Envenoming...
Where’s the toxicologist, antivenom and helicopter?

Geoff Isbister
Troublemaker
Calvary Mater Newcastle and University of Newcastle

ED Leadership Forum
Friday May 31 2013
ASP....

...what’s new and who have I offended lately?

Man dies trying to kill snake

ADELAIDE, Tuesday. — A tractor driver was killed yesterday when his tractor overturned as he tried to run over a snake.

He was Colin Gardner Goode, 45, an employee of Mr. Reginald Michael, of Barunga Gap, 82 miles north of Adelaide.
Toxinology Critical Care

In severe and life-threatening envenomning the most important thing is …

ABC …. CPR

The most important first aid treatment for envenomning is …

ABC …. CPR
ToxiCology Critical Care

In severe and life-threatening poisoning the most important thing is …

ABC …. CPR

The most important first aid treatment for poisoning is …

ABC …. CPR
You can sleep now…

**Snake envenoming**
usually managed in an ED observation unit

**Distribution:**
Tigers south; Browns north, east and west

**VDK:**
Adds little to clinical care - expensive

**Antivenom:**
Early
1 vial and no re-dosing

**Suspected snake-bite**
Most of the work!
Australian Snakebite Project

…ASP

Prospective study of snake-bites
Serial data collection with venom/antivenom levels to determine:
ANTIVENOM: EFFECTIVENESS, SAFETY and DOSE
END-POINTS for TREATMENT
RANDOMISED CONTROLLED TRIAL of antivenom for Red-bellied black snake envenoming

CONTACT ASP number: 1800 676 944
• Geoff Isbister 0438 466 471
• Simon Brown (WA) 0419 796 678
Australian Snakebite Project

Dec 2001 to Jan 2013
1300 snakebites
644 envenomed

- Brown Snake  260
- Tiger Snake  92
- Red-bellied black snake  84
- Rough-scaled snake  39
- Taipan  30
- Mulga snake  25
- Death Adder  22
- *Hoplocephalus* spp.  20

12 deaths = 5%

2 deaths
<table>
<thead>
<tr>
<th>Snake Type</th>
<th>Number of Cases</th>
<th>%</th>
<th>AV</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown snake</td>
<td>248</td>
<td>41%</td>
<td>236</td>
<td>95%</td>
</tr>
<tr>
<td>Tiger snake</td>
<td>87</td>
<td>14%</td>
<td>84</td>
<td>97%</td>
</tr>
<tr>
<td>Red-bellied black snake</td>
<td>78</td>
<td>13%</td>
<td>34</td>
<td>44%</td>
</tr>
<tr>
<td>Rough-scale snake</td>
<td>39</td>
<td>6%</td>
<td>36</td>
<td>92%</td>
</tr>
<tr>
<td>Taipan</td>
<td>29</td>
<td>5%</td>
<td>29</td>
<td>100%</td>
</tr>
<tr>
<td>Mulga snake</td>
<td>24</td>
<td>4%</td>
<td>19</td>
<td>79%</td>
</tr>
<tr>
<td>Death adder</td>
<td>21</td>
<td>3%</td>
<td>19</td>
<td>90%</td>
</tr>
<tr>
<td>Clinical Syndromes</td>
<td>Number of Cases</td>
<td>%</td>
<td>AV</td>
<td>%</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>-----------------</td>
<td>----</td>
<td>-----</td>
<td>----</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>520</td>
<td>85%</td>
<td>475</td>
<td>91%</td>
</tr>
<tr>
<td>Complete VICC</td>
<td>354</td>
<td>58%</td>
<td>433</td>
<td>99%</td>
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<tr>
<td>Partial VICC</td>
<td>100</td>
<td>16%</td>
<td>81</td>
<td>81%</td>
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<tr>
<td>Anticoagulant</td>
<td>66</td>
<td>11%</td>
<td>42</td>
<td>64%</td>
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<tr>
<td>Major Haemorrhage</td>
<td>5</td>
<td>1%</td>
<td>5</td>
<td>100%</td>
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<tr>
<td>Neurotoxicity</td>
<td>73</td>
<td>12%</td>
<td>72</td>
<td>99%</td>
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<tr>
<td>Mild</td>
<td>42</td>
<td>7%</td>
<td>41</td>
<td>98%</td>
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<tr>
<td>Myotoxicity</td>
<td>56</td>
<td>9%</td>
<td>46</td>
<td>82%</td>
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<td>Thrombotic microangiopathy</td>
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<td>8%</td>
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<tr>
<td>Renal Toxicity</td>
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<td>68</td>
<td>97%</td>
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<tr>
<td>Acute renal failure</td>
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<td>35</td>
<td>97%</td>
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<td>Abnormal Creatinine</td>
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<td>6%</td>
<td>33</td>
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## Clinical Syndromes

<table>
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<tr>
<th>Snake</th>
<th>Coags</th>
<th>Neurotoxicity</th>
<th>Myotoxicity</th>
<th>NSS</th>
<th>TMA</th>
<th>CVS effects</th>
<th>AV</th>
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</thead>
<tbody>
<tr>
<td>Brown Snake</td>
<td>VICC</td>
<td>Rare/mild</td>
<td>-</td>
<td>&lt;50%</td>
<td>10%</td>
<td>Collapse (33%) Cardiac arrest (5%)</td>
<td>Brown</td>
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<tr>
<td>Tiger snake</td>
<td>VICC</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Common</td>
<td>5%</td>
<td>Rare</td>
<td>Tiger</td>
</tr>
<tr>
<td>Rough-scale</td>
<td>VICC</td>
<td>Uncommon</td>
<td>Uncommon</td>
<td>Common</td>
<td>&lt;5%</td>
<td>Rare</td>
<td>Tiger</td>
</tr>
<tr>
<td>Hoplocephalus</td>
<td>VICC</td>
<td>-</td>
<td>-</td>
<td>&lt; 50%</td>
<td>-</td>
<td>-</td>
<td>Tiger/</td>
</tr>
<tr>
<td>Mulga snake</td>
<td>AC</td>
<td>-</td>
<td>Common</td>
<td>Common</td>
<td>-</td>
<td>-</td>
<td>Brown</td>
</tr>
<tr>
<td>RBBS</td>
<td>AC</td>
<td>-</td>
<td>Common</td>
<td>Common</td>
<td>-</td>
<td>-</td>
<td>Black</td>
</tr>
<tr>
<td>Death Adder</td>
<td>-</td>
<td>Common</td>
<td>-</td>
<td>Common</td>
<td>-</td>
<td>-</td>
<td>Tiger</td>
</tr>
<tr>
<td>Taipan</td>
<td>VICC</td>
<td>Common</td>
<td>Rare</td>
<td>Common</td>
<td>5%</td>
<td>Uncommon</td>
<td>Taipan</td>
</tr>
</tbody>
</table>
Resources

Therapeutic Guidelines
Toxicology and Wilderness

Poison Centre
131126
ASP
1800 676 844
Toxicology Service

- If presenting to a health care facility that does not have critical care and on-site pathology facilities with antivenom, maintain basic life support, apply PBI and arrange urgent transfer.

1. Give antivenom; monoclonal antivenom based on geography, clinical effects and VDK.
2. Be prepared for anaphylaxis
3. Release PBI after antivenom

- Laboratory or clinical evidence of envenomation develops?
  - Yes
  - PBI biological isolation and vials [NB3]
  - 1 hour after removing PBI and 6 and 12 hours after bite
  - Repeat bloods at 6, 12 and 24 hours [NB4] to check for recovery of coagulopathy and development of complications such as kidney impairment
  - Further treatment of neurotoxicity, myotoxicity or thrombotic microangiopathy may require intensive care and clinical toxicology advice
- No
  - Discharge in daylight hours with advice on serum sickness [NB5]
case 1

A 34 year old female presents after a snake bite with vomiting, abdominal pain and headache. The hospital has no laboratory but does have antivenom. The hospital is located in Eastern NSW. The patient has a pressure bandage on.
Q1. What action would you take?

A. Treat with metoclopramide and intravenous fluids.
B. Transfer to another hospital
C. Give one vial of tiger and one vial of brown snake antivenom.
D. Remove the bandage and observe for 12 hours
E. Give a vial of polyvalent antivenom
Issues

• What is the likely snake?
• Indications for antivenom:
  • Are systemic symptoms enough?
• What are the risks of giving antivenom?
• What are the benefits of giving antivenom?
Bite distribution

Brown snakes

Tigers snakes
Bite distribution

RBBS snakes       Rough-scaled snakes       Hoplocephalus

Legend
X. bitorquatus
H. bungaroides
H. stephensi
Bite distribution

Other snakes:

Death adder
  • mainland Australia

Taipan –
  • Northern Australia
  • Captive snakes; snake handlers

Mulga:
  • Where the RBBS are not…
  • Central/Western Australia
# Clinical Syndromes

<table>
<thead>
<tr>
<th>Snake type</th>
<th>Major clinical effect</th>
<th>Other clinical effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown snake</td>
<td>VICC</td>
<td>• often asymptomatic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• thrombocytopenia</td>
</tr>
<tr>
<td>Tiger snake group</td>
<td>VICC</td>
<td>• systemic symptoms</td>
</tr>
<tr>
<td>Tiger snake</td>
<td></td>
<td>• myotoxicity and neurotoxicity</td>
</tr>
<tr>
<td>Rough-scale snake</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stephen’s banded snake</td>
<td>VICC</td>
<td>• often asymptomatic</td>
</tr>
<tr>
<td>Red-bellied black snake</td>
<td>systemic symptoms</td>
<td>• anticoagulant coagulopathy</td>
</tr>
<tr>
<td>Mulga snake</td>
<td></td>
<td>• myotoxicity</td>
</tr>
<tr>
<td>Death adder</td>
<td>neurotoxicity</td>
<td>• systemic symptoms</td>
</tr>
<tr>
<td>Taipan</td>
<td>VICC</td>
<td>• systemic symptoms</td>
</tr>
<tr>
<td></td>
<td>neurotoxicity</td>
<td></td>
</tr>
</tbody>
</table>
CSL Venom Detection Kit

Adds little to geography + clinical

Source:  
- Wound (best site)  
- Urine (high rate of false+)

False positives and negatives

Determines which venom from 5 snake types

for selection of antivenom

ONLY for envenomed patients
TIGER: sVDK results

44 bite sites tested
- 33 positive (75%)
- 4 negative (3 Urine + tiger)
- 2 positive tiger/brown

5 positive brown
- 3 got brown snake AV
- 1 got brown and tiger snake AV

12 not tested:
- 4 Urine VDK +ve tiger
- 4 expert ID
- 4 Tasmania

### Venom Identification

<table>
<thead>
<tr>
<th>Well</th>
<th>Venom Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tiger snake venom</td>
</tr>
<tr>
<td>2</td>
<td>Brown snake venom</td>
</tr>
<tr>
<td>3</td>
<td>Mulga snake venom</td>
</tr>
<tr>
<td>4</td>
<td>Death adder venom</td>
</tr>
<tr>
<td>5</td>
<td>Taipan venom</td>
</tr>
<tr>
<td>6</td>
<td>Negative control</td>
</tr>
<tr>
<td>7</td>
<td>Positive control</td>
</tr>
<tr>
<td>8</td>
<td>Blank well</td>
</tr>
</tbody>
</table>

![Image showing samples and test results]
Red-bellied black snake

MOST LIKELY SNAKE
# Indications for antivenom

## Absolute indications:
- History of sudden collapse, seizure or cardiac arrest
- Abnormal INR
- Any evidence of paralysis with ptosis and/or ophthalmoplegia being the earliest signs

## Relative Indications:
- Systemic symptoms (vomiting, headache, abdo pain)
- Leukocytosis
- Abnormal aPTT
- CK > 1000U/L
Indications for antivenom in RBBS

Unknown

Unresponsive to symptomatic treatment
ie. anti-emetics, pain relief, intravenous fluids

Specific end-points:
To prevent myotoxicity (CK>1000)
Anosmia and changed smell
Reversal of non-specific systemic effects
### Myotoxicity: red-bellied black snake envenoming

<table>
<thead>
<tr>
<th></th>
<th>AV &lt; 6 hr</th>
<th>AV &gt; 6 hr or nil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Myotoxicity</td>
<td>0</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>Venom Cmax (ng/mL)</td>
<td>84 (43 to 157)</td>
<td>19 (12 to 45)</td>
</tr>
</tbody>
</table>

56 patients with envenoming:
- Non-specific systemic effects 95%
- **Anticoagulant coagulopathy** 61%
- Myotoxicity 12%

Churchman et al Med J Aust 2010
Antivenom Reactions

1. Early reaction in 48 cases (25%)
   38 mild or moderate
   10 severe

2. Commonest feature:
   generalised erythema or urticaria in 44 cases (92%)

3. Hypotension
   9 of 10 severe cases.

4. Respiratory manifestations:
   uncommon with wheeze in 7, stridor in one and hypoxaemia in 3.

<table>
<thead>
<tr>
<th>Antivenom</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown</td>
<td>9 (10%)</td>
</tr>
<tr>
<td>Tiger</td>
<td>24 (41%)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Death Adder</td>
<td>4 (44%)</td>
</tr>
<tr>
<td>Taipan</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>Polyvalent</td>
<td>9 (41%)</td>
</tr>
</tbody>
</table>
## Treatment of Antivenom Reactions

1. **Stop antivenom infusion**
2. Lie patient flat, high flow O₂, support airway and ventilation
3. For hypotension - 1L normal saline (20 ml/kg in children) rapidly
4. For hypotension, hypoxaemia, wheeze/upper airway obstruction:
   - adrenaline *intramuscularly*, 0.01 mg/kg to 0.5 mg OR I.V.
5. Consider I.V. infusion of adrenaline – avoid BP surges
   - severe coagulopathy
   - If no response to steps 1-4,
     - 1mg in 100mL: Start at 0.5 mL/kg/hour and titrate
6. Persistent hypotension, repeat fluid bolus
7. Bronchospasm, consider nebulized salbutamol
8. Upper airway obstruction, consider nebulized adrenaline
Treatment of Antivenom Reactions

Premedication
Not recommended in Australia
One RCT in Sri Lanka showed benefit for adrenaline
BE PREPARED for anaphylaxis

Antihistamines and Steroids
No evidence for use for premedication or treatment

Serum Sickness
Probably occurs in 30% to 40% of cases
Warn the patient – treatment with steroids
benefit versus risk

Benefit of preventing myotoxicity

Risk of reactions
Treatment

Red-bellied black snake
Tiger snake antivenom

What if ? brown snake or tiger snake group
Add brown snake antivenom

EMPIRICAL TREATMENT
1 vial tiger and 1 vial brown snake antivenom
OR retrieve and send bloods
benefit versus risk
You are called about advice and retrieval for a brown snake bite in a remote hospital. POC INR and POC dDimer are both normal and the patients is asymptomatic. The hospital has 1 vial of brown snake and 1 vial of tiger snake antivenom but no sVDK.
Q9. Which is the appropriate action?

A. Reassure that the patient is likely non-envenomed and can be observed overnight repeating the INR and dDimer.

B. Give 1 vial of brown snake antivenom and 1 vial of tiger snake antivenom.

C. Send the blood in a taxi to the closest lab 2 hours away to recheck the INR.

D. Retrieve the patient and reassess in your ED

E. Give 1 vial of brown snake antivenom and 1 vial of tiger snake antivenom and retrieve the patient.
## Point of Care – INR or d-Dimer

<table>
<thead>
<tr>
<th>Age</th>
<th>Snake species</th>
<th>Clinical effects</th>
<th>iSTAT© INR</th>
<th>Analyser INR</th>
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<tbody>
<tr>
<td>37</td>
<td>Brown</td>
<td>Hypotensive collapse</td>
<td>3.2</td>
<td>&gt;10</td>
</tr>
<tr>
<td>68</td>
<td>Brown</td>
<td>Systemic symptoms</td>
<td>0.8</td>
<td>1.8</td>
</tr>
<tr>
<td>2</td>
<td>Taipan</td>
<td>Neurotoxicity; myotoxicity; TMA</td>
<td>1.5</td>
<td>&gt;10.0</td>
</tr>
<tr>
<td>30</td>
<td>Brown</td>
<td>Nil</td>
<td>1.2</td>
<td>&gt;10</td>
</tr>
<tr>
<td>27</td>
<td>Tiger</td>
<td>Nil</td>
<td>1.2</td>
<td>&gt;10.0</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>No</td>
<td>2.5</td>
<td>1.0</td>
</tr>
</tbody>
</table>
TO treat snake bite / envenomning

You NEED:
Hospital with medical staff
Antivenom
• Ability to treat anaphylaxis
Laboratory that can do an INR/PT
  • not POC
  • not WBCT

Limiting Factor
Question 3

You are asked to review the hospital supply of snake antivenom in Western Sydney.
Q3. What antivenom should you keep?

A. 1 vial of brown snake and 1 vial of tiger snake

B. 2 vials of brown snake, 4 vials of tiger snake and 1 vial of polyvalent antivenom

C. 5 vials of tiger snake, 4 vials of tiger snake, 1 vial of black snake and 1 vial of death adder antivenom.

D. 1 vial of brown snake, 1 vial of tiger snake, 1 vial of black snake and 1 vial of death adder antivenom
What snakes?

Brown snake

Red-bellied black snake

Snake-handler:

Every major snake

Death Adder

Tiger snake/Hoplocephalus

Brown Snake AV

Tiger Snake AV

Polyvalent AV

Polyvalent AV

Tiger Snake AV
POLYVALENT antivenoms

Commercial monovalent antivenoms in Australia are polyvalent

Margaret A. O'Leary a, Geoffrey K. Isbister a, b, c, *

POLYVALENT (LARGE VOLUME)
Taipan, death adder, black
All large volumes and uncommon snake bites

LOW VOLUME POLYVALENT
Brown + Tiger
<table>
<thead>
<tr>
<th>Batch No.</th>
<th>Expiry date</th>
<th>Vial volume (ml)</th>
<th>Units/vial</th>
<th>Vials</th>
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<td></td>
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<td></td>
<td>BSAV</td>
<td>TSAV</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1000</td>
<td>3000</td>
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<td>2612</td>
<td>3000</td>
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<td></td>
</tr>
<tr>
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<td>5/93</td>
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<td>4951</td>
<td>8756</td>
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<td>7429</td>
<td>12987</td>
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<td>17070</td>
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<td>Death adder antivenom</td>
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<td>052-1</td>
<td>7/90</td>
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<td>6/95</td>
<td>25.0</td>
<td>1631</td>
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<td>3/98</td>
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<td>1719</td>
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<td>8/01</td>
<td>27.0</td>
<td>2073</td>
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<td>06901</td>
<td>5/03</td>
<td>22.0</td>
<td>2465</td>
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<td>11/06</td>
<td>52.0</td>
<td>9219</td>
<td>8575</td>
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<td>07701</td>
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<td>8802</td>
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<td>Black Snake antivenom (Mulga snake)</td>
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<td>12/90</td>
<td>38.2</td>
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<tr>
<td>04901</td>
<td>4/94</td>
<td>46.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>06001</td>
<td>7/00</td>
<td>46.9</td>
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<td>06601</td>
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<td>07201</td>
<td>9/06</td>
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<td>07301</td>
<td>7/07</td>
<td>55.7</td>
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<td>Polyvalent antivenom</td>
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<tr>
<td>16301</td>
<td>3/08</td>
<td>29.87</td>
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<tr>
<td>16501</td>
<td>7/09</td>
<td>35.93</td>
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</tr>
<tr>
<td>Snake Type</td>
<td>Vial</td>
<td></td>
<td></td>
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<tr>
<td>----------------------------------</td>
<td>------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown Snake</td>
<td>1 vial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiger Snake/Rough Scale</td>
<td>1 vial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black Snakes: Mulga Snake</td>
<td>1 vial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red-bellied Black Snake</td>
<td>1 vial tiger/black</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taipan</td>
<td>1 vial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death Adder</td>
<td>1 vial</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
How much antivenom?

Need to treat one case only

Therefore:

1 vial brown snake AV
1 vial tiger snake AV
Access to 1 vial polyvalent AV
• Major referral centre, retrieval etc.
Question 5

A 45 year old male presents to a hospital in Northern Coastal NSW with vomiting and headache. His first INR is unrecordable and he is treated with tiger snake antivenom. 4 hours later the RMO reports that he has ptosis.
Q5. Which is the appropriate action?

A. Get the RMO to re-examine the patient
B. Give a further vial of tiger snake antivenom
C. Retest the sVDK and give 1 vial of brown snake antivenom
D. Observe carefully over the next 6 hours for bulbar or progressive neurotoxicity
E. Give polyvalent antivenom
Question 6

One vial of tiger snake antivenom is given. The RMO calls 2 hours later to say the INR is still unrecordable now 8 hours post-bite.
Q6. Which is the appropriate action?

A. Get the RMO to re-collect the bloods and repeat the coags.
B. Give 4 units of FFP
C. Give a further vial of tiger snake antivenom and recheck bloods in 2 hours
D. Get the RMO to examine for any external bleeding or evidence of major haemorrhage
E. Give polyvalent antivenom
Issues

What is VICC?
What is the dose of antivenom in VICC?
Antivenom and neurotoxicity

Just give more if it hasn’t worked yet ....
What is Snake Bite Coagulopathy?

Venoms contain a procoagulant toxin:
Prothrombin activator
Causes a clot in vitro

VICC: Venom-induced consumption coagulopathy
Clotting factor consumption in vivo
Specific factor deficiencies:
• Fibrinogen
• Factors V and VIII

Most Australasian elapids:
Brown snake, tiger snake and taipan
Venom induced consumption coagulopathy (VICC)

**Complete:**
Consumption coagulopathy with undetectable fibrinogen and/or a raised D-Dimer (at least 10 times the assay cut-off or >2.5mg/L) and an international normalised ratio (INR) >3.0

**Partial:**
Incomplete consumption coagulopathy with low but detectable fibrinogen, elevated D-Dimer and a maximum INR <3.0
Recovery of Factors

Recovery to INR<2 = median 14.4h (IQR 11.5-17.5 h)
Recent “Current” practice

Unrecordable INR = severe coagulopathy
Increasing doses of antivenom required
Commence with a larger dose of antivenom
Antivenom needs to be titrated:
Repeat coags 1 to 3 hours post-AV, fibrinogen best
• IF abnormal repeat dose antivenom
Regular coagulation testing
Continue antivenom until coagulation normal
Does NORMAL = measurable fibrinogen, normal INR and aPTT, or even normal D-dimer?
Antivenom Dose:
CSL’s original recommendation

<table>
<thead>
<tr>
<th>Snake Type</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown Snake</td>
<td>$\frac{1}{2}$ vial</td>
</tr>
<tr>
<td>Tiger Snake/Rough Scale</td>
<td>1 vial</td>
</tr>
<tr>
<td>Black Snakes: Mulga Snake</td>
<td>1 vial</td>
</tr>
<tr>
<td>Red-bellied Black Snake</td>
<td>1 vial tiger/black</td>
</tr>
<tr>
<td>Taipan</td>
<td>1 vial</td>
</tr>
<tr>
<td>Death Adder</td>
<td>1 vial</td>
</tr>
</tbody>
</table>
## Antivenom Dose:
1990s to ~2007

<table>
<thead>
<tr>
<th>Snake Type</th>
<th>Antivenom Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown Snake</td>
<td>4 to 10 vials</td>
</tr>
<tr>
<td>Tiger Snake/Rough Scale</td>
<td>4 vials</td>
</tr>
<tr>
<td>Black Snakes: Mulga Snake</td>
<td>1 vial</td>
</tr>
<tr>
<td>Red-bellied Black Snake</td>
<td>1 vial tiger/black</td>
</tr>
<tr>
<td>Taipan</td>
<td>3 vials</td>
</tr>
<tr>
<td>Death Adder</td>
<td>1 vial</td>
</tr>
</tbody>
</table>

**All these snakes cause a consumptive coagulopathy; VICC ??**
Increasing Dose of Brown Snake Antivenom

CSL initially recommended 500 U
Now equivalent to $\frac{1}{2}$ vial

CSL antivenom handbook:
3 to 4 vials

Toxicologists in 2006:
5 vials (Eastern States)
10 vials (WA) = 20 x initial CSL dose
Antivenom dosing in 35 patients with severe brown snake (Pseudonaja) envenoming in Western Australia over 10 years

Justin M Yeung, Mark Little, Lindsay M Murray, George A Jelinek and Frank FS Daly

There is conflicting advice about the appropriate dosing of antivenom for patients envenomed by brown snakes in Australia, with recommended initial doses ranging from one to four ampoules.\(^1\)\(^-\)\(^3\)

Determining the dose required to neutralise the venom in a given case is difficult, because there is no clear end-point against which to titrate antivenom. The two brown snakes in Western Australia — the dugite (Pseudonaja affinis) and the western brown snake or gwardar (P. nuchalis) (Box 1) — both produce defibrination coagulopathy (in severe cases, afibrinogenaemia), but few other clinical features. Unlike the common or eastern brown snake (P. textilis), they rarely cause neurotoxicity in humans. Patients envenomed by brown snakes in Western Australia are often asymptomatic. Even when venom is neutralised by antivenom, there is a delay before fibrinogen is produced, so determining the dose required is difficult. An objective method for determining the neutralising dose based on ELISA measurement of venom concentrations in blood has been reported, but at present this is not available for the brown snakes in Western Australia.

Main outcome measure: The dose of antivenom required to neutralise venom, defined prospectively as afibrinogenaemia (<0.3 g/L) after a bite by a brown snake (genus Pseudonaja).

Results: Of 88 patients with brown snake envenoming admitted over the 10 years, at least 35 had severe envenoming. Afibrinogenaemia persisted for 10 hours (range, 1.4–68 hours) after the first dose of antivenom; in four patients afibrinogenaemia lasted more than 24 hours. The dose of antivenom given before venom neutralisation ranged from one to 23 ampoules. In two-thirds of cases, venom was neutralised with five ampoules, and 89% had venom neutralised with 10 ampoules. Two patients died, and another had serious bleeding complications. Another patient died during the study period from intracerebral haemorrhage, but did not have fibrinogen levels measured.

Conclusions: Patients received initial doses of antivenom too small to neutralise circulating venom, and remained afibrinogenaemic for prolonged periods, with serious consequences. The authors now use 10 ampoules as an initial dose in severe brown snake envenoming.

MJA 2004; 181: 703–705
### Clinically relevant venom concentrations

<table>
<thead>
<tr>
<th>Snake</th>
<th>N</th>
<th>Venom Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown</td>
<td>118</td>
<td>1.5 ng/mL (0.2-210)</td>
</tr>
<tr>
<td>Tiger</td>
<td>50</td>
<td>2.9 ng/mL (0.15-152)</td>
</tr>
<tr>
<td>Taipan</td>
<td>11</td>
<td>10 ng/mL (0.3-3212)</td>
</tr>
<tr>
<td>Rough-scale</td>
<td>23</td>
<td>17 ng/mL</td>
</tr>
<tr>
<td>Red-bellied black snake</td>
<td>37</td>
<td>19 ng/mL (3-360)</td>
</tr>
</tbody>
</table>
In vivo binding...after antivenom

- **Brown snake***
  - No venom detected in any sample; 9 with only 1 vial
  - 106 cases; only 2 with very low levels of venom in any sample; 18 with on 1 vial

- **Rough-scale snake***
  - No venom detected except one patient after minimal antivenom

- **Tiger snake**
  - No venom detected after antivenom in 56 cases; 10 with only 1 vial

- **Taipan**
  - No venom detected after antivenom; 7 with only 1 vial
  - Kulawickrama et al Toxicon 2010
Recovery of coagulopathy

Delay between venom neutralisation and coagulopathy resolving:
Re-synthesis of coagulation factors
Will antivenom speed this process?

INCORRECT ASSUMPTION:
Ongoing coagulopathy = insufficient antivenom
BASED ON:
• Antivenom will treat the coagulopathy
## Antivenom Dose

<table>
<thead>
<tr>
<th>Snake Type</th>
<th>Antivenom Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown Snake</td>
<td>1 vial</td>
</tr>
<tr>
<td>Tiger Snake/Rough Scale</td>
<td>1 vial</td>
</tr>
<tr>
<td>Black Snakes: Mulga Snake</td>
<td>1 vial</td>
</tr>
<tr>
<td>Red-bellied Black Snake</td>
<td>1 vial tiger/black</td>
</tr>
<tr>
<td>Taipan</td>
<td>1 vial</td>
</tr>
<tr>
<td>Death Adder</td>
<td>1 vial</td>
</tr>
</tbody>
</table>

Can we trust the science OR do we just give more because it makes us feel better

**False attribution of FAILURE to not enough antivenom and SUCCESS to giving the antivenom**
Recovery of VICC

![Graph showing the relationship between antivenom dose (vials) and hours until INR < 2.](image1)

![Graph showing the proportion of recovery over time for different antivenom doses.](image2)
Do we need to re-dose?

Once all venom (toxins) bound no further doses are required:

i.e. no venom detectable in serum

Assumes:

No ongoing absorption of venom

Can only be determined with venom concentrations:

• Not possible in real time
• Establish dose in large prospective studies (ASP)
Why do clotting studies?

Previously:
Decide on re-dosing antivenom

Now:
… Is the patient coagulopathic?

Bleeding
• Do they need FFP

Asymptomatic
• Can they be sent home?
What you really worry about...

Table 1. The proportions of patients given antivenom at various times after envenoming requiring intubation, and their survival

<table>
<thead>
<tr>
<th>Time between bite and antivenom administration (h)</th>
<th>No. of patients</th>
<th>No. intubated</th>
<th>No. surviving</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2</td>
<td>18</td>
<td>6 (33%)</td>
<td>18</td>
</tr>
<tr>
<td>2–4</td>
<td>42</td>
<td>9 (21%)</td>
<td>42</td>
</tr>
<tr>
<td>4–6</td>
<td>24</td>
<td>16 (66%)</td>
<td>24</td>
</tr>
<tr>
<td>6–8</td>
<td>19</td>
<td>12 (63%)</td>
<td>19</td>
</tr>
<tr>
<td>8–12</td>
<td>14</td>
<td>8 (57%)</td>
<td>12</td>
</tr>
<tr>
<td>&gt;12</td>
<td>24</td>
<td>17 (71%)</td>
<td>23</td>
</tr>
<tr>
<td>5.25a</td>
<td>15</td>
<td>9 (60%)</td>
<td>15</td>
</tr>
</tbody>
</table>

*a Patients received 2 vials of antivenom; time shown is the median time to administration of the first vial.
Question 4

An 11 year old boy presents after feeling a sting while walking in a park. He is brought in by his parents 2 hours after the event.
Q4. Which is the appropriate action?

A. Apply a pressure bandage and collect admission bloods
B. Collect admission bloods and observe for 6 hours
C. Reassure parents that this is unlikely to be a snake bite
D. Swab the bite site and apply a pressure bandage
Issues

How long do we observe?

24hr
4hr
12hr

Pressure bandage:
When to put on?
Serial laboratory changes in envenomed versus non-envenomed snakebite patients: when can we safely exclude envenoming?

Ireland et al Med J Aust 2010

To determine:

• Which laboratory tests are first associated with severe envenoming;
• When they become abnormal; and
• Whether this can determine a safe observation period following suspected snakebite.
All severe envenoming...240 cases

Lab abnormalities and/or neurotoxicity present in:

- 213/220 (97%) by 6 hours
- 238/240 (99.2%) by 12 hours
Suspected snake-bite

all cases should be observed with serial blood testing for 12 hours to exclude severe envenoming using the following pathway.
Therapeutic Guidelines
Toxicology and Wilderness

If presenting to a health care facility that does not have critical care and on-site pathology facilities with antivenom, maintain basic life support, apply PBI and arrange urgent transfer.

Observe in a critical care area. Life-threatening envenoming? [NB1]

Yes

1. Resuscitate
2. Give antivenom immediately (before transfer if possible);
   monovalent antivenom based on clinical effects and
   geography (if consider polyclonal antivenom)
3. Release PBI after antivenom

No

1. Take bloods [NB2]
2. Swab bite site, but don’t test

Laboratory or clinical evidence of envenoming?

Yes

1. Take bloods [NB2]

No

1. Release PBI
2. Do neurological examination and
   repeat bloods [NB3] 1 hour after removing
   PBI and 6 and 12 hours after bite

Laboratory or clinical evidence of envenoming develops?

Yes

1. Give antivenom; monovalent antivenom based on geography,
   clinical effects and VDK
2. Be prepared for anaphylaxis
3. Release PBI after antivenom

No

Discharge in daylight hours

Repeat bloods at 6, 12 and 24 hours [NB4] to check for
recovery of coagulopathy and development of complications such as kidney impairment
2. Further treatment of neurotoxicity, myotoxicity or
   thrombotic microangiopathy may require intensive care
   and clinical toxicology advice

Discharge in daylight hours with advice on serum sickness [NB5]
Resources

Therapeutic Guidelines
Toxicology and Wilderness

Poison Centre
131126
ASP
1800 676 844
Toxicology Service