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Notes

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New developments in management of snake envenomation and tick paralysis

Ellie Leister & Andrew Padula

Introduction

The most common snake species responsible for severe envenomation of dogs and cats in Australia are the brown snakes (*Pseudonaja sp*), tiger snake (*Notechis scutatus*) and red-bellied black snake (*Pseudechis porphyricus*). This section will focus on these three snake species and the diagnosis and management of the resulting envenomation.

Snakebite Incidence

A nationwide survey of Australian veterinary practices in 1996 found that brown snakes (76%), tiger snakes (13%) and black snakes (6%) accounted for 95% of reported snakebite cases in dogs and cats. A separate survey published in 2005 of veterinarians in NSW found the species responsible to be red-bellied black (44.6%), brown snakes (40.4%), tiger snakes (7%), copperhead (1.6%), mulga (1.3%) and others (1.3%).

The key issues that contribute to domestic pet death from snake envenomation in veterinary medicine are a combination of the following:

- Ratio of venom to body weight (generally they are much smaller than your average human and they receive multiple bites rather than a human just receiving one bite)
- Time delay between bite and treatment
- The wrong type of antivenom administered and/or insufficient antivenom given

- Misdiagnosis/missed diagnosis
- Inadequate supportive care
- Elective euthanasia

With every envenomation case that we treat we should be thinking about the points listed above during our diagnosis, treatment and supportive care to maximise patient survival rate.

Differential diagnosis

Other causes of lower motor neuron (LMN) paralysis including:

Tick paralysis – normally slower onset, cranial nerves generally not involved and if they are, usually unilateral and associated with a tick on the head. No associated coagulopathy.

Organophosphate/carbonate poisoning – initial stages muscarinic signs (diarrhoea, urination, vomiting, salivation, bradycardia, bronchospasm and miosis) nicotinic signs can then progress to muscle weakness. No coagulopathy.

Acute onset sepsis (especially in the cat) – profound weakness, hypothermia, tachypnoea, bradycardia, hypotension, pale mm, increased capillary refill time.

Polyradiculoneuritis – slower onset. No coagulopathy.

Myasthenia gravis – usually improves temporarily with rest, exacerbated with exercise. No coagulopathy.

Tetrodotoxin & Ciguatera result in hind leg paresis and vomiting (must have access to reef fish, toad fish, puffer fish, newts or blue ringed octopus). No coagulopathy.

Red-back spider bite – may cause vomiting, agitation, muscle weakness, incoordination, muscle tremors and tachycardia may be present. No coagulopathy.

Thromboembolism – usually one body area affected (either both pelvic limbs or a thoracic limb). Cats are usually very painful!!, affected muscles are usually firm and painful with lack of perfusion.

Meningitis/myelitis - can present with a variety of neurological presentations. No coagulopathy.

General toxic components of snake venom

Snake venoms contain a wide range of toxic and non-toxic components including:

Neurotoxins: cause a progressive flaccid paralysis of voluntary and respiratory muscles which can eventually result in respiratory failure and death. Most neurotoxins act pre-synaptically by blocking acetylcholine (ACh) release into the neuromuscular junction after depolarisation. Phospholipase A2 is a major component of pre synaptic neurotoxins, binding to and hydrolysing the phospholipid membrane of the motor nerve terminal, causing degeneration of the nerve terminal and distal motor axon, depleting synaptic vesicles and preventing recycling of ACh following exocytosis. This action is delayed and doesn't become evident for 30-60 minutes. Antivenom cannot reverse pre-synaptic binding of toxin. This highlights the importance of prompt administration of the correct antivenom and the appropriate amount. Post synaptic neurotoxins block acetylcholine receptors and tend to be easier to reverse with antivenom than pre-synaptic toxins. Onset of complete paralysis may take 3-18hrs. These pre-synaptic acting neurotoxins explain why some animals need mechanical ventilation for days after appropriate antivenom.

Procoagulants: trigger off the coagulation cascade or what we now know as the cell-based model of coagulation with prothrombin activators. Prothrombin activators are classified into 4 groups (A-D). Australian elapids contain the C and D prothrombin activators which are serine proteases. Group C are found in the brown snake and taipan, they resemble the prothrombinase complex (FXaVa) which converts prothrombin to thrombin. Group D toxins are found in tiger snakes and contain a toxin similar to FXa, without the FVa cofactor. This leads to a consumptive coagulopathy which may result in complete defibrination (within < 30 minutes of bite). In the early stages this coagulopathy may result in brief clot formation in critical cardiac vessels which can cause cardiac collapse, usually soon after the bite. Then, the secondary fibrinolytic process results in clot lysis and consumption of all clotting factors. The progression of coagulopathy may result in bleeding tendencies from wounds, IV catheter sites and

venipuncture sites. They may also bleed into GIT tract, lungs, bladder and other sites which may manifest as haematemesis, haematuria, haemoptysis, or hyphaema. This coagulopathy isn't reversible with antivenom and won't resolve until either re-synthesis of factors occurs over 12-48hrs or there is replacement of factors with an appropriate volume fresh frozen plasma. Catastrophic pulmonary bleeds have been seen multiple times by the author in South Eastern Queensland, these dogs can walk into the clinic and acutely deteriorate in minutes.

Anticoagulants: causes a rapid reversible coagulopathy without defibrination. Inhibitory actions against FX, FII, and platelets. This may be reversible with antivenom.

Myolysins: Myotoxins bind to muscle fibres, causing progressive destruction of the muscle cells with the release of breakdown products. The process may take hours to days to become evident by which time irreversible damage has been done. The result is progressive muscular weakness and pain with myoglobinuria. Secondary acute renal failure may occur from acute tubular necrosis due to myoglobin obstruction of renal tubules. Muscle damage can be identified from elevated creatine kinase (CK), AST +/- ALT and presence of muscular pain. Monitoring for hyperkalaemia and hypocalcaemia is also important. The muscle damage can't be reversed but can be attenuated with appropriate antivenom.

Haemolysins: cause haemolysis via phospholipase A2 damage to the RBCs membrane. This results in direct lysis or indirect via the formation of spherocytes and removal via the reticuloendothelial system. (Spherocytes have been documented on day one of envenomation). Intravascular haemolysis may result in marked haemoglobinuria/uria with possible secondary renal failure if renal pigment load is severe. Secondary hyperbilirubinaemia may develop after extravascular haemolysis. Ensuing anaemia may be mild to severe, requiring blood transfusions.

Nephrotoxins: there are no specifically isolated nephrotoxins in any Australian snake venom (nephrotoxins have been documented in some exotic snake venoms). However, acute kidney injury is reported in both humans and animals. The mechanisms are unclear but may include both direct toxic effects on the kidney and secondary damage as a result of hypotension, myolysis, haemolysis or coagulopathy.

Renal histopathology has indicated that tiger snake venom was directly nephrotoxic, causing acute tubular necrosis. This was documented as early as one hour after envenomation and did not seem to be closely related to the occurrence of either haemoglobinuria or myoglobinuria.

Cardiac Toxin: This is typically specific for Taicatoxin from the Taipan, and it has been shown to inhibit calcium channels in the myocardium, leading to prolonged repolarisation and arrhythmias. Caution is used in relation to possible fluid overload due to its effects as a negative inotrope and chronotrope, and positive lusitrope. Other cardiac toxins have not been ruled out from other elapids, though are weak in nature if present.

Cytotoxins: some snake venom (mostly black snakes and whip snakes) cause a local cytotoxic reaction (cell death and necrosis) at bite site resulting in pain, swelling and inflammation that may take days to resolve. Antibiotics aren't indicated.

Tiger Snake (*Notechis scutatus*)

Scalation: 17 to 21 rows at midbody, 140-190 ventrals, single anal scale, 35-65 subcaudals all single.

Appearance: solid snake with a large broad flat head, colour variable with many shades from light grey to olive, brown though to black. Cross bands of lighter scales continue down the length of the body. Belly lighter than main colour, usually cream or grey, often darker on throat and under tail.

Toxins: very potent, contains pre and post-synaptic neurotoxins, myolysins, haemolysins and procoagulants. Major toxic component 'notexin'.

Clinical Signs: paralysis, rhabdomyolysis, haemolysis and consumptive coagulopathy. Dogs may present after pre-paralytic signs (collapse due to hypotension, vomiting, salivation, defecation, trembling and tachypnoea). They will then progress to paralytic stage with skeletal muscle paralysis, coagulopathy, oliguria with or without haemoglobinuria or myoglobinuria. Acute tubular necrosis has been documented in the dog and may be exacerbated by myolysis +/- intravascular haemolysis. Megaesophagus persisting for up to 6 weeks post envenomation has been reported in the dog (not feline or humans) and this may be attributed to the fact that the human and

feline oesophagus is mostly smooth muscle which isn't affected by the myotoxic component of the venom. Some cases may require PEG feeding tubes. These cases are at very high risk of aspiration pneumonia which can be life threatening.

Antivenom: Tiger-Brown anti venom

Brown Snake (*Pseudonaja sp*)

Scalation: the emporolabial scale is fused to the last (6th) supralabial scale. A divided anal scale, more than 35 divided subcaudals and 17 or 19 mid body scales. Rarely a few of the most caudal sub caudals may be single.

Appearance: Colour can range from pale tan through orange, russet, dark brown and almost black, sometimes with cross-body banding. Belly is usually cream, yellow or orange with scattered orange or grey blotches. Hatchling and juveniles particularly vary in colour, frequently having dark heads or neck bands, or being completely banded along the body length.

Toxin: Procoagulants, neurotoxins (pre and post synaptic). Major toxic component 'textilotoxin' and 'pseudonajatoxin'. There has been the suggestion of cardiotoxins, but this has not been classified as yet.

Clinical Signs: Paralysis and consumptive coagulopathy +/- mild haemolysis. Myolysis does not occur. AKI has been documented in human and canine cases hypothesised due to procoagulant microthrombotic effects or secondary to hypotension and hypoxia.

Dogs: if a lethal dose is received, they often show pre-paralytic signs – vomiting, salivation, transient collapse and mydriasis followed by apparent recovery lasting 30-120 minutes. They can then suddenly deteriorate and present with any of the following: vomiting, haematemesis, haematoptysis, trembling, salivation, excitement, weakness, mydriasis, ptosis, initial posterior paresis, dyspnoea, tachypnoea, shallow respiration, flaccid paralysis, coma and death.

Cats: will often initially show a weakness and ataxia. Other signs are inconsistent or transient and include: intermittent weak struggling, lethargy, tachypnoea, dyspnoea, haematuria, vocalisation, absent papillary light reflex, disorientation, mydriasis, generalised paresis.

Antivenom: Tiger-brown or monovalent brown snake antivenom

Note: studies have demonstrated that QLD (Gold Coast) eastern brown snakes are more venomous than South Australia eastern brown snakes. This is due to a combination of larger venom yield per bite and also higher coagulation potential per unit of venom.

Red Bellied Black Snake (RBBS) (*Pseudechis porphyriacus*)

Scalation: squarish rostral shield, 2+2 temporals, 17 rows at mid body, 180-215 ventrals, divided anal plate. 48-60 subcaudal, the anterior scales are single and the posterior scales are generally divided (sometimes all subcaudals are single)

Appearance: uniform glossy black above along whole body except tip of snout which is paler brown. Belly has a red or pink flush, brighter on the sides and paler in the middle.

Toxins: neurotoxin, myotoxin, cytotoxin, haemolysin, weak anticoagulants. Major toxic component 'pseudexin'.

Clinical Signs: Intravascular +/- extravascular haemolysis resulting in anaemia (can be marked). Phospholipase A2 hydrolyses the RBC phospholipid membrane causing direct lysis (intravascular haemolysis) or damage to the membrane and spherocyte formation (extravascular haemolysis). Rhabdomyolysis – increase in CK and AST, often very painful! The cardiac muscle can be affected resulting in arrhythmias. They can cause a flaccid paralysis (weak presynaptic neurotoxin) – very occasionally they present in respiratory arrest requiring intubation and intermittent positive pressure ventilation (IPPV). Defibrination coagulopathy is not seen, but there may be slight elevation of clotting times due to anticoagulants in the venom. Small haematomas at peripheral injection sites are seen. Secondary renal failure has been reported from haeme and/or myoglobin protein precipitation in the renal tubules and formation of casts causing functional tubular blockage and direct toxicity via oxidative injury and the formation of free radicals. Ischaemic damage to the nephron may also occur.

Antivenom: Tiger-brown or monovalent Black Snake antivenom

Snakebite Diagnosis

Generally based on either known access or potential access to a snake (often the owners find a dead snake in the yard or witness envenomation) or consistent clinical signs. Perform a thorough physical examination paying close attention to neurological status. Is a coagulopathy present?

Cats are rarely presented for treatment during the pre-paralytic stage of snake envenomation. The most common clinical signs are generalised weakness or flaccid paralysis. Signs in dogs are generally more severe and may be attributed to a combination of the following:

- Cats are three times less sensitive to tiger snake venom and brown snake venom than dogs
- Cats generally have greater agility and so are less likely to receive full strike
- Cats with multiple lethal doses may die without being observed and owners attribute it to being hit by a car or running away.

Snake ID refer to snake identification charts.

SVDK

The snake venom detection kit (SVDK) is a rapid in vitro sandwich enzyme immunoassay that enables detection of venom from the five major genera of snakes within Australia (Tiger, Brown, Black, Death Adder and Taipan). It takes 20 mins to complete.

The SVDK was developed as a tool for human medicine to use for bite site swabbing to determine the most appropriate antivenom to administer. Venom concentrations at bite sites are often 100 to 1,000 times higher than in either serum or urine.

Murdoch University Veterinary Hospital looked at the specificity of SVDK on urine and found no false positives in both dogs (50) and cats (25), thus 100% specificity. Ensure instructions are followed closely and no fibre matter from paper towels come in contact with the wells. (False positives have been reported because of this).

False negatives do arise and the three main reasons for this are:

- Insufficient time for venom to concentrate in urine (actual time from envenomation to presence of venom within the urine may vary with envenomation amount, bite site and absorption). Positive results have occurred within 15 mins but may take hours.
- Venom levels below the detection limit of the test (subclinical envenomation or long delay to presentation)
- Very high levels of venom concentration result in saturation of the binding antibodies in the kit and the labelled conjugate is removed in the washing step, resulting in a negative result.

Note: cross reactivity can occur, make sure that you closely monitor the wells for colour change. The first well to change colour is the positive snake ID. Commonly the black snake well go positive initially quickly followed by tiger snake well. This still indicates a red-bellied black snake (Brisbane area so no Mulga snakes). The dog hasn't been bitten by both black snake and tiger snake! If the negative control has a colour change the SVDK is invalid.

SVDK does not identify the snake species – instead the test identifies the immunotype of the snake venom and which antivenom is indicated

In house diagnostics: Minimum database for a suspect snakebite bite should include:

- PCV/TP and blood smear for platelet evaluation.

Evidence of anaemia maybe present due to the presence of haemolysis

- Venous blood gas (if available)

Assess electrolytes, acid base, lactate and PvCO₂. Metabolic acidosis can occur due to release of intracellular contents for rhabdomyolysis and haemolysis.

Coagulation parameters

Activated Clotting Time (ACT) or (Activated Partial Thromboplastin Time/Prothrombin Time aPTT/PT) If performing ACT, it is recommended to have a standardised method of collection and assessment of clot formation. Or a standardised procedure. We have a Haemochron 401 which warms and senses clot formation and will record an exact second time till clot formation.

Biochemistry

- CK and AST are measured to determine the significance of rhabdomyolysis and if ongoing muscle damage is occurring. CK can take 2 hrs to rise after envenomation, and half-life of CK is approx 3-6 hrs and AST 12 hrs.
- UREA and CREA are used to determine if there are any delayed effects from envenomation, and if there is impaired renal function. This can be due to effects from pigmenturia, hypovolaemia or direct nephrotoxins though the latter are not described yet.
- TBIL can also be measured to monitor effects of haemolysis and possible renal tubular damage

Voided urine sample – avoid cystocentesis if coagulopathic

- SVDK – Gentle bladder expression or soft temporary urinary catheter
- Baseline, USG, urinalysis, sediment exam and pigmenturia assessment

Treatment

Initial stabilisation

Airway/Breathing: – is the patient breathing and moving air? Upper airway paralysis can occur before respiratory paralysis causing an upper airway obstruction. Swab and/or suction the pharynx. Provide oxygen via flow by or mask. Avoid intra nasal oxygen catheters initially (because of risk of haemorrhage from traumatised nasal mucosa and coagulopathy)

If the patient is still in respiratory distress despite initial stabilisation, consider intubation and commencing manual ventilation. Some patients present in respiratory arrest and need immediate intubation and ventilation. Patients can be so severely paralysed that intubation is possible without sedation/anaesthesia. Otherwise use low dose of a short acting anaesthetic, e.g. alfaxan, propofol or diazepam/ketamine. Continue with stabilisation, baseline bloods, SVDK and antivenom if snake ID known.

Circulation: assess heart rhythm and rate, peripheral pulses, mm colour and refill

Gain IV access and blood sample for baseline diagnostics – see above.
Avoid jugular sticks due to risk of haemorrhage.

Assess volume status – if hypovolaemic/hypotensive give appropriate crystalloid bolus 10mls/kg then reassess and keep repeating as necessary. As hypotension resolving, HR decreasing, pulses improving continue on 2-4 times maintenance fluids.

Snake patients can be hypertensive on presentation – monitor and avoid adrenaline

Once initial stabilisation is underway START ANTIVENOM ASAP

To premedicate or not?

Pre-medication prior to administering antivenom is controversial in the human field. There is some conflicting evidence and opinion with uncertainty about ‘best practice’. Studies outside Australia have provided evidence showing premedication using antihistamines and/or hydrocortisone are either ineffective, or possibly effective to a variable extent. Similar contradictory evidence applies to adrenaline premedication within and outside Australia.

Currently in the veterinary field pre-medication is not indicated unless that patient has previously received antivenom and had a hypersensitivity or anaphylactic reaction. If a reaction occurs treat appropriately. See below.

Which antivenom and how fast?

If pre-paralytic signs occurred or clinical signs are present, then antivenom is required. Pre-paralytic signs indicate a lethal envenomation. Don’t delay antivenom to see if they become neurological.

If there is no snake for a definite identification start running a SVDK.
If the patient is deteriorating or critical give a vial of Tiger-Brown.

Once you have a positive snake ID for brown snake envenomation you can change to the monovalent brown snake antivenom if further vials are needed.

If your patient is dying and you suspect impending arrest, then give antivenom quickly!

Otherwise dilute ideally 1:10, this is often a large volume for smaller animals so ratio can be decreased.

Speed: Start slowly and monitor closely for reaction. Increase the rate and infuse over 10-20 mins.

1. Mild: (skin and s/c tissues only) – generalised erythema, urticaria, peri orbital oedema, or angioedema
2. Moderate: (features suggesting respiratory or cardiovascular or gastrointestinal involvement) – dyspnoea, stridor, wheeze, nausea, vomiting, abdominal pain
3. Severe: (hypoxia, hypotension or neurological compromise) – cyanosis or SpO₂ <92% at any stage, hypotension, collapse, loss of consciousness or incontinence.

If a transfusion reaction occurs STOP the antivenom and provide supportive care, O₂, fluid bolus if hypotensive. Adrenaline if indicated 0.01mg/kg IV +/- CRI. Consider chlorpheniramine 1mg/kg SC if cutaneous signs then re-commence at a slower rate and monitor patient closely.

When do you just monitor your patient?

If the patient isn't showing any clinical signs of envenomation and coagulation studies are normal, hospitalise on intravenous fluids and continue to monitor neurological status every hour (make sure you get the patient out of the cage to assess). Examine voided urine for pigmenturia and monitor coagulation (ACT) every 6 hours. Dry bites do occur. If dogs are still normal in 12 hrs then envenomation is unlikely, if cats are still normal after 24 hrs then envenomation is unlikely. (However never say never as both species have had delayed onset of envenomation reported).

When do you know you have given enough antivenom?

This has been a hot area of research in the human vial with the recommended amount of antivenom drastically decreasing after the Australian Snake Bite Project down to 1600 – 3200 units (1-2 vials of monovalent antivenom).

We have been analysing pre and post serum and urine venom (and antivenom) levels in Eastern Brown and RBBS envenomations in south eastern Queensland. We have documented some massive envenomations (3600ng/ml in a dog envenomated by an Eastern Brown, Human cases have reports of 200ng/ml). Currently for Eastern Brown Envenomations we recommend 2 vials of polyvalent Tiger Brown antivenom and 1-2 vials for RBBS. The antivenom used in this research as Padula Serums Tiger 4000IU Brown 4000IU polyvalent antivenom. These recommendations may change with further research and debate on antivenom dosing will continue!

SVDK on urine post antivenom?

This method has been used to titrate antivenom and try and ensure no further circulating venom before giving blood products. However, it is likely an ineffective method because of the possibility of residual venom in the bladder or the fact that the ELISA measuring bound venom (IgG + venom complex) not free venom. We no longer use or recommend this use of SVDK on urine post-antivenom to determine if more antivenom is necessary as we have had multiple case that are still SVDK positive on urine, however there is no circulating venom detectable in blood (serum).

Aftercare and continued monitoring – you have given antivenom what now?

1. Intravenous fluids – ensure an appropriate fluid rate. Dependant on the patient's other underlying disease (heart disease etc) we often administer fluids at 1.5-2 maintenance after correcting any hypovolaemia or fluid deficits to induce diuresis if pigmenturia is present.
2. Oxygenation – monitor SpO₂, respiration rate and effort

3. Ventilation – ETCO₂ (if intubated), PvCO₂ on blood gases, excursions, respiration rate and effort. If CO₂ is increasing and > 60 this is an indication that the patient needs ventilation. Some patients maybe just holding acceptable oxygenation and ventilation but they have an “unsustainable work of breathing”; this is another indication to intubate and ventilate. If they look like they can’t maintain that respiratory effort then they probably can’t and respiratory arrest is imminent.
4. Bloods – monitor PCV/TP, electrolytes, CK, urea, creatinine, coags q 4-6 hrly initially then frequency decreasing as patient stabilises
5. Recumbent nursing care – if the patient is paralysed and unable to move they will need soft warm bedding, eye care, bladder care (manual expression or foley catheter), regular physio and turning, maintenance in a sternal position. These patients need constant monitoring and regular checking of vitals/TPRs.
6. If they are intubated and ventilated, they require intensive nursing including all of the above and mouth care to prevent tongue swelling or mouth ulcers. The need continuous monitoring of blood pressure, temperature, HR, ventilator settings, urine output, SpO₂, PaO₂/CO₂, ETCO₂ and electrolytes q 4-6 hrly.
7. Nutrition – if patient doesn’t recover quickly and start eating and drinking then ongoing nutritional requirements need to be addressed.

Complications

Aspiration: if the patient is unable to protect its own airway it is at risk of aspiration which will initially cause a pneumonitis then to progress to aspiration pneumonia needing further intervention. Appropriate antibiotics, nebulisation, coupage, oxygen if SpO₂ <94%. Mechanical ventilation is indicated if aspiration is severe and the patient is still hypoxic despite intranasal oxygen, PaO₂ <60, SpO₂ < 90-92%. Some patients may present with a history of acute onset of vomiting and aspiration before presentation to the clinic.

Corneal ulceration: if the animal presents paralysed, they often have a very reduced or absent blink reflex and are prone to superficial (which can become deep very quickly) ulceration. Regular eye care and

lubrication is essential. Any snake patient requiring mechanical ventilation will often have contact lenses placed to protect the cornea during ventilation as these patients are very difficult to keep eyes closed and lubricated because of the complete muscle paralysis.

Megaesophagus: has been reported as a complication in tiger snake envenomation due to myolysis (in theory this is a possible complication in any snake envenomation case that causes myopathy). The megaesophagus develops due to myolysis of the skeletal muscles in the oesophagus and may take up to 6 weeks to resolve. Placement of a PEG tube may be required. Aspiration pneumonia is frequently a complication.

Oesophagitis: inflammation of the oesophagus from reflux/regurgitation or megaesophagus.

Local cytotoxicity: depends on species of snake. Common with black snakes and whip snakes. They typically cause venom-induced chemical cellulitis around the bite site, with erythema, pain and swelling. This may peak at 1-3 days post bite and slowly resolve over subsequent days. Antibiotics aren't usually indicated.

Respiratory muscle paralysis/fatigue: ideally prompt adequate antivenom is indicated to prevent progression to full pre-synaptic paralysis. If this wasn't possible because of a delay between bite and seeking veterinary treatment then monitor SpO₂, PaCO₂, PvCO₂, ETCO₂ (if intubated), and excursions. If they look unsustainable or too shallow/non-existent – then they probably are. Intubate and commence IPPV.

Myolysis: Management: firstly, antivenom is used to neutralise circulating myotoxins, secondly supportive treatments to help minimise potential complications. IVFT to support renal function, monitor and control hyperkalaemia as this can cause lethal cardiotoxicity. Monitor CK - half live 3.5hrs, reduction of CK levels indicative of resolving myolysis

Pain: myolysis is painful! Ensure adequate opioid analgesia. If pain is severe consider methadone and placing a fentanyl patch. If mild pain is present buprenorphine may be adequate. AVOID NSAIDs as kidneys may already be compromised dealing with pigmenturia.

Intravascular haemolysis (RBBS) – if severe it can result in an anaemia PCV<20, if clinical signs of the anaemia include tachycardia, tachypnoea, hyperdynamic pulses consider PRBCs transfusion once you have ensured appropriate amount of antivenom and no further unbound venom is present.

Secondary acute renal failure: if haematuria/myoglobinuria is present then place urinary catheter to closely monitor urine output (UOP). At least twice maintenance crystalloid fluids. Monitor UOP. If the patient is becoming oliguric and/or anuric closely monitor for fluid overload. These patients require intensive monitoring. Ensure adequate volume expansion. Consider mannitol for its effect as a proximally acting diuretic, potent renal vasodilator and potential reducer of haeme iron-induced oxidant stress. (0.25 – 0.5gm/kg over 15 -20minutes. If urine is produced we will often continue with a mannitol CRI 0.1-0.2gm/kg/hr). Consider sodium bicarbonate to promote alkalinisation of the urine as this may facilitate a reduction in precipitation and cellular uptake of haemoglobin and myoglobin and therefore result in greater excretion of these pigments. The use of sodium bicarbonate for urinary alkalinisation is now in question and controversial. Anuric patients also often have a metabolic acidosis. Care with frusemide as it may cause increased urinary acidification due to inhibition of the sodium-hydrogen pump in the distal tubule. However, if complete anuria frusemide may be indicated as urine production is essential. If pigmenturia alone is present without oliguria/anuria we will often just monitor UOP without the use of mannitol (clinician dependant).

When to give FFP for VICC?

Good question! No one knows this answer yet but some good clinical information is coming from the Australian Snakebite Project (ASP) <https://www.newcastle.edu.au/research-and-innovation/centre/health-medicine/clinical-toxicology/research/australian-snakebite-project>

Venom-induced consumption coagulopathy is a major clinical syndrome of envenomation in brown snakes (*Pseudonaja spp.*), tiger snakes (*Notechis spp.*) and the coastal taipan (*Oxyuranus spp.*). The venom in these elapid snakes has a potent prothrombin activator which activates the clotting pathway causing complete consumption of fibrinogen, factor V and FVIII. This results in markedly prolonged

clotting times, and often no clot time is recorded. Antivenom is the main treatment for VICC, it neutralises the procoagulant toxins by binding to circulating venom components, preventing further consumption. (However, often by the time they present for treatment complete defibrination has already occurred). The re-synthesis of clotting factors can take the liver 12-48 hrs. Therefore, our patients remain at risk of major haemorrhage and complications for a significant time period after antivenom treatment. This has prompted the use of clotting factor replacement in VICC, despite limited evidence for its safety and effectiveness in human medicine. Factor replacement has been suggested for the treatment of snakebite, to rapidly restore clotting factor levels and consequently reduce the risk of major haemorrhage. However, there is a concern that the provision of clotting factors will worsen the coagulopathy, or 'fuel the fire' if there is any un bound venom present as more substrate will be available for the procoagulant toxins present in the venom to activate. Ensure antivenom is given before FFP administration.

The Australian Snakebite Project recruited 65 human patients from 28 hospitals with VICC between March 2008-June 2012 for a randomised controlled trial of FFP for treating VICC in cases of Australian Snake bite. They found that FFP administration after antivenom administration results in more rapid restoration of clotting function in most patients, but no decrease in discharge time. Patients who didn't receive FFP clotting times still returned to normal but just took longer (average of 14 hours compared to FFP group which was 6 hrs). One patient in the FFP group with brown snake envenomation suffered an intracranial haemorrhage. She was hypertensive on admission and developed a headache 6hrs after FFP administration and died 1 day later. They also found that early administration of FFP (<6-8 hrs) post bite was less likely to be effective. This may be attributed to the presence of active clotting factors in the initial period of resolution of VICC. The current human recommendations of use of FFP is it is only indicated in coagulopathic patients who have received appropriate antivenom and are at risk of catastrophic bleeding.

Another study published in *Anaesthesia and Intensive Care* in 2005 looked at the replacement of clotting factors with fresh frozen plasma. They gave 11 dogs given 1ug/kg brown snake venom, 30 min later brown antivenom, another 30 mins 2 units FFP or saline. Of the six study dogs given antivenom plus FFP, two died at around 60 to 90

minutes post-venomation, at the end of the FFP infusions, and all but one of the survivors had persistent afibrinogenaemia. Of the five study dogs given antivenom and no FFP, all but one had return of detectable fibrinogen at eight hours after envenoming. None died. Post mortem examinations of dogs that died during dosage and administration studies showed massive intracardiac clots.

The decision about whether or not to give FFP for venom induced coagulopathy is still very much a grey area in both human and veterinary medicine. Watch this space. Clinically at both PetICU, Animal Emergency Service and Veterinary Specialist Services we approach venom induced coagulopathy in a similar way to what is currently recommended in the human field. We ensure that appropriate amount and type of antivenom is given and unless clinically bleeding or PCV is dropping we will monitor coagulopathy. If the patient has active bleeding, we will ensure that an appropriate amount of antivenom has been administered (currently 1-2 vials of Tiger-brown polyvalent antivenom). Then we will give fresh frozen plasma and make owners aware of risks of FFP – transfusion reaction, transfusion related lung injury and volume overload. We have had a few cases of catastrophic bleeding in coagulopathic brown snake envenomation patients who have had severe pulmonary blood loss resulting in death. We now immediately administer antivenom and then bolus liquid plasma (FFP that has been thawed at 4 degree and stores for 14 days) or whole blood. Human studies have found that at least 10 mL/kg of FFP is needed to replace clotting factors or until coagulation testing returns to normal.

Complications - a few days down the track

Continued Haemolysis

A problem that occurs with some RBBS cases is development of a continued haemolysis (and spherocytosis) despite the administration of antivenom. It is not clear why this happens but may be related to the use of tiger snake antivenom to neutralise RBBS venom; but perhaps not all the haemolytic toxins are neutralised. Experience has shown that additional antivenom may be required to arrest ongoing haemolysis in RBBS cases.

Serum Sickness

Serum sickness has been reported commonly in within 2-14 days post antivenom administration in humans but is rarely observed in animals. Large doses of antivenom are causally associated in humans. It is a type III hypersensitivity reaction which is IgG or IgM mediated. It is an immune response to antibody complexes being deposited on endothelial surfaces.

Presentation: urticaria, cutaneous oedema, lymphadenopathy, polyarthropathy and proteinuria can develop. Treatment is immunosuppressive doses of prednisolone then tapering after a few days depending on response.

The ones that need referral – mechanical ventilation –what do I do?

If you have a severe envenomation patient that you have had to intubate and ventilate while giving antivenom and the patient isn't taking any spontaneous breaths after appropriate antivenom then contact your nearest referral centre that can provide 24hr care and ventilation. Transport methods can be arranged to provide IPPV during transport. Owners need to be committed financially to be able to ventilate. Pre-synaptic paralysis may take days to resolve. Some patients are ventilated for at least 2-3 days, sometimes longer.

Conclusion

Snakebite by either brown, tiger or RBBS can have potentially fatal consequences for dogs and cats. Prompt, aggressive and appropriate therapy is required to ensure good patient outcomes.

Further Reading

Heller J, Bosward KL, Hodgson DR, Pottie R. Case Report: Anuric renal failure in a dog after Red-bellied Black snake (*Pseudechis porphyriacus*) envenomation. *Australian Veterinary Journal*. 2006; 84(5): 158-162

Heller J, Bosward KL, Hodgson JL, Cole FL, Reid SWJ, Mellor DJ. Snake envenomation in dogs in New South Wales. *Australian Veterinary Journal*. 2005; 83(5) 286-292

Hopper K, Beck C, Slocombe RF. Megaoesophagus in adult dogs secondary to Australian tiger snake envenomation. *Australian Veterinary Journal*. 2001;79(10):672-675

Isbister GK, Buckley NA, Page CB, et al. A randomized controlled trial of fresh frozen plasma for treating venom-induced consumption coagulopathy in cases of Australian snakebite (ASP-18). *Journal of Thrombosis and Haemostasis*. 2013;11:1310-1318

Isbister GK, O'Leary MA, Elliott M, Brown SGA. Tiger snake (*Notechis* spp) envenoming: Australian Snakebite Project (ASP-13). *Medical Journal of Australia*. 2012;197(3):173-177

Lenske, E., A. M. Padula, E. Leister and S. Boyd (2018). Severe haemolysis and spherocytosis in a dog envenomed by a red-bellied black snake (*Pseudechis porphyriacus*) and successful treatment with a bivalent whole equine IgG antivenom and blood transfusion. *Toxicon* **151**: 79-83.

Leong, O. S., A. M. Padula and E. Leister (2018). Severe acute pulmonary haemorrhage and haemoptysis in ten dogs following eastern brown snake (*Pseudonaja textilis*) envenomation: Clinical signs, treatment and outcomes. *Toxicon* **150**: 188-194.

Mirtschin PJ, Masci P, DC Paton, Kuchel T. Snake bites recorded by veterinary practices in Australia. *Australian Veterinary Journal*. 1998; 76(3)195-198

Ong RKC, Swindells K, Mansfield CS. Prospective determination of the specificity of a commercial snake venom detection kit in urine samples from dogs and cats. *Australian Veterinary Journal*. 2010;88(6):222-224

Padula A, Winkel K. Case Report: Fatal presumed tiger snake (*Notechis scutatus*) envenomation in a cat with measurement of venom and antivenom concentration. *Toxicon*. 2016; 113:7-10

Padula A, Winkel K. Case Report: Red-bellied black snake (*Pseudechis porphyriacus*) envenomation in the dog: Diagnosis and treatment of nine cases. *Toxicon*. 2016; 117: 69-75

Padula AM, Ong HM, Kelers K. Snake Envenomation in Domestic Animal Species in Australia. *Clinical Toxicology*. 2016

Padula, A. M. and E. Leister (2017). Eastern brown snake (*Pseudonaja textilis*) envenomation in dogs and cats: Clinical signs, coagulation changes, brown snake venom antigen levels and treatment with a novel caprylic acid fractionated bivalent whole IgG equine antivenom. *Toxicon* **138**: 89-97.

Padula, A. M. and E. M. Leister (2017). Severe neurotoxicity requiring mechanical ventilation in a dog envenomed by a red-bellied black snake (*Pseudechis porphyriacus*) and successful treatment with an experimental bivalent whole equine IgG antivenom. *Toxicon* **138**: 159-164.

Notes: