via mobilisation of vesicles
- ECF [Ca$^{2+}$ ] controls quantal release of ACh
- Ca$^{2+}$ release is limited by Ca$^{2+}$-activated K$^{+}$ channels
- Ca$^{2+}$ entry explains post-tetanic potentiation
- Calcium channels (P-type and L-type) responsible for ACh release
NMJ: Calcium Channels

- *Voltage dependent P channels* are found only at nerve terminals.
- Located immediately adjacent to active zones.
- Targeted in Eaton-Lambert Syndrome.
- Antagonised by bivalent inorganic cations eg Mg$^{2+}$.
- Explains rationale behind Mg$^{2+}$ use in pre-eclampsia.
- Not affected by calcium channel blockers, which block *L-type channels*.
- Prolonged n.m block with non-depolarising agents and calcium channel blockers.
NMJ: Synaptic Vesicles

- 2 pools of vesicles:
  - VP1 = reserve store
  - VP2 = readily releasable store
- Calcium docks to vesicle wall and causes ACh exocytosis
- Most vesicles fuse with release sites (VP2 stores)
- SNARE protein mediated (soluble N-ethylmaleimide-sensitive attachment protein receptors)
  - Synaptobrevin = vesicle protein
  - Syntaxins = plasma membrane proteins
  - Synaptotagmin = neuronal calcium receptor bridge
NMJ: ACh Release
NMJ: Acetylcholine Receptor

- Mature / junctional form:
  - 2 α, β, δ and ε sub-units
  - ε = shorter open times, high-amplitude channel currents
- Immature / extra-junctional form:
  - 2 α, β, γ and δ sub-units
  - γ = long open times, low amplitude channel currents
- Receptor = 250,000Da molecular weight
- α units = ACh binding sites
- Anchored to end-plate membrane by protein = rapsyn
ACh Receptor
NMJ: Electrophysiology of Neurotransmission

- ACh receptor normally closed by approximation of sub-units
- ACh binds both α sub-units to open channel
- Cations flow down concentration gradients:
  - Influx: Na⁺, Ca²⁺
  - Outflux: K⁺
  - Anions excluded from channel
- Ion current depolarises muscle membrane
- Each quantum of ACh opens 500,000 channels (picoamps)
- Non-depolarising blockers competitively block this action
Neurotoxicity

- \( \beta \)-Neurotoxins
  - Highly specific **pre-synaptic** calcium channel blockers (P-type)
  - Inhibit vesicle availability irreversibly
  - Multiple agents from different species:
    - Single chain: Notexin (tiger snake)
      Pseudexins (black snake)
      Acanthoxin (death adder)
    - Multi-chain: Taipoxin, Taicatoxin (taipan)
      Textilotoxin (brown snake)
  - All phospholipase A\(_2\) inhibitors

- \( \alpha \)-Neurotoxins
  - Non-lethal **post-synaptic** acetylcholine receptor antagonists
  - “curare-mimetic” agents
Role of Clotting Factors

- Factor I: Fibrinogen
  *Activates fibrin clot*

- Factor II: Pro-thrombin
  *IIa activates factors I,V,VII,XIII, protein C, platelets*

- Factor III: Tissue factor
  *Co-factor for VIIa*

- Factor IV: Calcium
  *Required for clotting factors to bind phospholipid*

- Factor V: Pro-accelerin, labile factor
  *Co-factor of X, forms pro-thrombinase complex*

- Factor VI: Defunct
Role of Clotting Factors

- Factor VII: Stable factor (cothromboplastin)
  *Activates IX, X*

- Factor VIII: Anti-haemophilic factor
  *Co-factor of IX, with which it forms the tenase complex*

- Factor IX: Christmas factor

- Factor X: Stuart-Prower factor
  *Activates II, forming pro-thrombinase complex with V*

- Factor XI: Plasma thromboplastin antecedent
  *Activates XII, IX and pre-kallikrein*

- Factor XII: Hageman factor
  *Activates pre-kallikrein and fibrinolysis*

- Factor XIII: Fibrin-stabilising factor
  *Cross-links fibrin*
Role of Clotting Co-factors

- **Von Willebrand Factor:**
  - Binds VIII, mediates platelet adhesion

- **Pre-Kallikrein:**
  - Activates XII and self; Cleaves HMWK

- **High Molecular Weight Kininogen (HMWK):**
  - Supports reciprocal activation of XII, XI and pre-kallikrein

- **Fibronectin:**
  - Mediates cell adhesion

- **Anti-thrombin III:**
  - Inhibits IIa, Xa and other proteases
Fibrinolysis

Tissue plasminogen activator (tPA)

Plasminogen activator inhibitor 1 & 2

Urokinase

PLASMINOGEN

Factor XIa, XIIa Kallikrein

α2-antiplasmin

α2-macroglobulin

FIBRIN

FIBRIN DEGRADATION PRODUCTS

THROMBIN

Thrombin-activatable fibrinolysis inhibitor
Role of Clotting Co-factors

- **Protein C:**
  - Inactivates Va, VIIIa
- **Protein S:**
  - Co-factor for activated protein C (inactive bound to C4b)
- **Protein Z:**
  - Mediates thrombin adhesion to phospholipids, degrades X
- **Plasminogen:**
  - Converts to plasmin, lyses fibrin and other proteins
- **Tissue plasminogen activator, urokinase**
  - Activate plasmin
- **a2-antiplasmin**
  - Inhibits plasmin
Haemotoxins

- Fibrinogen clotting enzymes
- Fibrinogen degrading enzymes
- Plasminogen activators
- Protein C activators
- **Activators of factors V, IX, X and prothrombin**
- Anticoagulants
- GIIb/IIIa receptor antagonism
- Complete defibrination can be seen in <20 minutes
- Profound secondary haemorrhagic effects
Australian Elapids

- **Group 1:**
  - Eastern Brown snake
  - Western Brown snake (Gwardar)
  - Dugite
  - Peninsula Brown snake
  - Speckled Brown snake
  - Ingram’s Brown snake
Eastern Brown Snake
*Pseudonaja textilis*
Gwardar (Western Brown)
*Pseudonaja nuchalis*
Dugite
Pseudonaja affinis
Speckled Brown Snake
Pseudonaja guttata
Brown Snake Venom

- Leading cause of snakebite deaths throughout Australia
- Coagulopathy, renal failure and haemolytic anaemia
  - Early deaths from shock and coronary thrombus
- Paralysis and neurotoxicity incredibly rare
Brown Snake Venom

- Venom-induced activation of coagulation cascade
- Brown snake venom contains a factor X-like protein that activates prothrombin in the presence of factor V, calcium and phospholipid.
- Leads to production of thrombin and consumption of fibrinogen (i.e. consumption coagulopathy).
  - Decreased fibrinogen and platelets (sometimes)
  - Raised INR, APTT, FDPs
Australian Elapids

- **Group 2:**
  - Common Tiger snake
  - Black Tiger snake
  - Western Tiger snake
  - Lowlands Copperhead
  - Highlands Copperhead
  - Pygmy Copperhead
  - Rough scaled snake
  - Broad-headed snake
  - Pale-headed snake
  - Stephen’s Banded snake
  - Eastern Small-eyed snake
Black Tiger Snake

*Notechis ater*
Mainland Tiger Snake

*Notechis scutatus*
Perth’s Tiger Snake
Copperhead
*Austrelaps superbus*
Rough Scaled Snake
*Tropidechis carinatus*
Broad Headed Snake
*Hoplocephalus bungaroides*
Pale Headed Snake

Hoplocephalus bitoquatus
Stephen’s Banded Snake
*Hoplocephalus stephensi*
Eastern Small Eyed Snake
Rhinocephalus nigrescens
Tiger Snake Venom

- Venom-induced activation of coagulation cascade
  - Rapid onset, factor V-like prothrombin activator

- Neurotoxicity and paralysis
  - Slow in onset (up to 24 hours)
  - Associated with rise in creatine kinase
  - Descending flaccid paralysis
  - Anti-venom arrests progression but not reversible
Australian Elapids

- **Group 3:**
  - Mulga (King Brown snake)
  - Butler’s Mulga
  - Collett’s snake
  - Red-bellied Black snake
  - Spotted / blue-bellied Black snake
Mulga (King Brown)
*Pseudechis australis*
Red-Bellied Black Snake

*Pseudechis porphyriacus*
Collett’s snake
*Pseudechis colletti*
Blue-bellied Black Snake
*Pseudechis guttatus*
Black Snake Venom

- Mild anti-coagulant effect but NO pro-coagulation
  - Normal fibrinogen and FDPs
  - Mildly raised INR, APTT
- Myolysis
  - Causes renal failure
  - Local swelling and necrosis at bite site
- Paralysis
  - Variable extent
- Possible direct cardiotoxin with Mulga envenomation
Australian Elapids

- **Group 4:**
  - Common Taipan
  - Inland Taipan (fierce snake)

- **Group 5:**
  - Common Death Adder
  - Desert Death Adder
  - Northern death Adder
Common Taipan

*Oxyuranus scutellatus*
Fierce Snake (Inland Taipan)

*Oxyuranus microlepidotus*
Death Adders

*Acanthophis antarcticus, A. praelongus, A. pyrrhus*
Other Elapid Snake Venoms

- **Taipans**
  - Aggressive snakes with high rate of envenomation
  - Similar spectrum of toxicity to tiger snakes
    - Activation of coagulation cascade
    - Factor V-like prothrombin activation
    - Neurotoxicity and progressive flaccid paralysis
    - Myotoxicity with raised CK

- **Death Adders**
  - Neurotoxicity
    - Potent post-synaptic blockade
    - No CK rise
  - Paralysis:
    - Reversed with anti-venom
    - Temporarily reversed with neostigmine
  - No effect on coagulation cascade
  - No myolytic toxin
  - *Little M et al. MJA 1998;169: 229-30*
Limitation of Data

- **Extensively studied:**
  - Common death adder
  - Mainland tiger snake
  - Coastal taipan
  - Mulga
  - Eastern brown snake

- **Lethal and not studied:**
  - Black headed death adder
  - Northern death adder
  - Desert death adder
  - Highland copperhead
  - Ingram’s brown snake
  - Broad headed snake
  - Stephen’s banded snake
  - Butler’s snake
Clinical Manifestations of Snake Bite

- **Local effects:**
  - Local necrosis
  - Oedema

- **Systemic effects:**
  - Anti-haemostatic and thrombotic
  - Coagulopathy
  - Progressive paralysis
  - Shock, hypovolaemia
  - Direct cardiac toxicity
  - Rhabdomyolysis, acute renal failure
Management of Snake Bite

- First aid:
  - Pressure-immobilisation principle (lymphatic spread)
    - Pressure bandage over entire limb
    - Immobilisation of limb and whole patient
  - Do not wash snake bite area
  - Aim of first aid is to delay absorption of venom from bite site until the patient is in a facility that can administer adequate doses of anti-venom if required
Hospital Management

- First aid and non-removal of PIB
- Transfer to appropriate facility
  - Clinical expertise, laboratory facility, sufficient anti-venom
- Assessment of likely envenomation
  - Coagulation, neurological examination, respiratory function
  - Envenomation is a clinical decision, not from venom detection kits
- History
  - Geographical area, snake description, bite characteristics
- Lab tests:
  - Coagulation, CK, U&Es, myoglobinuria
- Anti-venom
- Ancillary therapy
Snake Species Detection

- Snake captured or correctly identified
- Geographical location
- Local and systemic effects
- Presence or absence of paralysis
- Coagulopathy (defibrination or anti-coagulation)
- Snake venom detection kits
  - ELISA test (affinity-purified venom specific antibodies)
  - Urine / bite site / blood
  - Detects 2.5ng/ml venom in 25min
- Australia has only commercially available test in world
Differences in Snake Venom

- **Brown:**
  - Life threatening coagulopathy
  - Paralysis
  - Thrombocytopenia

- **Black (including Mulga):**
  - No pro-coagulants in Mulga (anticoagulant toxin only)
  - Paralysis
  - Myolytic toxins
  - Possible cardiotoxin (Mulga)
  - Less toxic but high volume
Differences in Snake Venom

- Tiger snake:
  - Pro-coagulant
  - Paralysis
  - Myolytic toxin

- Taipan:
  - Profound paralysis
  - Potent pro-coagulant
  - Myolytic toxin

- Death Adder:
  - Paralysis – common
  - Coagulopathy - rare
Anti-venom

- F\textsubscript{ab} fraction of immunised horse serum
- First utilised in 1897
- 21 labs produce anti-venom worldwide
- Powerfully immunogenic to humans but more cost effective because of high yield
- Liquid or lyophilised preparation
- Mono-specific: Safer, smaller dose, species dependent
- Poly-specific: Higher risk of reaction, species independent
Anti-venom

Types available:

- Death adder (6,000u/vial: $1,582.25)
- Brown snake (1,000u/vial: $381.96)
- Black snake (18,000u/vial: $1,963.14)
- Taipan (12,000u/vial: $2,395.49)
- Tiger snake (3,000u/vial: $480.78)
- Sea snake (1,000u/vial: $1314.61)
- Polyvalent (40,000u/vial: $2,621.96)

Amount standardised to neutralise in vitro average yield of venom for each snake
Indications for Anti-venom

- Shock
- Spontaneous systemic bleeding
- Incoaguable blood
- Paralysis
- Acute renal failure or myoglobinuria
- Extensive, progressive local swelling
  - Especially in digits or fascial compartments and necrotic venom
- Anti-venoms all highly immunogenic
- Controversy over use of adrenaline pre-medication
Anti-Venom Adverse Effects

- Amount required highly variable depending on degree of envenomation
- Equine serum:
  - Risk of anaphylaxis high
  - Viral transmission possible
  - Anaphylactoid reactions with other equine serum
- Complement fixation
- Delayed serum sickness
Anti-Venom Hypersensitivity

- 1978 – 2003: 17 anti-venom adverse reactions
  - Polyvalent: 6
  - Brown: 4
  - Tiger: 3
  - Black: 3
  - Death Adder: 2
  - Taipan: 0
  - Sea snake: 2 minor

- No deaths
Ancillary Therapy

- Thorough supportive care required to maintain cardiovascular, respiratory and renal function while definitive treatment (anti-venom) is given.
- ICU management
- Intubation and ventilation
- CVVHF / haemodialysis
- Controversies:
  - Use of blood products
  - Adrenaline and anaphylaxis precautions before anti-venom
  - Role of fasciotomy in local necrosis
Snakes are rare cause of venomous creature bites but carry high mortality if incorrectly treated

Up to 50% bites may be dry (no venom)

6 broad categories of dangerous snakes

Identification of snake difficult and may be avoidable

Mixed neuro- and haemo-toxicity most serious effects

Envenomation and need for anti-venom <50% cases

Management of envenomed patients is an enormous challenge and requires transfer to adequate facility and ICU

Appropriate first aid therapy can be life saving

Limited data available on venom composition and pharmacology
Any Questions?