LIFE THREATENING COMPLICATIONS OF SNAKE BITE

Dr Jenna L Taylor
MBChB DA(SA) FCA(SA)
Specialist Anaesthesiologist – Inkosi Albert Luthuli Central Hospital, Durban KZN
Clinical Lecturer – UKZN Department of Anaesthesia & Critical Care
Member – National Snakebite Advisory Group (NSAG)

INTRODUCTION

Snakebite is referred to as a neglected tropical disease of global importance. Morbidity & mortality remains high in resource poor, rural communities. [1]

The clinical presentation of snake bite is a spectrum. It varies from no symptoms at all to a severe, life threatening, multisystem disease. Other speakers have dealt with the types of venom and local wound complications. This talk focuses on life threatening complications of snake bite which include:

1) Neurotoxicity and respiratory failure
2) Haemodynamic instability
3) Coagulopathy
4) Acute kidney injury

The goal of this talk is to:

1) Educate regarding these life-threatening complications
2) Teach early recognition of complications
3) Prevent complications
4) Show when to refer

Note that any of these life-threatening complications can become significant very abruptly if a tourniquet is released suddenly, resulting in a rush of venom into the systemic circulation. Neurotoxicity and cardiovascular instability are the commonest culprits of cardiac arrest in this scenario.

The classic division of pure neuro / cyto / haemotoxins is simplistic. Most snake venoms consist of a delicate mix of these components, which can be affected by snake locality & diet.

VENOM ACTIONS

The following toxins can be present within snake venom: [2]

1) Neurotoxins
- Pre or postsynaptic effect at the neuromuscular junction (acute flaccid paralysis)
- E.g. mambas & cobras

2) Myotoxins
- Local or systemic
- Rhabdomyolysis with resultant raised creatinine kinase, myoglobinuria and acute renal failure (classically in sea snake venom)

3) Coagulotoxins
- Anticoagulants & haemorrhagins
- Back fanged snakes (boomslang, vine snake) as well as adders (puffadder & gaboon)

4) Nephrotoxins
- Primary renal damage e.g. Puff Adder

5) Necrotoxins
- Range of effects from mild to massive limb necrosis (direct venom effect)

6) ***Cardiotoxins***
    - Direct cardiac toxicity (any arrythmia)
    - E.g. Sarafotoxins – coronary vasoconstriction (atractaspis species)

NEUROTOXICITY

Neurotoxicity is a characteristic of Southern African elapid snakes: cobras and mambas. It can range from mild symptoms to respiratory paralysis, hypoxia and cardiac arrest. Severe untreated neurotoxicity is an important cause of mortality; and of out of hospital cardiac arrest. [3] Importantly, it is recognised that these out of hospital cardiac arrests result in erroneously low snakebite statistics worldwide. [3]

Neurotoxic bites can produce life threatening effects within 1-8 hours. [4] Early signs include nausea, vomiting, abdominal pain and "gooseflesh". [5] Later, ptosis, blurred vision, myokymia (twitching), circumoral tingling, tinnitus, slurred speech, difficulty swallowing, drooling, shortness of breath & respiratory distress occurs. Central effects include altered level of consciousness, seizures and smell & taste disturbance (from cranial nerve involvement, classically from berg adder bites).[6] Many patients can be tachypnoeic due to stress and anxiety. So when should one become concerned? Not all patients exhibiting weakness go on to develop respiratory compromise. [1] Desaturation and hypoxaemia are very late signs. Where possible, a pre-emptive approach is safer.

Occasionally, intubation is required not for respiratory paralysis but rather for airway obstruction from vomitus in the airway, particularly in the case of a low level of consciousness.

Antivenom is the mainstay of treatment of neurotoxicity. However, antivenom can only neutralise unbound venom, hence early administration is paramount.
Importantly, a lack of antivenom does not kill patients with neurotoxic snakebite. Hypoxia and its complications kill these patients. Therefore, it is vitally important that the potential for hypoxia is recognised early and managed appropriately.

Hypoxaemia = low oxygen content in the blood
Hypoxia = lack of oxygen at a cellular level

Acute respiratory failure is an absolute indication for intubation & ventilation.

Type 1: hypoxaemic
- PaO_2 reduced (< 60mmHg or 8kPa)
- $PaCO_2$ normal or reduced (< 50mmHg or 6.7kPa)
- $P_{A\text{-}a}O_2$ reduced

Type 2: hypoxaemia with hypercarbia
- PaO_2 reduced (< 60mmHg or 8kPa)
- $PaCO_2$ increased (> 50mmHg or 6.7kPa)
- $P_{A\text{-}a}O_2$ normal

Oxygenation and ventilation are the primary goals. This can be achieved by a variety of means:

1) ***Mouth to mouth ventilation***
    a. If no equipment is available. Important to consider infection control
2) ***Bag mask ventilation***
    a. Via BVM with face mask
    b. Can be simple, can be challenging in certain patients (BONES – beard, obese, no teeth, elderly, snorers)
    c. Risk of stomach insufflation, regurgitation & aspiration
3) ***Ventilation via a supraglottic airway device***
    a. Such as the LMA / iGEL / Combitube / Laryngeal Tube
    b. Can be difficult to insert in certain patients but require less skill than intubation
    c. Risk of stomach insufflation, regurgitation & aspiration

4) ***Intubation and positive pressure ventilation – gold standard***
    a. Secures the airway definitively
    b. Protects from aspiration (due to ETT cuff)
    c. Allows for leak free IPPV

Whatever the method – **OXYGENATE AND VENTILATE**

Technical skills related to intubation & ventilation will be taught in the practical session

Early appropriate administration of antivenom is the gold standard in the treatment of neurotoxic snakebite. In this way ventilation may be avoided completely or minimised. Complications arise with prolonged mechanical ventilation such as Ventilator Associated Pneumonia (VAP) which contribute to morbidity & mortality. [7]

It is important to note that severe neurotoxic envenomation can mimic brain death [8] Absent respiratory efforts, fixed dilated pupils, areflexia and absent dolls eye movement have been documented in bites. This is particularly concerning in patients presenting unconscious following purely neurotoxic snakebite (such as a black mamba or in India, a krait). There will be minimal evidence of snake bite with puncture marks not always seen and no necrosis or limb swelling. Snake bite must therefore feature on the differential diagnosis of any coma of unknown aetiology. If there is any doubt, electroencephalogram (EEG) or cerebral angiography can help to differentiate neurotoxicity from brain death. [8]

The Black Mamba – Dendroaspis polylepis
The black mamba is regarded as WHO category 1 snake in 17 African countries, which refers to snakes of the "highest medical importance." [5] Neurotoxicity can be profound and rapid (within 15 minutes). Importantly, mamba venom consists of dendrotoxin which is unique in that it potentiates the release of acetylcholine pre-synaptically resulting in an excitatory effect (much like suxamethonium). This produce the hallmark fasciculations of black mamba envenomation.[5]
Additionally, mamba venom contains 3 finger toxin which has the following effects:
- Alpha neurotoxin – nicotinic cholinergic receptor at the motor end plate
- Muscarinic toxins – bind to muscarinic receptors
- Fasciculins – acetylcholinesterase inhibitors. [5]

Other toxins present in mamba venom include:
- Calciseptine – inhibits voltage gated calcium channels [1]
- Mamba intestinal toxin (prokineticin) – gut spasm, hyperalgesia and central effects [9]

Autonomic instability and arrythmias are well described from mamba bites. [4]

The Role of Neostigmine
Neostigmine is a cholinesterase inhibitor which is used for the reversal of competitive non-depolarising neuromuscular blockade. In the case of neurotoxic snake bite, particularly with venoms with competitive, postsynaptic effects, neostigmine can improve the symptoms of neurotoxicity. [1, 10, 11] The role of neostigmine has been described in either cases of poor response to antivenom o in cases where antivenom is unavailable or contraindicated. [4] Neostigmine must be co-administered with an anticholinergic such as atropine or glycopyrrolate in order to negate the muscarinic effects of neostigmine (bradycardia, hypersalivation, bronchospasm etc).
Dosage:
- Adults: Neostigmine 2.5mg; glycol 0.6mg / atropine 1mg
- Paeds: take adult dose, dilute to 7ml and give 1 ml per 10 kg

Delayed Neurotoxicity
Occasionally patients may develop delayed neurotoxicity (2 weeks to 6 months following the bite). Mechanisms include characteristics of the venom itself (example Krait venom) or Guillain Barre syndrome. This may be difficult to distinguish from Critical Illness Neuropathy. [1]

Importantly, patients may need intubation & ventilation for indications other than neurotoxicity, including

- Fluid overload (acute renal failure)
- Acute Respiratory Distress Syndrome (ARDS) [12]
- Shock

HAEMODYNAMIC INSTABILITY

Shock is life threatening circulatory failure. It is defined as a state of cellular and tissue hypoxia due to reduced oxygen delivery and / or increased oxygen consumption or inadequate oxygen utilisation.
Shock is divided into distributive (which includes septic shock), cardiogenic, hypovolaemic and obstructive.
The causes of shock are multi-fold in the victim of snake bite. Mechanisms include: [13]

- ***Hypovolaemic shock***
  - extravasation of fluid into the bitten limb
  - generalised capillary leak from metalloprotease release [2]
  - vomiting
  - blood loss (in the case of coagulopathy)
- ***Direct cardiovascular effects***
  - Puff Adder - bradycardia
  - Gaboon adder [4]
  - Mambas – autonomic instability and calcium inhibition [1]
  - Atractaspis - sarafotoxins – coronary vasoconstriction
- ***Autopharmacological effects (Vasomotor dysfunction)***
  - Angiotensin – renin – bradykinin system
  - Natriuretic peptides resulting in hypotension [9] (e.g. BNP in green mamba venom)
- ***Anaphylaxis*** (from the venom itself of in response to antivenom administration) [14]
- ***Septic shock*** – which may occur later in cases of neglected bites

In puffadder bites, the risk of shock is high. The mechanisms of haemodynamic instability in these patients includes:

- Myocardial depression
- Vasodilatation
- Increased vascular permeability [2]

Unrecognised or mismanaged shock can have devastating effects including death, hypoxic brain damage, acute kidney injury and myocardial injury. A high index of suspicion is essential in victims of snakebite so that shock can be prevented or treated timeously.

Warning signs include tachycardia with a maintained blood pressure, reduced urine output and rising lactate on the arterial blood gas. Tachypnoea and altered mental state are also worrying. It is best to recognise patients at this point, rather than acting only when cardiovascular collapse necessitates emergency intervention.

Clinical examination of hydration status is important. Skin turgor, capillary refill & urine output are simple yet important signs to observe. Obtain baseline heart rate, BP and CVP if possible. Perform a passive leg raise (ideally with 2 people lifting both legs) and hold the limbs up. This autotransfusion can help to show if the patient is fluid responsive or not.
Management includes:

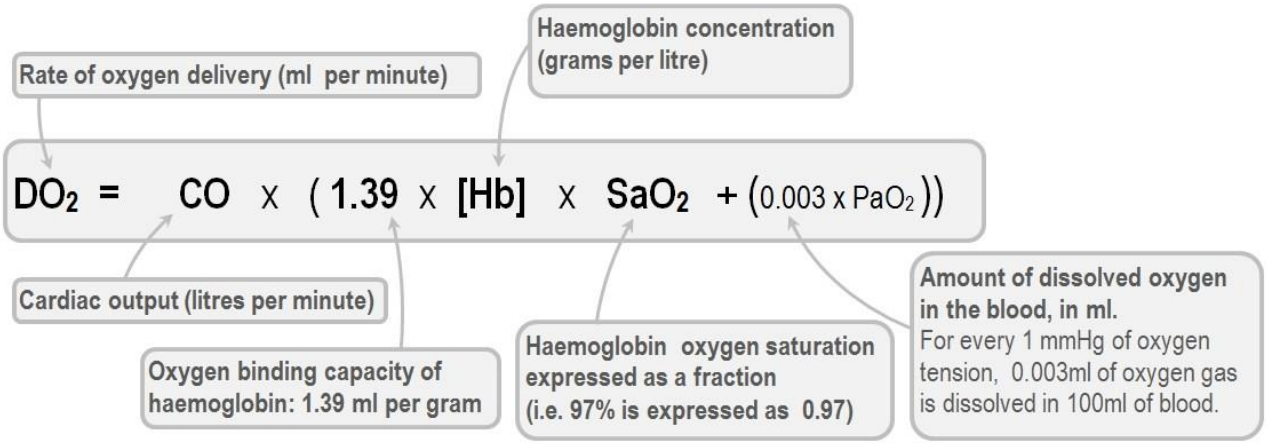
- Insertion of IV line and fluid administration
- Insertion of urinary catheter (aim for 0.5-1ml/kg/hr in adults; 1.5ml/kg/hour in children)
- Continuous monitoring of NIBP, ECG and saturation
- Oxygen administration via face mask in order to assist with tissue hypoxia (initially, intubation & ventilation may be required later)

- Arterial blood gas analysis paying particular attention to pH, Base deficit, bicarb and lactate (i.e. markers of tissue hypoperfusion)
- If possible – invasive monitoring to guide fluid therapy
    - Central venous catheter – as a TREND monitor only
    - invasive arterial blood pressure
    - cardiac output monitoring
- Cardiovascular support with inotropes (adrenalin)

Adrenalin Administration:
Dosage range – 0.05 – 1 mcg/kg/min
Need infusion pump (ideal) or flow regulator on giving set
Adults: e.g. 70kg
- 8 ampoules adrenalin in 200ml NaCl (40mcg/ml)
- 5 – 105ml/hour (start at 55ml/hour)

Children:
- Take 0.3mg/kg adrenalin and mix in a 50ml syringe
- 5ml / hour = 0.5mcg/kg/min; 10ml/hour = 1mcg/kg/min

In summary:
DO_2 = Cardiac output x (Saturation x Hb x 1.39) x (PaO_2 x 0.03)
Shock is the failure of oxygen delivery (DO_2). At all times, DO_2 needs to monitored and maintained.
Shock is therefore managed by:
- optimising cardiac output
    - determined by heart rate & stroke volume
- Optimising oxygenation (supplemental oxygen, IPPV)
- Optimising oxygen carrying capacity (haemoglobin)



COAGULOPATHY

Coagulation disorders characterise the back-fanged species, namely the boomslang and vine snake. They can also occur in puff adder bites as well as gaboon adder envenomation. Coagulopathy can be profound and very difficult to manage once established.

The mechanisms include proteinase activation, procoagulants (thrombin activators) leading to disseminated intravascular coagulation (DIC), protein C activation and phospholipid degradation. [2] Accelerated fibrinolysis is also a common pathology. [15] Haemorrhagins affect endothelium, contributing to increased permeability and local bleeding in the area of the bite. [15]
The final coagulation disturbance depends on the delicate balance of procoagulant, anticoagulant, fibrinolytic and fibrinogenolytic components in the venom. [2]

The most common mechanism appears to be Venom Induced Consumptive Coagulopathy (VICC). [16, 17] The mechanism is much like DIC; where fibrinogen and factors V & VIII are consumed.

Mortality increases significantly in patients with coagulopathy as well as hypothermia and acidosis (the so-called lethal triad) One should treat coagulopathy aggressively and prevent other components of the lethal triad from aggravating this already life-threatening situation.

Death can occur as either an effect of blood loss & hypovolemic shock (which should not happen if the patient presents to hospital timeously) or from haemorrhage into vital structures (particularly intracerebral haemorrhage and pituitary haemorrhage; possibly causing Sheehan syndrome). [3, 15, 17]
The mainstay of treatment of coagulopathy is early antivenom administration. This neutralisation of the venom coupled with supportive therapy (blood product administration) is the only way to manage the coagulopathy. Haemotoxic venoms in general are notoriously difficult to manage and can be fatal. Patients managed with component therapy only can survive but do tend to have a protracted (and expensive) course.
Bleeding can be aggravated by haemolysis which occurs because of phospholipase A2 release (classic with puffadder venom). [2]

Assessment of Severity:

1) Clinical Assessment

- Assessment of puncture sites and the bite site for bleeding
- Spontaneous haemorrhage – mucosa (gums, vagina, eyes, nose, GIT) [2]
- Spontaneous haemorrhage – solid viscus (brain, liver, spleen, kidneys etc)

2) Basic tests

- 20-minute whole blood clotting test – use a plain glass tube, fill with blood, leave at room temperature and start a timer. After 20 minutes, gently invert the tube to see if clotting has taken place. This is a crude test but is excellent as a screening tool. [4, 13-15, 17]
  If the blood fails to clot within 20 minutes, this is associated with fibrinogen < 0.5g/L. [9]
- FBC – Hb and platelets (thrombocytopaenia may occur from consumption in DIC)
- INR – checks the
- aPTT
- Fibrinogen

3) Advanced testing

- Tests such as a TEG or ROTEM (dynamic tests of coagulation) are probably the gold standard; as they reflect in vivo coagulation. They can also be performed at the bedside with results within 20 minutes. The drawback is the cost of the machine & reagents.

Diagnosis:

If the diagnosis is not overtly clinically obvious, an objective scoring system can be used.

Table 1 - International Society on Thrombosis and Hemostasis DIC score: [18]

Factor	Level (score)	Level (score)	Level (score)
Platelets	Over 100 000 (0)	50 -100 000 (1)	< 50 000 (2)
FDP	No change (0)	Moderate rise (2)	Strong rise (3)
PT prolongation	3 seconds or less (0)	3 – 6 seconds (1)	Over 6 seconds (2)
Fibrinogen	> 1 (0)	< 1 (1)	

Score 0-4: DIC not overt, repeat tests in 1-2 days

5-8: DIC probable

Management of Coagulopathy

- Ideally one should transfuse blood products based on point of care testing. However, when this is not available, the following approach is acceptable:

1) Correct the coagulopathy FIRST before giving packed cells
2) Correct any secondary factors that aggravate coagulopathy
3) Correct the haemoglobin once bleeding is controlled (unless the patient is hypovolaemic and anaemic in which case blood is required during resuscitation)

1) Direct management of the coagulopathy

a. Antivenom administration – mainstay of treatment [15, 17]
b. Plasma – 15ml/kg as a slow infusion (over 20 minutes). Faster administration can cause haemodynamic instability because of the citrate toxicity (citrate in the plasma chelates calcium which is essential for myocardial contractility) (1 bottle FDP = 200ml / 50ml). One should be careful of administering plasma before starting antivenom as there is a risk of providing more substrate for the process of VICC. [17]
c. Platelets – 5ml/kg will raise the count by 30 – 40 000. (1 Bag = approx. 500ml)
d. Cryoprecipitate – plasma that is higher in fibrinogen. 5ml/kg (1 bag = 30ml)
e. Vitamin K 0.5-5mg IVI stat (depending on severity of the haemorrhage).
f. No role for the administration of heparin or antifibrinolytics. [17]

Must repeat measurements of coagulation indices every 6 hours (ideally) until parameters return to normal (as one needs to ascertain if additional doses of antivenom are required). [19]

Table 2 – Dosages of Blood Products

Agent	Amount in Bag	Dose per kg	Dose in 70kg adult	Volume
Plasma	200ml	15	1050	5 bottles
Platelets	400 - 500ml	20	1400	3 pools
Cryoprecipitate	30ml	5	350	12 bags
Vitamin K	2mg/amp	/	4mg	2 amps

2) Correct secondary factors

a. Acidosis
    - Treat the cause
b. Hypothermia
    - Actively warm the patient

c. Hypocalcaemia
    - Calcium is an essential co-factor in coagulation
    - Ionised above 1mmol/L essential for coagulation
    - If no lab available – give 0.5ml/kg calcium gluconate slow IV (over 10 min). If bleeding is profound & active – give 1ml/kg

3) Transfuse packed cells

a. 4ml/kg will increase by 1g/dL (packed cells)
b. 8ml/kg will increase by 1g/dL (whole blood). Whole blood is preferable if available, but it is a rarity.

ACUTE KIDNEY INJURY

Acute kidney injury carries a high morbidity in victims of snakebite. It is also an important cause of delayed mortality. [3, 20, 21] Some patients never regain their kidney function. The spectrum of kidney affectation from snake venom is diverse. It can range from mild haematuria & proteinuria to severe acute kidney injury (AKI) [22] AKI appears to be an under-recognised complication of snake bite. [3]

Fortunately, although AKI can occur with any medically significant snakebite, it is far more common in snakes from Asia & South America. [2]

The mechanisms of acute kidney injury in snake bite are multifactorial. The majority of cases of AKI are due to acute tubular necrosis (ATN). [23] Mechanisms include:

- Ischaemia mediated / indirect causes
    - Hypovolaemia & hypotension
    - Hypoxia
    - Anaemia
    - Abdominal compartment syndrome (overzealous fluid, capillary leak) [24]
    - Sepsis [2]
- Direct tubular injury (myoglobinuria from rhabdomyolysis) [22]
- Coagulation disorders & enzymatic effects [2, 20, 23]
    - Metalloprotease activation causing distension, oedema & capillary rupture
    - deposition of fibrin
    - haemolysis & haemolytic uraemic syndrome (uraemia, haemolysis & thrombocytopaenia). [15]
- Iatrogenic (administration of nephrotoxins e.g. NSAIDS)
- Aggravation of pre-existing renal disease
- Less common but documented pathologies include
    - Cortical necrosis (Proatheris superciliaris, Russels Viper)[22] Carries a high mortality. [2]
    - Interstitial nephritis (which may occur with puff adder bites) [2, 23]
    - Glomerulonephritis (puff adders) [2]

The incidence of AKI internationally ranges from 5% (myotoxic) to 29% (haemotoxic). In the international literature, combined cyto & haemotoxic bites [such as those from Bothrops (pit vipers) & Crotalus (rattlesnakes)] have the highest incidence of AKI [20] By extrapolation, one could assume that puff adders & gaboon vipers carry the highest risk in the Southern African setting.

Definitions:

Table 3: KDIGO Criteria (Kidney Disease: Improving Global Outcomes)

	Stage 1	Stage 2	Stage 3
Creatinine values	↑ by 26.5µmol/l within 48 hours	/	Total create > 354 or acute increase >44 µmol/l
Creatinine relative increase	1.5 – 2 x baseline within 7 days	2 – 3 x baseline	≥ 3 x baseline
Urine output	< 0.5ml/kg/hour for 6-12 hours	< 0.5ml/kg/hour for > 12 hours	< 0.3ml/kg/hour for 24 hours OR anuria for 12hr

Practically speaking; the following is an approach to the detection & diagnosis of AKI

- Clinical examination – renal angle tenderness may precede AKI [2]
- Urine catheter insertion for all significant bites
    - Close monitoring of urine output (hourly documentation)
    - Documentation of urine colour
- Serum urea & creatinine
    - Baseline
    - 6 hourly
- Creatinine kinase [12]
- Coagulation profile
- Urine testing:
    - Urinalysis
        - Protein
        - Haemoglobin
        - Myoglobin
    - Urine microscopy [12]

Management

1) ***Prevention***
    a. Recognise that all patients with snakebite are at risk for AKI, especially cytotoxic bites
    b. Antivenom – the timing of AV administration is crucial in the prevention of AKI. The earlier it is given; the lower the risk of AKI. [2, 12, 20, 24, 25]
    c. Prevent secondary kidney injury:
        i. Maintain oxygen delivery
            1. Cardiac output
            2. Haemoglobin
            3. Oxygen saturation
        ii. Avoid nephrotoxins
            1. NSAIDS, contrast, aminoglycosides etc
2) ***Supportive***
    a. Fluid therapy
    b. Furosemide – controversial
        i. Promotes urine output
        ii. Contraindicated in hypovolaemia
        iii. Acts by inhibiting the Na-K-Cl co-transporter therefore reduces renal oxygen consumption
    c. Sodium bicarbonate
        i. Urine alkalinisation – prevents precipitation of myoglobin in rhabdomyolysis [2, 21]

3) Directed

a. Renal replacement therapy – dialysis
b. Indications:
    i. Fluid overload
    ii. Refractory hyperkalaemia
    iii. Refractory metabolic acidosis
    iv. Uraemic symptoms

Table 4 – Clinical Predictors of AKI in Snakebite [20]

Feature	Non AKI	AKI	P value
Haemorrhagic manifestation	22	62	0.001
Local lesion	24	172	0.022
Altered PT	9	88	0.005
Altered aPTT	8	71	0.042

In summary:
One should have a high index of suspicion in the following patients:

- Cyto & haemotoxic bites
- Severe systemic manifestations
- High urea & creatinine on admission
- Low haemoglobin
- Elderly patients [25]

The mainstay of prevention and treatment is

- Early effective antivenom administration
- Supportive care (to prevent secondary renal injury) [12]

Most patients will make a good recovery but those with Stage III AKI have a poor prognosis [12]

SUMMARY

It is important to note that these complications should be seen as a continuum and not as discrete entities. Haemolysis contributes to bleeding as well as being a risk factor for AKI. Cardiotoxicity aggravates shock as well as secondary acute renal injury. Respiratory failure, by means of hypoxia, aggravates coagulopathy (via anaerobic metabolism and acidosis) as well as cardiovascular instability and renal injury.
For patients without overt systemic shock, neurotoxicity or coagulopathy, Darryl Wood and team developed a simple scoring system, the Zululand Snakebite Score, which flags patients who require an active treatment intervention. [26]
These include (1 point each):

- Children < 14
- Duration > 7 hour (between bite & admission)
- WCC > 10x 10^9 /L
- INR > 1.2
- Platelets < 92 x 10^9 / L
- Haemoglobin < 7.4 g/dL

Patients scoring 4 or more should be flagged as those who require aggressive treatment & monitoring (because of a higher risk of complications).

Mortality and significant morbidity from snakebite is preventable

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