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Antivenom Therapy in the Americas

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Abstract

Envenomations are an important cause of injury in the Americas. While supportive care alone may result in an acceptable outcome, antivenom offers a specific therapy that can significantly reduce the injury and symptoms of the envenomation. Antivenoms are hyperimmune sera collected from animals immunised with venom. The antibodies contained in the serum bind and inactivate venom components. This leads to cessation or reversal of the toxic effects of the venom. The serum is often processed to increase the level of antibodies directed against venom components and decrease the amount of inactive proteins that may cause allergic reactions. The processing may include precipitation of inactive proteins, chromatographic methods and cleavage of the immunoglobulins to form antibody fragments known as Fab or $F(ab)_2$.

In the Americas, antivenoms are produced to treat crotalid and *Micrurus* snake envenomations, *Latrodectus* and *Loxosceles* spider envenomations and *Centruroides* and *Tityus* scorpion envenomations. The indications, method of administration and incidence of adverse reactions differ greatly for each antivenom. The adverse effects encountered when using antivenoms are primarily allergic in nature. Anaphylaxis, which may be life threatening, is a major concern. Preparations to treat anaphylaxis must be made before initiating antivenom therapy. Serum sickness is also common with many of the antivenom preparations.

Envenomation of humans by animals may produce severe pain, extensive tissue injury and occasionally result in death. In 1996, there were almost 20 000 bites or stings involving snakes, spiders or scorpions reported to US Poison Centers.[1] Clinically significant envenomations are even more common in other American countries. In Costa Rica, the annual number of hospital admission for snakebites has been estimated to be as high as 22.4 per 100 000.[2]

While pain can be controlled and local injury mitigated with excellent supportive care, specific therapy with antivenom offers definitive therapy for many of these envenomations. The purpose of this review is 3-fold: to review the envenomations that may require antivenom therapy; to describe the process of antivenom production; and to discuss antivenom therapy using the antivenoms currently available in the Americas.

1. Envenomation Syndromes that Respond to Antivenom Therapy

1.1 Crotalidae

The family Crotalidae (Pit vipers) includes the genera *Crotalus* (rattlesnakes), *Bothrops*, *Bothriechis*, *Agkistrodon* (copperheads and water moccasins), *Lachesis*, *Porthidium* and *Sistrurus* (pygmy rattlesnakes and massasauga). Because these snakes are found throughout North and South America, crotalid snake bite is the most common snake envenomation encountered in the Americas. The snakes in this family range from a length of less than 1 metre to over 2.5 metres.[3] Larger snakes can deliver more venom. However, the degree of injury does not always correlate with the size of the snake.

Crotalid venom is a complex mixture of proteins, peptides and biogenic amines that cause injury to local tissue, vascular tissue, the coagulation system and the peripheral nervous system. Local injury results from proteolytic enzymes, hyaluronidases, phospholipases and collagenases. These enzymes disrupt cell membranes, cause microvascular platelet aggregation and attract inflammatory cells.[4]

Crotalid venom initiates activation of the coagulation system, but the resulting clot is not stable and is rapidly degraded by the endogenous fibrinolytic system and fibrinolytic enzymes in the venom. Platelet counts and fibrinogen levels may drop to extremely low levels. Fibrinolytic enzymes interfere with blood clotting thereby allowing bleeding into injured local tissues and occasionally haemorrhage. Adequate antivenom therapy prevents or reverses crotalid venom–induced coagulopathy and thrombocytopenia.[5-8]

Other peptides and metalloproteins increase vascular permeability and can cause hypovolaemic shock by allowing fluid to leak from the intravascular compartment.[3] Neurotoxic effects include fasciculation, weakness and paraesthesia.

While many crotalid venoms contain neurotoxins,[3] the Mojave rattlesnake (*C. scutulatus*) and the tropical rattlesnake (*C. durissus terrificus*) are reported to cause significant neurotoxicity, including paralysis. Mojave A toxin and crotoxin are structurally similar proteins that directly inhibit presynaptic acetylcholine release in motor neurons.[9] The neurotoxic effects of the Mojave have been reported to be resistant to the currently available antivenoms,[10] but respond to a polyvalent Fab antivenom therapy.[11]

In summary, crotalid envenomation may result in local tissue, haematological, cardiovascular and neurological toxicity. Individual manifestations are determined by the relative amount and activity of the components in the venom from the snake.

1.2 Elapidae

The coral snakes make up the genus *Micrurus* and are the only Elapidae indigenous to the Americas. Coral snakes are small (usually less than 1 metre), rarely aggressive and have smaller mouths and fangs than crotalids. This makes effective envenomations of humans difficult.

The toxic components of coral snake venom are the alpha neurotoxins. These toxins block acetylcholine binding to nicotinic receptors, resulting in

weakness and paralysis.[12] Once the venom is bound to the receptors, the effects appear reversible using *in vitro* studies,[12] but treatment has not been demonstrated to be uniformly effective in preventing progression of symptoms or reversing symptoms.[13] Elapid venom is also rich in acetylcholine esterase,[3] but this component does not appear to be responsible for the neuromuscular toxicity of these venoms. These venoms do not typically produce local tissue injury. Early administration of antivenom has been reported to decrease the probability of systemic toxicity, but prospective, randomised data are lacking.[13]

1.3 *Latrodectus*

The genus *Latrodectus* includes the widow spiders. These spiders range throughout North and South America, except in areas with extremes of temperature. They favour warm, dark environments and are not considered aggressive. Both sexes produce venom, but only females are capable of human envenomation.

Latrodectus venom contains a protein that increases the permeability of neurons to calcium. Calcium moves into the neurons and stimulates release of the neurotransmitters from the presynaptic nerve. The released neurotransmitters trigger the postsynaptic neurons, resulting in muscle spasm (motor neurons), localised diaphoresis and piloerection (cholinergic neurons) and hypertension (adrenergic neurons). Because *Latrodectus* venom lacks enzymes that cause significant tissue injury, local symptoms are minimal.[14]

Latrodectus antivenom is very effective at relieving acute pain and systemic symptoms, and administration 30 hours post envenomation was associated with resolution of pain.[15]

1.4 *Loxosceles*

The brown recluse spider and its relatives make up the genus *Loxosceles*. This genus is thought to be the major cause of necrotic arachnidism in the Americas. Several *Loxosceles* species are present in the North America, while *Loxosceles laeta* is found in South America. These spiders are not considered aggressive, and the bite often goes unnoticed initially.

The major toxin of *Loxosceles* venom is sphingomyelinase D. Other components include hyaluronidase, esterase, protease and collagenases.[16] Sphingomyelinase D is a phospholipase that lyses cell membranes, resulting in activation of the inflammatory cascade. This leads to platelet aggregation and thrombosis of the local capillaries. The clinical effect is necrosis of local tissues resulting in a slowly healing wound. Sphingomylinase D occasionally causes intravascular haemolysis by lysing red blood cells.

Loxosceles antivenom has not proven to be effective in animal models in the US,[17] but is reportedly available in South America.[18]

1.5 *Centruroides*

Centruroides scorpions are found in the southwestern US and Mexico. They are not considered aggressive, and most stings occur when the scorpion is disturbed (often after the scorpion seeks shelter in a sleeping bag or pile of clothing). *Centruroides* venom binds and partially activates neuronal sodium channels, resulting in uncontrolled neuron firing. Repeated firing of pain fibres causes pain in the affected area. The pain migrates centrally, and is often triggered by tapping the area of envenomation. Repeated firing of adrenergic nerves results in hypertension and tachycardia while increased parasympathetic stimulation results in increased salivation, and repeated motor neuron firing causes uncontrollable muscular activity.[19] Antivenom therapy has been shown to rapidly reverse the neurological effects of this toxin, with most patients showing a response within 1 hour of infusion.[19,20]

1.6 *Tityus*

Tityus scorpions are found in South America and the Caribbean. One hospital in Brazil reported 3866 patients admitted for envenomations over a 16-year period.[21] The toxins cause activation of sodium channels resulting in dysfunction of the nervous, cardiovascular and respiratory system.[22]

The clinical effects include local pain, vomiting, tachycardia, dysrhythmias, hypertension and pancreatitis.[21-23] It has been reported that after the development of antivenom the mortality of Tityus envenomations has decreased.[23]

2. Preparation and Purification of Antivenom

The term antivenom describes a serum product that contains a mixture of antibodies that bind and inactivate the components of venom. The antibodies are produced by animals immunised with small amounts of the target venom. The animal's serum is then collected and processed to produce antivenom. When the venom of one species is used to immunise the animal, the venom is termed monovalent. Polyvalent antivenom is produced by injecting the venom from several species, or mixing the serum from several animals injected with different venoms. Polyvalent antivenom is manufactured to be effective against several local species. This allows treatment using effective antivenom without an exact identification of the envenoming species.

Horses are often used to produce antivenoms. They are large, which allows the collection of several litres of serum at frequent intervals. They are also easy to care for and rapidly produce antibodies to venom proteins. Unfortunately, many people are sensitised to horse proteins. This has led some investigators to produce antivenom in rabbits or goats.[24] More recently, sheep have been used because they are easy to maintain, and some investigators have suggested that sheep derived antivenoms may be less immunogenic than horse-derived antivenoms.[25] The use of sheep in many countries may be limited by the theoretical potential for transmission of prion mediated infection.

The ideal antivenom would contain only the specific antibodies that bind the active components of venom. Nonessential components that may trigger allergic reactions would be eliminated. Ammonium sulphate treatment of antivenom has been used since 1939 to decrease the amount of nonfunctional protein present in antivenom. This process removes much of the albumin from the serum. Unfortunately, some of the neutralising antibody is also lost. For example, final protein level of IgG in Antivenin (Crotalidae) Polyvalent Wyeth is only 15 to 25%, and not all of this is IgG that binds the venom toxin.[26]

Affinity chromatography is another method of antibody purification. In this process, venom components are bound to a chromatography column. The antiserum is passed through the column. Antibodies that bind to venom components are retained in the column, while other proteins pass through. The column is treated to release the antibodies, which are collected and concentrated. *In vitro* and animal models demonstrate increased activity of the antivenom, presumably by increasing the concentration of proteins that inactivate venom. Studies of animals sensitised to horse serum suggest that antivenom prepared this way causes fewer anaphylactic reactions.[27]

The latest development in improving antibody therapy has been the development of antibody fragment therapy. Antibody fragments are produced by partial enzymatic digestion of IgG. The resultant antibody fragments can be either Fab or $F(ab)_2$, depending on the technique. $F(ab)_2$ consists of 2 Fab fragments that remain connected to a portion of the Fc fragment. Antibody fragments retain the ability to bind and inactivate venom, but are smaller and lack the most immunogenic portions of the antibody.

Antibody fragments have a larger volume of distribution than IgG. This suggests that tissue penetration of antibody fragment antivenom would be better than IgG preparations.[28] Animal studies also indicate that antibody fragments are less likely than whole IgG to induce an antibody response.[28] A recent study reported an increased incidence of adverse reactions to Fab antivenom compared to a $F(ab)_2$ preparation. However, this likely resulted from an inadequate purification technique.[29] A study of crotalid Fab antivenom reported a much lower incidence of adverse reactions.[30]

Fab therapy used for digoxin poisoning also demonstrates that these preparations are very safe.

Post-marketing surveillance of 717 patients treated with digoxin specific Fab reported allergic reactions in only 6 patients.[31] Currently, the only Fab antivenom available in the Americas is used in Brazil.[21] Crotalid Fab antivenom (CroTab®) is currently pending approval in the US. A *Micrurus* Fab antivenom has been developed but is not commercially available.[32]

Recent animal studies that have compared Fab and $F(ab)_2$ suggest that there may be significant differences in the mechanism of action and the pharmacokinetics of the 2 types of antivenom. Fab has a larger volume of distribution than $F(ab)_2$. Fab is also rapidly cleared by renal excretion, while $F(ab)_2$ is not cleared significantly by the kidneys. The redistribution and clearance of Fab from the vascular compartment may lead to the reappearance of toxic venom levels following administration of a single dose of Fab. This does not occur with $F(ab)_2$.[33,34]

Clinical recurrence of coagulopathy been reported for patients that received Fab and whole antibody therapy for crotalid envenomations.[35,36] These data suggest that Fab may require multiple doses to provide effective clearance of venom and to prevent recurrence of venom effects.

A potential advantage of the small size of Fab relative to $F(ab)_2$ is that the antibody fragments may be able to bind and inactivate venom more effectively in tissue and prevent local injury. However, data comparing the efficacy of Fab and $F(ab)_2$ antivenoms in humans are not available for most antivenoms.

Table I. Antivenoms manufactured in North America and their uses[a][61]

Antivenom	Target species
Antivenom production Laboratories - APL (US)	
Centruroides sculpturatus antivenom (goat serum)	*Centruroides sculpturatus, C. gertschi, C. limpidus, C. noxius, C. suffusus*
Instituto Nacional de Higiene (Mexico)	
Polyvalent Snake Antivenom	All Mexican Crotalid sp, *Bothrops asper, Crotalus basiliscus, Agkistrodon bilineatus*
Grupo Pharma S.A. (Mexico)	
'ANTIVIP' Polyvalent Snake Venom	All *Crotalus* and *Bothrops* species of Mexico, Central and South America *Porthidium nummifer*
Polivalent Scorpion Antivenom (Alacramyn)	*C. limpidus, C. noxius, C. suffusus*
Gerencia General de Biologicos y Reactivos (Mexico)	
Suero Antiviperino Polivalente Equino	*C. basiliscus, B. asper*
Suero Antialacran	*C. limpidus, C. noxius, C. suffusus*
Merck Sharpe & Dohme (US)	
Antivenin (*Latrodectus mactans*)	*Latrodectus mactans*
Therapeutic antibodies (US)	
Crotab[b] (Ovine Fab)	All North American pit vipers except *Agkistrodon* (Copperhead)
Wyeth-Ayerst Laboratories (US)	
Wyeth Antivenin Polyvalent	All New World pit vipers
Wyeth Antienin N. American Coral Snake Antivenom	*Micrurus fulvius fulvius, Micrurus f. tenere*

a All products are equine-derived IgG preparations unless noted.
b Pending FDA approval.

3. Antivenom as Therapy

The indications for the use of antivenom vary by species, geographic location and patient symptoms. Antivenoms and their target species are provided in tables I to III.

Crotalid antivenom is indicated for progression of clinical findings. These include progression of local swelling, coagulopathy (low platelet count or elevated clotting times), persistent hypotension or increasing weakness. Patients that lack these symptoms after 8 to 12 hours are not likely to require antivenom therapy.[37,38]

Elapid antivenom is indicated for patients with venom effects, skin penetration or a history of 'chewing' on the affected limb. Patients should be treated before they develop symptoms. This recommendation is based on a limited case series that suggested that patients that are treated before symptoms develop have shorter duration of symptoms.[13] Unfortunately, these recommendations may result in administration of antivenom to patients with insignificant envenomation.

Latrodectus antivenom should be administered to patients who fail to respond to analgesics, or con-

Table II. Antivenoms manufactured in South America and their uses[a][61]

Antivenom	Target species
Instituto Nacional de Microbiologia (Argentina)	
Bothrops Bivalent	*Bothrops alternatus, B. neuweidi, B. ammodytoides*
Tropical Trivalent	*Bothrops alternatus, B. neuweidi, Crotalus durissus terrificus*
Bothrops tetravalent	*Bothrops alternatus, B. neuweidi, B. jararaca, B. jararacussu*
Antimicrurus	*Micrurus frontalis, M. corallinus*
Anticrotalus	*C. durissus terrificus*
Ejercito Argentino (Argentina)	
Antibothrops	*Bothrops sp.*
Antimicrurus	*Micrurus sp.*
Instituto Butantan (Brazil)	
Antibothropico	*Bothrops jararaca, B jararacussu, B. cotiara, B. moojeni, B. alternatus, B. neuweidi*
Anticrotalico	Snakes of the genus *Crotalus*
Antibothropico-anticrotalico	Snakes of the genus *Crotalus* or genus *Bothrops*
Antielapidico	Snakes of the genus *Micrurus*
Antibothropico-Laquetico	*Bothrops* sp. or *Lachesis muta*
Antiarachnidico	Spider of the genus *Loxosceles* or scorpions of the genus *Tityus*
Antiloxoscelico	Spider of the genus *Loxosceles*
Antiscorpionico	Scorpions of the genus *Tityus*
Instituto Vital Brazil (Brazil)	
Soro antibotropico	*Bothrops jararaca, B. jararacussu, B. coitara, B. moojeni, B. alternatus, B. neuweidi, B. pradoi*
Soro anticrotalico	*C. durissus terrificus*
Soro antiofidico polivalente	*B. jararaca, B jararacussu, B. cotiara, B. moojeni, B. alternatus, B. neuwiedi, B. pradoi, C. durissus terrificus*
Fundacao Ezequiel Dias- FUNED (Brazil)	
Antibotropico	*B. jararaca B. neuwiedi, B jararacussu, B. moojeni, B. alternatus*
Anticrotalico	*C. durissus terrificus*
Antibotropico crotalico	*B. jararaca B. neuwiedi, B jararacussu, B. moojeni, B. alternatus, C. durissus terrificus*
Antibotropico laquetico	*B. atrox, L. muta*
Antiscorpion (Fab_2)	Scorpions of the genus *Tityus*
Grupo de Sueros Instituto Nacional de Salud (Colombia)	
Antiveneno Polivalente	*Bothrops* sp. native to Colombia, *C. durissus terrificus*, *L. muta* in high doses
Antiveno Monovalente	*Bothrops* sp. native to Colombia
Instituto Nacional de Higiene Y Medicina Tropical (Ecuador)	
Anti-Bothrops	*B. asper*
Instituto Nacional de Salud (Peru)	
Suero Antibotropico	*B. atrox, B. brazili, B. pictus, B. castelnaudii, B. barnetti, Bothriopsis taeniata, B. bilineata, Porthidium nummifer*
Suero Antilachesico	*L. muta*
Suero Anticrotalico	*C. durissus terrificus*
Instituto de Higiene (Uruguay)	
Suero antifidico bivalenteAntibothropico	*B. alternatus, B. neuwiedi*
Universidad Central de Venezuela (Venezuela)	
Suero antiofidico polyvalent	*B. atrox, C. durissus cumanensis*

a All products are equine derived IgG preparations unless noted.

tinue to require parenteral opioids after a reasonable observation period.[39] It has also been recommended for pregnant patients and those at the extremes of age.[40]

Centruroides antivenom is used for patients who develop skeletal muscle dysfunction or cranial nerve findings and do not respond to supportive care.[19,41] These symptoms are much more common in patients less than 2 years old.[42]

Tityus antivenom is indicated for patients that develop systemic symptoms. Patients with local pain are treated with local anaesthetics and systemic analgesia.[23]

4. Administration of Antivenom

The initial step of antivenom therapy is to determine the amount of antivenom required and the amount of antivenom available. Many facilities have minimal or no antivenom stores.[43] If it is determined that the amount available is not sufficient, more antivenom should be procured or the patient should be transferred.

Antivenom is a potentially dangerous therapy. The major life threatening complication of antivenom is anaphylaxis. Because anaphylactic reactions can occur during skin testing, preparation to treat anaphylaxis should be made prior to skin testing. The patient should have 2 functioning intravenous (IV) catheters. Equipment and personnel to manage the patient's airway must be accessible, and the patient should be placed on oxygen. Medications for anaphylaxis, including epinephrine (adrenaline), diphenhydramine and steroids should also be immediately available. Optimally, antivenom is administered in a critical care setting such as an intensive care unit, emergency department, or post-anaesthesia care unit.

In the US, skin testing has become routine prior to the use of antivenom, while in other countries skin testing is not performed. Skin testing is an imperfect indicator of allergic reactions, and many antivenom manufacturers do not recommend routine skin testing.[21,44] A report of 100 patients treated with Antivenin (Crotalidae) Polyvalent Wyeth stated 80% of the patients that responded 'unfavourably' had negative skin tests.[45] In a smaller series of 26 patients treated with crotalid antivenom, 10% of patients with a negative skin test had an immediate hypersensitivity reaction to antivenom.[46] However, this study included a rash without other systemic symptoms as an immediate reaction. Two-thirds of patients with positive skin reactions did not have immediate hypersensitivity reactions. A study of 25 patients from Nigeria and Thailand treated for snake envenomation reported that none of 12 anaphylactic reactions were predicted by skin testing.[47]

Table III. Antivenoms manufactured in Central America and their uses[a][61]

Antivenom	Target species
Instituto Clodomiro Picado (Costa Rica)	
Anti-Coral Polyvalent	*Micrurus nigrocinctus, M. Carinicauda. M. fulvius, M. alleni, M. dumerilii*
Polyvalent (horse or sheep serum)	*Bothrops asper, Crotalus durissus, Lachesis muta, Porthidium* sp. All small pit vipers of Central America

a All products are equine-derived IgG preparations unless noted.

Our experience indicates that a positive skin test increases the chance that a patient will have a serious reaction, and therefore it is a worthwhile procedure.[48] Skin testing is not used for the crotalid Fab antivenom (CroTab®).

In summary, the skin test is of questionable value in managing the envenomed patient. While a positive skin test may provide warning of a potential life-threatening reaction, a negative skin test should not reassure the clinician that the patient will not have a hypersensitivity reaction. Perhaps the strongest argument for skin testing is that it is recommended by the antivenom producer, and failure to skin test could be considered failure to use the product as directed.

Skin testing should only be performed after the physician has determined antivenom therapy is indicated. Antivenom therapy should not be delayed for skin testing in critically ill patients. When skin testing is performed, the manufacturer's protocol should be followed. Most protocols use a separate testing solution, but some physicians use the mixed

antivenom diluted to 1 : 100 concentration. The recommended amount of solution, (usually 0.02ml) should be administered intradermally, the technique commonly used for tuberculin skin testing. The area should be circled with a marking pen and observed for 30 minutes. A positive test results in induration of more than 10mm. Erythema alone is not considered a positive test. Obviously systemic allergic symptoms, such as hypotension, bronchospasm vomiting or flushing, also constitute a positive test.

The dose of antivenom differs for each antivenom. In general, therapy is titrated to a desired endpoint. Antivenom for crotalid envenomation is administered until systemic symptoms have resolved, haematological parameters are normal and local progression has stopped.[4] *Micrurus* bites receive prophylactic treatment, with more antivenom administered if symptoms occur.[13] Initial therapy for *Latrodectus* envenomation using the Merck antivenom is usually 1 vial.[14] If symptoms do not resolve following 2 vials, the diagnosis should be reconsidered. *Centruroides* antivenom is titrated to resolution of the neuromotor symptoms, with most patients requiring 1 or 2 vials.[19]

Many antivenom preparations are lyophilised and must be reconstituted to produce a solution. The proper method is gentle agitation of the vials after addition of the provided diluent or sterile saline. This process can take 30 to 60 minutes. Shaking the vials will result in the formation of foam, and may cause the proteins to denature. If only 1 or 2 vials of antivenom are to be infused, the antivenom is diluted in 100ml of saline or 5% dextrose solution. If a greater amount of antivenom is to be infused, then each 5 to 10 vial 'round' of antivenom is diluted to a total of 250 to 500ml in normal saline or 5% dextrose. In children the antivenom should be reconstituted in a volume of fluid that yields a total of 20 ml/kg to be administered (up to a maximum of 250ml).[49]

Because it is impossible to predict with certainty which patients will experience anaphylactic reactions, the infusion should be started slowly.[45] A slow initial rate will allow early detection of anaphylaxis. Rapid infusion also increases the number of patients who will complain of flushing, nausea or anxiety.[45] We recommend beginning the infusion at 25 to 50 ml/h. If there is no evidence of reaction after 5 minutes, the rate is doubled. As long as the patient remains asymptomatic, the rate is doubled every 5 minutes until the volume is infused. The patient must have continuous cardiac, blood pressure and oximetry monitoring during the infusion. Many experts recommend that the initial dose is infused within 60 minutes, although some data suggest that the rate of severe early reactions may not be decreased by slower infusion.[47,49]

5. Complications of Antivenom

Positive skin reactions indicate hypersensitivity to the antivenom. If there is an effective alternative to antivenom (i.e. opioid pain medications for *Latrodectus*), a positive skin test is an indication to withhold antivenom therapy. If there is no effective alternative (i.e. crotalid envenomation with extensive local effects), positive skin reactions are not considered an absolute contraindication to therapy.

Although conclusive data demonstrating a benefit from pretreatment in preventing or modifying anaphylaxis to antivenom are not available, we believe that the risk to benefit ratio favours pretreatment for patients with a positive skin test. Patients who demonstrate a wheal and flare reaction may be pretreated with histamine H_1 and H_2 receptor antagonists (e.g. diphenhydramine and cimetidine), which have been shown to help decrease the number of anaphylactic reactions to several agents.[50] Epinephrine should be ready to administer (see hypotension section below), and preparations made to manage the patient's airway. Finally, the antivenom should be diluted in a volume of 1000ml and the initial infusion rate should be 10 to 25 ml/hour. Patients who have no reaction to the infusion should have the rate doubled as described in section 4.

Airway swelling or bronchospasm require immediate cessation of the infusion. Patients with symptoms of airway obstruction should be placed on high-flow oxygen, and treated with 0.3ml of epi-

nephrine (1 : 1000) subcutaneously (paediatric dose 0.01 mg/kg), IV diphenhydramine 50mg (paediatric dose 1 mg/kg) and cimetidine 300mg IV (paediatric dose 5 mg/kg). Patients with imminent airway obstruction must be intubated; cricothyroidotomy may be required in severe cases. Bronchospasm also may be treated with a nebulised β_2-agonist.

Hypotension is the hallmark of anaphylactic shock, the most life threatening complication of antivenom therapy. It is due to vasodilation and capillary leakage.[51] The antivenom infusion is stopped and the patient receives 20 ml/kg of crystalloid. Patients with severe manifestations or those who do not respond immediately to these measures should receive intramuscular or IV epinephrine. The usual intramuscular dose is 0.3ml of a 1 : 1000 solution for adults and 0.01 mg/kg for children. IV epinephrine is usually given by infusion rather than bolus to avoid ventricular dysrhythmias. The recommended dose is 0.1ml of 1 : 1000 diluted in 100ml of saline given over 10 minutes.[52] Patients refractory to epinephrine may benefit from cimetidine 300mg IV.[53] Glucagon has been used to reverse hypotension refractory to epinephrine in patients on β-blocker therapy.[54]

The incidence of acute reactions is not well described. Jurkovich[46] reported a 23% incidence of anaphylaxis in patients treated with Antivenin (Crotalidae) Wyeth, but 50% of the patients with 'anaphylaxis' had only skin reactions. Immediate hypersensitivity reactions were reported in 87%, 37% and 56% of patients treated for *Bothrops* envenomations using Butantan, Vital Brazil and FUNED antivenom respectively.[7] The rate of early allergic reactions with crotalid Fab antivenom (CroTab®) was 20%, most of which were mild (RC Dart, unpublished data). One of 17 patients treated with Wyeth Antivenin (*Micrurus fulvuis*) had an anaphylactic reaction.[13] One death has been reported from Merck *Latrodectus* antivenom.[39] *Centruroides* antivenom from Antivenom Production Laboratories (APL) caused immediate hypersensitivity reactions in 8% of patients.[55] A very large study of patients treated in Mexico with *Centruroides* polyspecific antivenom reported no immediate reactions.[44] However, this appears to be an anecdotal study and no formal reporting methods are described.

Another type of hypersensitivity reaction is serum sickness, a type III hypersensitivity reaction due to the formation of antigen-antibody complexes. Studies report an incidence of 50 to 75% for patients treated with Wyeth antivenom for crotalid envenomation.[45,46] Mild symptoms such as itching, nausea, urticaria, low-grade fever and malaise have been treated with diphenhydramine or other H_1 antihistamines.[45,46] Up to 35% of patients reported severe reactions including persistent urticaria, vomiting, arthralgias, myalgias, syncope or angioedema.[45] Glomerulonephritis and neuritis are rare complications of serum sickness from antivenom therapy.[56] The incidence of serum sickness with Antivenom (*Crotalidae*) Wyeth Polyvalent appeared to increase after infusion of more than 3 vials. The onset is from 1 day to 3 weeks. The onset of serum sickness appears to be positively correlated with the number of vials administered.[45] Preliminary studies of crotalid Fab antivenom (CroTab®) have found the rate of serum sickness is less than 10% (RC Dart, unpublished data).

10% of patients treated with *Micrurus* antivenom developed symptoms of serum sickness that prompted them to seek medical attention.[13] Limited data suggest that serum sickness is rare following Merck *Latrodectus* antivenom administration.[39,57] Much larger studies of *Latrodectus* antivenom in Australia have also reported a very low incidence of serum sickness, but this rate of reaction may not apply to other *Latrodectus* antivenoms.[58]

The incidence of serum sickness following APL antivenom therapy for *Centruroides* envenomation has been reported to be as high as 58%.[20] Other authors report a much lower incidence.[19] Information on the incidence of serum sickness for *Centruroides* envenomation using antivenom in Mexico is not available.[41]

Treatment of serum sickness is directed at patient's symptoms. Patients with urticaria or pru-

ritus should be treated with antihistamines. Patients with low-grade fever, myalgias, or arthralgias should receive mild analgesics and antipyretics. A 7- to 10-day course of high dose steroids (prednisone 40mg/day) is indicated for all symptomatic patients.[56]

6. Conclusions

Antivenom is a powerful therapy for significant envenomations. Recent studies have reported 'successful' management of crotalid envenomations without antivenom.[59,60] These authors claim that the risk of antivenom outweighs the benefits. However, many of the patients reported in these series did not appear to have significant envenomations or were bitten by snakes that rarely cause effects significant enough to warrant antivenom therapy.

We advocate consideration of the risks and benefits of antivenom therapy when treating an envenomed patient. While it is true that antivenom may not be required for many patients with minor envenomations, antivenom provides specific therapy that can rapidly reverse venom effects. When the potential benefits are considered, antivenom often offers the most reasonable therapeutic option for treating these patients.

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