The role and use of antivenom in Papua New Guinea

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Introduction

Although antivenoms were first developed in France in 1894, Australia only starting using them in the 1930's and in PNG they were not available for routine use until the 1960's. During the early 1960's, PNG snakebite patients who developed paralysis often received up to four ampoules each[1,2]. Since then antivenom use has become more frugal as antivenom costs have increased, although in the 1980's and early 1990's the majority of patients received at least one ampoule[3,4].

Our recent studies at PMGH indicate that the treatment focus has switched from high antivenom availability and usage with lower rates of ventilation, to one of low antivenom availability and consequent high rates of ventilation. This is despite clear evidence that snakebite deaths in PNG may be prevented by more widespread availability of antivenom[5]. Regrettably, PNG is not alone in the shortage of antivenom supplies, an international problem that is particularly acute in the Indo-Pacific[6-8]. This chapter will discuss the use of antivenom and highlight ways in which scarce supplies can be used most effectively.

As explained in Chapter 2 only six of the venomous snakes described in the PNG/Solomon Island archipelago are considered potentially lethal. Antivenom produced in Australia by CSL Ltd is the only specific treatment for envenomation by these venomous snakes. The decision to use antivenom should be based on the patient's history, examination and pathologic findings, and the type of antivenom used will depend on geographic, clinical and pathologic factors. Antivenom is only indicated if there is clear evidence of systemic envenomation, and it should be given by the intravenous route.

Initial recommended doses of antivenom are based on the average venom yields from each of the snakes concerned. There is evidence that these doses may be insufficient to reverse coagulopathy associated with the bites of several venomous snakes, notably the brown snake and the taipan. Larger initial doses should be considered if there is evidence of severe envenomation (multiple bites, rapidly progressive symptoms, large snakes) and the earlier it is given the better. Children should receive exactly the same dose as adults.

As antivenoms are animal products, acute and delayed adverse reactions (anaphylaxis and serum sickness) can occur and premedication should be considered. The patient should be monitored for their response to antivenom and multiple doses may be required. Other treatments such as clotting factor replacement, supplemental oxygen and, sometimes, mechanical ventilation may be indicated. All patients should receive appropriate tetanus prophylaxis and consideration should be given to antibiotic prophylaxis if the bite wound is contaminated.

Anticholinesterase inhibitors such as neostigmine and edrophonium might also be useful in the diagnosis and emergency management of death adder envenomation. When antivenom supply is limited, there may be some therapeutic value in the prolonged use of pressure-immobilisation bandaging for death adder bites.

Recent Snakebite Studies at PMGH

Together with Kenny Aaron and Gertrude Didei, we recently examined mortality and morbidity records at PMGH, and found that snakebite places a greater burden on PMGH ICU ventilators than all other conditions combined, and that the duration of dependency in cases of snakebite was significantly longer, undoubtedly adding to treatment costs. So far as the authors are aware, this represents the highest proportional ventilator load yet reported for snakebite in any hospital globally.

The second major finding related to the worsening outcomes for paediatric snakebite inpatients. A study of snakebite in children during the 1980's found that only 29.6% of children admitted to the PMGH ICU with envenomation required intubation; 91% received antivenom; and the case fatality rate was 7.7%[9]. In contrast 85.4% of children admitted to the ICU in this study were intubated and ventilated; antivenom use was only documented for 50% of the paediatric fatalities; and the paediatric case fatality rate was 14.6%. Ventilation was also a key feature in the management of the adult ICU admissions (See Chapter 13).

Increased reliance on ventilation may be a consequence of inadequate antivenom supplies due to rising costs influenced partly by the floating of the Kina, and its subsequent devaluation against the Australian Dollar[6,7,10] (Table 1). The cost issue is even more extreme when considering direct antivenom purchases from Port Moresby pharmacies by individuals, when PMGH stocks have been depleted. Purchasing of less expensive monovalent antivenoms, in combination with appropriate diagnostic use of the simple 20WBCT and CSL's Venom Detection Kit (VDK), should not only generate significant unit cost savings, but also result in increased stock availability. It is hoped that this course will facilitate improved use of scarce antivenom based on more rational purchasing and prescribing habits.

Previous studies have found that delays in the administration of antivenom significantly increased the necessity to intubate snakebite patients at PMGH[4,11]. Patients who received antivenom within four hours post-bite were:

- Three times less likely to require intubation;
- Exhibited more rapid resolution of neurotoxicity; and,
- Had shorter hospital stays.

Unfortunately, despite the fact that many cases in our study arrived at a health facility, either a peripheral clinic or PMGH itself, within four hours of the bite, very few received antivenom within that period (Table 2).

Despite clear guidelines for appropriate antivenom administration, their relevance becomes questionable in the absence of adequate antivenom supplies, and consequently antivenom is often reserved for moribund patients, or only partial ampoules given and its use may be delayed until significant deterioration has occurred[12,13]. Given the concern about intracranial haemorrhage in the context of a bleeding diathesis, use of products such as fresh frozen plasma might appear reasonable. Blood products are, however, scarce, expensive and their value in the treatment of snakebite coagulopathy is unclear and potentially hazardous. Moreover, previous studies have demonstrated that systemic bleeding generally resolves rapidly after administration of appropriate amounts of specific antivenom[4].

TABLE 1: The cost of antivenom purchased in PNG (1985-2003): comparison of prices (per ampoule) for CSL polyvalent and taipan antivenoms to the PNG Department of Health. Costs are given in PNG Kina (K) with equivalent Australian Dollar (A$) prices (at effective K/A$ exchange rates).

	Type Of Antivenom			
	CSL Polyvalent		*CSL Taipan*	
Year	**K**	**A$**	**K**	**A$**
1985[10]	212	300	173	245
1987[10]	367	580	352	556
1992	803	1180	730	1073
1995	1739	1758	1604	1620
1998	2352	1811	2338	1800
2000	2960	1835	1740	1079
2003	3575	1833	3075	1577

TABLE 2: Time of use of antivenom in the 60 fatal cases of snakebite treated at PMGH 1/1/92 – 31/12/01. This compares the time of arrival of patients at either a primary health clinic or Port Moresby General Hospital with the number of each subset who received antivenom at those times. Note that most patients who arrived in either the hospital or clinic within 4 hours of snakebite did not receive antivenom within those 4 hours.

	Clinic Records (n=29)		**PMGH Records (n=60)**	
Time Post-bite (Hours)	*No. of Patients*	*No. Given Antivenom*	*No. of Patients*	*No. Given Antivenom*
<4	24	1	19	2
4-10	4	1	22	10
>10	1	2	19	16
Total	29	4	60	28

Hospital care of snakebite patients

General/ supportive care

Once the patient reaches hospital, initial management consists of venous cannulation and resuscitation if required. Where possible, a careful history and examination should be undertaken with reference to the features of envenomation described above, as well as previous envenomations and allergies to antivenom or to horse serum. This will assist in diagnosis and aid decision-making with respect to definitive treatment, and is covered in more detail elsewhere in these notes. Samples for venom detection and for pathology testing should be obtained, and an attempt made to identify the genus of snake, if possible (see below).

When an intravenous line is *in situ* and antivenom and resuscitation facilities, including adrenaline, are assembled, then first aid measures may be removed. If the patient has not developed any symptoms or signs of envenomation, nor any indication of coagulopathy or myolysis on blood taken 4-6 hours after the removal of first aid (or after the bite if no first aid was used) then the patient has probably not sustained a significant envenomation, although delayed onset of symptoms (especially neurotoxicity) up to 24 hours after bites have been described. Overnight observation is desirable, especially if the patient comes from a remote area.

Ideally, envenomed patients should be admitted to hospital and observed for a period of at least 24 hours, depending on the clinical circumstances. Regular (i.e.: at least hourly) neurological observations should be performed and basic pathology studies (such as 20WBCT and Multistix urine tests for blood or protein) repeated regularly to monitor progression of the illness. The 20WBCT should be repeated as discussed in Chapter 9. After circulating antivenom has been neutralised, it may be several (4-6) hours before reconstitution of plasma clotting factors has occurred sufficiently to return clotting times towards normal. A lack of improvement in clotting times on retesting may therefore represent insufficient antivenom or insufficient time before re-testing. Improvement in clotting times may represent the efficacy of antivenom, or the natural history of the disease. Worsening of coagulopathy on testing, however, is an indication that circulating procoagulants remain un-neutralised, and that further antivenom is required.

The potential therapeutic value of pressure-immobilisation bandaging

Several studies suggest that there may be some therapeutic value in the prolonged use of pressure-immobilisation bandaging. Dr Struan Sutherland, who developed the technique in the late 1970's, noted that the monkeys who received this type of first aid for experimental tiger snake envenomation generally developed a less severe coagulopathy. In addition funnel-web spider venom-induced neurotoxicity was abrogated by pressure-immobilisation first-aid[14]. Building on these observations, Dr John Oakley, an Australian GP working at Rumginae Hospital in Western Province, examined the outcome of patients given prolonged PIB after death adder bites[15]. His retrospective, uncontrolled study suggested that prolonged use of PIB, followed by graded cautious release, was effective at managing most cases of death adder envenomation.

In John Oakley's study, which was conducted between 1994 and 1999, 44 patients with unequivocal signs of envenomation were all managed with pressure bandaging, strict bed rest and close observation. The bandages were kept in place for at least 24 hours and the graded release commenced when there were no longer signs of envenomation. Three cases (7%) required antivenom for severe central muscle weakness and there were no deaths. It is also

important to note that no significant local complications occurred as a consequence of the prolonged bandaging. Whilst not strictly comparable, from a series of 18 definite death adder envenomations managed at PMGH between 1990 and 1992, 13 (72.2%) received antivenom and 5 (27.7%) required intubation and ventilation[16].

Thus, if antivenom is limited, prolonged use of pressure-immobilisation first-aid may help to reduce the severity of the neurotoxicity after death adder envenomation. Note that it is critically important to get pressure applied just right. It has to be firm, but not uncomfortable and should cover almost the entire limb – leaving enough space to regularly test capillary return to the toes or fingers. The place of the prolonged use of this technique after other PNG snakebites is less clear. This is because, generally speaking, local tissue damage due to the venom is least likely after death adder bites than after taipan, black snake and small-eyed snakebite.

Adjunctive Therapies

Other treatments such as analgesia (avoid sedating agents such as morphine if possible), plasma volume expanders and fresh frozen plasma may be required; but **blood products should only be given after antivenom** has been used and the coagulopathy has been arrested.

In severe envenomations resulting in respiratory compromise, supplemental oxygen and, sometimes, mechanical ventilation, are indicated. Incipient renal failure may be treated with volume replacement and diuretics, but dialysis may occasionally be required, particularly in cases where treatment has been delayed. Hyperkalaemia secondary to rhabdomyolysis may be treated with calcium, insulin and glucose, salbutamol, frusemide and IV fluids, and resonium.

All patients should receive appropriate tetanus prophylaxis (after resolution of coagulopathy) and consideration should be given to antibiotic prophylaxis if the bite wound is contaminated. Rarely, the snake's fangs may break and become embedded in the wound, acting as a foreign body and a nidus for infection. Crystalline penicillin is the first-line of treatment in such cases[12].

Anticholinesterases

(See Chapter 12)

Antivenom

Antivenom is the only specific treatment for effective bites by venomous PNG snakes. In Australia, prior to the availability of antivenom, death ensued in approximately 90% of taipan envenomations. The decision to use antivenom should be based on the patient's history, examination and pathologic findings, and the type of antivenom used will depend on geographic, clinical and pathologic factors as described above.

Indications for antivenom

Antivenom is indicated if there is specific evidence of **systemic envenomation**

Such evidence includes specific symptoms or signs such as collapse, cranial nerve weakness, abnormal bleeding, generalised muscular pain and tenderness, or grossly discoloured urine (red or dark brown). Laboratory investigations consistent with systemic envenomation include incoagulable blood in whole blood clotting test (20WBCT)[21], a grossly elevated serum creatine kinase level, haematuria, haemoglobinuria or myoglobinuria, or a positive SVDK test

on a urine sample in the presence of non-specific or specific symptoms or signs of envenomation.

If pressure-immobilisation first aid is in place, symptoms or signs of envenomation, including laboratory signs, may only become apparent when first aid measures are removed.

Puncture marks, and lymphadenopathy and other non-specific symptoms and signs of envenomation are not indications *per se*, for antivenom, as these can occur in bites from non-venomous snakes, or in cases where little or no venom is injected. Similarly, a positive SVDK result (see below) from a bite site is not in itself an indication for antivenom, as venom may be present on the skin or clothing, but not in sufficient quantity in the circulation to cause systemic envenomation. A positive SVDK result from a urine sample is an indication that venom is present in the circulation and that antivenom is indicated.

If the blood remains incoagulable (20WBCT positive) 6 hours after the first dose, a second dose of antivenom is indicated.

TABLE 3: Non-specific and specific signs of probable envenomation in approximate order of occurrence; these must be present in conjunction with a history of actual or suspected snakebite.*

Type	Indication
Neurotoxic signs and symptoms	Early – [1-3 hours] cranial nerve signs: such as droopy eyelids, double vision, reduced or paralysed eye movements, difficulty with swallowing, talking and tongue protrusion Late – [>3hrs] limb and respiratory muscle paralysis leading to respiratory failure
Haemostatic abnormality	Spontaneous bleeding from wound, gums, mouth, nose, vomitus, rectum/stool and urinary tract or evidence of non-clotting blood via the WBCT20
Cardiovascular abnormality	Shock, hypotension, cardiac failure, pulmonary oedema, arrhythmias and ECG abnormalities
Depressed consciousness	Including confusion and coma
Generalised rhabdomyolysis	Muscle aches and pains, red, brown, black or 'Coca-cola' urine
Likely renal failure	Uraemia, hypercreatininaemia, oliguria, and acidosis

* Adapted from:
Warrell, DA. (1990) Treatment of Snakebite in the Asia-Pacific region: a personal view. In: Gopalakrishnakone, P, Chou, LM. *Snakes of Medical Importance (Asia-Pacific Region)*, Venom and Toxin Research Group, National University of Singapore,
Warrell DA & Lalloo DG. (1996) Snakebite and its treatment in PNG, In: O'Shea M. 1996. *A guide to the snakes of Papua New Guinea*. Independent Publishing, Port Moresby, p23-30.

The **indications for antivenom are**, thus, specific symptoms or signs such as

- early collapse,
- cranial nerve weakness,
- abnormal bleeding,
- generalised muscular pain and tenderness,
- grossly discoloured urine (red or dark brown),

or the pathology test results of

- incoagulable blood, by the whole blood clotting test (20WBCT)[21],
- a grossly elevated serum creatine kinase level,
- haematuria, haemoglobinuria or myoglobinuria, or
- a positive SVDK test on a urine sample in the presence of non-specific or specific symptoms or signs of envenomation.

Choice of Antivenom

Selecting the correct antivenom is crucial to the successful treatment of envenomation. Monovalent antivenoms are much less expensive than polyvalent antivenom, and are associated with a reduced risk of adverse antivenom reactions. Their disadvantage, however, is that they are only intended for use against the bites of a particular species, rather than all species (which is the advantage of polyvalent antivenom). Unless the precise identity of snake responsible for the envenomation can be confirmed, the use of monovalent antivenom can be hazardous.

If the identity of the snake cannot be determined, then the appropriate antivenom to use, in all circumstances, is CSL polyvalent antivenom.

There are ways in which the choice of antivenom can be narrowed down and two methods are discussed here.

Snake Identification

The difficulties of identifying snakes have been discussed in detail in Chapter 2.

Identification of the offending snake will aid in the choice of the appropriate antivenom and alert clinicians to particular features characteristic of envenomation by that species of snake. In many cases a snakebite victim will not have seen the snake, or only glimpsed it briefly as it fled after the bite. An identification of a snake made by a patient, or those accompanying them, should be treated with scepticism, although a clear description of the offending animal (such as describing a “blacksnake with a red back”: Papuan taipan) may assist you in narrowing the possibilities.

Even seemingly experienced snake handlers can misidentify some snakes. Identifications by the general public or by hospital staff are frequently unreliable, and a formal identification by a professional herpetologist is the ideal approach, but seldom available in Papua New Guinea.

It is possible to use of some basic information about the snakebite to make a presumptive identification with enough confidence to make prudent antivenom choices (*see algorithm table on next page*). For example, it is possible to split Papua New Guinea into three broad regions on the basis of the number of highly venomous snakes which occur naturally in

particular provinces, and then combine this knowledge with the clinical signs of envenoming that are present in order to select appropriate antivenom.

Algorithms, such as the simple one offered here, **must to be used with care**:

- You must ensure that the 20WBCT was properly performed to ensure a valid test result of either 'positive' or 'negative' for incoagulable blood.
- Any description obtained must be offered without prodding or suggesting answers, ie. ask only open-ended questions. For example, do not ask a patient/relative "*Did the snake have a red back*", just ask "*What did the snake look like*?".
- Ensure that the clinical signs have been properly elucidated, and use signs that you have observed or elicited, rather than less reliable symptoms reported by the patient/relative.
- Record the answers you reach for each question in the algorithm to ensure that the decision-making process is clear to you and to others who treat the patient.

Use the algorithm cautiously, and if you still have doubts, select the general purpose CSL polyvalent antivenom.

Presumptive selection of appropriate antivenoms

The following algorithm uses information about the snakebite in order to enable conservative selection of an antivenom product. This technique of antivenom selection is evidence-based, but should be used with care. ***If you are in doubt about the identity of the snake after using this algorithm, and if it is available, you should use CSL polyvalent antivenom***.

1. Where in PNG did the bite occur?

(a) MBAY, ORO, CENT, NCD, GULF, WEST?	Go to 2
(b) MOR, SIM, E.HIGH, S.HIGH, W.HIGH, ENGA, SAND, E.SEP, MAD?	Go to 4
(c) MAN, WNB, ENB, N.IRE, N.SOL?	Go to 6

2. What was the result of the 20WBCT?

(a) Positive test (unclotted at 20 min.)	Go to 3
(b) Negative test (clotted at 20 min.)	Go to 4

3. Was there a description of the snake that referred to it having "*a red stripe on the back*" or being a *"blacksnake with a red back"*?

(a) Yes	**CSL taipan antivenom** (Papuan taipan)
(b) No	**CSL polyvalent antivenom** (Papuan blacksnake, brown snake or small-eyed snake)

4. Are there observed or elicited signs of ptosis, diplopia, or other neurotoxicity?

(a) Yes	Go to 5
(b) No	Observe and reassess the patient hourly for 24 hours

5. Is there generalised muscle pain, muscle tenderness or dark coloured urine?

(a) Yes	**CSL polyvalent antivenom** (Small-eyed snake)
(b) No	**CSL death adder antivenom** (death adder)

6. Did the bite occur in the ocean, close to the ocean foreshore or in a coastal river?

(a) Yes	**CSL seasnake antivenom** (Sea krait or true seasnake)
(b) No	Go to 4

Snake Venom Detection Kits

(See also Appendix: CSL Snake Venom Detection Kits)

Australia and Papua New Guinea are the only countries in the world that have potential access to commercially available snake venom detection kits. At the moment, these kits are not being used in Papua New Guinea, however this may change soon.

The introduction of snake venom detection kits (SVDK) will provide a major improvement in the ability to choose the most appropriate antivenoms. This will have several advantages including:

- Significantly reducing the costs of treating many snakebites.
- Increasing the purchasing power of health authorities so that more vials of appropriate antivenoms are available without necessarily spending more money.
- Improving the prognosis for patients through greater antivenom availability.
- Greater specificity and potentially reduced risks of adverse serum reactions.

SDVKs consist of a rapid two-step enzyme immunoassay in which wells are coated with antibodies to the major Australian snake venom groups. Venom from a bite site swab or a urine sample will react with the antibodies in one specific well, resulting in a colour change indicating the snake group involved. This information is used to help select the type of snake antivenom that may be required. Note that the primary purpose of the venom detection kit is not to decide whether envenomation has occurred (i.e.: whether antivenom is indicated), but to help to choose the appropriate antivenom if required:

- A positive SVDK result is not, in itself, an indication for antivenom.
- Venom detected at the bite site may be present in insufficient quantity in the circulation to cause significant illness.
- Venom detected in a urine sample indicates that venom is present in the circulation and that the indicated antivenom is the correct one to be given.
- A negative SVDK result does not mean that envenomation has not occurred; the venom may have been washed off or diluted at the bite site, or may not have reached the urine, but still be present in the circulation.

Bite site swabs are considered to be the most reliable sample for use with venom detection kits. Venom may also be obtained from clothing, or even from the fangs of the dead snake. Note that very high concentrations of venom in the sample may cause false positives, with multiple test wells turning blue, either simultaneously or sequentially. If this occurs, the sample should be diluted tenfold and the test repeated. Blood and urine samples may also be used in the venom detection kit, but are less reliable than bite site swabs. Urine, in particular, may be used if there has been some delay in presentation, if no bite site can be identified, or it has been washed. Blood (serum) is the least reliable.

The kit has 'built-in' positive and negative controls that need to be checked to validate the test results. In addition, after the final wash, the test wells need to be continuously observed for the **first well to turn blue**. Snake Venom Detection Kit results should be used in conjunction with other information (such as clinical presentation, knowledge of snakes in the geographic area, identification of snakes brought to hospital with the patient) to determine which antivenom to use if the patient is significantly envenomed.

If a reliable identification cannot be made, then polyvalent snake antivenom (or the appropriate combination of monovalent antivenoms for the locality) should be used.

Antivenoms for PNG snakes

At present only 6 of the 25 species of terrestrial elapids described in the PNG/Solomon Island archipelago are considered potentially lethal[21] – the antivenom requirements for these major groups, together with sea snakes, are discussed in more detail below. However, it should be noted that there are a variety of other snake species of potential medical importance.

Firstly, the bite of non-venomous snakes may be confused with those of venomous species. Non-venomous species (See Chapter 2) include the tree and water pythons, ground and tree boas and file snakes. As the bitten patient may develop the non-specific symptoms of anxiety, breathlessness, dizziness, headache, nausea or vomiting, it can be difficult to exclude envenomation. Hence, even if the bite of a non-venomous snake is suspected, such cases should be managed as for a venomous snakebite until proved otherwise. Attention should, therefore, be paid to the specific indications for snake antivenom to avoid unnecessary antivenom use. Note that any animal (or human!) bite may be complicated by infection. This is an uncommon problem after snakebite in Australia but may be more frequent in PNG. This issue is discussed further in adjunctive therapies section above.

Secondly, a variety of species, classified as 'mildly venomous rear-fanged snakes', may cause troublesome local effects or pose a significant hazard in very young children. These include the mangrove, mud, water and cat (tree) snakes. It is unknown whether CSL antivenoms have any value in treating such cases, but as they are primarily arboreal or semi-aquatic species, significant bites are unlikely.

The third group, representing potentially dangerous 'front-fanged terrestrial' venomous snakes, includes many very poorly researched species. Some of these are known to be quite dangerous and others are suspected to be. This includes New Guinea forest snakes, the brown headed snake, the Solomon's and Bougainvillean coral snakes, the Solomon's small-eyed snake, the Australian small-eyed snake, the New Guinea crowned snake and Papuan whip snakes. In the absence of information about the VDK reactivity of these venoms and in cases of definite envenomation from one of these snakes (i.e.: satisfying one of other of the indications for antivenom described above, it is recommended that CSL polyvalent antivenom be given.

The following highly venomous snakes (*See Chapter 2 for further detail*) are capable of causing human deaths. The bites of any of these snakes can be treated with **CSL polyvalent antivenom**, although the monovalent antivenoms shown below are not only effective but much more cost efficient, and should be used if the identification is reliable and the particular monovalent antivenom is available:

Papuan Taipan (*Oxyuranus scutellatus canni*)

This nervous and highly venomous snake is only found in southern PNG from Milne Bay to Western province (including Daru Island). It also occurs in the Merauke region of Irian Jaya. It is the longest venomous snake in PNG and has the most efficient bite. The clinical syndrome includes neurotoxicity, coagulopathy and rhabdomyolysis. Prior to the development of antivenom, effective bites from taipans were almost invariably fatal. Papuan taipan venom is neutralised with **CSL Australian taipan antivenom** if given early after a bite, but antivenom efficacy declines as neurotoxicity becomes established. The reasons for this reduction in antivenom efficacy have been discussed at length in Chapter 3, and relate to the physiological nerve damage caused by the toxins, rather than actual inability of the antivenom to neutralise the venom itself.

Death adders (Genus *Acanthophis)*

The death adders are found throughout PNG to an altitude of 1800m as well as on Manam and Karkar islands in Madang Province, the island of Geelvinck Bay and those west of Vogelkop in Irian Jaya. They are readily identified by their short, squat, viperine appearance. They are ambush predators, and unlike most snakes, will not necessarily retreat from humans. They may therefore be trodden on or disturbed by the unwary, and bite defensively. The venom contains predominantly postsynaptic neurotoxins, with some mild anticoagulant and possibly myolytic activity (the latter two characteristics are not seen with most Australian death adders). At least one case of renal failure has been described after a PNG death adder bite. This venom's neurotoxicity is readily reversed with **CSL death adder antivenom**.

The Blacksnakes (*Pseudechis papuanus* and *Pseudechis cf. australis*)

Mulga snakes (*Pseudechis australis*) (also known as king brown snakes) are the largest venomous snakes in Australia and may reach 3 metres in length; however the New Guinean race is much smaller and rarely attains 1.3 metres. Large Australian specimens have had the highest recorded venom outputs of any snake. This species is only known from the far south-western corner of Western province and from adjoining southern Papua, but may eventually be found further east on the Oriomo plateau. The name "king brown" snake may lead to confusion and to the incorrect use of brown snake antivenom, and is therefore best avoided. The Papuan black snake (*Pseudechis papuanus*) is an uncommon cause of snakebite, and the species is rarely encountered. Its conservation status in the eastern two-thirds of southern PNG is unknown. No live or recently dead specimens have been collected in Central province since the early 1990's. Mulga snake and Papuan blacksnake venoms contain neurotoxins, myotoxins and mild anticoagulants that are neutralised by **CSL black snake antivenom**.

Brown snakes (*Pseudonaja cf. textilis*)

The eastern brown snake (*Pseudonaja cf. textilis*) has been recorded from Western, Central, Milne Bay and Oro Provinces of PNG, and from southern Papua. Bites are very uncommon and this is in marked contrast to Australia where brown snakes are responsible for the majority of snakebites and snakebite deaths. Coagulation disturbance is common in brown snakebites, but there exists the potential for significant neurotoxicity. Myolysis is not a feature of brown snake envenomation, although renal failure may ensue putatively as a result of direct nephrotoxicity. The possibility of direct cardiotoxicity has also been suggested, as several brown snakebite deaths have been associated with early cardiovascular collapse, but this is more likely due to the venom procoagulants causing temporary coronary artery blockage by thrombosis. The venom is neutralised by **CSL brown snake antivenom,** although recent Australian experience is that multiple ampoules may be needed in cases of profound coagulopathy.

The New Guinean small-eyed snake (*Micropechis ikaheka*)

The PNG small-eyed snake is distributed widely throughout PNG and neighbouring Irian Jaya at altitudes of 0–1500 m[21,22]. It is also found on Karkar Island in Madang Province and on the islands of Geelvinck Bay and those west of Vogelkop in Irian Jaya. Although the species has been implicated in human deaths and serious illness, reports of bites are few[22-25] and, in some cases, identification of the snake was unverified[23-25]. In one recent series[22] of 11 cases with two fatalities, reliable attribution of bites to *M. ikaheka* was made by enzyme immunoassay of serum, bite site swabs and urine from victims. In these cases, typical symptoms of envenomation included neurotoxicity, generalised myalgia, spontaneous haemorrhage,

incoagulable blood and passage of dark urine. One of the victims who died had hypotension associated with untreated respiratory paralysis.

The New Guinean small-eyed snake (*Micropechis ikaheka*) is not related to the Australian small-eyed Snake (*Rhinoplocephalus nigrescens*). Although no specific antivenom exists for the bite of the New Guinean small-eyed snake *Micropechis ikaheka*, there are reports of some patients who appear to have benefited from treatment with CSL polyvalent antivenom, but not CSL death adder antivenom[22]. These observations are consistent with our recent *in vitro* and *in vivo* neutralisation studies[27] that found that CSL polyvalent antivenom and to a lesser extent, CSL Blacksnake antivenom, could neutralise this venom's toxicity. *In vitro* immunoreactivity tests suggest that the monovalent blacksnake antivenom component is the most active of the five monovalent components of CSL polyvalent antivenom. At this stage, **CSL polyvalent antivenom** is recommended as the antivenom of choice for New Guinean small-eyed snake envenomation.

Sea snakes (Family *Hydrophiinae* & *Laticaudidae*)

At least 20 species of sea snakes have been recorded in PNG waters, both coastal and estuarine. All sea snakes are dangerously venomous, with neurotoxicity and myolysis, leading to renal failure, being the major features. The bite itself is not particularly painful, and may go unnoticed, distinguishing it from envenomation by stinging fishes or jellyfish, both of which cause immediate, and often excruciating, pain. Bites may occur whilst swimming, on the beach or during fishing activities, as sea snakes may be caught in nets and bite when handled. It is rarely encountered as a medical problem in PNG and supplies of sea snake antivenom are very limited. Envenomation should be treated with **CSL sea snake antivenom,** but if this is not available, then CSL polyvalent antivenom may be useful. In the case of the latter, two (2) ampoules should be given initially.

Administration of antivenoms

Where there is clinical evidence of systemic envenomation, the most appropriate available antivenom should be administered as soon as possible. If the appropriate antivenom is not on hand, it will be necessary to either:

1. Obtain the appropriate antivenom from the closest source (perhaps a nearby health centre or hospital) or,
2. Transport the patient without delay to another health centre or to a hospital that does have stock of the appropriate antivenom.

Giving the wrong antivenom simply because it is the only one available may do more harm to the patient, and should be avoided. There have been a number of deaths in Papua New Guinea that were the result of patients having been administered the incorrect antivenom on the basis of misidentification by the bitten person or their relatives. This commonly occurs when health centre staff accept a claim that the snake responsible was a 'Papuan black' and give CSL Blacksnake antivenom, when in reality the species that caused the bite was a Papuan taipan.

Route of administration

Snake antivenoms are given by the intravenous route. Antivenoms that are given intravenously should be diluted in at least 100ml of either normal saline, 5% dextrose, or Hartmann's solution immediately prior to administration. If giving CSL polyvalent antivenom it is advisable to dilute 1 in 10 for adults, or 1 in 5 for children (to avoid fluid overload).

Premedication

Adrenaline

In rural health centres patients should be premedicated with subcutaneous adrenaline prior to the intravenous administration of antivenom.

Dosage: Adults: 0.25 mg subcutaneously
Children: 0.005 mg/kg subcutaneously

Adrenaline premedication should never be given intravenously. This is to avoid hypertension in the coagulopathic patient with the potential for bleeding, as this has been documented to cause deaths from intracerebral bleeding. Similarly, it should not be administered intramuscularly, as this may also lead to hypertension, as well as to haematoma formation in the presence of coagulopathy.

Additional adrenaline should also be drawn up into a syringe and kept on hand for immediate use in the event of an early adverse antivenom reaction (see below).

Antihistamines and hydrocortisone

Although both antihistamine (typically Phenergan - promethazine) and hydrocortisone are traditionally used in the premedication of patients prior to antivenom administration, their use in Australia has now been widely discontinued.

There is no current proven benefit to giving either antihistamine or hydrocortisone as premedication before antivenom use. They do have a role in the treatment of allergy and this is discussed later.

Antivenom dosages

The following table gives the initial monovalent antivenom dosages for the bites of Papua New Guinean snakes. Additional doses may be required, so use this table as a guide only:

TABLE 4: Initial doses of antivenoms for snake bites. Use this information when the snake has been positively identified by SVDK, for example. Severe envenomation may require more than one dose of antivenom. Dosage for children is the same as that for adults. ***If the snake is unidentified, use CSL polyvalent antivenom***.

Snake	Appropriate Antivenom	Initial Dose
PNG small-eyed snake *(Micropechis ikaheka)*	Polyvalent antivenom	1 vial
Papuan death adder *(Acanthophis spp.)*	Death adder antivenom	6,000 units (1 vial)
Papuan Taipan *(Oxyuranus scutellatus canni)*	Taipan antivenom	12,000 units (1 vial)
Eastern Brown snake *(Pseudonaja textilis)*	Brown snake antivenom	1,000 units (1 vial)
Papuan Black snake *(Pseudechis papuanus)*	Black snake antivenom	18,000 units (1 vial)
King brown (Mulga snake) *(Pseudechis australis)*	Black snake antivenom	18,000 units (1 vial)
Sea snake (multiple species)	Sea snake antivenom, or Polyvalent antivenom	1,000 units (1 vial)

One ampoule of CSL polyvalent snake antivenom (Australia/Papua New Guinea) contains:

Tiger snake antivenom	3.000 units	Taipan antivenom	12,000 units
Brown snake antivenom	1,000 units	Black snake antivenom	18,000 units
Death Adder antivenom	6,000 units		

Note: If stored at 2-8°C, antivenoms have a shelf life of three years; but they should not be frozen.

The initial doses of antivenom shown in Table 4 are based on the average venom yields from each of the snakes concerned. There is evidence, however, that these doses may be insufficient to reverse coagulopathy associated with the bites of several venomous species, notably the brown snake (*Pseudonaja cf. textilis*) and the Papuan taipan (*Oxyuranus scutellatus canni*). Larger initial doses should be considered if there is evidence of severe envenomation (multiple bites, rapidly progressive symptoms, description of large snakes).

The dose of antivenom for children should not be reduced according to their weight, since the amount of venom injected by the snake is independent of patient body size. Patients should be monitored for their response to antivenom, and additional antivenom may be required (*See Table 3 for indications for repeated doses of antivenom*).

Note: The antivenom requirements of patients will vary considerably. Some patients with minimal envenoming will require no antivenom, while more severely envenomed patients may require multiple doses of antivenom. Detailed information is packaged with the individual antivenoms.

Rate of administration

Administer the whole dose of antivenom (the contents of the entire vial) and diluent over a period of 30-60 minutes.

Early adverse antivenom reactions

Antivenoms are foreign proteins, and it is possible for a patient to experience a reaction to antivenom administration that can range from mild to severe. According to the manufacturer, adverse reactions to antivenoms can include:

Type of reaction	Frequency	Conditions
Hypersensitivity & skin	Common	Urticaria Rash Welts or local swellings Hypotension Bronchospasm Anaphylaxis
	Uncommon	Angioedema
Neurological	Common	Headache
Musculoskeletal	Uncommon	Arthralgia Myalgia
Gastrointestinal	Uncommon	Abdominal pain Vomiting
Cardiovascular	Uncommon	Chest pain Cyanosis
General	Common Uncommon	Pyrexia Pain at the infusion site

If the patient reacts to the antivenom, the rate may need to be slowed or the infusion ceased temporarily. If the reaction is more severe, then treatment with adrenaline, antihistamines, corticosteroids, plasma volume expanders and ß-agonists should be undertaken as required.

Skin testing for allergy to antivenom is not recommended, as it is unreliable and may delay urgent therapy. The decision to recommence antivenom should always be based on the clinical state of the patient. Special care needs to be taken if the patient has a known allergy to equine (horse) serum or to antivenom. Antivenom should not be withheld from these people; however it is important to have adrenaline and other drugs at hand in case they are needed, and to be in a situation where resuscitation and airway protection are immediately possible.

Issues surrounding the use of premedication

The issue of premedication has been controversial, and until recently, definitive evidence for its efficacy had been lacking. A randomised, double-blind, placebo controlled trial of the efficacy of low dose subcutaneous adrenaline to prevent acute adverse reactions to snake antivenom in Sri Lanka demonstrated a four-fold reduction in such reactions. No adverse reactions (such as intracranial haemorrhages) were observed in the premedicated patients[28]. This study strongly suggests the efficacy and safety of low dose subcutaneous adrenaline.

Despite this good evidence, there are conflicting opinions about the role of adrenaline as a premedication before giving antivenoms. In Australia's toxinology textbook[29], Drs Struan Sutherland and James Tibballs considered the evidence available up to 2001 and concluded that *"premedication with subcutaneous adrenaline is recommended (0.25 mg for an adult, 0.005 mg/kg for a child) before antivenom therapy"*. In contrast, in a recent review, Dr Bart Currie concluded: *"with the very low rate of severe reactions to antivenom seen in Australia . . . and the ability of emergency medicine physicians to adequately manage reactions that may occur, a policy of withholding premedication but always having adrenaline drawn up and ready is now recommended by many authorities and is policy in the Northern Territory"*[30]. In the middle is Australia's antivenom manufacturer, CSL Limited (Product information: ANG/Polyvalent snake antivenom, 2000): *"Some authorities have advocated premedication with subcutaneous adrenaline and intravenous antihistamine, particularly in those patients who are known to be at risk, but such use is controversial"*. Readers should consult the references for further details of the respective arguments and the history and evolution of the manufacturer's recommendations[31,32].

Although it is likely that well staffed major hospitals can, if it is recognized early, readily and rapidly manage antivenom reactions, such events can be severe, progressive and are not necessarily remediable[33]. Therefore, it is the small rural centres, with more limited staffing and facilities, that may benefit most from the apparent efficacy of adrenaline premedication[28,29,32]. If any premedication is to be given, currently the best evidence is that it should be **subcutaneous** adrenaline[28].

Thus, premedication with subcutaneous adrenaline is especially recommended prior to the intravenous administration of antivenoms in smaller centres. Adults should receive 0.25 mg of adrenaline by the **subcutaneous route** (0.005 mg/kg SC for a child).

Adrenaline premedication should never be given intravenously.

This is in order to avoid hypertension in the coagulopathic patient with the potential for bleeding. Similarly, it should not be administered intramuscularly, as this may also lead to hypertension, as well as to haematoma formation in the presence of coagulopathy. Alternatively, a treatment dose of adrenaline should be drawn up in a syringe ready for use (1 in 1000 – see anaphylaxis section below).

The traditional the role of antihistamines in premedication is less clear. On one hand a recent, well conducted, but underpowered, study from Sri Lanka[34] documented a reduction in mild-to-moderate acute reactions to antivenom with an antihistamine bolus in conjunction with a hydrocortisone infusion. However, with respect to the clinically important endpoints of moderate and severe reactions, there was insufficient power in this study to confirm a trend toward fewer reactions in the hydrocortisone-containing regimens. This study is in contrast to a previous study from Brazil that failed to demonstrate any difference in early antivenom reactions with prophylactic promethazine alone[35].

Adverse reactions to antivenom

Acute adverse reactions and/or anaphylaxis

Snake antivenoms are derived from antibodies of immunized animals; in the case of CSL snake antivenoms, the animals are horses. The rates of reactions to antivenoms appear to vary with the species of antibody origin, the extent of enzymatic digestion of the antibody molecules, the presence of molecular aggregates and the total protein content of the product[36,37]. It has been presumed that most acute reactions relate to the extent of complement activation from Fc receptor binding[37,38], with improvements in quality having largely resulted from enhancements in antivenom processing[36].

The antivenoms made in Australia by CSL Ltd, which are also used in Papua New Guinea, are amongst the safest in the world. The acute reaction rates to these antivenoms are reported as 10% in the absence of premedication[31] and 4.6% with premedication[32]. Three cases (3.8%) of delayed serum sickness were reported from 79 adequately followed up patients in one study[32]. A more recent survey of returned (but not followed up) antivenom usage report forms found a total of 14 adverse reactions (6%) to antivenom from 232 snakebite cases over 46 months. These figures probably underestimate the true adverse reaction rate to Australian antivenoms, but nonetheless compare favourably with figures from overseas, where adverse reactions to antivenoms have been reported in up to 80% of patients.

Many patients, even those with a past history of reaction to equine proteins, such as snake handlers, have had minimal or no problems with repeat antivenom therapy after premedication. All antivenoms however, contain foreign proteins (CSL snake antivenoms are comprised of approximately 17% equine IgG), and the possibility of allergic reactions, including life-threatening anaphylaxis, should always be considered. This is especially so if the patient has allergic/atopic disease (asthma, hay fever or eczema), if they have a history of prior exposure to equine serum (eg. anti-tetanus serum or antivenom for a previous snakebite), or have been given multiple doses of antivenom, especially if this was polyvalent antivenom.

Facilities should be available for dealing with complications such as anaphylaxis before the administration of antivenoms. The patient should be monitored closely for acute reactions (most occur within the first 30 minutes after starting antivenom administration). These signs include generalised feelings of anxiety, warmth, itching, progressive erythematous or urticarial rash, oedema of face/neck/soft tissues, vomiting, wheeze and shortness of breath, fever, hypotension, collapse and other evidence of shock. Adrenaline (*See next page for dosages and injection routes*) is the immediate treatment of choice for anaphylactic and anaphylactoid reactions, in conjunction with cessation of antivenom administration, oxygen by face mask, bronchodilators, H_1 receptor blockers, fluid replacement and corticosteroids.

Once the episode has been treated antivenom administration can be cautiously recommenced.

Adrenaline dosages for adverse serum reactions or anaphylaxis

The following initial doses of adrenaline should be given by the intramuscular route (IM).

Adrenaline concentration	Patient weight/age	Dosage
1 in 1,000	Small adults (< 50 kgs)	0.25 ml IM
	Average adults (50-100 kgs)	0.5 ml IM
	Large adults (> 100 kgs)	0.75 ml IM
1 in 10,000	Children (< 25 kgs)	10 µg/kg up to 250 µg IM

Only if there is little or no response to the initial dose should the same amount (diluted to 1 in 10,000) be given slowly via an intravenous line. It is important to establish radio contact with a consultant at PMGH while treatment with adrenaline is being undertaken and to seek qualified advice specific to the particular reaction that has occurred.

Serum Sickness

Serum sickness, due to the deposition of immune complexes, is a recognized complication of the administration of foreign protein solutions such as antivenoms. Symptoms include fever, rash, arthralgia, lymphadenopathy and a flu-like illness. Serum sickness following the administration of Australian antivenoms was reported in 3 out of a total of 70 cases in one series, although this is may be an underestimate due to loss to follow up of some patients.

Serum sickness typically **occurs between 5-10 days after antivenom** has been administered.

The possibility of serum sickness, and the usual symptoms and signs, should be discussed with the patient prior to discharge, so that it may be recognized and treated early. If a large amount of antivenom (i.e. polyvalent antivenom or multiple doses of monovalent antivenom) was given, then corticosteroid treatment should be considered. This may also be advisable if the patient has a past history of exposure to equine protein.

Both the incidence and severity of delayed serum sickness may be reduced by the having the patient take prednisone, at a dose of 50 mg (adult), or 1 mg/kg (child) for five days after the administration of the antivenom.

Quantity of antivenoms to be held by hospitals

The following is a suggested guide to the minimum amounts of antivenoms that should be held by health centres and hospitals at all times.

Regional Hospitals

1. Adequate antivenom to treat **six (6) to eight (8) serious cases** of envenomation by the major venomous snake species found in that province, i.e. a minimum of twelve (12) to sixteen (16) vials of appropriate relevant monovalent antivenoms; and
2. Eight (8) ampoules of polyvalent antivenom that should be held for the treatment of cases in which the snake has not been positively identified.

Urban Clinics and Rural Health Centres

The ability of clinics and health centres to maintain stocks of antivenom depends entirely on whether or not adequate cold chain storage is available and can be maintained. The shelf life of antivenom is three years when stored protected from light at between 2^0C to 8^0C. Antivenom must not be frozen.

1. Adequate antivenom to treat **two (2) serious cases** of envenomation by the major venomous snake species found in that region, i.e. a minimum of four (4) vials of appropriate relevant monovalent antivenom; and,
2. Four (4) ampoules of polyvalent antivenom that should be held for the treatment of cases in which the snake has not been positively identified.

Rural health centres that treat large numbers of snakebites each year should stock the same minimum quantities as large regional hospitals.

In areas where snakebite is infrequent and where there is **reasonable timely access** to a larger health centre or hospital, it may not be necessary for all small centres to stock antivenom. In these circumstances there should, however, be a clear medical evacuation strategy for transferring a snakebite patient to the larger centre for treatment with minimal delay.

All health centres and hospitals should have clear procedures for replacing antivenom stock as and when it is used from the appropriate Area Medical Store.

Provincial Antivenom Requirements

The medically important snake species in Papua New Guinea have natural distributions that vary from one type of snake to another. While some species are widespread and common throughout that distribution, other types of snakes may only be found in some parts of the country, and may not be common throughout those places (*See Chapter 2 for more information on individual species*).

Antivenoms are extremely expensive and it is prudent to conserve resources by planning for the most appropriate distribution and use of antivenoms, according to which species of venomous snake occur in particular parts of Papua New Guinea. Until the introduction of snake venom detection kits across PNG makes it possible to select monovalent antivenoms for all envenomations, the Provincial antivenom stocking recommendations made on the following two pages which are based on the current scientific knowledge of the natural distribution of Papua New Guinea snakes, and should be used as a basis for stocking antivenom and supplying it to health centres and hospitals in each province.

Recommended antivenoms for snakebites in PNG Provinces

This chart recommends appropriate antivenoms for each of the provinces throughout Papua New Guinea. The chart can be used in conjunction with the antivenom selection algorithm on page 11.8 to choice the antivenoms in the absence of SVDK testing.

Province	Native Species	Antivenoms Needed
Western	Papuan taipan	CSL taipan antivenom
	Death adder	CSL death adder antivenom
	Papuan blacksnake Papuan mulga snake Small-eyed snake Brown snake	CSL polyvalent antivenom
Gulf	Papuan taipan	CSL taipan antivenom
	Death adder	CSL death adder antivenom
	Papuan blacksnake Small-eyed snake	CSL polyvalent antivenom
Central & NCD	Papuan taipan	CSL taipan antivenom
	Death adder	CSL death adder antivenom
	Papuan blacksnake Brown snake Small-eyed snake	CSL polyvalent antivenom
Milne Bay	Papuan taipan	CSL taipan antivenom
	Death adder	CSL death adder antivenom
	Papuan blacksnake Brown snake Small-eyed snake	CSL polyvalent antivenom
Oro (Northern)	Death adder	CSL death adder antivenom
	Small-eyed snake Brown snake	CSL polyvalent antivenom
Morobe	Death adder	CSL death adder antivenom
	Small-eyed snake	CSL polyvalent antivenom
Eastern Highlands	Death adder	CSL death adder antivenom
	Small-eyed snake	CSL polyvalent antivenom
Simbu	Death adder	CSL death adder antivenom
	Small-eyed snake	CSL polyvalent antivenom
Southern Highlands	Death adder	CSL death adder antivenom
	Small-eyed snake	CSL polyvalent antivenom

Recommended antivenoms for snakebites in PNG Provinces

This chart recommends appropriate antivenoms for each of the provinces throughout Papua New Guinea. The chart can be used in conjunction with the antivenom selection algorithm on page 11.8 to choice the antivenoms in the absence of SVDK testing.

Province	Native Species	Antivenoms Needed
Western Highlands	Death adder	CSL death adder antivenom
Enga	Death adder	CSL death adder antivenom
Sandaun	Death adder	CSL death adder antivenom
	Small-eyed snake	CSL polyvalent antivenom
East Sepik	Death adder	CSL death adder antivenom
	Small-eyed snake	CSL polyvalent antivenom
Madang	Death adder	CSL death adder antivenom
	Small-eyed snake	CSL polyvalent antivenom
Manus		CSL Sea snake antivenom
West New Britain		CSL Sea snake antivenom
East New Britain		CSL Sea snake antivenom
New Ireland		CSL Sea snake antivenom
North Solomons		CSL Sea snake antivenom

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