THE NORTHERN HOSPITAL

SNAKE BITE

"Death of Cleopatra", Jean André Rixens, Oil on canvas 1874. Musee des Augustins, Toulouse, France

"The thing had been quickly done. The messengers came at full speed, and found the guards apprehensive of nothing; but on opening the doors, they saw her stone dead, lying upon a bed of gold, set out in all her royal ornaments. Iras, one of her women, lay dying at her feet, and Charmion, just ready to fall, scarce able to hold up her head, was adjusting her mistress's diadem."

Plutarch, Life of Antony 75 A.D

On hearing of the death of Mark Antony at the battle of Actium, Cleopatra kills herself from the bite of a deadly "Asp" It is said that the old Roman republic had only ever feared two people, Hannibal and Cleopatra.

SNAKE BITE

Tiger Snake

Brown Snake

Red Bellied Black Snake

Copperhead Snake

The four venomous snakes of the State of Victoria.

Introduction

Australia has some of the most deadly venomous snakes in the world.

Although most snakebites do not result in clinical envenoming because insufficient venom is injected (i.e, a dry bite) or because the snake is non-venomous, snake bite in Australia is nonetheless a true medical emergency, as it is a potentially life threatening envenomation.

Death is primarily from coagulopathy and neurotoxicity.

The time course of envenomation is typically several hours, however there is great variation in any given individual case, ranging from sudden collapse shortly after a bite to up to 12 hours.

Treatment is both supportive and specific with the use of snake antivenom.

Appropriate **immobilization and pressure** treatment first aid is extremely important in the field, and once this has been achieved then the patient must be transferred immediately to a hospital Emergency Department that is able to treat snakebite by having adequate stocks of snake antivenom, 24 hour laboratory services, and facilities and staff expertise for monitoring and resuscitation.

The traditional Venom Detection Kit (VDK) has been found to be unreliable and its use is no longer recommended.

A **single** vial of antivenom is recommended for patients with clinical and/ or laboratory evidence evidence of envenomation, along with supportive measures, as clinically indicated.

Any patient who develops evidence of toxicity should be discussed with an expert clinical toxinologist, to guide ongoing treatment.

The Venomous Snakes of the State of Victoria

The four venomous land snakes of **Victoria** (see above) are:

1. Tiger Snake.
2. Common Brown Snake.
3. Red Bellied Black Snake
4. Copperhead.

Habitats

Habitat ranges of the venomous snakes found in the State of Victoria

Pathophysiology

Australian Snake Toxins:

There are 4 main types of toxins present in Australian snake venoms:

1. Neurotoxins:

   - Pre-synaptic inhibitors:

     These are the predominant neurotoxins seen in tiger and taipan venom.

     These inhibit the release of neurotransmitter. They are highly toxic and cause a progressive neuromuscular paralysis. They take relatively longer to act than post synaptic inhibitors.

     Antivenom may prevent paralysis but cannot reverse neuronal damage that has already occurred.

     Damaged neurons may take weeks to recover.

   - Post-synaptic inhibitors:

     These are the predominant neurotoxins seen in death adder venom.

     These produce a non-depolarizing competitive block at post synaptic receptors.

     These toxins tend to be less potent, but are more rapidly acting than pre-synaptic inhibitors and are more readily reversed by anti-venom.

   - The usual pattern of both neurotoxins shows cranial nerve involvement, first, followed by paralysis of large limb muscles, then ultimately paralysis of the respiratory muscles.

2. Myotoxins:

   - These cause rhabdomyolyis which can result in hyperkalemia in the short term and renal failure due to myoglobinuria in the longer term.

3. Hemotoxins:

   - Coagulopathy is a leading cause of death in human snake bite.

   - Hemotoxins consist of :

     ♥ **Procoagulants** (ie prothrombin activators) which result in a Venom Induced Consumptive Coagulopathy (or **VICC**) that manifests as defibrination or a DIC type picture, (*Brown, Tiger and Taipan snakes*)

     ♥ Direct anticoagulants which result in a “pure” anti-coagulation type picture, (*Black Snakes*)

4. Direct Acting toxins:

- These are less well defined, but possibly involve toxins that have direct effects on the myocardium (myocardial toxins) and on the kidney (nephrotoxins).

Determinants of the severity of envenomation:

The course of clinical envenomation can vary considerably depending on a number of factors including:

1. The site and vascularity of the tissues penetrated, including direct vessel penetration.

2. The body mass of the victim, (children are more susceptible than adults)

3. The actual amount of venom that is injected.

    - The majority of bites will actually contain little venom and most in fact will not require anti-venom.

4. The number of bites received.

5. The effectiveness of the initial first aid that is delivered.

6. The species of snake that delivered the bite.

Clinical Features

Most snakebites do not result in clinical envenoming because insufficient venom is injected (i.e, a dry bite) or because the snake is non-venomous.

Features of clinical envenoming may include:

1. Local and regional effects

2. Systemic symptoms

3. Sudden collapse/ cardiac arrest

4. Toxin syndromes:

    - Coagulopathy:

        - ♥ **Venom-induced consumption coagulopathy (VICC)**

        - ♥ Thrombotic microangiopathy

        - ♥ Anticoagulant coagulopathy:

    - Myotoxicity

- Neurotoxicity

Local and regional effects:

Local effects:

1. Wound:

   - It is vital to note that snake bite wounds can be extremely variable. The likelihood of a bite *cannot* be based on the "typical" appearance of paired fang marks.

   - Bites may show the "typical" appearance of paired puncture wounds, but they may also appear as a single puncture wound, or merely as a scratch mark, occasionally as a frank laceration.

   - On occasions no bite wound may be apparent at all.

2. Pain:

   - The degree of local pain varies with the species. Pain can range from relatively painless to moderate.

3. Local reaction:

   - Again this is variable and will depend to some degree on the species of snake involved.

     Some mild swelling or bruising may be observed.

     Overall however local effects are *uncommon* in Australian snakebite and are minimal for bites by brown snakes, which cause most major cases of systemic envenoming in Australia.

Regional effects, (Less commonly):

4. Prominent regional swelling may be observed after bites by snakes that cause myotoxicity, (including black and tiger snakes).

5. Local lymphadenopathy may be seen.

Systemic symptoms

Non-specific systemic symptoms which may be observed include:

1. Diaphoresis

2. Headache

3. GIT upset:

- Nausea, vomiting, abdominal pain, diarrhoea.

Sudden collapse:

Collapse or syncope occurring within an hour of the bite may be seen:

Features include:

- Collapse associated with transient hypotension and possible loss of consciousness
  - ♥ Spontaneous recovery usually occurs within minutes.
- A minority of these patients (about 5%) may have a seizure or even a cardiac arrest.

Venom-induced consumption coagulopathy (VICC):

Activation of the clotting pathway by prothrombin activator toxins and consumption of clotting factors (**fibrinogen, factor V** and **factor VIII**) lead to a consumptive coagulopathy known as **Venom-induced consumption coagulopathy (or VICC).**

Coagulation studies reveal:

- INR is high or unrecordable
- aPTT is prolonged
- Fibrinogen level is low or undetectable
- D-dimer level is very high

Two degrees of severity are recognized:

- Complete or severe VICC:

  This is defined as:

  - ♥ Undetectable fibrinogen level
  - ♥ INR > 3.0 (most often unrecordable)
  - ♥ Abnormal aPTT (outside the laboratory's reference interval)
  - ♥ Very high D-dimer level (100 - 1000 times assay cut-off)
- Partial VICC (or less severe changes):

  This is defined as:

- ♥ Low but detectable fibrinogen level (< 1.5 g/L)
- ♥ INR < 3.0

Clinical evidence of abnormal coagulation may include:

- Bleeding from the bite site, cannula site, oral cavity

or from occult sites:

- Gastrointestinal, urinary tract and intracranial

Anticoagulant coagulopathy:

Note that VICC should be distinguished from Anticoagulant coagulopathy, which is a biochemical abnormality, usually without clinical consequences.

This condition provides a good marker of envenoming (especially for black snakes and mulga snakes) but is not clinically important.

Here there is:

- aPTT is moderately abnormal (1.5 - 2.5 times laboratory's reference interval)
- No or mild elevation of INR (> 1.3)
- D-dimer and fibrinogen levels which are normal

Thrombotic microangiopathy:

This condition is always associated with VICC

Features of this syndrome include:

- A microangiopathic haemolytic anaemia, (presence of **fragmented red blood cells on blood film**).
- Thrombocytopenia
- A rising creatinine level (> 120 mmol/L), which may lead to acute renal failure requiring dialysis.

Myotoxicity:

Myotoxicity can be local or generalised.

There is myalgia and/or muscle tenderness.

Biochemical features include:

1. Elevated CK levels:

   CK level is usually normal (within the laboratory's reference interval) on admission but rapidly rises over the ensuing 24 - 48 hours (peak ranges from 1000 U/L in mild cases to > 100,000 U/L in severe cases).

2. Potassium levels may also be elevated (> 5.0 mmol/L) in severe cases.

3. Renal impairment may develop from myoglobinuria.

Neurotoxicity:

This is characterised by **a descending flaccid paralysis.**

It classically first involves the:

1. Eye muscles (ptosis, ophthalmoplegia, diplopia)

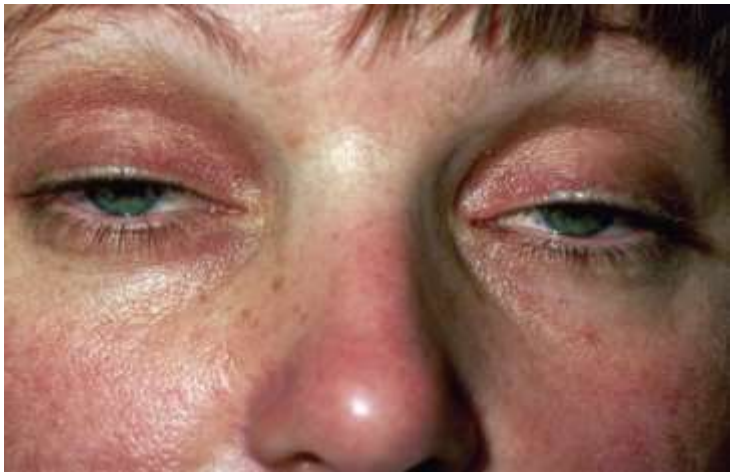
   - To properly test for ptosis, get the patient to look upwards for a **full minute.**

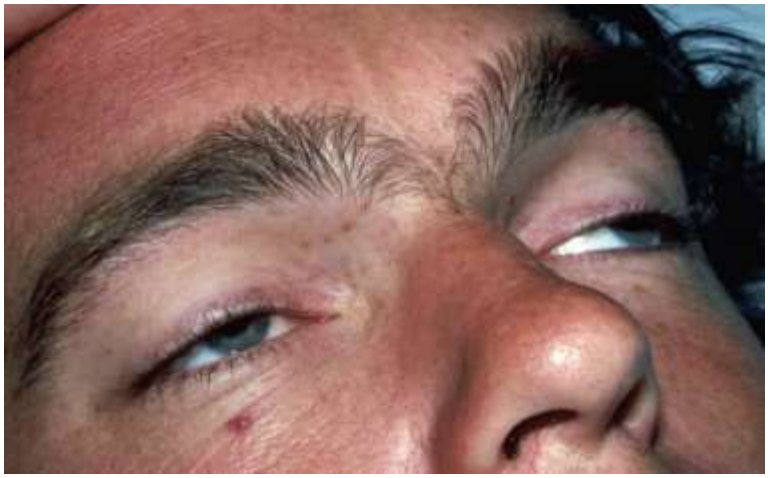
and is followed by:

2. Bulbar muscle paralysis

3. Limb paralysis

4. Respiratory muscle paralysis





Left: Ptosis following a Tiger Snake bite. Right: Ptosis and partial gaze paralysis following Death Adder bite, (NSW Health, 2007).

Time course of Systemic Effects:

The "typical" or average time course of toxicity is over 2-3 hours, however there can be great variation in any particular individual case, depending on the factors that determine severity, (listed above) and can range from sudden collapse shortly after a bite to up to 12 hours following a bite.

An "average" time course of progressive envenomation may be as follows:

1. Within the first hour:
    - Headache.
    - Nausea and vomiting.
    - Collapse/ transient hypotension.
    - Coagulopathy.
    - Restlessness/ confusion.
2. 1-3 Hours:
    - **Cranial nerve paralysis**, the first evidence of this is usually **ptosis** and **diplopia,** followed by **dysarthria**.
    - Increasing agitation/ confusion.
    - Hypertension and tachycardia.
3. After 3 Hours:
    - Paralysis of larger limb muscles.
    - Respiratory paralysis.
    - Cardiovascular collapse.
    - Rhabdomyolysis.
    - Renal failure
    - Coma.

Investigations

Blood tests:

Note that there is currently **no** *specific* biomarker available that diagnoses the presence of venom in the body.

Instead indirect evidence of tissue damage is sought via the following markers:

1. FBE and blood film:
    - Low hemoglobin.
    - A non-specific leukocytosis and lymphopenia can occur with systemic envenoming.
    - **Thrombocytopenia** and **red cell fragmentation** on a **blood film** indicate a diagnosis of **thrombotic microangiopathy.**
2. U&Es / glucose:
    - Check for hyperkalemia in particular.
3. Clotting Profile:
    - **INR & aPPT**
    - Decreased fibrinogen levels.
    - Elevated fibrin degradation products, (d-dimers).
4. **CK:**
    - An elevated creatine kinase (CK) level is a clinically important indicator of myotoxicity but, compared with clinical muscle injury, may lag by up to 24 hours**.**
5. Myoglobin:
    - May be measured in blood or urine, but is not usually *routinely* done.
6. Group and save serum
7. LDH:
    - An elevated lactate dehydrogenase level may assist in diagnosis of thrombotic microangiopathy.

TEST	**VICC** -Venom induced Consumptive Coagulopathy) - (a Defibrination/DIC).	**Anticoagulant coagulopathy**

INR	Increased	Increased
APTT	Increased	Increased
Fibrinogen	Decreased	Normal
FDPs / d-Dimers	Increased	Normal
Platelets	Decreased	Normal
Response to antivenom.	Very difficult to reverse.	Relatively easier to reverse.

Summary of VICC versus Anticoagulant coagulopathy

Urinalysis:

FWT may show positive for "blood".

This may be due to hemoglobin due to hemolysis, but more commonly it will in fact be due to **myoglobin**, indicating rhabdomyolysis.

Snake Venom Detection Kit (SVDK):

The Snake Venom Detection Kit (SVDK; CSL Ltd) was designed to **assist** in determining the appropriate antivenom to use in envenomed patients.

However research has shown that the kit is unreliable producing both false negative and false positive results.

The VDK is no longer recommended for use by Clinical Toxicologists in the State of Victoria.

Management

Pressure Bandage and Immobilization First Aid:

Sutherland's method of pressure bandage & immobilization (PB&I) is *vital* as initial management in any snake bite victim.

This method acts by limiting the lymphatic spread of the venom.

Bandaging:

- The bandage needs to be **broad (15 cm)** and preferably **elasticised**, (e.g "Tubigrip") rather than the previously recommended crepe bandage, (though this can be used if nothing else is available).

- Bandaging is applied over the bite site first, then to the rest of the *entire* limb, (work from the bite site to the fingers and toes, then reflect back proximally to cover the entire limb.

  The limbs are the most commonly bitten area, but if the trunk is involved, then firm pressure should still be applied over the wound.

- The bandage is applied at a pressure similar to that used for a sprained ankle.

- Note that the wound should **not** be washed, (as venom on the skin can be tested for)

- In the *wilderness* setting bandaging should be left in place for at least 24 hours pending evacuation.

- The use of PBI more than 4 hours **after** the bite is unlikely to be effective.

Immobilization:

- It is important to recognize that bandaging is only *half* the treatment.

  Immobilization is also vital in limiting the spread of venom.

  This may be achieved by additional splinting and/or instructing the patient to remain as still as possible.

- If a patient presents to the ED without bandaging, this should be put on immediately.

- Once bandaging is removed there is potential for sudden systemic envenomation. Bandaging should never be removed until the patient has IV access and anti-venom is on hand.

- If there are sudden signs of envenomation then bandaging should be reapplied.

Removal of bandaging:

The PB&I can be removed when:

- The initial clinical and laboratory assessment shows no evidence of envenoming

And

- The patient is in a facility where antivenom is available.

For patients with envenoming:

- The PB&I can be **removed after administration of antivenom**.

As there are reports of cases where envenoming appears to be delayed by early application of a PBI but becomes evident soon after its removal, careful observation of the patient in the hour after PBI removal is essential.

For further details of the technique see separate document.

Transfer to definitive care

Once a patient has been given appropriate first aid at the scene, they must then be immediately transferred to a hospital Emergency Department that has the *capability* of treating snakebite, i.e.

- There must be a supply of antivenom.
- There must be a 24/7 hour laboratory service.
- There must be appropriate facilities and clinical expertise for close monitoring and resuscitation.

Ongoing monitoring of patients with suspected snake bite

Recent research has established the optimal investigation pathway for patients who have suspected snake bite.

Baseline blood tests are taken on presentation to the ED

If blood tests are **normal and the patient has no clinical features of envenomation**, then remove pressure bandage, and observe closely for signs of envenomation.

At **1 hour** post removal, check INR, aPPT, and CK

If no clinical features of envenoming occur within an hour of PBI removal, patients can then be moved to a general clinical area (e.g an SSU) and observed there.

Repeat blood tests at **6 hours** INR, aPPT, and CK post bite, (unless already > 6 hours)

Take final blood tests - INR, aPPT, and CK at **12 hours** post bite.

If the patient remains without signs of clinical envenomation and the INR, aPPT and CK are all normal at 12 hours, then the patient is safe to be discharged.

If at any time the patient develops clinical features of envenomation or the blood tests become abnormal, then the patient must be given antivenom.

Dedicated charts are available for:

- **Medical and Nursing clinical observation**
- **Biochemical investigation**

The Envenomed Patient: Antivenom:

The most important aspect of initial management remains ABC and CPR, followed by supportive care as required.

Antivenom (Equine IgG Fab fragments) - if given *early* - provides additional benefit.

Antivenom can *prevent* certain envenoming syndromes if used early.

Once major envenoming syndromes are established however, antivenom may *not* be nearly so effective.

Patients receiving antivenom must be monitored closely in a resuscitation area.

In **Victoria** polyvalent antivenom is not necessary as **Tiger** and **Brown Snake antivenom** between them are sufficient for the **four toxic species encountered**.

Note that some antivenoms are effective against *more than one* species of snake.

Brown Snake antivenom will treat:

- Brown snake envenomation

Tiger Snake antivenom will treat:

- Tiger snake antivenom
- Copperhead
- Red bellied black snake.

If the bite has been from an "exotic" snake, (e.g. in snake handlers of pets or in zoo keepers) then supplies of antivenom for the particular species can be obtained from CSL

The optimal dosing of snake antivenom has been the subject of much recent research.

The large numbers of vials quoted in the past were probably unnecessary.

Current expert opinion is that **one** vial is sufficient to treat envenomation. Anything further than this is not adding any benefit.

One vial of the relevant snake monovalent antivenom is required to treat both **children** (*you are neutralizing an amount of snake venom, which is independent of the patient's weight*) **and adults** for all snake types.

One vial of antivenom is designed to provide sufficient antivenom to completely neutralise the **total maximum venom load** from one snake, (which is extremely unlikely to be injected in any given snakebite).

The use of more than one vial or repeat doses of antivenom is no longer recommended.

Premedication with adrenaline, antihistamines and corticosteroids are not recommended in Australia, unless there has been a well documented previous **serious** allergic reaction.

Indications for antivenom:

Absolute and relative indications have been established for antivenom

Absolute indications include:

- Reported sudden collapse or seizure
- Cardiac arrest
- Abnormal international normalised ratio, (INR).
- Any clinical evidence of paralysis, with ptosis and/ or ophthalmoplegia being the earliest signs

Relative indications include:

- Systemic symptoms (vomiting, headache, abdominal pain, diarrhoea)
- Leukocytosis
- Abnormal activated partial thromboplastin time (outside laboratory's reference interval)
- Creatine kinase level > 1000 U/L

Contraindications to Antivenom:

There are **no** *absolute* contraindications to the administration of antivenom to those who require it.

It can be given in both pregnancy and lactating patients.

It is safe to give in children

Administration of Antivenom:

1. Patients receiving antivenom must be closely monitored in a **resuscitation cube**.

2. IV access with normal saline running.

3. Pre-medication with adrenaline is *not* necessary, with the high grade antivenoms now used in Australia, unless there is a specific history of a prior life-threatening allergic reaction to antivenom.

4. Tiger and brown snake antivenoms come in ampoules of approximately10 mls.

    - **Ampoule should be diluted 1:10 (i.e. approximately 100 mls of normal saline) and infused over 15-30 minutes, (but may be given quicker depending on how unwell patient is).**

    When the snake species is *uncertain* in the State of Victoria, then one vial of *both* Brown and Tiger Snake Antivenom are given.

    Both ampoules can be diluted together into 200 mls of normal saline and infused over 15-30 minutes, (but may be given quicker depending on how unwell patient is).

    The need for any further dosing should be guided by the advice of an expert toxinologist.

5. The dose is the same for a child as an adult.

6. Following the administration of antivenom:

    - The patient's clinical status must be continuously closely monitored

    - Blood tests are repeated at 6 and 12 hours, and then 12 hourly until normalized.

    Even with adequate antivenom administration it may take 10-20 hours for coagulation studies to return to normal in patients with VICC.

End points to antivenom treatment

Generally one ampoule is sufficient for most bites from most snakes.

VICC lasts a median of around 14 hours (and can last up to 36 hours) before the INR returns to less than 2. Its *duration* is almost certainly not affected by antivenom and so INR is no longer used to "titrate" antivenom response.

Of more use is demonstrating a **rise in the levels of fibrinogen**, at least **3-6 hours** after the administration of antivenom.

If the patient is clinically well and fibrinogen levels are **rising**, then further antivenom should not be necessary, just ongoing close laboratory (and clinical) monitoring.

Coagulopathy treatment:

To treat coagulopathy:

- Antivenom is indicated for any evidence of coagulopathy.
- If there is also **life threatening** bleeding, then this should be treated aggressively with FFP in addition to antivenom.
- FFP in the absence of significant bleeding is an area of controversy at present.

  It is **not** currently given in the *absence* of significant bleeding, however there may be special circumstances where it is considered, and the decision to give it should be guided by consultation with an expert clinical toxinologist.

Complications of Antivenom

Allergic Reactions:

If an allergic reaction occurs to antivenom:

1. Stop antivenom infusion:
   - Many reactions will resolve simply with this step, and the infusion can then be restarted at a **slower rate.**
2. Lie the patient flat, commence high-flow oxygen, support airway and ventilation if required.
3. Hypotension:
   - For hypotension, give fluid resuscitation. Give rapid infusion of 1 liter normal saline (20mL/kg in children).
   - Lie the patient flat or in the Trendelenburg position, with head down and legs elevated
4. **Adrenaline:**
   - For hypotension, hypoxaemia, wheeze or upper airway obstruction, give intramuscular adrenaline (0.01 mg/kg to a maximum of 0.5 mg).
   - Consider a cautious intravenous infusion of adrenaline.

Note that patients with envenoming may be severely coagulopathic, and high blood pressure may cause or worsen intracerebral haemorrhage, although in severe allergic reactions the patient will be hypotensive.

Some patients however can have exaggerated, hypertensive responses to intramuscular bolus adrenaline, especially to second doses and so caution must be exercised.

5. For bronchospasm, consider nebulised salbutamol.

6. For upper airway obstruction, consider nebulised adrenaline.

Serum Sickness:

Serum sickness occurs in about a third of patients given antivenom and is characterised by influenza like symptoms with:

- Fever
- Myalgia
- Arthralgias
- Rash

It generally develops around 4- 14 days after administration of antivenom.

All patients who have received antivenom should be warned about the possibility of serum sickness

It can be treated with oral prednisolone **25 mg (- 50 mg) daily for 5 - 7 days.** [1]

Tetanus immunoprophylaxis

Tetanus immunoprophylaxis is given as clinically indicated.

Disposition

Patients with suspected snake bite but who do not have signs or symptoms or laboratory evidence of envenomation may be admitted to a Short Stay Unit (SSU) for their period of observation.

Patients with mild symptoms of envenomation can be managed in an SSU unit, providing experienced staff are available.

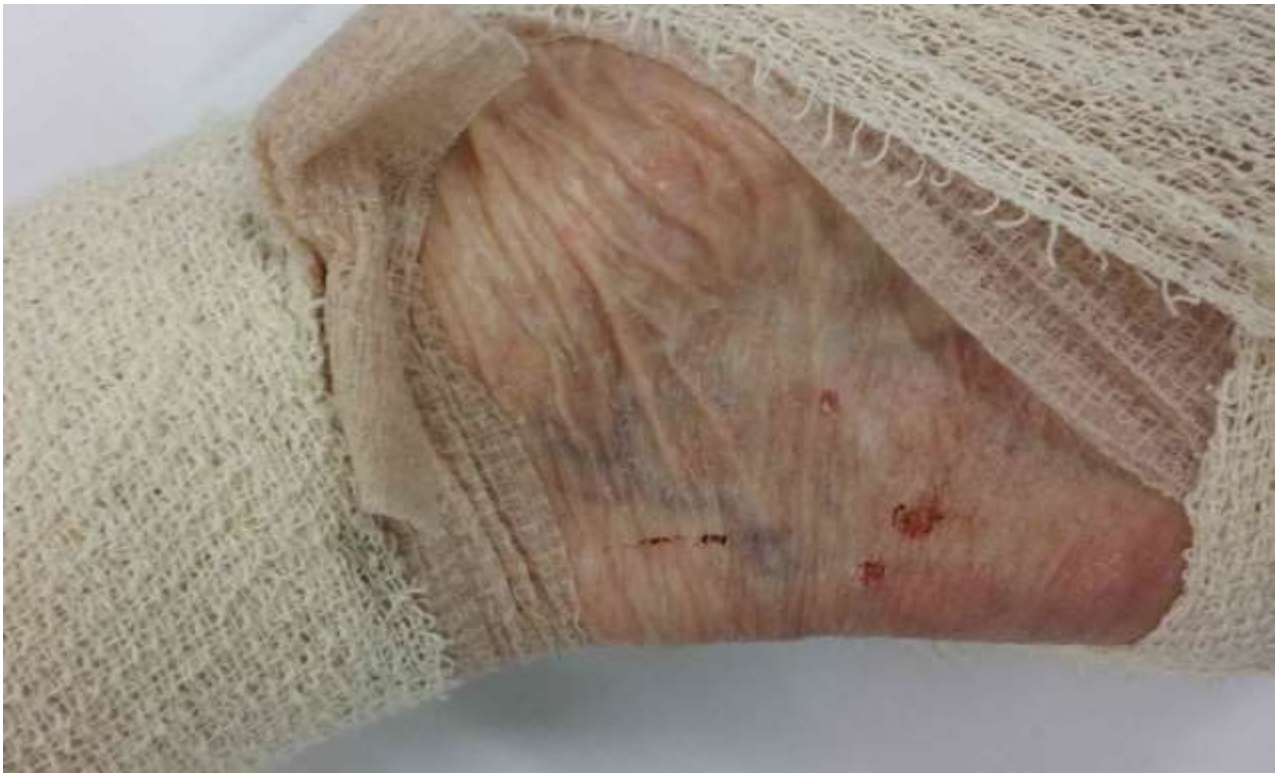
Admission to an intensive care unit is only necessary for patients with major complications, including those with neurotoxic paralysis, thrombotic microangiopathy or severe myotoxicity requiring mechanical ventilation.

Specialist Advice:

Any patient who develops signs or symptoms or laboratory evidence of envenomation, should be discussed with a toxinologist.

For specialist advice concerning any Australian envenomation contact:

Poisons Information Center : 13 11 26



Two fang marks seen – in this case that of a Red Bellied Black Snake bite sustained by an 88 year old lady, who trod on a 4 foot snake. She developed severe systemic symptoms after a few hours but fortunately survived with timely PB&I and a single vial of Tiger Snake antivenom, (Clinical photograph, courtesy Dr Mike Taylor).

References

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3. Christopher I Johnston et al. The Australian Snakebite Project, 2005 - 2015 (ASP-20). MJA 207 (3) 7 August 2017.

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