

# Pit Viper Snakebite in the United States

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Pit viper snakebite is a relatively uncommon medical emergency which must be adequately diagnosed and treated to minimize local tissue destruction and systemic complications and to prevent death. Severity is highly variable and may range from minimal local pain and swelling to marked pain, edema, tissue necrosis, hemorrhage, shock, and death within one hour. By far, the most common complication is local tissue destruction often resulting in loss of function. Pit viper venom is extremely complex, containing factors which directly destroy muscle, blood vessels, and renal tissues. Other components anticoagulate blood and cause hypotension, local edema, and pain. Neurotoxicity is unusual, but respiratory paralysis may follow Mojave rattlesnake bites.

Proper first aid consists of a proximal mildly constricting tourniquet, superficial incision at fang marks, and constant suction. Medical management consists of early intravenous antivenin in adequate dosage, after hypersensitivity testing. Other measures are largely supportive. The early use of corticosteroids is controversial. Cryotherapy is to be avoided. Fasciotomy may be necessary when edema is severe and impairs arterial perfusion. Promising developments include immunization trials against pit viper venom as well as studies on the antivenom activity of rattlesnake plasma.

Poisonous snakebite is a subject long clouded by myth and superstition.<sup>1</sup> Even today, the lay and medical literature on this subject remains somewhat confused and at times contradictory. Nevertheless, physicians throughout the United States should have a general understanding of this

relatively uncommon medical emergency. Even in areas far removed from the snake's natural habitat, poisonous snakebite still occurs among amateur herpetologists, exotic dancers, and religious cultists.

Only ten percent of the snakes in the United States are poisonous. The vast majority are pit vipers (subfamily Crotalidae). They account for 98 percent of all poisonous snakebites in this country. Pit vipers include rattlesnakes (genus *Crotalus*), cottonmouths and copperheads (genus *Agkistrodon*), plus the massasauga and pigmy rattler

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(genus *Sistrurus*). At least one species is found in each of the 48 contiguous states except Michigan, Maine, and Delaware. In general these poisonous snakes are more prevalent in rural areas of the South and Southwest. In the United States pit viper bites are seldom fatal. Of approximately 7,000 snakebites treated annually, there are fewer than 12 deaths per year.<sup>2,3</sup> By far the most common and persistent complication is local tissue destruction leading to loss of function, deformity, or even amputation. At times undue emphasis on the deadly potential of snake venom has resulted in unnecessary, heroic measures often worsening local damage.

The remaining poisonous snakebites—less than two percent—are accounted for by coral snakes.<sup>2,4</sup> These are small snakes, found in the southern and southwestern United States, possessing a neurotoxic venom. A specific antivenin is now commercially available for the treatment of coral snake envenomation. These snakes will not be discussed further.

## General Principles

It is initially important to determine whether or not a poisonous snakebite has actually occurred. Only poisonous snakes have fangs and when a strike is effective, two fang marks result. The size of the serpent is roughly proportional to the distance between marks; however, a glancing blow may leave only one mark or merely scratch the skin. At times thorns and other vegetation may cause confusing puncture wounds. Visual identification of the attacker is often helpful, as pit vipers can be distinguished by the presence of a triangularly shaped head, fangs, vertical elliptically shaped pupils, and heat-sensing pits located between the eye and nostril. Rattlesnakes also have a tail of interlocking horny segments which resembles a rattle and is used to produce a hissing sound similar to that of escaping steam.<sup>5</sup>

The severity of pit viper snakebite is highly variable. In 20 percent of these bites no clinical envenomation occurs because the snake fails either to pierce the skin or to inject venom.<sup>3,6</sup> Actual

envenomation almost always causes burning pain and rapidly spreading edema at the bite site, usually within five minutes. Other early systemic effects include sweating, weakness, faintness, vertigo, numbness, cramps, and tingling of the scalp or face. Fever, nausea, vomiting, and regional lymphadenopathy may soon follow.<sup>3,4</sup> If burning pain or edema more than 2 cm from the fang marks does not develop within one hour, there has probably been no significant pit viper envenomation.<sup>4</sup> The amount of venom injected is usually greater in hungry, agitated, and larger snakes, although juvenile rattlesnakes have been found which contained highly concentrated venom.<sup>7</sup> Severity is often increased in bites to the trunk, face, and those penetrating large blood vessels; fortunately, over 95 percent of all bites are located on the extremities.<sup>2,8-10</sup> Children generally suffer more serious reactions because of the proportionately greater venom dose they receive per kilogram, although mortality has not been found to be appreciably higher.<sup>8</sup> The wide variability in individual sensitivity to venom is unexplained.

Pit viper venom potentially contains many toxic substances which will be discussed later. Nevertheless, they are seldom if ever all present in significant concentration in the venom of any single snake. In fact, the composition and potency of venom is highly variable and differs not only among species, but also among individual snakes.<sup>7,11,12</sup> Despite this, several generalizations can be made. The eastern and western diamondback rattlesnakes are potentially extremely dangerous. They cause 95 percent of all pit viper fatalities, but are responsible for only one tenth the total number of bites.<sup>4</sup> The cottonmouths and other United States rattlers are moderately dangerous.<sup>13</sup> Copperheads inflict 3,000 bites yearly because of their propensity to invade the human habitat. However, their bites are less dangerous and fatalities are extremely rare.<sup>10,14</sup> The pigmy rattlesnake and the massasauga are not generally considered deadly.

Snake venoms are among the most complex of all poisons.<sup>14</sup> Recent advances in biochemistry have spawned increased research and have provided clearer understanding of the action of the many venom components. Previously, the numerous enzymes of crotalid venom were held responsible for its toxicity.<sup>15</sup> It is now clear that nonenzymatic, low molecular weight proteins are the



primary toxic principles, and that the venom enzymes play secondary, albeit important, roles.<sup>12,16</sup>

## Complications of Pit Viper Snakebite

### *Bleeding Complications*

Bleeding is not an infrequent complication in pit viper envenomation. This is caused by a venom hemorrhagic factor which may act in concert with a venom anticoagulant enzyme. As a result of the latter, nonclotting blood is found in the victims of snakebites from many different crotalid species,<sup>17-20</sup> which include the eastern diamondback, Pacific, and timber rattlesnakes found in the United States.<sup>21-27</sup> This phenomenon is caused by thrombin-like venom arginine ester hydrolases known as procoagulant esterases, which directly convert fibrinogen to "fibrin" more readily than thrombin.<sup>18-20,25-29</sup> They rapidly split off fibrinopeptides A, AP, and AY, but hydrolysis of fibrinopeptide B does not take place.<sup>28,30,31</sup> Unlike thrombin, the procoagulant esterases do not activate factor XIII or factors of the extrinsic clotting system, and their action is not inhibited by heparin.<sup>23,27,29,30,32</sup> In vitro, they convert fibrinogen to a less easily polymerized fibrin monomer which forms a friable fibrin clot or gel which readily lyses.<sup>27,29</sup> Paradoxically, the clinical result is that both crude venom and the purified procoagulant fraction exhibit powerful anticoagulant activity by depleting available fibrinogen without producing intravascular clotting.<sup>23,25-27,29</sup> Large amounts of fibrin degradation products are formed by this mechanism.

The defibrination state may develop in a matter of a few hours and can persist for several days.<sup>17,22,23,25,29,33</sup> When present as an isolated entity, it is a relatively benign condition in which hemorrhage develops infrequently.<sup>17,29,33</sup> Affected individuals are usually asymptomatic, but laboratory studies show markedly elevated prothrombin and partial thromboplastin times, low or undetectable fibrinogen levels, and high titers of fibrin split products. Platelet concentration, and hemoglobin and hematocrit levels are generally within normal limits.<sup>23,32,34</sup> Procoagulant esterases do not significantly aggregate platelets.<sup>29</sup> Experimentally, loose

platelet aggregates may be induced, but neither formation of platelet adenosine diphosphate (ADP) nor viscous metamorphosis or fusion of the platelets takes place.<sup>32,35</sup>

Although ecchymosis, followed by hemorrhagic vesiculations, is commonly seen near fang punctures, overt bleeding occurs only when the venom contains a specific hemorrhagic principle found in many species of Asiatic and New World pit vipers. In the United States this activity is most pronounced in the eastern diamondback, but is also seen in western diamondback and timber rattlesnakes, copperheads, and cottonmouths.<sup>36,37</sup> Initially, petechiae, local bleeding or hematomas, and later hematuria, hemoptysis, hematemesis, epistaxis, bloody diarrhea, and melena may occur.<sup>27,38-40</sup> Oozing of blood through the skin, intracerebral and intracardiac hemorrhages, and shock may develop in extreme cases.<sup>16</sup> Rarely noted is yellow vision or blindness secondary to retinal hemorrhage.<sup>41</sup>

The hemorrhagic factors or hemorrhagins are nonproteolytic, nonenzymatic proteins which are directly toxic to the vascular wall.<sup>16</sup> Although histamine and bradykinin markedly increase vascular permeability they neither cause nor potentiate hemorrhage as previously believed.<sup>42-45</sup> Some species appear to contain multiple distinct homogeneous hemorrhagic factors which may differ in potency and possibly in location of primary vascular toxicity.<sup>43,44</sup> The venom of many North American pit viper species has been shown to cause endothelial cell disintegration associated with prominent hemorrhages in the perimysium and endomysium of muscle in the vicinity of the venom injection site. Hemorrhage beneath the endothelium, necrosis of smooth muscle fibers of the media, and formation of mural thrombi were seen in small arteries, with similar but less severe changes seen in small veins.<sup>37</sup> A recent study employing electron microscopy revealed that hemorrhage may occur within two minutes of an injection of western diamondback venom. Early changes in endothelial cells included dilated perinuclear space and endoplasmic reticulum. Rupture of the plasma membrane with extravasation of erythrocytes through the disintegrating endothelial cells followed. Platelet aggregations without fibrin plugged gaps in vessel walls, often completely occluding capillary lumina.<sup>46</sup> Mechanical erythrocyte destruction due to damaged mi-



circulation probably accounts for instances of hemolysis, as crotalid venom lacks direct *in vivo* hemolytic activity.<sup>15,16,45,47</sup> Hyaluronidase, which is nonhemorrhagic itself, appears to increase the area of hemorrhage.<sup>44</sup>

If both hemorrhagic and anticoagulant activity are present in the venom a victim receives, they will act synergistically to produce dose-related hemorrhage, anticoagulation, and thrombocytopenia.<sup>27,38,39,47</sup> Antivenin is the only effective treatment. It will rapidly neutralize both the procoagulant esterases and hemorrhagic factors.<sup>27,33,46</sup> It will not, however, reverse myonecrosis and vascular injury which has already occurred. Therefore, it is important to use antivenin early in cases of potentially serious envenomation.<sup>46</sup>

### Shock

Local pain and progressive limb edema are hallmarks of significant pit viper envenomation. In severe bites acute hypotension will occasionally develop as well. North American pit viper venoms apparently cause these responses by triggering the release of vasoactive substances in their victims.<sup>11,48</sup> Venom arginine ester hydrolases rapidly convert circulating plasma kininogen to bradykinin which is subsequently inactivated by plasma kininases.<sup>11,16</sup> Early transient hypotension seen in severe rattlesnake bites is believed to be primarily due to the potent vasodilator effect of bradykinin, although histamine and venom phosphodiesterase may play secondary roles.<sup>48,49</sup> Experimentally, immediate hypotension occurs in animals after the intravenous injection of rattlesnake venom, primarily due to blood pooling in the pulmonary, and to a lesser degree, the splanchnic, vasculature.<sup>50,51</sup> The drop and recovery of the systemic arterial pressure was found to parallel the explosive release and later disappearance of bradykinin.<sup>48,52</sup> Bradykinin probably contributes to local pain, stimulates visceral smooth muscle, and may provoke abdominal cramping, nausea, and vomiting.<sup>16</sup> Bradykinin stimulation of parasympathetic centers may be responsible for the pronounced miosis seen in severe rattlesnake envenomation.<sup>36</sup>

A common finding in the recovery phase is elevation of hemoglobin and hematocrit levels.<sup>50,52</sup> However, after interim improvement in blood pressure, circulatory collapse may develop because of hypovolemia and/or hemorrhage. Venom-liberated histamine and to a lesser extent bradykinin act to greatly increase permeability in the microcirculation, probably at the level of the small venules rather than the true capillaries.<sup>45,48,53</sup> In human victims this may result in significant loss of plasma volume into the tissues of the involved limb, hypovolemia, and hemoconcentration. In severe cases, shock may ensue, unless circulating plasma volume is restored.

Recently, low molecular weight proteins isolated from the venom of eastern diamondback and canebrake rattlesnakes have been shown to cause severe myocardial ischemia.<sup>54</sup> In animal studies the degree of myocardial damage and resultant cardiovascular compromise appeared dose-related. Myocardial ischemia and necrosis was demonstrated by serum enzyme elevation and histopathologic evaluation.<sup>54,55</sup> Another recent report states that the venom of all North American pit vipers contains varying amounts of a myocardial depressor protein (MDP).<sup>56</sup> Administration of MDP to animals induces dose-related myocardial failure as evidenced by decreased cardiac output, systemic arterial pressure, left ventricular systolic and mean pressures, and elevated left ventricular end diastolic and pulmonary wedge pressures.<sup>56</sup> The effect of these factors on the circulatory status of human victims has not yet been determined.

### Allergy

Pit viper venom is a potent allergen capable of causing rhinitis, conjunctivitis, and asthma, even in technicians without an allergic history who infrequently handle dry venom. In these individuals both intradermal testing and passive transfer of reaginic activity were positive.<sup>57,58</sup> Recently, serum IgE antibody against eastern rattlesnake venom has been demonstrated by solid phase radioimmunoassay.<sup>58</sup> A study of snakehandlers who had received multiple pit viper bites showed that although no permanent immunity to venom developed, hypersensitivity to crotalid venom was



frequent.<sup>59</sup> Hypersensitivity to venoms of related crotalid species indicating antigenic similarity was reported.<sup>57,60</sup> Compared to controls, venom-sensitized mice showed greatly increased susceptibility to cottonmouth venom as well as antivenin-neutralized venom.<sup>61</sup> In human subjects with prior hypersensitivity to crotalid venom, accidental snakebite by a related species has resulted in severe asthma and systemic anaphylaxis.<sup>57,62</sup> Although the incidence of allergic reactions to snake venom is no doubt low, anaphylaxis should be considered in circulatory collapse immediately following rattlesnake bite when there is a history of prior exposure to snakes and snake venom.<sup>62</sup>

### *Neurotoxicity*

The Mojave rattlesnake found in northern Mexico and southwestern United States is an infrequent attacker, but possesses the most deadly venom of all North American pit vipers.<sup>4,63</sup> Its venom lacks anticoagulant and hemorrhagic activity and may cause little, if any, swelling or edema. However, it has marked neurotoxicity and may cause respiratory paralysis and death within five to ten hours in the absence of antivenin and medical care.<sup>4,16,64</sup> Recently, several investigators have reported success in isolating neurotoxic factors in Mojave venom. Tentative data discloses these to be proteins with molecular weights which have differing chemical and pharmacologic properties.<sup>65-67</sup> Since snakebites of other pit viper species cause minor neurologic symptoms after envenomation, it is reasonable to expect that they may possess neurotoxic factors in low concentration. Indeed, purified basic proteins from the venom of the eastern diamondback, Pacific, and timber rattlesnakes have been shown experimentally to possess varying degrees of neurotoxicity.<sup>68-70</sup>

### *Myonecrosis*

Disfigurement and loss of function not uncommonly result from extensive tissue destruction in a

snakebitten extremity. This is primarily because most pit viper venoms possess a potent non-proteolytic protein which is directly myonecrotic.<sup>16,37</sup> A study of electron microscopical (EM) changes has shown marked muscle changes within three hours after prairie rattlesnake envenomation. Focal areas of myonecrosis were abundant. Injured fibers contained dilated sarcoplasmic reticulum, disoriented, coagulated myofilamentous components, and condensed, rounded, enlarged mitochondria. In focal areas of hemorrhage where erythrocytes were tightly packed between muscle fibers, hemolysis was discernible. Disruption of the external lamina and sarcolemma and pronounced degeneration of muscle fibers also developed in these areas.<sup>71</sup> A subsequent EM study using purified myotoxic factor showed that skeletal muscle was altered specifically. The primary site of action was the sarcoplasmic reticulum. These results correlated well with the previous study; however, the purified component did not affect endothelial cells, erythrocytes, or connective tissue cells, and hemorrhage did not occur.<sup>72</sup>

### *Renal Failure*

Shock is probably the most important etiologic factor in acute renal failure which may develop following severe rattlesnake bite.<sup>40</sup> However, some rattlesnake venoms have been found to have direct renal toxicity. A recent study has shown that western diamondback rattlesnake envenomation directly causes ultrastructural damage to the renal corpuscles and proximal convoluted tubules of mice within hours.<sup>73</sup> At present the role of free hemoglobin and myoglobin in snakebite has not been determined. Management of acute renal failure may require hemodialysis for successful treatment.<sup>3,40</sup>

## **Management of Pit Viper Snakebite**

### *First Aid*

Initial first aid measures should include reas-



surance, avoidance of unnecessary exertion, and direct transportation to medical care. To reduce systemic absorption of venom, the affected limb should be immobilized and a mildly constricting tourniquet should be applied 10 to 15 cm proximal to the bite. The tourniquet should obstruct only lymphatic and superficial venous flow.<sup>74</sup> Some authors recommend that it be loosened for 90 seconds every 20 to 30 minutes;<sup>3,13</sup> others disagree, noting that this causes additional venom to be propelled from the limb.<sup>36,74</sup> Complete removal of the tourniquet prior to antivenin therapy is ill advised because of the ensuing rapid systemic absorption of unneutralized venom.<sup>75,76</sup>

Prior to arrival at a medical facility, prompt incision and suction (I and S) should be instituted if feasible. Proper technique calls for superficial longitudinal skin incisions through each fang mark paralleling the direction of entry. These should be approximately 5 mm in length and 2 mm in depth to avoid tendon, nerve, and blood vessel injury. Cruciate incisions are strongly discouraged because they offer no added value and lead to poor wound healing.<sup>74,77</sup> Next, constant suction should be applied for thirty minutes<sup>75</sup> preferably with a rubber suction cup. However, mouth suction has been employed in the absence of oral lesions, as swallowed venom is not harmful.<sup>39</sup> When begun within three minutes after subcutaneous envenomation, almost fifty percent of injected venom can be retrieved.<sup>74,75,78</sup> Venom recovery is much less successful after intramuscular deposit of venom or delayed I and S. Although the wisdom of recommending incision and suction to the layman has been questioned, reviews of large numbers of case reports found actual complications relatively infrequent.<sup>79,80</sup>

### Cryotherapy

Cryotherapy is the practice of packing the site of envenomation in ice or immersing it in ice water for hours to days in order to inhibit tissue destruction.<sup>81,82</sup> Experimentally it has shown no benefit, and in fact causes markedly increased local tissue destruction and prolonged disability.<sup>83-86</sup> Clinically there is a strikingly high rate of amputation in snakebite victims treated with cryotherapy. The use of cryotherapy has repeatedly been con-

demned by experts and has largely been abandoned even by previous advocates.<sup>75,80,87,88</sup>

### Surgery

The role of surgery in the treatment of snakebite is controversial. Early excision of the bite site is performed by some authors in an effort to retrieve injected venom.<sup>76,89</sup> Excision of the bite site one inch equidistant from the fang marks in an elliptical fashion to muscle fascia has been shown experimentally in dogs to recover a substantial amount of venom if performed within two hours of envenomation.<sup>74</sup> However, this method is not suitable for some anatomic sites and there are no data to show greater efficacy than properly performed incision and suction as an adjunct to antivenin therapy. In cases of minimal envenomation this treatment may cause more morbidity than the bite itself.

For the treatment of most rattlesnake bites, some surgeons advocate the early longitudinal excision of necrotic and hemorrhagic tissue down to the fascia which is incised widely if the underlying muscle is edematous, hemorrhagic, or necrotic. Following fasciotomy, the wound is left open or covered with loose gauze pending skin closure five to ten days later.<sup>90-92</sup> Other experts feel that with rare exception surgical intervention during the acute phase of snakebite poisoning is contraindicated.<sup>3,93,94</sup> In cases of severe edema with high compartmental pressures and compromised arterial perfusion, surgery is warranted.<sup>95</sup> Recently, the Doppler ultrasonic flowmeter was successfully used to evaluate arterial flow in a series of antivenin-treated snakebite victims with marked edema and nonpalpable extremity pulses. In these individuals arterial perfusion was demonstrated and fasciotomy was avoided.<sup>96</sup> In cases in which relief of tension is imperative, an effective method consists of multiple short transverse skin incisions three to four inches apart followed by blunt dissection to the deep fascia, which is then incised longitudinally between the transverse incisions. This preserves the skin and subcutaneous tissues as a barrier preventing herniation of nerve, muscle, and tendon which could lead to functional impairment.<sup>95</sup>

Convalescent measures include surgical debridement of vesicles and superficial necrotic tis-



sue three to ten days after the bite. Physical therapy should be instituted early in the recovery from serious bites. Active and passive exercises are recommended the day following initial surgical debridement. Soon thereafter daily exercise of the injured extremity may begin in the whirlpool bath.<sup>63</sup>

### Early Hospital Management

Upon arrival the victim should be reassured and placed at bedrest. Details of the snakebite and a brief medical history noting serious illness, allergy, exposure to horse serum, or previous bites should be followed by a physical examination. Blood pressure, pulse, respiration, level of consciousness, and circumference of the involved limb should be recorded on admission and serially thereafter. A large bore intravenous line for the administration of antivenin and fluids should be established. A complete blood count, platelet count, prothrombin time, partial thromboplastin time, and urinalysis are performed, as well as the determination of blood urea nitrogen, glucose, and electrolyte levels. A type and crossmatch are performed initially because venom may alter the blood, making this technically impossible later.<sup>95</sup> Studies often helpful in significant envenomation include sedimentation rate, fibrinogen, fibrin degradation products, bleeding, clotting, and clot retraction times, serum bilirubin and protein levels, as well as arterial blood gases, and an electrocardiogram. Severe cases may require serial determinations of hemoglobin and hematocrit levels, platelet counts, clotting studies, electrolyte levels, and urinalysis.

Hypotension or shock can usually be managed with intravenous electrolyte solutions, plasma, or plasma expanders, although whole blood and vasopressors may occasionally be indicated.<sup>79</sup> Mojave rattlesnake bites have the potential to paralyze the respiratory system; consequently, equipment for the administration of oxygen, intubation, and assisted ventilation should be readily available. Analgesics, sedatives, and tranquilizers may be used as needed, though caution is urged in cases of potential respiratory depression.

The bite site should be cleaned appropriately and covered with a sterile dressing. If indicated, the affected extremity should be immobilized in a position of function on a well padded splint.<sup>97</sup> A broad spectrum antibiotic, such as tetracycline, erythromycin, or ampicillin, is recommended except in cases of mild snakebite.<sup>13,64</sup> This is reasonable in light of the varied bacterial flora, including histiotoxic Clostridia, found on fangs and in venom, compounded by the ample opportunity for early wound contamination.<sup>13,98</sup> Tetanus prophylaxis should be administered to all snakebite victims. Despite the fact that snake fangs and venom are free of *C. tetani*, clinical tetanus does develop following snakebite, although this is extremely rare.<sup>79,98</sup> This is probably the result of contaminant spores on the skin or clothing. Gas gangrene antitoxin is ineffective and not generally used.<sup>36,64,99</sup>

### Corticosteroids

Corticosteroids are commonly used in addition to antivenin in initial therapy of serious pit viper envenomation.<sup>90,100</sup> However, the benefit remains controversial. In contrast to an earlier report, corticosteroids failed to relieve pain, fever, edema, and the toxic state of envenomation, although they gave the impression of decreased morbidity.<sup>101,102</sup> Reports of experiments in animals have both confirmed<sup>52,61,103</sup> and denied<sup>104,105</sup> the efficacy of corticosteroids in severe envenomation. In a controlled study, prednisone failed to lessen either local or systemic effects of accidental Maylayan pit viper bites in human subjects.<sup>106</sup> At present the value of corticosteroids in managing the shock of severe envenomation is unclear.<sup>3,95</sup> The routine use of hydrocortisone in place of antivenin has been advocated by one author,<sup>92</sup> but is not generally accepted.<sup>107</sup>

Serum sickness may develop within three weeks of antivenin usage. The incidence in one series was 75 percent regardless of the dose or route of administration.<sup>95</sup> Corticosteroids are the standard treatment. They should be given early and continued until symptoms have resolved. Antihistamines are of value only for their sedative and antipruritic effects.<sup>64</sup>



## Antivenin

The use of antivenin is by far the most important factor in successful treatment of crotalid envenomation. Antivenin (Crotalidae) Polyvalent is a lyophilized powder of refined horse serum produced by Wyeth Laboratories. It is produced in horses by injecting them with ever increasing doses of the combined venoms of the eastern diamondback, western diamondback, tropical rattlesnake, and the fer-de-lance. These snake venoms contain the basic antigens of most crotalid venoms. The commercial antivenin has been refined, purified, standardized, and freeze dried. When reconstituted with sterile water, each vial yields 10 ml of concentrated serum.<sup>108</sup> Polyvalent antivenin has been proven very effective in neutralizing venom toxicity of copperheads, cottonmouths, and United States rattlesnakes, as shown in animal studies and clinical trials.<sup>3,52,75,83,99,109</sup> It also offers protection against the fer-de-lance, tropical rattlesnake, cantil, and bushmaster of Central and South America, as well as the habu of Okinawa and the Agkistrodon species of Japan and Korea.<sup>108</sup>

The importance of early administration of an adequate dosage of antivenin has been stressed repeatedly.<sup>36,65,109</sup> The logic behind this is that with time the venom causes destruction of the vascular system in the vicinity of the wound. This effective isolation prevents rapid neutralization of venom when antivenin is given.<sup>36</sup> Equally important is the fact that antivenin does not reverse any local or systemic injury which has already taken place. Animal studies show that by early administration of antivenin both systemic and local damage can largely be prevented.<sup>99,109</sup> The most practical and effective route of administration is by intravenous infusion. Experimentally when I<sup>131</sup> tagged antivenin was injected into dogs one hour after rattlesnake envenomation, less than two percent of the antivenin given intramuscularly was located in the envenomated leg as opposed to 85 percent after intravenous infusion.<sup>75</sup> Antivenin should not be injected locally, especially into a hand or finger as it is ineffective and potentially dangerous.<sup>76</sup>

A generally accepted guide to the initial evaluation of patients bitten by pit vipers has been proposed and subsequently modified.<sup>6,75,102</sup> Grade 0, or zero envenomation, describes an innocuous bite by a known poisonous snake; fang marks and minimal pain may be present. Grade 1, or minimal

envenomation, refers to minimal local edema and moderate pain, without systemic involvement. For grade 2 the characteristics of grade 1 develop more rapidly. In moderate envenomation, weakness, nausea, and vomiting may occur, as may local petechiae, ecchymoses, and a bloody ooze from the fang marks. Grade 3, or severe envenomation, describes the rapid progression through grade 2. Systemic involvement is significant. Grade 4 or very severe envenomation is seen infrequently. It was added to describe the profound changes which can develop after the bite of a large rattlesnake.<sup>75</sup> Marked rapidly spreading edema, which may involve the ipsilateral trunk, follows the sudden onset of local pain. Local ecchymoses, bleb formation, and necrosis develop, though these findings may be absent if the venom was injected intravascularly. Weakness, vertigo, numbness, fasciculations, muscular cramping, and paresthesias may appear within a few minutes. Progressive deterioration with nausea, vomiting, incontinence, hemorrhage, and the signs of shock may be followed by convulsions, coma, and death within one hour.<sup>75</sup> While this grading system provides a helpful framework for evaluating the patient on admission, all clinical and laboratory data, as they become available, should guide therapy.<sup>3</sup> Despite some variation among authors in grading systems and recommended antivenin dosage, certain guidelines emerge. Grade 0 bites do not require antivenin. In minimal envenomation antivenin is sometimes not given. This conservative approach avoids sensitization and appears logical especially when a snake handler has been bitten.<sup>4</sup> In other instances from 10 to 50 ml of antivenin are used. Moderate envenomation may require from 20 to 90 ml of antivenin. Severe and very severe envenomation, grades 3 and 4, require at least 50 to 90 ml, although from 100 to 200 ml are usually given for the highest grade.<sup>4,13,64,79</sup>

As noted previously, antivenin is most effective in preserving life and preventing tissue damage when given early and in adequate dosage. However, unless there is a clear contraindication, it may be used and be expected to provide some benefit when given within the first 12 to 24 hours following rattlesnake bite.<sup>109</sup> Certainly, if the signs and symptoms of envenomation progress after therapy, additional antivenin is indicated. Antivenin may be used in pregnancy, and its use may prevent snakebite-induced abortion.<sup>110</sup> Prior to



therapy, skin testing for allergy to horse serum is performed according to the package insert. When horse serum hypersensitivity is suspected a conjunctival test is performed initially. If testing is negative, cautious intravenous administration of diluted antivenin is started. Epinephrine should be readily available as the patient is observed for signs of impending anaphylaxis. Following a five to ten minute trial, the appropriate amount of antivenin may be given at its reconstituted strength.

In patients with a positive skin or conjunctival test, the relative risks of envenomation versus anaphylaxis must be weighed. Monovalent antivenin prepared from goat serum has been used successfully to overcome this problem, but it is not presently available.<sup>3,111</sup> Desensitization as described in the package insert may be attempted. However, in severe envenomation this method suffers because only small amounts of antivenin can be given when time is a critical factor. To overcome this problem, one technique incorporates 50 to 100 mg diphenhydramine hydrochloride (Benadryl) given intravenously, followed by slow infusion of antivenin for 15 to 20 minutes while the patient is closely observed. If no evidence of anaphylaxis appears, the rate of administration is then gradually increased. A promising method which requires considerable clinical experience and judgment involves titrating antivenin with epinephrine. Two intravenous lines in separate extremities are used. Antivenin is given by one line and epinephrine by the other, which is often also used for administration of electrolyte solutions. Beginning with a few drops of epinephrine, the two are alternated, working toward the point at which epinephrine is not needed with each dose of antivenin.<sup>64</sup>

### Promising Developments

Snakehandlers who have become sensitized to horse serum obviously work with a considerable risk. Attempts have been made to immunize patients against specific rattlesnake venom. Adequate titers of antibodies to the lethal fractions of the venom were produced. Unfortunately, the trials were not successful because nodular lesions

and necrosis developed at the venom injection site.<sup>112</sup> Another report describes a large scale immunization trial of residents on the Amami and Ryukyu Islands against the habu pit viper which is a frequent attacker. The immunization material was prepared by detoxifying habu venom with dihydrothioctic acid. Immunization resulted in varying degrees of local swelling and pain following initial injections and booster injections 6 to 12 months later. Adequate neutralizing antibody titers were produced in the immunized subjects. Case analysis of over 100 subjects who subsequently became habu victims demonstrated the effectiveness of the immunization program in minimizing tissue necrosis, although no reduction in mortality was seen.<sup>113</sup>

Another recent development is the clear demonstration of the antivenom activity of rattlesnake blood plasma. Crude plasma (detoxified by heat treatment) neutralized more rattlesnake venom than an equal volume of horse serum antivenin. This was true even though only a small amount of the total plasma protein has antivenom activity.<sup>114</sup>

Further efforts to isolate and analyze the antivenom factor(s) of rattlesnake plasma are in progress. Conceivably these efforts could lead to an effective antivenin product for use as a possible alternative to horse serum antivenin.

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