**Current Concepts**

**Bites of Venomous Snakes**

**Barry S. Gold, M.D., Richard C. Dart, M.D., Ph.D., and Robert A. Barish, M.D.**

Approximately 15 percent of the 3000 species of snakes found worldwide are considered to be dangerous to humans (Table 1). The last comprehensive survey of snake-venom poisoning, completed in the late 1950s, documented an average of 45,000 snakebites annually in the United States, 8000 of them by venomous snakes. During the past three years, the American Association of Poison Control Centers has reported an annual average of 6000 snakebites in the United States, 2000 of them by venomous snakes. Since reporting is not mandatory, many snakebites go unreported. Some victims do not seek treatment, and some treating physicians do not consult with a poison-control center. The true incidence of bites by venomous snakes in the United States is probably 7000 to 8000 per year, of which 5 or 6 result in death. The eastern and western diamondback rattlesnakes account for most fatalities. Deaths typically occur in children, in the elderly, and in victims to whom antivenom is not given, is given after a delay, or is administered in insufficient quantities.

Typically, victims are male and between 17 and 27 years of age. Ninety-eight percent of bites are on extremities, most often the hands or arms, and result from deliberate attempts to handle, harm, or kill the snake. Most bites occur between April and September, when snakes are active and humans are outdoors. Alcohol intoxication of the victim is a factor in many envenomations.

The majority of bites in the United States occur in the southwestern part of the country — in part because of the near-decimation of rattlesnake populations in the eastern United States. Few bites are now associated with agricultural activities, and more bites result from deliberate exposure to captive native and non-native snakes. This article focuses on the management and treatment of bites from venomous snakes encountered in North America; however, the principles of management apply to patients with bites seen in medical facilities worldwide.

**Venomous Snakes in the United States**

Of the approximately 120 species of snakes indigenous to the United States, approximately 20 are venomous. All are pit vipers (rattlesnakes, cottonmouths, and copperheads), with the exception of the coral snake, the only other native venomous snake (Fig. 1). At least one species of venomous snake has been identified in every state except Alaska, Maine, and Hawaii.

Minton described the management of 54 bites from at least 29 species of non-native venomous snakes that were kept in zoos or by amateur or professional collectors. The most common species was the cobra, which is perceived as the quintessential deadly snake. Cobras remain popular with zoos as well as with amateur snake keepers and are readily available in the animal trade.

**Venomous or Nonvenomous?**

Definitive diagnosis of snake-venom poisoning requires positive identification of the snake and clinical manifestations of envenomation. Although the snake is rarely available for identification, it may be brought into the health care facility — alive or dead, whole or in parts — for identification. Snake parts should not be handled directly, since the bite reflex in recently killed or decapitated snakes remains intact, rendering them capable of inflicting a bite. Specific characteristics of pit vipers and nonvenomous snakes aid in their identification (Fig. 2). Herpetologists from zoos or aquariums may be available to assist with positive identification.

In the assessment of a reported bite from a venomous snake, one must distinguish the bite from that of a nonvenomous snake or another animal (e.g., a rat) and from puncture wounds caused by inanimate objects. In the absence of positive identification, objective signs and symptoms of envenomation become the primary focus of diagnosis.

**Systemic Symptoms and Signs**

The most common reaction to snakebite is terror, which may cause nausea, vomiting, diarrhea, syncope,
tachycardia, and cold, clammy skin. Many people believe that any bite from a venomous snake will result in envenomation; in fact, 25 percent of all pit-viper bites are “dry” and do not result in envenomation. Autonomic reactions related to terror must be differentiated from systemic manifestations of envenomation.

Common characteristics of pit-viper bites include the presence of one or more fang marks, including puncture wounds and scratches. Local findings emerge within 30 to 60 minutes after most pit-viper envenomations. These findings include pain, edema, erythema, or ecchymosis at the site of the bite and in adjacent tissues. Localized pain is usually felt immediately and occurs in more than 90 percent of envenomations. An exception is envenomation by the Mojave rattlesnake, which may cause little or no pain. Edema from small-vessel injury usually appears within 30 minutes but may not become apparent for several hours. Bullae (serous or hemorrhagic) may be noted within several hours after the envenomation. There may be signs of lymphangitis, with tender regional lymph nodes and warmth in the injured body part. An ecchymosis may appear over the site of the bite within three to six hours after a bite by a rattlesnake (except the Mojave rattlesnake); ecchymoses are less common after copperhead bites. Early systemic manifestations include nausea, vomiting, perioral paresthesia, tingling of the fingertips and toes, myokymia, lethargy, and weakness. Victims may describe a “rubbery,” “minty,” or “metallic” taste after envenomation by some species of rattlesnake. More severe systemic effects include hypotension, tachypnea, respiratory distress, severe tachycardia, and altered sensorium. Bites by rattlesnakes may result in a consumptive coagulopathy manifested by a prolonged or unmeasurable international normalized ratio (prothrombin time) and activated partial-thromboplastin time, hypofibrinogenemia, the presence of fibrin-degradation products, or a platelet count of less than 20,000 per cubic millimeter.

Pit-viper venom increases the permeability of the capillary membranes, resulting in the extravasation of electrolytes, albumin, and red cells into the envenomated site. This process may also occur in the lungs, myocardium, kidneys, peritoneum, and rarely, the central nervous system. Altered permeability of red-cell membranes may result in hemolysis. Edema, hypoalbuminemia, and hemoconcentration are followed by pooling of blood and fluids in the microcirculation, resulting in hypovolemic shock and lactic acidosis. Renal failure may result from hypotension, intravascular hemolysis, a syndrome resembling disseminated intravascular coagulation, or nephrotoxic effects of components of venom.

General guidelines are available to help the physician assess the severity of envenomations by North American pit vipers (Table 2). The ultimate severity of a bite from any venomous snake depends on the size and species of the snake, the amount and degree of toxicity of the venom injected, the location of the bite, the first-aid treatments provided, the timing of definitive treatment, the presence or absence of underlying medical conditions, and the unique susceptibility of the victim to the venom.7

Coral-snake envenomations produce little or no

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**Table 1. Major Venomous Snakes of the World.**

<table>
<thead>
<tr>
<th>FAMILY</th>
<th>SUBFAMILY</th>
<th>DISTRIBUTION AND EXAMPLES</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viperida</td>
<td>Crotalinae (pit vipers)</td>
<td>North America: crotalus and sistrurus species (rattlesnake), agkistrodon species (cottonmouth, copperhead)</td>
<td>Heat-sensing foramen “pit” between each eye and nostril; elliptical pupils; retractable, canalized fangs</td>
</tr>
<tr>
<td></td>
<td>Viperinae (true vipers)</td>
<td>Africa, Europe, Middle East: Bitis arietans (puff adder), B. gabonica (Gaboon viper), B. nasicornus (rhinoceros-horned vipers)</td>
<td>No heat-sensing pit</td>
</tr>
<tr>
<td>Elapidae</td>
<td></td>
<td>Tropical and warm temperate zones: naja species (cobras), dendroaspis species (mambas), bungarus species (kraits), maticora species (coral snakes), and most venomous snakes of Australia</td>
<td>Short, fixed fangs; venom injected by succession of chewing movements</td>
</tr>
<tr>
<td>Hydrophiidae</td>
<td>Hydrophiinae (true sea snakes)</td>
<td>Indopacific region: Pelamis platurus (pelagic sea snake)</td>
<td>Fangs similar to those of elapidae; highly neurotoxic venom; rarely bite humans</td>
</tr>
</tbody>
</table>

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pain but may result in tremors, marked salivation, and changes in mental status, including drowsiness and euphoria. The neurologic manifestations are usually cranial-nerve palsies evidenced by ptosis, dysarthria, dysphagia, dyspnea, and respiratory paralysis. The onset of neurotoxic effects may be delayed up to 12 hours.\textsuperscript{14} Once manifestations appear, it may not be possible to prevent further effects or reverse the changes that have already occurred.

**PHARMACOLOGY OF VENOMS**

Snake venoms are chemically complex mixtures of proteins ranging from 6 to 100 kD.\textsuperscript{15} Many of the proteins have enzymatic properties (Table 3). Although
enzymes contribute to the deleterious effects of the venom, the lethal components may be the smaller low-molecular-weight polypeptides. The quantity, lethality, and composition vary with the species and age of the snake, the geographic location, and the time of year. Venom is highly stable and is resistant to temperature changes, drying, and drugs. 

Electron microscopy has demonstrated that these proteins damage endothelial cells of vascular walls, causing blebs in the endothelium, dilating the perinuclear space, and breaking down the plasma membrane. The peptides in venom appear to bind to multiple receptor sites in the prey. 

Components of pit-viper venom affect almost ev-

Figure 2. Comparison of Venomous Snakes (Pit Vipers) and Nonvenomous Snakes in the United States.
Table 2. Guidelines for Assessing the Severity of North American Pit-Viper Envenomations.*

<table>
<thead>
<tr>
<th>TYPE OF SIGNS</th>
<th>MINIMAL</th>
<th>MODERATE</th>
<th>SEVERE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>Swelling, erythema, or ecchymosis confined to the site of the bite</td>
<td>Progression of swelling, erythema, or ecchymosis beyond the site of the bite</td>
<td>Rapid swelling, erythema, or ecchymosis involving the entire body part</td>
</tr>
<tr>
<td>Systemic</td>
<td>No systemic signs or symptoms</td>
<td>Non-life-threatening signs and symptoms (nausea, vomiting, perioral paresthesias, myokymia, and mild hypotension)</td>
<td>Markedly severe signs and symptoms (hypotension [systolic blood pressure &lt;80 mm Hg], altered sensorium, tachycardia, tachypnea, and respiratory distress)</td>
</tr>
<tr>
<td>Coagulation</td>
<td>No coagulation abnormalities or other important laboratory abnormalities</td>
<td>Mildly abnormal coagulation profile without clinically significant bleeding; mild abnormalities on other laboratory tests</td>
<td>Markedly abnormal coagulation profile with evidence of bleeding or threat of spontaneous hemorrhage (unmeasurable INR, APTT, and fibrinogen; severe thrombocytopenia with platelet count &lt;20,000 per mm$^3$); results of other laboratory tests may be severely abnormal</td>
</tr>
</tbody>
</table>

*The ultimate grade of severity of any envenomation is determined on the basis of the most severe sign, symptom, or laboratory abnormality (e.g., systolic blood pressure <70 mm Hg in the absence of local swelling should be graded as a severe envenomation). INR denotes international normalized ratio, and APTT activated partial-thromboplastin time.

Table 3. Enzymes in the Venoms of North American Snakes.*

<table>
<thead>
<tr>
<th>ENZYME</th>
<th>CROTALUS</th>
<th>SISTRURUS</th>
<th>AGKISTRODON</th>
<th>MICRURUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteolytic enzymes</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Arginine ester hydrolase</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombin-like enzyme</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collagenase</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyaluronidase</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phospholipase A$_2$(A)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Phospholipase B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphonooesterase</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
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<tr>
<td>Phosphodiesterase</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetylcholinesterase</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RNase</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DNase</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5’-Nucleotidase</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAD-nucleotidase</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>1-Amino acid oxidase</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

*Data are from Russell. A plus sign indicates the presence of the enzyme, and a minus sign its absence; a blank space indicates that it is unknown whether the venom contains the given enzyme.

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Measurements at the same sites should be repeated and documented every 15 to 20 minutes until local progression (swelling) subsides. The time should be marked with an indelible marker at the advancing edge of swelling to serve as an index of local progression and a guide for the administration of antivenom. Base-line laboratory studies should include a complete blood count with platelet count, coagulation profile (international normalized ratio [prothrombin time], activated partial-thromboplastin time, and fibrinogen level), measurement of fibrin degradation products, electrolytes, blood urea nitrogen, and serum creatinine, and urinalysis. Laboratory studies should be repeated after each infusion of antivenom. In addition, testing such as measurement of creatine kinase, blood typing with cross-matching, chest radiography, and electrocardiography may be indicated on the basis of the victim’s age or medical history or the severity of the envenomation.

Since manifestations of envenomation can be delayed, particularly with the bites of Mojave rattlesnakes, it is recommended that all patients with pit viper bites be observed in the emergency department for a minimum of eight hours. If no clinical or laboratory manifestations have presented during this time, the patient may be discharged. A mild envenomation syndrome at one hour could progress to a severe syndrome within several hours and, without continuous observation, lead to death. Monitoring in an intensive care unit is recommended for all patients treated with antivenom. There have been no controlled trials to establish the efficacy of pretreatment with epinephrine, histamine H1- and H2-receptor blockers, or corticosteroids. Although we do not recommend pretreatment, some experts treat routinely.

Envenomations by copperheads are not considered to be as toxic as rattlesnake or cottonmouth bites and rarely require treatment; however, severe envenomations left untreated in children or elderly persons may result in death. Victims of bites by snakes confirmed to be coral snakes should be treated immediately with coral-snake antivenom. However, if the snake has not been found, victims of bites by snakes suspected to be coral snakes should be admitted to the hospital for 12 hours of observation, since the effects of envenomation may develop precipitously hours after a snakebite and are not easily reversed. Local necrosis and coagulopathy are not seen in persons with coral-snake envenomation. Because coral-snake venom has a potent neurotoxic component, monitoring should focus on neuropathic symptoms. Patients require frequent assessment of oxygen saturation and ventilatory function. Ventilatory support may be required.

The bites of non-native venomous snakes present their own challenge. When this type of emergency arises, expert consultation should be sought through a poison-control center or local zoo. Specific antivenoms are available to treat envenomations by most exotic snakes. Guidelines for management of envenomations by snakes native to Africa, Asia, and Central and South America are summarized in Supplementary Appendix 1 (available with the full text of this article at http://www.nejm.org).

ANTIVENOMS

Antivenin (Crotalidae Polyvalent [ACP], Wyeth, was introduced in the United States in 1954 and contributed to a remarkable decrease in the rate of mortality from crotaline (pit-viper) snakebites — from an estimated 5 to 25 percent in the 19th century to less than 0.5 percent today. According to ESI Lederle, the manufacturer, production of antivenoms for the bites of both crotaline and coral snakes is being discontinued. Another antivenom for bites of crotaline snakes, Crotalidae Polyvalent Immune Fab (Ovine) (FabAV), is now available. The two antivenoms are compared in Table 4.

FabAV is a mixed, monospecific, polyvalent antivenom produced by immunizing sheep with the venom of crotaline snakes. In animal testing, the new product was, on average, 5.2 times as potent as ACP (range, 3.0 to 11.7 times as potent).

FabAV has been evaluated in two prospective clinical trials in which a snakebite severity score was used to document objectively the severity of envenomation. In both studies, the mean snakebite severity score improved during the initial infusion of FabAV, and improvement continued through the 12-hour evaluation of efficacy. The decrease in severity was related to improvement in the components of the snakebite severity score that reflect effects on coagulation, the central nervous system, the gastrointestinal system, and the cardiovascular system, each of which showed improvement throughout the evaluation period. Thus, venom-induced abnormalities in these organ systems were reversible. In contrast, the component of the score representing local injury (pain, swelling, and ecchymosis) showed no significant change. This observation may be explained by the fact that such injury involves local hemorrhage, cell swelling, and cell death — processes that cannot be reversed quickly or at all.

An unexpected observation during the first clinical trial was the recurrence of effects of venom after the completion of FabAV treatment. Recurrence was defined as the return of any venom-related effect after that abnormality had resolved. Limb swelling recurred in some patients within 18 hours after treatment ended, and recurrence of hypofibrinogenemia
was found in one patient during a follow-up visit seven days after treatment was completed. On the basis of the findings of the second trial, a dosing schedule was established that effectively prevented recurrence. The schedule requires the administration of a loading dose of FabAV and, once initial control has been achieved, three maintenance doses 6, 12, and 18 hours later.

Safety

Products of animal serum can produce adverse reactions ranging from rash to death. Anaphylaxis or anaphylactoid reactions may occur during infusion or may be delayed, as in serum sickness. According to retrospective reports, the incidence of acute reactions to ACP ranges from 23 percent to 56 percent. The incidence of acute reactions to FabAV in clinical trials was 14 percent.

The incidence of serum sickness in reaction to ACP, according to retrospective reports, ranges from 18 percent to 86 percent. In the only prospective study of reactions to ACP, serum sickness developed in six of eight patients. The overall rate of serum sickness after the administration of FabAV was 16 percent; this rate has been lower in initial clinical experience.

Clinical Use

In the United States, indications for the use of antivenom have not been defined rigorously. After rattlesnake bites, the indications include progressive effects of venom, such as worsening local injury (pain, swelling, and ecchymosis), coagulopathy, or systemic effects (hypotension and altered mental status). Early administration of antivenom binds venom components, thereby reversing some manifestations of envenomation, such as hypotension and coagulopathy, and preventing further progression of local manifestations.

FabAV is administered according to the principle that initial control should be established, followed by scheduled therapy (Fig. 3). Control is defined as the reversal or marked attenuation of all effects of venom. In most reported cases, 8 to 12 vials were sufficient to establish initial control, but 22 vials were needed in one case.

FabAV is a lyophilized antivenom. Each dose must be reconstituted and then diluted to a volume of 250 ml in a crystalloid fluid before being administered. The initial dose is given by slow infusion for the first 10 minutes, and the infusion of the rest of the dose is completed over the course of 1 hour.

**FOLLOW-UP CARE**

An injured extremity should be maintained in a functional position. The wound should be cleansed and covered with a sterile dressing. Blebs, vesicles, and necrotic tissue may require surgical débridement after several days. Assessment and follow-up treatment should be aimed at the preservation of joint mobility and muscle strength.
Figure 3. The Clinical Use of Crotalidae Polyvalent Immune Fab (Ovine) (FabAV).
Each vial is reconstituted and the entire dose diluted to a volume of 250 ml in a crystalloid fluid and administered over the course of one hour.
COMPLICATIONS OF ENVENOMATION AND TREATMENT

It is inadvisable to attempt to correct a coagulopathy until sufficient quantities of neutralizing antivenom have been administered. The consumptive coagulopathy seen with rattlesnake envenomations is unresponsive to heparin and the replacement of coagulation factors (i.e., with fresh-frozen plasma) or other blood components while unneutralized components of venom are circulating. Treatment with coagulation factors or blood components adds more substrate for unneutralized venom, thus increasing the levels of degradation products, which are also anticoagulant.

Opioid analgesics should be avoided if the venom is known to have neurotoxic components (as do, for example, the venoms of coral snakes, Mojave rattlesnakes, and cobras), so as to avoid masking neurotoxic effects. Wound infections are rare after pit-viper bites; therefore, the prophylactic use of antibiotics is not recommended. Antibiotics should be administered if there is clinical and microbiologic evidence of wound infection.38

Severe envenomations by rattlesnakes may be associated with increased compartment pressure. The local reaction to envenomation, manifested as marked swelling, tenderness, tenseness, hyposthesia, and pain, may mimic a true compartment syndrome. In cases of suspected compartment syndrome, clinical diagnosis requires objective evidence of elevations in compartment pressure to more than 30 mm Hg. If compartment pressure is elevated, we recommend elevation of the bitten body part in conjunction with the administration of an additional four to six vials of FabAV over the course of one hour. Compartment syndrome in patients with envenomation by a rattlesnake is thought to be caused by myonecrosis related to the action of the venom components rather than to elevated compartment pressure that causes vascular insufficiency.36 Additional antivenom should effectively neutralize the venom components, thereby reducing compartment pressure.

If these measures fail to reduce compartment pressure within four hours and the patient has circulatory compromise, fasciotomy may be required to lower the compartment pressure.37 There is some debate regarding the use of fasciotomy, and evidence regarding its efficacy is sparse.35 It does not prevent the progression of envenomation, treat coagulopathy, or obviate the need for additional antivenom, yet it is considered to be routine practice in some areas of the United States. Fasciotomy may substantially lengthen the course of treatment and may be associated with nerve damage, disfiguring scars, contractures, and loss of limb function.19

Serum sickness is a type III hypersensitivity reaction that may occur 7 to 21 days after the completion of treatment. It is manifested as fever, rash, arthralgias, and lymphadenopathy and responds well to a tapering course of oral prednisone, starting at a dose of 60 mg per day.

ASSISTANCE IN MANAGING BITES OF VENOMOUS SNAKES

A regional poison-control center (which may be reached through the national hotline at 800-222-1222) should be contacted for assistance in treating patients who present after being bitten by a native or exotic venomous snake. These centers are staffed by persons who have been trained in all types of poisoning and maintain a list of consulting physicians throughout the United States who are experienced in the management and treatment of bites from venomous snakes.

Snake-venom poisoning is a complex medical emergency that not only involves the site of the bite but may involve multiple organ systems as well.7 The dynamic and erratic course of the envenomation syndrome requires close monitoring of the patient and careful clinical decision making.28 Consultation with a physician who is experienced in the diagnosis and treatment of bites of venomous snakes is essential.

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REFERENCES