

Extreme Snakeover



Antivenom Improvements
 Claire Prowse
 IH Technical Product Manager

CSL Biotherapies

Content is copyright to CSL Limited and cannot be reproduced without written permission.

CSL Biotherapies

Agenda


- Snakes
- Antivenoms
 - History
 - Manufacturing Improvements
 - Regulatory Compliance
 - Pharmacovigilance Compliance
 - Research and Development
 - Corporate Social Responsibility
- Diagnostic Tool - Snake Venom Detection Kit (SVDK) + Venom Practice Kit (VPK)
- Technical Support
- Snakebite Management – First Aid, Educational Material, Other Resources

CSL Biotherapies

Snake Venom Toxicity

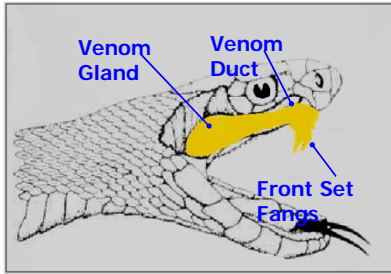
The severity of the envenomation depends on five main factors:

- Venom toxicity
- Venom yield
- Fang length or snake maturity
- Temperament
- Frequency of bite and the time since the snake's last venom injection



CSL Biotherapies

Family - Elapid



CSL Biotherapies

Snake Venom Toxicity

Snake	Average Venom Yield (mg)	Total Fatal Doses (LD50)	Max Venom Yield (mg)	Total Fatal Doses (LD50)
Inland Taipan	44	217,821	110	544,554
Taipan	120	94,488	400	314,961
Common Brown Snake	2	2,468	67	80,426
Chappell Island Tiger Snake	75	13,838	388	71,587
Indian Cobra	169	16,900	610	61,000
Death Adder	78	11,538	236	34,911
King Cobra	421	11,050	? 500	13,123
Eastern Diamond Back Rattlesnake	410	2,662	848	5,505

CSL Biotherapies

Australian Snakes - Venom Components

- Multiple Neurotoxins
- Enzymes(phospholipase A, hyaluronidase, L-amino oxidase, phosphodiesterase, cholinesterase)
- Haemolytic, Haemorrhagic and Pro- and Anti-Coagulant Factors
- Myotoxic Factors
- Cytotoxic Factors
- Nephrotoxic Factors
- Low Molecular Weight Components

CSL Biotherapies

Australian Snakes

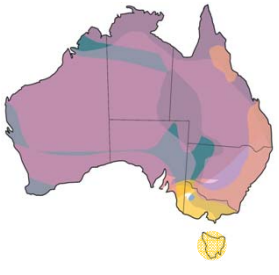


- 5 main land based immunotypes
- Visually difficult to identify
- Snake may not be seen
- Symptoms can be confused
- Which antivenom to treat with?



CSL Biotherapies

Australian Context




- Taipan Immunotype
- Death Adder Immunotype
- Brown Immunotype
- Tiger Immunotype
- Black Immunotype

CSL Biotherapies

CSL Antivenoms

LAND BASED

1930	Tiger Snake
1955	Taipan
1956	Brown Snake
1958	Death Adder
1959	Black Snake
1962	Polyvalent Snake (Australia New Guinea) (includes all of the above)




CSL Biotherapies

CSL Antivenoms


MARINE

1959	Stonefish
1960	Sea Snake
1970	Box Jellyfish



SPIDER

1956	Redback Spider
1981	Funnel Web Spider



CSL Biotherapies

CSL Monovalent Antivenom Specificities

Tiger Snake Antivenom	Tiger Snake (<i>Notechis scutatus</i>) Copperhead (<i>Austrelaps superbus</i>) Clarence River or Rough Scaled Snake (<i>Tropidechis carinatus</i>) Blue Bellied or Spotted Black Snake (<i>Pseudechis guttatus</i>) Pale Headed Snake (<i>Hoplocephalus bitorquatus</i>) Red Bellied Black Snake (<i>Pseudechis porphyriacus</i>) Broad Headed Snake (<i>Hoplocephalus bungaroides</i>) Stephen's Banded Snake (<i>Hoplocephalus stephens</i>)
Brown Snake Antivenom	Common or Eastern Brown Snake (<i>Pseudonaja textilis</i>) Dugite (<i>Pseudonaja affinis</i>) Gwardar or Western Brown Snake (<i>Pseudonaja nuchalis</i>)
Black Snake Antivenom	King Brown or Mulga Snake (<i>Pseudechis australis</i>) Red Bellied Black Snake (<i>Pseudechis porphyriacus</i>) Butler's Mulga Snake (<i>Pseudechis butleri</i>) Papuan Black Snake (<i>Pseudechis papuanus</i>) Blue Bellied or Spotted Black Snake (<i>Pseudechis guttatus</i>) Collett's Snake (<i>Pseudechis collettii</i>)
Death Adder Antivenom	Common Death Adder (<i>Acanthophis antarcticus</i>) Desert Death Adder (<i>Acanthophis pyrrhus</i>) Northern Death Adder (<i>Acanthophis praelongus</i>) Pilbara Death Adder (<i>Acanthophis sp</i>)
Taipan Antivenom	Taipan (<i>Oxyuranus scutellatus</i>) Inland Taipan, Small Scaled or Fierce Snake (<i>Oxyuranus microlepidotus</i>) Papuan Taipan (<i>Oxyuranus scutellatus carinii</i>)

Biotherapies

Venom Procurement

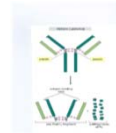
- Venom Supplies Pty Ltd
- Australian Reptile Park



CSL Biotherapies

CSL Antivenoms

- Manufacturing Principles
 - Hyper-stimulate immune system to produce high concentrations of antivenom in the plasma
 - Processing of plasma to cleave IgG, extract and purify the biologically active F(ab)₂ portion
 - Determine the Median Effective Dose (ED₅₀)
 - Quantity of antivenom that will protect 50% of the guinea pigs or mice
 - Measures the total ability of the antivenom to prevent DEATH from all venom components



CSL Biotherapies

CSL Antivenoms

- Manufacturing facility and process Improvements:
 - Plasmapheresis: *Hyperimmune Plasma Extraction*
 - Slower process but horses recover more quickly due to return of red blood cells
 - Strengthened aseptic controls
 - Filtration Improvements
 - Optimise purity and volume of the end Immunoglobulin concentrate



CSL Biotherapies

CSL Antivenoms

- Manufacturing Facility Improvements
 - Portable Mixing Vessels
 - Jacketed to maintain required temperature during dialysis of the Immunoglobulin concentrate



CSL Biotherapies

CSL Antivenoms

- Manufacturing Improvements
 - Quality Management Database
 - Securing venom procurement



CSL Biotherapies

CSL Antivenoms

- Regulatory Compliance
 - Continually evolving and increased compliance requirements, including adherence to:
 - The Code of Good Manufacturing Practice (cGMP)
 - Therapeutic Goods Administration (TGA) licence requirements
 - Product registration requirements
 - Nominated compendials, including British Pharmacopeia (BP), European Pharmacopeia (EP) Immunoserum Monograph

CSL Biotherapies

CSL Antivenoms

- Regulatory Improvement Projects
 - Generate increased data (stability trials, process and test validation) in support of products and production processes
 - Animal Ethics Considerations
 - Quality Control
 - Antivenom Analytical Assays
 - Test product purity, potency, specificity

CSL Biotherapies

CSL Antivenoms

- Pharmacovigilance (PhV) Compliance
 - Established Pharmacovigilance agreements (local and global)
 - Collection and analysis of information on Adverse Events (AE) to therapeutic goods
 - Increasing emphasis from global regulatory authorities to monitor PhV throughout the product life cycle

Suspected Adverse Reaction Report Form									
I. Source of report									
II. Patient Details & History									
Department	Service	Specialist	Sex	Age	Height	Weight	Temperature	Pulse	Respiratory rate
III. Suspect Medication Product Information									
Product Name	Strength	Formulation	Batch No.	Expiry Date	Lot No.	Manufacturer	Country of Origin	Indication	Route of Administration
IV. Details of Adverse Event									
Date of Onset	Time of Onset	Duration	Severity	Outcome	Investigation	Reporting Authority	Product Name	Strength	Formulation

CSL Biotherapies

CSL Antivenoms

- Research and Development
 - Investigations to improve animal dosing regimes and immunological responses
 - Antivenom Handbook
- Corporate Social Responsibility
 - Involvement in the WHO worldwide 'Standardisation of Antivenom Production and Control' project
 - Creation of guidelines for the worldwide production of Antivenoms
 - PNG Project Group
 - Aims to improve AV supply to PNG

CSL Biotherapies

CSL Snake Venom Detection Kit: SVDK

SVDK Purpose

- *In vitro* detection and immunological identification (immunotyping) of snake venom in snakebite cases
- Assist clinicians (and veterinarians) to select the most efficacious and lowest dose monovalent antivenom therapy and give clues to typical symptoms caused by species
- Detects common Australian elapid venoms and categorises them into one of five medically important snake immunotypes:
 - Tiger
 - Brown
 - Black
 - Death Adder
 - Taipan



CSL Biotherapies

The SVDK does NOT Speciate Snakes!

It does 2 things:

1. Detects the presence of snake venom in the sample under test
2. Indicates which monovalent antivenom will most effectively neutralise the detected venom

CSL Biotherapies

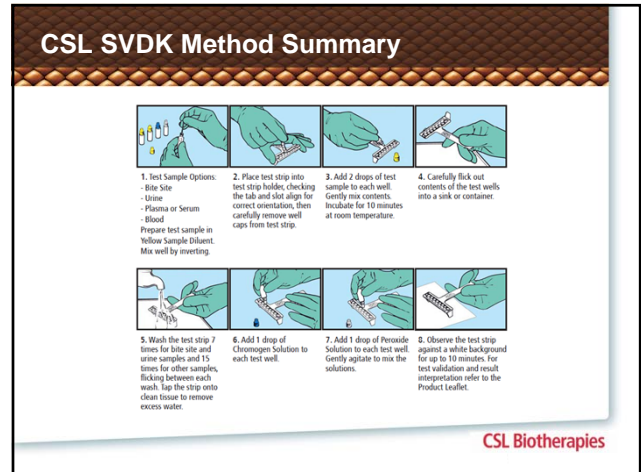
CSL Snake Venom Detection Kit: SVDK

Principle

The antibody causing the most colour binds the most venom *in vitro*. This antibody will most effectively bind and **neutralise** venom *in vivo*.



CSL Biotherapies



SVDK Prospective Study of Non-Envenomed Person

- Unpublished data of study conducted by Australian Venom Research Unit (AVRU)
- Prospective study of non envenomed person
- N = 80
- Samples: urine, blood, skin swab
- No false positives
- One positive reaction in the negative control well due to person with anti-rabbit antibodies – test invalidated

CSL Biotherapies logo is at the bottom right.


CSL Venom Practice Kit: VPK







VPK Purpose

- 6 simulated patient samples from human or veterinary cases
- From a range of Australian venomous snakes (geographically from across Australia)
- Display a range of reaction strengths
- Designed to be used with the SVDK
- Allows operators to gain experience using the SVDK and identifying the snake immunotype detected when a positive sample encountered
- Allows staff to be trained in use and assessed for competency

The image shows the VPK components, including a box and several small vials. The CSL Biotherapies logo is at the bottom right.

CSL Venom Practice Kit Result Sheet




Expected Results		Batch No. 1212 001 Expiry: 09/2008				
Sample No.	Snake Name (Latin Name)	Reaction Strength	Snake Identification (Common Name)	Snake Identification (Scientific Name)	Snake Illustration	Snake Source (Country)
1	Common Death Adder	Weak	Common Death Adder	<i>Acanthopis porteri</i>		Ethiopia - SA
2	Spine-tailed Snake	Strong	Common Tiger Snake	<i>Herpetus indicus</i>		Malaysia - SA
3	Black Snake (Asian or West I.)	Strong	King Brown or Ring Snake	<i>Pseustes condani</i>		Malaysia - SA
4	Brown Snake	Strong	Eastern or Common Brown Snake	<i>Pseudonaja textilis</i>		Barbados - SA
5	Tree Snake	Strong	Tiger	<i>Pseudonaja textilis</i>		Comoros - SA
6	Red Snake (Asian or West I.)	Strong	Red Bellied Black Snake	<i>Pseudonaja porphyria</i>		Malaysia

Prepared and packaged by CSL Limited, 45 Poplar Road Torrance 3022 Victoria Australia January 2008

CSL Biotherapies


Snake Venoms Courtesy of Peter Mirtschin at Venom Supplies - www.venomsupplies.com

First Aid – Pressure Immobilisation Bandage (PIB)




1


Bandage
prevent lymphatic return




2



3




4



5

Splint
prevent peristaltic pumping past bandage




CSL Biotherapies

Support Materials

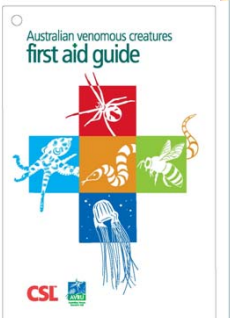
- CSL Medical Information contact details:
 - Phone: 1800 642 865
 - Email: medinfo.aust@csl.com.au
- CSL actively supports snakebite management education in Australia through education materials, workshops and presentations.
- CSL also supports PNG through the provision of first aid materials translated into local languages, donation of SVDKs for research and participation in workshops and conferences.

CSL Biotherapies

Support Materials: CSL Website & First Aid Guide



<http://www.csl.com.au/IH>



CSL Biotherapies

Support Materials: First Aid Information

CSL Biotherapies

Support Materials: Snakebite Management Posters

CSL Biotherapies

CSL Antivenoms

- Optimum treatment of the envenomed patient is the ultimate aim.
- CSL, as sole manufacturers of Antivenoms in Australia, continue to strive for and implement product improvements that will contribute to best patient outcomes and improved snakebite education.

CSL Biotherapies

CSL Antivenoms

- Acknowledgements
 - CSL Manufacturing
 - CSL Regulatory
 - Australian Venom Research Unit (AVRU)
 - Prof. Julian White

CSL Biotherapies

References

- Theakston RDG, Lloyd-Jones MJ, Reid HA. Micro-ELISA for detecting and assaying snake venom and venom-antibody. *Lancet* 1977; 2: 639-41.
- Sutherland SK. Treatment of snakebite and arachnid poisoning. CSL 1978.
- Sutherland SK, Lovering KE. Antivenoms: Use and adverse reactions over a 12-month period in Australia and Papua New Guinea. *Med J Aust* 1979; 2: 671-4.
- Sutherland SK. Rapid venom identification: availability of kits. *Med J Aust* 1979; 2: 602-3.
- Sutherland SK Deaths from Snakebites in Australia 1981-1991 *Med J Aust* 1992 Vol 157: 740-745)
- Coulter AR, Harris RD, Sutherland SK. Enzyme immunoassay for the rapid clinical identification of snake venom. *Med J Aust* 1980; 1: 433-5.
- Chandler HM, Hurrell JGR. A new enzyme immunoassay system suitable for field use and its application in a snake venom detection kit. *Clin Chem Acta* 1982; 121: 225-30.
- Hurrell JGR, Chandler HM. Capillary enzyme immunoassay field kits for the detection of snake venom in clinical specimens. *Med J Aust* 1982; 2: 236-7.
- Sutherland SK. Treatment of snakebite in Australia and Papua and New Guinea. *Aust Family Physician* April 1990; 21-42.
- Cox JC, *et al.* A novel format for a rapid sandwich EIA and its application to the identification of snake venoms. *J Immunol Methods* 1992; 146: 213-18.
- Sutherland SK. Antivenom use in Australia. Premedication, adverse reactions and the use of venom detection kits. *Med J Aust* 1992; 157: 734-739.
- Clancy AM, *et al.* The effect of species and geographical origin on the identification of their venom using a commercial assay. *Med J Aust* 1997; 166: 7.
- Williams D, *et al.* Venomous Bites and Stings in Papua New Guinea. AVRU Melbourne 2005.
- Winkel K.D, *et al.* Twentieth century toxinology and antivenom development in Australia. *Toxicon* 48 (2006) 738-754

CSL Biotherapies