Venomous Snakebite: Past, Present, And Future Treatment Options

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Abstract: ***Background:*** **Venomous snakebites continue to cause great morbidity, and treatment options are confusing the attending physician. In the United States approximately 45,000 snakebites occur each year, of which some 8000 are by 20 species of venomous snakes.**

Methods: **Information on venomous snakes and snakebite treatment was gathered from the libraries of the Wilderness Medical Society and the Rocky Mountain Center for Wilderness Medicine in Boise, Idaho (co-supported by the Boise State University and the Family Practice Residency of Idaho), as well as from current literature files of physicians practicing wilderness medicine.**

Results and Conclusions: **Three genera of venomous snakes account for the majority of poisonous snake envenomations in this country. Most hospitalized victims are bitten either by rattlesnakes or copperheads or by unidentified snakes. Most of these bites occur during the summer months and are found on the extremities. Field treatment focuses on the application of a vacuum extractor and transportation to the nearest medical facility. Although constriction band use can be helpful, tourniquets, incision and suction, and ice therapy are contraindicated. Electric shock therapy is of no use and could cause serious injury. Hospital management focuses on rapid clinical evaluation and laboratory tests to establish the degree of envenomation, looking for clotting abnormalities. If envenomation has occurred and is reactive, polyvalent antivenin should be administered according to the degree of envenomation. Errors in diagnosis and treatment result in increased morbidity and put attending physicians at risk for litigation. Prevention remains the most successful approach to snakebite management. (J Am Board Fam Pract 1992; 5:399-405.)**

There are approximately 2700 species of snakes worldwide, of which about 375 are considered venomous.[1] Venomous snakes are responsible for an estimated 75,000 human deaths annually.[2] In the United States approximately 45,000 snakebites occur each year, of which about 8000 are by 20 species of venomous snakes. Deaths do not exceed 10 to 12 per year.[1]

Background

The Snake

Five genera of venomous snakes are indigenous to the United States. Three genera belong to the family Crotalidae: *Crotalus* (15 species of rattlesnakes), *Sistrus* (pygmy rattlesnakes, massasauguas), and *Agkistrodon* (copperheads, cottonmouth moccasins). The other two (*Micruroides*, *Micrurus*) are coral snakes. At least one species of poisonous snake can be found in every state except Alaska, Hawaii, and Maine.[3]

This paper focuses on the treatment of crotalid envenomation. The Crotalidae are distinguished by facial pits, vertical elliptical pupils, a triangular head, a single row of subcaudal scales, and a venom apparatus. Further, the genus *Crotalus* is unique in possessing a rattle composed of loosely articulated, interlocking segments of keratin. Although the purpose of the rattle is a warning, it is not always sounded before a strike.[4]

Pit vipers are named for the paired, short-range, infrared-heat-sensitive pit organs located between the eye and nostril. Sensitive to temperature changes as little as 0.003°C, the organs allow for effective night hunting.[4]

The Venom

The venom apparatus consists of venom glands, ducts, and fangs. The paired venom glands, homologous to human parotid glands, are located behind the eye. They produce and store a quantity of venom relative to the size of the snake. Young snakes have concentrated venom and

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therefore are more toxic for their size. The gland is connected to the venom duct, which pierces the fang sheath and ends opposite the upper fang opening. The fang sheath stores part of the venom for transfer to the fang. The curved hollow fangs are 5 mm to 20 mm long and have an oval-shaped discharge orifice above the tip. Fangs are attached to a rotating maxilla, which enables them to swing from the resting position (folded against the roof of the mouth) to the biting position (perpendicular to the upper jaw). Fangs have a life span of 6 to 10 weeks and then are replaced by reserve fangs. During the change, there is a 4- to 5-day overlap when both can be functional.[4-6]

Venom is a yellow fluid, and its primary function is to immobilize, kill, and digest prey.[6] Venom contains metal ions, biogenic amines, lipids, free amino acids, large and small proteins, polypeptides, and enzymes.[5] Within a species, toxicity can vary with the snake's age, size, health, time of year, time of day, length of hibernation, length of time since last strike, geographical area, and the individual animal. The median lethal dose (LD_{50}) for humans varies considerably among species from a low of 0.23 mg/kg in the Mojave rattlesnake to a high of 10.92 mg/kg for the copperhead.[5]

Snakes can strike from any position and with considerable force. The S-shaped defensive position allows a maximum strike length of up to three-quarters of the snake's length, although usually less than one-half is used.[4] The strike of vipers can be directed in any position including vertically. During the lunge, the mouth is opened, fangs are erected, and if contact is made, the palatine muscles contract to inject the venom. In human victims, venom is usually deposited in dermal or subcutaneous tissues but can be left subfascially.[7] The amount of venom injected in prey is well controlled, but during a defensive bite, the amount might not be so well controlled. Consequently, 20 to 30 percent of Crotalidae bites in humans contain no venom.[8]

Epidemiology

Of hospitalized snakebite victims, 0.5 percent of bites were inflicted by coral snakes, 7.3 percent by cottonmouths, 28.6 percent by copperheads, 29.8 percent by unidentified snakes, and 33 percent by rattlesnakes.[3] Of rattlesnakes, the western diamondback, prairie, Pacific, timber, pygmy, and eastern diamondback were responsible for most bites, with diamondbacks causing the most fatalities.[5]

The highest number of bites occurs in North Carolina, followed in descending order by Arkansas, Texas, Georgia, West Virginia, Mississippi, Louisiana, Oklahoma, and Arizona. Arizona has the highest mortality.[3]

There has been a remarkable change in the demography of snakebites. Early studies (1929) showed 28.3 percent of bites occurring in those aged 1 to 10 years, 43.1 percent in those aged 10 to 30 years, and 28.6 percent in those aged 30 to 80 years. By 1979, 82.5 percent occurred in the 10- to 30-year age group.[5] Early studies showed a 2:1 male-female ratio, but now that ratio is much greater, 7–9:1. Snakes, because they are poikilothermic, are most active in hot weather. As a result, more than 95 percent of bites occur between April and October, and 77 percent occur during daylight hours, times also of greatest human activity.

Ninety-seven percent of bites occur on the extremities.[3] Although the majority historically were found on the lower extremities, snakebites are now found predominantly on the upper extremities (85 percent).[9] This shift in location might reflect a higher number of illegitimate bites, i.e., those bites that occur when victims have chosen to expose themselves to the risk of bite (pet snakes, handling of snakes).[4] Legitimate bites happen when the victim has no intention of indulging in so unnecessary a risk. In 1980, 75 percent of bites were legitimate.[5] In 1988, 43 percent were legitimate, and 28 percent of victims appeared intoxicated.[9]

Field Treatment

Recommended first aid for snakebite has changed through the years but has been generally directed toward removing the venom and preventing spread systemically. Popular past methods have ranged from amputation, alcohol, application of various materials, such as split chickens, scrapings of crocodile teeth, or the saliva of a fasting man, to various plant cures.[4]

Even now controversies exist. Russell[5] summed it up when he said, "I feel the first-aid hubbub has been created and nourished under the old idiom, 'You've got to do something.' "

Controversies center primarily around the uses of tourniquets or constriction bands, incision and suction, cryotherapy, pressure wrappings, and the electric stun gun. Experts do agree, however, on the following recommendations:[10,11]

1. Move the victim out of the snake's territory
2. Place the victim at rest
3. Reassure the victim
4. Cleanse the wound
5. Withhold alcohol and drugs, which could camouflage clinical information
6. Attempt to identify the snake
7. Immobilize the affected part in a functional position
8. Transport to the nearest medical facility for definitive care as quickly as possible

Controversies in Field Management

Tourniquets have long been promoted to prevent the proximal spread of venom but now are no longer recommended. Venom uptake occurs through the lymphatics, yet tourniquets occlude venous and arterial flow, leading to lymphedema, ischemia, necrosis, gangrene, arteriovenous fistula formation, and peripheral neuritis.[2] Further, the release of a tourniquet can lead to rapid dispersal of venom and tissue debris, causing hypotension and shock.[12]

Recently a constriction band to occlude only lymphatic flow has been advocated.[8] The band should be 2.5 to 5.0 cm wide and placed 2 to 4 inches proximal to the bite, allowing enough room to slip one finger beneath. Distal pulses should remain palpable, and capillary refill should be brisk. Decreased venom dispersion has been demonstrated in dogs using this procedure.[2] Intermittent release of the band could propel venom from the bite site and lead to a higher rate of shock. The band can be loosened as swelling occurs.[2]

In the past, incision and suction (oral or mechanical) have been advocated for the removal of the venom pool from the site of deposit. Proponents have based this advice on experimental as well as anecdotal experience.[12] Opponents, however, note several problems:[8,9]

1. No controlled experiments have been done on humans
2. Survival of experimental animals has not been affected
3. The venom pool can occur anywhere within the area of a circle, the radius of which is determined by the length of the fangs, thereby making accuracy of location, direction, and depth of the incision difficult
4. In inexperienced hands great damage can be done to underlying arteries, veins, tendons, and nerves
5. Use of unsterile technique can result in secondary infection
6. Under field conditions, a 5 to 6 percent retrieval is probably realistic

The newest device on the market is a suction pump that delivers approximately 1 atmosphere of negative pressure. If applied within 3 minutes and left on for 30 minutes, it is capable of removing up to 35 percent of venom.[13] Commercial suction devices are readily available (Sawyer Extraction Pump™) and should replace the old method of incision and suction. No incision is necessary with this vacuum device. Human studies are underway. (Michael Callahan, M.S., personal communication, July 1991.)

Cryotherapy, including ice, ice water immersion, and cold sprays, is no longer recommended.[8] Animal studies have shown ice to be effective at retaining venom at the inoculation site, but rapid venom dispersal following removal of the ice has produced shock.[14] Exposure to cold produces vasoconstriction in already compromised tissues; prolonged exposure can result in gangrene, and the victim could require amputation.[8] The American Red Cross and the Committee on Trauma of the American College of Surgeons recommend against its use.[15]

Electric shock treatment for snakebite dates back to 1899 but was most recently popularized after its successful use on the Waoroni Indians of Ecuador.[16] Seventy-eight percent of the tribe, however, were positive for snake venom antibodies as determined by enzyme-linked immunosorbent assay, indicating at least partial immunity.[19] In controlled animal studies, electric shock therapy has shown no effect.[17,18] Venom was not inactivated using electric current from a commercial stun gun directly applied to a rattlesnake venom solution in an electrolysis cell.[20] Electric shock treatment is not recommended and should not replace vacuum suction and rapid

transport to medical facilities for evaluation and antivenin.

Hospital Management

Appropriate hospital management depends on understanding the pathophysiology of envenomation. Lethal venom proteins (low molecular weight peptides) damage endothelial cells and result in increased microangiopathic permeability, edema, hemoconcentration, and lactic acidosis, ultimately causing shock and death. Proteolytic enzymes damage muscle and subcutaneous tissues, and hyaluronidase allows venom to spread through tissues. Phospholipase A_2 provokes histamine release, hemolysis, and necrosis of muscle fibers. Thrombinlike enzymes promote unstable fibrin clot, afibrinogenemia, thrombocytopenia, and an increase in fibrin split products.[21] Platelets are actively sequestered at the bite site and are consumed by intravascular clotting.[22,23]

As a result of the various interactions between venom and host, a fairly typical clinical picture develops. Blood oozing from the wound and numbness around the bite characterize a poisonous snakebite. Swelling, discoloration, ecchymosis, and painful lymph nodes develop. Bullae and blisters associated with bleeding can be severe. Systemic reactions, such as orthostatic changes, paresthesia, nausea, and vomiting, can occur and can be associated with a change in laboratory markers. Increased creatine phosphokinase (CPK), proteinuria, and hematuria can be seen. A marked coagulopathy with hypofibrinogenemia, thrombocytopenia, increased fibrin split products, and a prolongation of prothrombin time (PT) and partial thromboplastin time (PTT) is seen with moderate and severe envenomations (Table 1).[9]

After arrival in the patient care setting, a rapid clinical assessment should be made, the snake should be identified, if possible, and the following laboratory tests should be ordered: complete blood count (CBC), platelet count, fibrinogen, PT, PTT, fibrin split products, blood urea nitrogen (BUN), creatinine, CPK, and urinalysis. The circumference of the extremity at the area of edema and 4 inches proximal to the bite should be measured and remeasured hourly.[9]

The severity of envenomation should be determined. Severity varies somewhat with the amount and kind of venom (species), field treatment, and length of time before medical management. Up to 25 percent of rattlesnake bites contain no venom. Systemic reactions, physical findings, and laboratory abnormalities allow the clinician to establish the degree of envenomation, which facilitates planning for antivenin administration (Table 2).[24 p 491] The bite is graded according to the most severe symptom or sign, and its status will change over time and with antivenin administration.[9]

If no signs or symptoms develop and all laboratory tests are normal after 6 hours, the patient can be reassured that no envenomation has taken place and can be discharged from medical care.

As in all puncture wounds, tetanus immune status should be assessed and brought up to date.

If envenomation has occurred, one then determines the need for antivenin. The amount of (Crotalidae) polyvalent antivenin (Wyeth) administered initially is based on the severity of envenomation (Table 3).[25] The initial dose of antivenin that is decided on from the clinical examination should be repeated every 2 hours until the patient shows clinical improvement (decreased swelling, fasciculations, paresthesia). There is no maximal dose, and therapy is measured by clinical response.[9] To be most effective, antivenin should be given during the first

Table 1. Signs and Symptoms of Envenomation in 227 Patients.*

Symptoms	Percent	Signs	Percent	Abnormal Laboratory Values	Percent
Weakness	80	Fang marks	100	Fibrinogen	35
Nausea, vomiting	70	Swelling	98	Fibrin split products	39
Paresthesias	73	Ecchymoses	27	Prothrombin time	15
Pain	60	Fasciculations	19	Proteinuria	9
		Hypotension	11	Hematuria	8
		Bullae	6		
		Necrosis	4		

*Treated at the Los Angeles County–University of Southern California Medical Center, 1975–1985.[9]

Table 2. Degree of Crotalid Envenomation.

Envenomation	Signs and Symptoms
No envenomation	Fang marks No local or systemic reaction
Minimal	Fang marks No systemic reactions Local swelling
Moderate	Fang marks Swelling and pain beyond the site of bite Systemic reactions: nausea, vomiting, paresthesias, orthostatic changes Laboratory markers change: hemoconcentration, mild coagulation abnormalities
Severe	Fang marks Swelling and pain in the extremity Systemic reactions: nausea, vomiting, paresthesias, orthostatic changes; subcutaneous ecchymosis Laboratory markers change: hemoconcentration, marked coagulopathy with thrombocytopenia, hypofibrinogenemia, prolonged PT and PTT, increased fibrin split products, increased CPK, proteinuria and hematuria[24 p491]

PT = prothrombin time, PTT = partial thromboplastin time, CPK = creatine phosphokinase.

6 hours after a bite. Antivenin administration is useful up to 24 hours after a bite and should be tried even later if coagulation defects continue to cause active hemorrhage.[5,25]

Skin testing for horse serum sensitivity should be performed prior to administration of antivenin, but only for those who will definitely need antivenin. Unnecessary skin testing and antivenin administration sensitizes the patient to these proteins and puts the patient at risk should antivenin be needed at a later date. Delaying testing until the decision is made to use antivenin does not delay antivenin administration.[26] Skin-testing materials are supplied, along with instructions, with each vial of antivenin. Testing should not be done with the more potent antivenin. Acute anaphylaxis should be anticipated even though the test is negative.

Victims who are skin-test-positive can be premedicated intravenously with diphenhydramine, and the antivenin can be administered intravenously along with epinephrine. Diluted antivenin is administered initially, and the dose is gradually increased in strength until a full dose is achieved.

Clinical reactions to antivenin can be both acute and chronic.[27] An immunoglobin E mediated acute anaphylaxis or an anticomplement reaction resembling anaphylaxis can occur, resulting in nausea, vomiting, urticaria, abdominal cramps, hypotension, and bronchospasm, which can be treated with diphenhydramine and epinephrine. Theophylline also might be required. A delayed serum sickness can develop within 1 to 3 weeks and is associated with fever, malaise, edema, and headache. Arthralgia, arthritis, and myalgia are frequent, and lymphadenopathy is one of the most constant features. Symptoms subside rapidly with corticosteroid therapy.[27]

Because snake mouths contain anaerobic and gram-negative organisms, a broad-spectrum antibiotic, such as ceftriaxone, is indicated.[28] The wound should be cultured, and sensitivities should direct future antibiotic treatment. Wounds should be cleaned three times daily with hydrogen peroxide (dilute) after debridement. The limb is immersed for 1 hour three to four times daily in Burrow solution (1:20 solution of aluminum acetate) with oxygen bubbled through an aquarium air stone at 6 L/min (hydro-oxytherapy).[29]

Surgical intervention (fasciotomy) should be entertained only in cases of demonstrated abnormalities in intracompartmental pressures.[5] Most edema is subcutaneous, and fasciotomy is not recommended as primary therapy. Creatine phosphokinase measurements and compartmental pressure monitoring are useful in those cases where doubt exists concerning neurovascular viability of the involved extremity. In animal studies researchers have demonstrated successful reduction of intramuscular pressure and superior survival and preservation of muscle function with antivenin alone when compared with antivenin plus fasciotomy or fasciotomy alone.[7,30]

Table 3. Initial Antivenin ([Crotalidae] Polyvalent [Wyeth]) Dose According to Grade of Severity.

Envenomation	Amount Administered
No envenomation	None
Minimal	0 to 5 vials
Moderate	10 to 20 vials
Severe	20 or more

Place 5 vials (50 mL) in 200 mL of 0.5 normal saline; infuse at 1 mL/min for first 10 minutes.[25]

Deaths are unusual (10 to 12 per year), although death resulted from extended periods of hypotension in many of the nine cases reported from Arizona.[31] More vigorous treatment with intravenous fluids and larger amounts of antivenin might have been helpful.

Numerous assessment and treatment errors have been cited as reasons for increasing morbidity and subsequent litigation[24] (Table 4). Careful study of these oversights is indicated for those physicians caring for patients envenomated by pit vipers.

What can we look forward to in the future to help us manage these complex problems associated with snake envenomation? Work on a new antivenin continues. The active component of crude antivenin is the immunoglobulin (IgG) β-2 fraction, which accounts for only about 20 percent of the protein content of crude antivenin. This active IgG fraction has been extracted using high-yield affinity chromatography.[24] Animal study results confirm the superior efficacy of this product. The next step is to prepare F(ab) fragments of the purified IgG antibody. The smaller fragments are readily distributed to more tissue sites to neutralize venom more effectively and do not cause the acute and delayed side effects of current preparations. The antibody fragments with bound venom are more rapidly excreted through the renal system, rather than by the much slower reticuloendothelial system for larger molecules. Commercial preparation of this potentially beneficial antivenin has not yet been undertaken.

Administration of the antivenin is not innocuous, and early débridement, fasciotomy, and bite excisions leave large wounds with delayed healing. We can only hope for more assistance in the future from these new developments.

Table 4. Errors in Diagnosis and Treatment of Crotalid Envenomation.

Not considering snake venom poisoning in the case of an edematous, ecchymotic extremity in a child who was playing in an area where snakes can be found
Not looking for fang marks at the site of pain
Not considering that envenomation grade can change with time and thus that the clinical status of the patient can worsen over time
Not checking initial coagulation studies and not repeating these studies within 12 hours
Not considering the diagnosis of envomation because a snake was not seen
Not administering antivenin early in the envenomation course in the face of progressive signs and symptoms
Not considering administration of broad-spectrum prophylactic antibiotics
Not realizing that antivenin can successfully reverse coagulopathy more than 24 hours after envenomation
Leaving a constriction band or tourniquet on an extremity for a prolonged period
Not doing a skin test appropriately; that is, not administering the proper dose of horse serum intradermally
Doing a skin test with horse serum when there is no intention to administer antivenin
Performing a fasciotomy without measured substantial elevation in intracompartmental pressure[24]

Prevention

Because treatment of any type is fraught with complications, it makes sense to teach prevention to our patients. The following list summarizes recommendations to prevent snakebites:[4,5,32]

1. Do not place any part of your body where you have not first looked
2. Do not use your hands to lift anything a snake could be under
3. Gather firewood in the daylight
4. Do not place your camp, boots, or clothes near brush, rubbish, rock piles, cave entrances, or swampy areas
5. Do not disturb, capture, or attempt to kill snakes unless you are experienced in handling them
6. Do not move suddenly when you hear a rattlesnake sound; locate the snake and carefully move away. Remember, there could be others nearby
7. Take along a friend when traveling in snake habitat
8. Stay on paths and avoid tall grass and heavy undergrowth
9. Wear adequate protective clothing, including tall boots with pant legs worn on the outside
10. Do not handle freshly killed snakes or the heads of decapitated snakes, which have been known to bite reflexively up to one-half hour after death
11. Carry a flashlight at night
12. Watch for snakes at altitudes of up to 9500 feet in warm climates, up to 11,000 feet in California, and up to 14,500 feet in central Mexico

13. Do not avoid snake habitats out of fear, but be careful
14. Do not keep poisonous snakes as pets or consume alcohol when handling them

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