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North American snake envenomation: diagnosis, treatment, and management

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Few animals have captured the human imagination more than the snake. Beginning with the Garden of Eden, world cultures have cast the snake in symbolic roles. It has been seen as a symbol of life, love, health, virtue, wealth, procreation, wisdom, and immortality. Alternatively, it has represented death, hate, disease, sin, and poverty. Humans can become obsessed with snakes—we fear them, worship them, and exploit them—but perhaps it is our fear of being bitten that lies at the core of our obsession. This obsession leads to one of the most multifaceted problems confronted by physicians—the management and treatment of individuals bitten by venomous snakes. Snake venom poisoning is a complex medical emergency that has local effects at the bite site and can affect every major organ system primarily or secondarily.

Epidemiology

Approximately 15% of the 3000 species of snakes found worldwide are considered dangerous to humans [1]. The commonly encountered venomous species of snakes are members of several families. The largest family is the Viperidae, which includes the African, European, and Middle-Eastern vipers. Within this family is the subfamily of Crotalinae (pit vipers), comprising the rattlesnakes, cottonmouths, and copperheads of North

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America, the fer-de-lances of Central and South America, and the Asiatic pit vipers. The other major family is the Elapidae, consisting of cobras, mambas, kraits, coral snakes, and all venomous snakes of Australia. Less frequently encountered are the Hydrophidae (true sea snakes) and the Lacticaudidae (sea kraits) families and members of the Colubridae, including the boomslang, bird snake, and keelback [2].

Approximately 45,000 snakebites occur annually in the United States, 8000 of which are from venomous snakes [3]. Envenomation can cause morbidity of significant extent and duration [4] and accounts for five to six deaths per year [5]. Deaths typically occur in children, the elderly, and in those for whom treatment is not given, is postponed, or is administered in insufficient quantities. Deaths are also seen among members of fundamentalist religious sects who handle venomous snakes during religious rites [6].

The victim profile has changed little since the late 1950s, when Parrish conducted his snake venom poisoning survey of the United States [3]. The majority of victims remain men between the ages of 17 and 27 years [7]. Alcohol intoxication is a contributing factor in many envenomations [7]. More than 95% of the bites are on extremities, and most occur between April and October, the peak months being July and August. These months coincide with the times when native snakes are active and humans are more prone to be bitten during outdoor activities.

Parrish found that North Carolina, Arkansas, Texas, Georgia, West Virginia, Mississippi, Louisiana, and Oklahoma had the highest bite rates per 100,000 population. In the decades since his study there has been a shift in prevalence toward the southwestern United States. This change is attributed to migration of the population westward along with the near-decimation of rattlesnake populations in the East and Northeast. Other trends are a lower percentage of bites associated with agriculture and a higher percentage of bites from captive native and nonnative snakes [6].

Venomous snakes in the United States

Only 25 of the more than 120 species of snakes indigenous to the United States are venomous [8]. The majority of these snakes belong to the subfamily Crotalinae (pit vipers: rattlesnakes, cottonmouths, and copperheads [Fig. 1]). The coral snake (Elapidae) is the only other native venomous snake. At least one species of indigenous poisonous snake has been identified in every state except Alaska, Maine, and Hawaii [3]. Exotic venomous snakes found in zoos, schools, snake farms, and amateur and professional collections account for an increasing number of bites [9].

*Pit vipers (*Crotalids*)*

Pit vipers are named for the heat-sensitive foramen (pit) located between each eye and nostril (Fig. 2), which senses the location and presence of

warm-blooded prey or predators and guides the direction of the strike. Pit vipers have a triangular head, owing to the venom glands in both temporal regions. The pupils are elliptic. These snakes have two curved, canalized fangs, each surrounded by a membranous sheath. The fangs are long and moveable and retract posteriorly when the mouth is closed. At least three pairs of replacement fangs lie behind each functional fang. These fangs are in various stages of development and ready to move forward to replace shed or broken fangs. Fangs are replaced through the life cycle of the snake; consequently, no fangless or defanged snake remains harmless indefinitely [6]. Based on their ability to sense the size of their prey using their pit, venomous snakes can regulate the amount of venom they excrete. The amount of venom discharged in defensive bites is less controlled [1].

*Rattlesnakes (*Crotalus *and* Sistrurus*)*

Sixteen species of rattlesnakes have been identified, making up two genera—*Crotalus* and *Sistrurus*. The genus *Crotalus* includes the larger species; *Sistrurus* includes the smaller pygmy rattlesnakes and massasaugas. The cardinal characteristic of the rattlesnake is the tail rattle, which is formed by a group of interlocking keratin rings that vibrate against each other, producing the characteristic buzzing sound when the snake is aroused. It is speculated that the rattle functions as a warning device to predators [10]. Throughout history, the myth has persisted that rattlesnakes always "rattle" before striking. In fact, many strikes occur without warning. Juvenile rattlesnakes might lack functional rattle segments and are often soundless.

Rattlesnakes are native to every state with the exception of Alaska, Hawaii, Maine, and the District of Columbia. Most bites result from the eastern diamondback rattlesnake (*C adamanteus*), the western diamondback rattlesnake (*C atrox*), the prairie and Pacific rattlesnakes (*C viridis*), the timber rattlesnake (*C horridus*), and the pygmy rattlesnake (*S miliarius*). The eastern and western diamondback rattlesnakes account for the most fatalities [6].

*Moccasins (*Agkistrodon*)*

There are two species of moccasins—the cottonmouth (*A piscivorus*) and the copperhead (*A contortrix*). Native to the southeastern and south central sections of the country, the cottonmouth is a semiaquatic snake that can be identified by dark olive to black coloring. It derives its descriptive name from the pale white color of the oral mucosa, which is highly visible when the mouth is fully opened. The cottonmouth is considered to be pugnacious and is capable of biting while submerged.

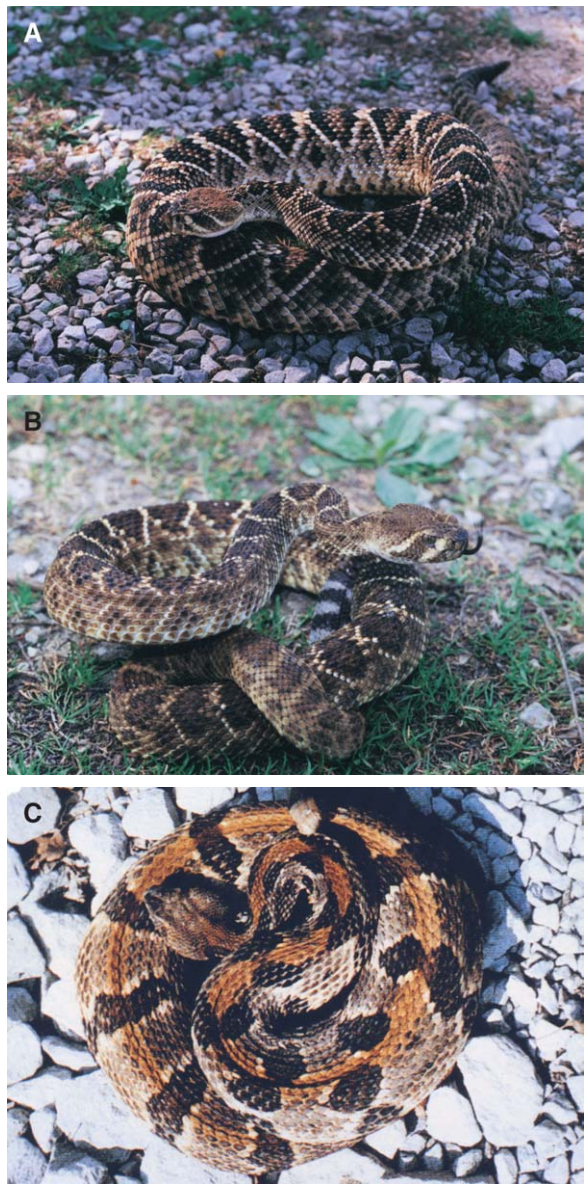

Fig. 1. Venomous snakes of North America. (*A*) Eastern diamondback rattlesnake (*Crotalus adamanteus*). (*B*) Western diamondback rattlesnake (*C atrox*). (*C*) Timber rattlesnake (*C horridus*). (*D*) Cottonmouth (*Agkistrodon piscivorus*). (*E*) Copperhead (*A contortix*). (*F*) Eastern coral snake (*Micrurus fulvius fulvius*). (*From* Gold BS, Dart RC, Barish RA. Bites of venomous snakes. N Engl J Med 2002;347(5):347–58; with permission; Panels *A*, *B*, and *F* courtesy of Kristen Wiley, Kentucky Reptile Zoo, Slade, Kentucky.)

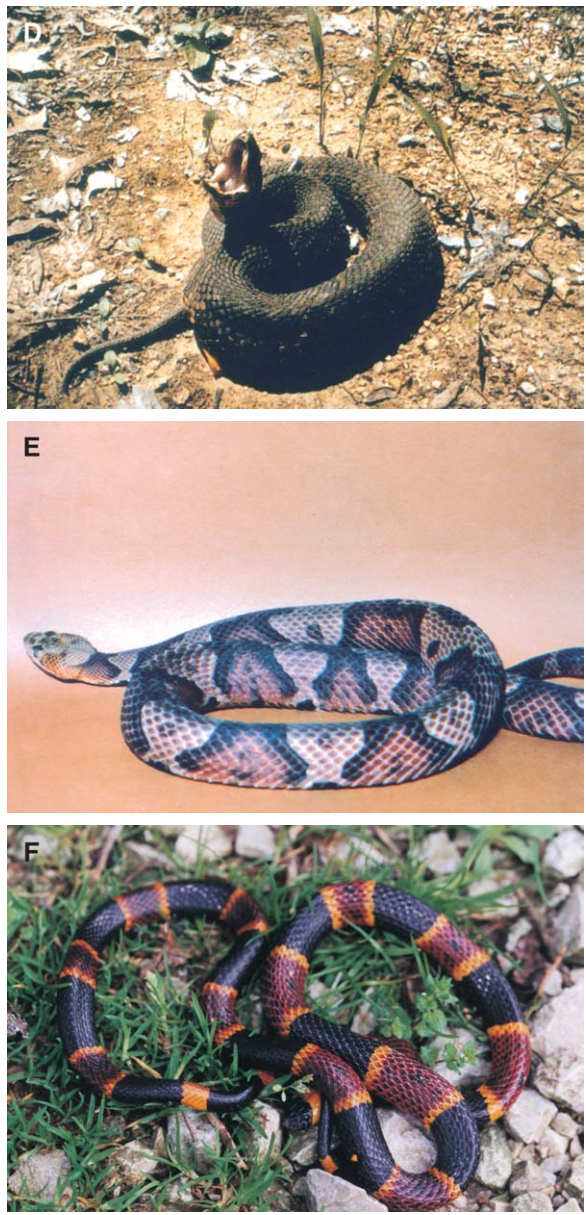

Fig. 1 (*continued*)

The copperhead can be identified by hourglass or inverted "y" markings on the body and a reddish brown to copper-colored head. These snakes inhabit the eastern two thirds of the country, sometimes residing within city limits. Copperhead bites are not considered to be as toxic as rattlesnake or

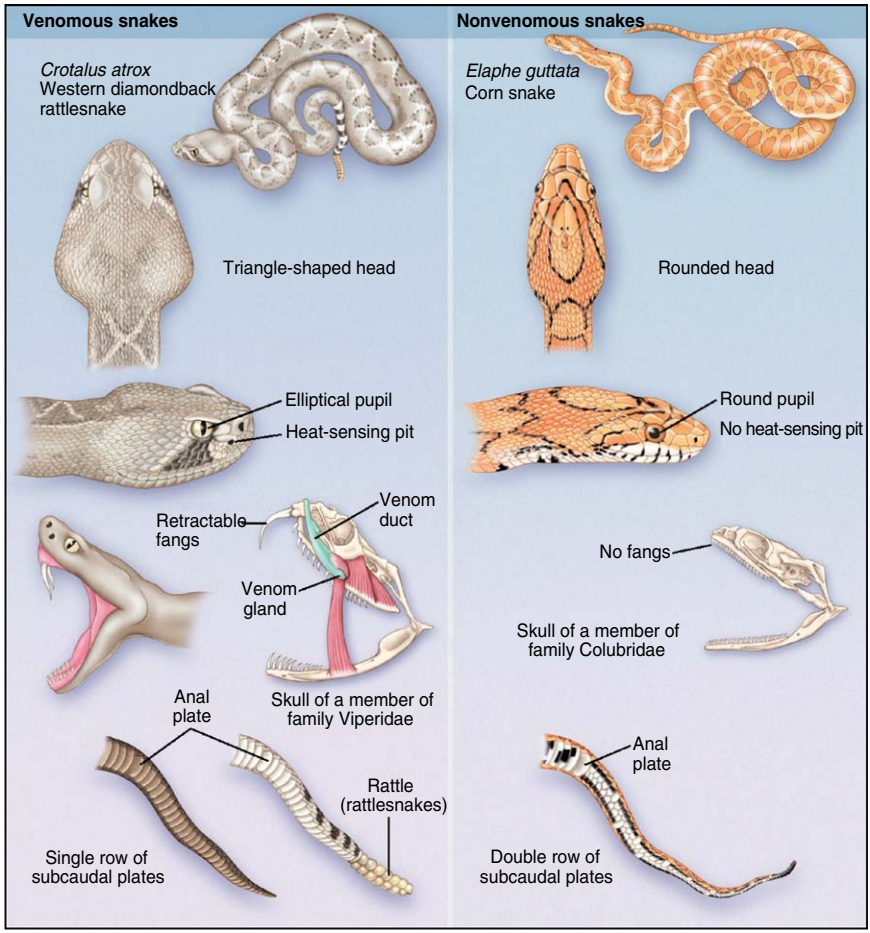

Fig. 2. Comparison of venomous snakes (pit vipers) and nonvenomous snakes in the United States. (*From* Gold BS, Dart RC, Barish RA. Bites of venomous snakes. N Engl J Med 2002;347(5):347–58; with permission.)

cottonmouth bites and rarely require treatment; however, severe envenomations left untreated in children and the elderly can result in death.

*Coral snakes (*Micruroides *and* Micrurus*)*

The coral snakes are members of the Elapidae family, with two genera of coral snake native to the United States, *Micruroides* and *Micrurus*. The Arizona or Sonoran coral snake (*Micruroides euryxanthus*), a small snake with an average length of 15 to 20 inches, is found in Arizona and New Mexico. The eastern coral snake (*Micrurus fulvius fulvius*) and the Texas coral snake (*Micrurus fulvius tenere*) are larger, with average lengths of 20 to

45 inches. They are native from North Carolina southward to Florida and through the Gulf states to Texas.

Although various color phases such as black and albino have been identified, coral snakes in the United States can be identified by characteristic broad red and black bands separated by yellow (or cream) bands on their bodies. A number of harmless snakes can mimic the coral snake, which has given rise to the rhyme "red on yellow will kill a fellow; red on black venom lack." This rhyme applies only to coral snakes native to the United States. Coral snakes in the United States possess black snouts and round pupils but lack facial pits. Their fangs are short and fixed, and they inject their venom by a succession of chewing movements. These snakes are shy, secretive, and nocturnal. They are not aggressive and account for only 20 to 25 bites per year [11].

Nonnative venomous snakes (exotic species)

Because of the increasing popularity of herpetoculture as a business and a hobby, the incidence of snakebites inflicted by nonnative venomous species in the United States is increasing. Between 1977 and 1995 Minton reported that he consulted on 54 cases of bites from nonnative venomous snakes involving at least 29 species [12]. The most common species was the cobra, which constituted 40% of the group [12]. The popularity of the cobra seems to arise from its perceived reputation as the ultimate deadly snake. They are popular with zoos and amateur snake keepers and are readily available in the animal trade.

Cobras are members of the Elapidae family. The majority of cobras belong to the genus *Naja,* of which the monocellate cobra (*Naja kaouthia*) appears to be the species that is most available in the United States. Other popular species include the Chinese cobra (*N atra*), the Indian cobra (*N naja*), and the African Cape cobra (*N nivea*). Cobras have a pair of short, fixed fangs in the front of their mouth, which allows them to bite a victim and maintain a hold while injecting venom in a succession of chewing movements.

Other popular species of nonnative snake are the African vipers belonging to the family Viperidae. These snakes are in the genus *Bitis* and include the puff adder (*B arietans*), the gaboon viper (*B gabonica*), and the rhinoceros viper (*B nasicornis*). These large, heavy snakes tend to have colorful markings, which make them popular in zoos and with amateur collectors. The brightly colored, nonnative, arboreal vipers are also commonly maintained in captivity.

Venomous or nonvenomous?

The essential components of a definitive diagnosis of snake venom poisoning are positive identification of the snake and clinical manifestations

of envenomation. In the assessment of a reported venomous snakebite, one must distinguish the bite from one from a nonvenomous snake, bites from other animals (eg, rat), and puncture wounds caused by inanimate objects. The victim or companion might be able to make a positive identification. The snake—alive, dead, or in parts—can be brought in with the victim. It is important to remember when handling recently killed or decapitated snakes that the bite reflex remains active for several minutes, rendering the snake capable of inflicting a bite [13]. Snake parts should not be handled directly; if possible they should be placed in a canvas bag or container. Expert assistance for establishing a positive identification is available by contacting herpetologists from zoos or aquaria. About 25% of all pit viper bites and 50% of all coral snakebites in the United States do not result in envenomation and are considered "dry" bites [14]. In the absence of positive identification, objective symptoms and signs of an envenomation become the focus of diagnosis.

Systemic symptoms and signs

The most common reaction to any snakebite is impending doom. Many people believe that bites from a venomous snake inevitably will result in death. Consequently, victims might appear emotionally unstable and exhibit extreme lethargy and withdrawal. Fear might cause symptoms such as nausea, vomiting, diarrhea, fainting, tachycardia, and cold, clammy skin. Thus, it is important to differentiate these autonomic reactions from systemic symptoms and signs resulting from the envenomation. Confusion could lead to unwarranted treatment.

The primary local clinical findings after most pit viper bites emerge within 30 to 60 minutes. Common characteristics of crotaline envenomation include the presence of one or more fang marks—including evidence of puncture wounds and scratches, pain, edema, erythema, or ecchymosis of the bite site and adjacent tissues. Localized burning pain and early progressive edema around the bite site are common. Pain, which is usually evident within 5 minutes following envenomation, is probably the result of edema, swelling, and the release of substance P. Pain is present in more than 90% of pit viper envenomations, with the exception of bites from the Mojave rattlesnake (*Crotalus scutulatus*), which might cause little or no pain. Edema, both proximal and distal to the bite site, appears within 10 minutes, is rarely delayed more than 30 minutes following the envenomation (but occasionally does not appear for several hours), and is the result of small vessel and capillary injury. Occasionally, bullae might be noted within several hours of the envenomation and can be serous or hemorrhagic. There might be signs of lymphangitis with tender regional lymph nodes along with increased temperature over the injured part. Ecchymosis might appear over the bite site within 3 to 6 hours. Ecchymosis is most severe following bites by

eastern and western diamondbacks and prairie, Pacific, and timber rattlesnakes. It is less severe after copperhead and cottonmouth bites. Systemic manifestations usually include nausea, vomiting, perioral paresthesia, tingling of the fingertips and toes, fasciculations, lethargy, and weakness. Subjective complaints of a rubbery, minty, or metallic taste are frequent after envenomation by some larger species of rattlesnake. More severe systemic effects include altered mental status, severe tachycardia, tachypnea, respiratory distress, and hypotension (systolic blood pressure <80 mmHg). Coagulopathy frequently occurs following bites by rattlesnakes and can result in a consumptive coagulopathy manifested by hypofibrinogenemia, prolonged prothrombin time (PT), decreased or unmeasurable activated partial thromboplastin time (A-PTT) with a platelet count of less than $20{,}000/mm^3$, or a combination of these signs. Pit viper venom alters capillary membrane permeability, resulting in loss of electrolytes, albumin, and red blood cells into the bite site, manifested clinically as edema and erythema. Altered red blood cell membrane permeability can cause hemolysis. Initially, hypoalbuminemia and hemoconcentration occur, followed by pooling of blood and fluids in the microvasculature, resulting in hypovolemic shock and acidosis; however, this process can occur concomitantly in other organs such as the lungs, myocardium, kidneys, peritoneum, and, rarely, central nervous system. Renal failure might be secondary to hypotension, hemolysis, consumptive coagulopathy, or the nephrotoxic effects of the venom components themselves.

An essential element in the evaluation of snakebites by North American pit vipers is assessing the severity of the envenomation (Box 1). Multiple factors influence the severity of any venomous snakebite: the species and size of the snake, the amount and toxicity of the venom injected, the location of the bite, first aid treatments performed, timing of definitive treatment, comorbid conditions, and the victim's unique susceptibility to the venom [6].

Coral snake envenomations produce a paucity of local effects, but there might be tremors, marked salivation, and altered sensorium, including drowsiness and euphoria. The neurologic signs are usually cranial nerve palsies manifested by ptosis, dysarthria, dysphagia, dyspnea, and seizures. The ultimate cause of death is paralysis of the respiratory musculature. The onset of clinical manifestations might be delayed up to 12 hours following the envenomation [15]. Once signs and symptoms have appeared, prevention of neurotoxicity and reversal of changes that have already occurred might not be possible and might require airway management.

Pharmacology of venoms

Snake venoms are chemically complex mixtures of proteins, many of which possess enzymatic properties. These enzymes contribute to the deleterious effects of the venom, but the lethal components might be small

Box 1. Guidelines for assessing severity of North American pit viper envenomations*

Minimal envenomation
Local: swelling, erythema, and/or ecchymosis confined to the site of the bite
Systemic: no systemic signs or symptoms
Coagulation: no coagulation abnormalities; no other significant laboratory abnormalities

Moderate envenomation
Local: progression of swelling, erythema, and/or ecchymosis beyond the site of the bite
Systemic: non–life-threatening signs/symptoms (nausea, vomiting, perioral paresthesias, fasciculations, mild hypotension)
Coagulation: mildly abnormal coagulation profile without clinically significant bleeding; mild abnormalities on other laboratory tests

Severe envenomation
Local: rapid swelling, erythema, and/or ecchymosis involving the entire extremity
Systemic: markedly severe signs and symptoms (hypotension [systolic blood pressure <80 mmHg], altered sensorium, tachycardia, tachypnea, or respiratory distress)
Coagulation: markedly abnormal coagulation profile with evidence of bleeding or threat of spontaneous hemorrhage (markedly prolonged prothrombin time, unmeasurable activated partial thromboplastin time, severe hypofibrinogenemia, severe thrombocytopenia with platelet count <20,000/mm^3, and the presence of fibrin degradation products)

*The ultimate grade of severity of any envenomation is determined on the basis of the most severe sign, symptom, or laboratory abnormality (eg, systolic blood pressure <80 mmHg in the absence of local swelling should be graded as a severe envenomation).

Adapted from Gold BS, Dart RC, Barish RA. Bites of venomous snakes. N Engl J Med 2002;347(5):347–56; with permission.

low-molecular-weight polypeptides. Quantity, lethality, and composition vary with the age and species of the snake and with the time of year, the geographic location, and the snake's diet. Venom is a highly stable substance, refractory to temperature fluctuations, desiccation, and drugs [16]. Venom proteins include transaminase, hyaluronidase, phospholipase,

phosphodiesterase, and endonucleases and range in molecular weight from 6000 to 100,000 daltons (Table 1) [17]. Electron microscopy shows that these proteins damage capillary endothelium, resulting in blebs, dilation of the perinuclear space, and plasma membrane destruction [18]. Plasma and erythrocytes leak into the tissues, resulting in massive accumulation of fluid in intracellular spaces, which is manifested as edema and erythema or ecchymoses. Plasma loss reduces the circulating blood volume and leads to hypovolemic shock, hemoconcentration, and lactic acidosis. The peptides of snake venom appear to bind to multiple receptor sites in the prey [19].

Crotaline venom components have the most deleterious effects on the cardiovascular, respiratory, hematologic, respiratory, and nervous systems. Consequently, attempting to label a venom as a "neurotoxin," "hemotoxin," "cardiotoxin," or "myotoxin" is misleading [20].

Treatment

Field and prehospital treatment

Following a bite from a venomous snake, the victim should be moved beyond striking distance, placed at rest, reassured, kept warm, and transported to the nearest medical facility as soon as possible. The injured area should be immobilized in a functional position below the level of the

Table 1
Enzymes in North American snake venoms

	Crotalus	*Sistrurus*	*Agkistrodon*	*Micrurus*
Proteolytic enzymes	+	+	+	0
Arginine ester hydrolase	+	NK	+	NK
Thrombin-like enzyme	+	NK	+	NK
Collagenase	+	NK	+	NK
Hyaluronidase	+	NK	+	NK
Phospholipase A_2(A)	+	NK	+	+
Phospholipase B	?	NK	NK	NK
Phosphomonoesterase	+	NK	+	NK
Phosphodiesterase	+	+	+	NK
Acetylcholinesterase	0	0	0	NK
Rnase	+	NK	NK	NK
Dnase	+	NK	NK	NK
5′-nucleotidase	+	NK	+	NK
NAD-nucleotidase	0	0	+	NK
L-amino acid oxidase	+	+	+	NK
Lactate dehydrogenase	NK	NK	NK	NK

NK, not known.

From Russell FE. Snake venom poisoning. Great Neck (NY): Scholium International; 1983. p. 179; with permission.

Modified from Gold BS, Dart RC, Barish RA. Bites of venomous snakes. N Engl J Med 2002;347(5):347–56.

heart. All rings, watches, and constrictive clothing should be removed. No stimulants such as caffeine or alcohol should be administered. Signs and symptoms of an envenomation might not develop immediately, which makes transportation to the nearest medical facility essential to ensure prompt and ongoing evaluation and necessary treatment if envenomation has occurred. Previously recommended first aid measures involving the use of tourniquets, incision and suction, cryotherapy, and electric shock therapy are strongly discouraged [6,21]. Paramedical personnel should focus treatment on support of airway/breathing, circulation, administration of oxygen, establishment of intravenous (IV) access on the contralateral side, and transportation of the victim to the nearest medical facility. Tourniquets that are not producing limb-threatening ischemia and constriction bands that have been placed as first aid should be left in place until the victim is evaluated in the hospital and, if necessary, antivenom infusion has been initiated.

Emergency department treatment

The principles of treatment of persons bitten by venomous snakes are aggressive supportive care and administration of antivenom. When airway, breathing, and circulation have been established, a rapid, detailed history should be obtained. Key points include the time of the bite, a general description of the snake, first aid measures employed, comorbid medical conditions, drug/food allergies, allergy to horse or sheep products, and history of snakebites and consequent therapy. The physical examination should be complete, with special attention paid to the cardiovascular, pulmonary, and neurologic systems. The bite site should be examined for fang/tooth marks and scratches. Baseline circumferential measurements at several points above and below the bite site should be documented. These measurements should be repeated and documented every 15 to 30 minutes throughout treatment. Any advancing edge of swelling should be marked with the time with an indelible marker. This mark serves as an index of local progression and a guide for additional antivenom administration [20]. Baseline laboratory studies should include complete blood count with platelet count, coagulation profile (PT, A-PTT, fibrinogen), electrolytes, blood urea nitrogen, serum creatinine, and urinalysis. Additionally, testing such as creatinine kinase, blood typing with crossmatching, chest radiography, and electrocardiography might be indicated based on age, comorbid history, or severity of the envenomation [14]. Tetanus prophylaxis/immunization should be administered based on the patient's history. It should be emphasized that a bite might appear to be innocuous at first. An essentially unremarkable presenting physical and laboratory examination is not a reliable indicator of the severity of the envenomation. Because the onset of signs and symptoms can be delayed, all crotaline snakebite patients should be observed in the emergency department for a minimum of 8 hours

[21], similar to patients who have other diseases for which observational medicine is warranted. If no clinical or laboratory abnormalities are observed during this time, the patient can be discharged. It is important to recognize that a mild envenomation syndrome at 1 hour could progress to severe within several hours and lead to death without continuous observation for progression and appropriate treatment. Therefore, monitoring in an intensive care unit (ICU) is recommended for all patients treated with antivenom. There have been no controlled trials to establish efficacy of pretreatment with histamine H_2 receptor blockers or corticosteroids in the acute phase of treatment. One controlled trial established the efficacy of pretreatment with epinephrine [22]. Mild sedation with a benzodiazepine is recommended for moderate to severe envenomations. Analgesia should be based on the severity of the pain. Pain can usually be managed with opioid analgesics. Aspirin and other nonsteroidal anti-inflammatory drugs, which can augment bleeding, should be avoided. Sedation and opioids should be avoided in all victims of coral snake envenomations and in Mojave and eastern diamondback rattlesnake poisonings because of their potent neurotoxic venom effects.

The same general protocol applies to coral snakebite victims. For a confirmed coral snakebite, treatment should be initiated immediately. Once the neurotoxic effects of coral snake envenomation have become manifest, they are difficult to reverse with antivenom and can last 3 to 6 days despite treatment. If the snake is not recovered but coral snakebite is suspected, the individual should be admitted for 24 to 48 hours of observation because the venom effects can develop hours after envenomation and are not reversed easily. Because of the potent neurotoxic component, ventilatory support might be required. These patients require frequent monitoring of oxygen saturation and baseline and serial pulmonary function, with special attention paid to peak flow and vital capacity.

Antivenoms

Two commercial antivenoms are available for the treatment of North American pit viper envenomations. Since 1954 Wyeth Laboratories (Philadelphia) has produced Antivenin (Crotalidae) Polyvalent (ACP) (equine), which contributed to a marked decrease in mortality rate from crotaline snakebite—from 5% to 25% in the nineteenth century to less than 0.5% for patients treated with antivenom in a health care facility [19]. In October 2000 a new antivenom for crotaline snakebite, Crotalidae Polyvalent Immune Fab (Ovine)/(CroFab™, Savage Laboratories, Melville, New York), was approved by the U.S. Food and Drug Administration. Characteristics of the two antivenoms are compared in Table 2. Current supplies of Wyeth antivenom for coral snakebite are expected to last at least 2 years. Foreign companies that produce antivenoms for nonindigenous coral snakes are investigating opportunities to import their products.

Table 2
Comparison of Antivenin (Crotalidae) Polyvalent and Crotalidae Polyvalent Immune Fab (Ovine)

	Antivenin (Crotalidae) Polyvalent	Crotalidae Polyvalent Immune Fab (Ovine)
Animal source	Horse	Sheep
Venoms used to immunize animal	*Crotalus adamanteus* (eastern diamondback) *C atrox* (western diamondback) *C durissus terrificus* (tropical rattlesnake) *Bothrops atrox* (fer-de-lance)	*C adamanteus* (eastern diamondback) *C atrox* (western diamondback) *C scutulatus* (Mojave) *Agkistrodon piscivorus* (cottonmouth)
Immunoglobulin (molecular weight)	IgG (150,000 daltons)	Fab (50,000 daltons)
Purification method	Ammonium sulfate precipitation	Sodium sulfate precipitation and affinity purification
Constituents		
Total protein	2.1 g/vial	<1.5 g/vial
Albumin	Albumin 120 mg/vial (6% w/w)	Albumin (<0.5% w/w)
Total antibody	IgG (18.9% w/w)	Fab (>85% w/w) Fc (<3% w/w)
Color	Yellow	White

w/w, weight per weight.

From Gold BS, Dart, RC, Barish RA. Bites of venomous snakes. N Engl J Med 2002;347(5):347–58; with permission.

FabAV is an ovine immune serum produced by immunizing sheep with four species of crotaline venom. The serum is then harvested and digested with papain to produce antibody fragments, Fab and Fc. The Fc portion is eliminated during purification, yielding two individual Fab fragments that are combined to form FabAV. The new product was an average of 5.2 times (range 3.0–11.7) more potent than ACP when tested in animals using 14 different crotaline venoms [23].

FabAV has been evaluated in two prospective trials [24,25]. The trials used a clinical research tool, the snakebite severity score (SSS), to document the severity of envenomation more objectively than in previous work [26]. In both studies the mean SSS improved during the initial infusion of FabAV and continued through the 12-hour efficacy evaluation. The decrease in the severity of illness, as represented by the SSS, was related to improvement of the components reflecting the coagulation, central nervous system, gastrointestinal, and cardiovascular systems. Each of these score components improved during the initial infusion and continued to improve throughout the evaluation period. Thus, venom-induced abnormalities in these organ systems were reversible. In contrast, the local injury (pain, swelling, ecchymosis) component of the score improved slightly, but the change was not statistically significant. This observation might be explained by the

fact that this injury involves local hemorrhage, cell swelling, and cell death, processes that are not quickly reversible.

An important and unexpected observation during clinical trials was recurrence after completion of FabAV treatment. Recurrence was defined as the recrudescence of any venom effect after that abnormality had resolved. Edema at the envenomated site recurred at the bite site within 18 hours of treatment, and recurrence of hypoprothrombinemia was found in one patient during a 7-day follow-up visit.

A new dosing schedule was devised and tested in the second trial, which compared a single dose of FabAV to a loading dose followed by three maintenance doses at 6, 12, and 18 hours after initial control was achieved. This study inadvertently became the first prospective evaluation of the recurrence phenomenon in the United States; however, recurrence has been described following the use of antivenoms around the world [27]. In addition, other reliable data show the phenomenon occurred in the United States before the study.

Safety of antivenoms

Animal sera products can produce a wide range of adverse events ranging from cutaneous reactions to death from anaphylaxis. Reactions can occur during infusion, such as anaphylactoid reactions or anaphylaxis, or they might be delayed, as in serum sickness. Based on retrospective data, the incidence of acute reactions following administration of ACP ranges from 23% to 56% [28–30]. The incidence of acute reactions to the FabAV in clinical trials was 14.3% (occurring in 6 of 42 patients) [31].

Retrospective studies by Jurkovich et al [30] and Downey et al [32] documented an incidence of serum sickness with ACP ranging from 18% to 86%. In the only prospective study of ACP reactions, serum sickness developed in six of eight patients [33]. Following administration of FabAV, the rate of serum sickness was 16% (occurring in 6 of 38 patients); however, five of the reactions were associated with one early lot of the study antivenom in which Fc had been retained inadvertently.

Clinical use of antivenoms

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

Because ACP is derived from horse serum, intended recipients should be skin tested for sensitivity before administration of the antivenom, as

recommended by the manufacturer; however, skin testing has no predictive value [34]. A negative skin test does not guarantee lack of hypersensitivity; conversely, a positive skin test does not predict the development of an acute reaction. Therefore, careful monitoring during subsequent antivenom administration is vital. In a patient who has an envenomation that is considered to be threatening to life or limb who has a positive reaction to the preliminary skin test, pretreatment with H_1 and H_2 blockers followed by antivenom should be administered in a critical care setting equipped to treat anaphylaxis. If a reaction occurs, the infusion should be stopped immediately (early reactions usually result from too rapid an infusion rate). After administration of epinephrine, H_1 and H_2 blockers, and isotonic fluids, the antivenom should be further diluted and the infusion resumed at a slower rate.

ACP is most effective when given within the first 4 hours after envenomation and is less effective after 12 hours; however, it has reversed coagulopathies after 24 hours. The amount of the initial dose should be guided by the severity and progression of local effects, systemic symptoms and signs, and results of coagulation studies. In general, patients who have minimal rattlesnake envenomation require no antivenom, moderate cases usually require 10 to 15 vials (100–150 mL) initially, and severe cases at least 15 vials ($\geq$150 mL). Patients who have profound circulatory collapse should receive 20 vials (200 mL) initially. In contrast to rattlesnake bites, bites from cottonmouths (water moccasins) usually require smaller doses of antivenom. Antivenom is unnecessary for most copperhead and pygmy rattlesnake bites, except in children, the elderly, and patients who have debilitating conditions such as diabetes mellitus or coronary artery disease.

Reconstituted ACP antivenom should be diluted in 250 to 1000 mL of normal saline or 5% dextrose in water and given by IV drip, slowly, at 50 to 75 mL/hour for the first 10 minutes. If no reaction occurs, the remainder can be infused over 1 hour. Antivenom should never be injected into the finger or toe. Administration of IV fluids should be minimized in children and the elderly unless shock or hypovolemia is present.

The need for additional antivenom doses should be guided by monitoring for progression of local, systemic, or coagulopathic abnormalities. If local findings, other signs, or laboratory test results progress, the initial dose of antivenom is repeated every 1 to 2 hours.

When coral snake (*Micrurus fulvius*) envenomation is proven or strongly suspected, five vials of coral snake antivenom should be administered immediately. If symptoms develop, an additional 10 to 15 vials might be necessary and the patient should be monitored in an ICU for respiratory depression.

FabAV is administered according to the concepts of initial control and maintenance therapy (Fig. 3). A large FabAV dose (four to six vials) is administered to achieve initial control, defined as reversal or marked attenuation of all venom effects: local injury, systemic effects, and coagulopathy. In the majority of cases, 8 to 12 vials is sufficient to provide

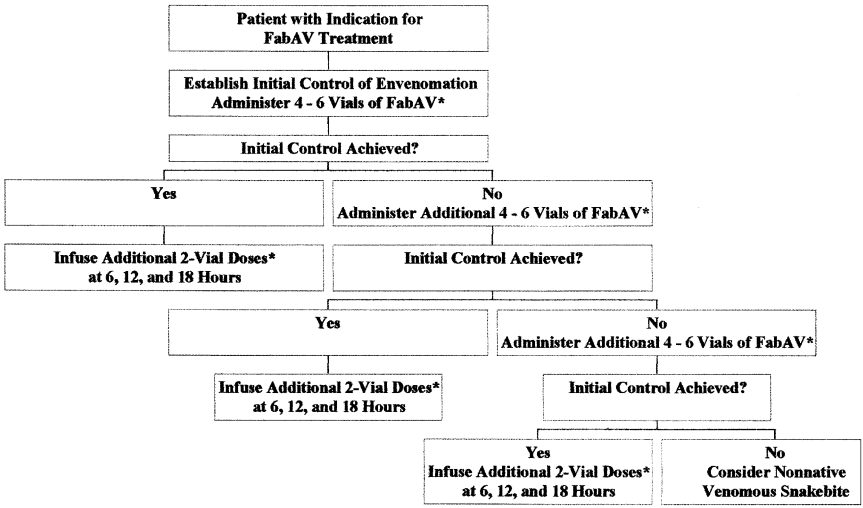

Fig. 3. The clinical use of Crotalidae Polyvalent Immune Fab (Ovine). *Reconstitute each vial, dilute the entire dose in a crystalloid fluid to a total volume of 250 mL, and administer over the course of 1 hour. (*Modified from* Gold BS, Dart RC, Barish RA. Bites of venomous snakes. N Engl J Med 2002;347(5):347–58; with permission)

initial control; however, 22 vials were needed in one case [35]. After control has been established, an additional two vials are infused at 6, 12, and 18 hours to prevent local recurrence. The regimen is based on a randomized comparative trial of two dosage schedules. In the arm of the trial that did not include maintenance doses, 8 of 16 patients in the ''as-needed'' group required treatment with additional (unplanned) antivenom doses for recurrent venom effects. None of the scheduled patients received additional doses outside the protocol [25]; however, optimal dosing schedules for FabAV are still being reviewed.

A concern with lyophilized antivenoms involves reconstitution. When the decision to treat has been made, any time lost to antivenom preparation risks worsening of venom effects. A 1-hour delay needed to reconstitute vials of ACP can be life-threatening in a patient who has a rapidly progressing envenomation. Reconstitution time was documented during the clinical trials of FabAV. All vials were judged ready for infusion within 30 minutes [25]. In the clinical trials, the initial dose of FabAV was diluted to a volume of 250 mL in a crystalloid fluid and the total dose was infused over 1 hour. After slow infusion for the first 10 minutes, the rate was increased to complete the infusion within 1 hour.

Follow-up care

The wound should be covered with a sterile dressing and the affected extremity maintained in a functional position. After the third day, blebs,

vesicles, and necrotic tissue might require debridement. The goals of follow-up treatment are preservation of function, joint mobility, and muscle strength.

Complications of envenomation and treatment

Wound infections are surprisingly rare following pit viper bites. Therefore, antibiotics are recommended only when there is clinical and microbiologic evidence of wound infection. The choice of antibiotic should be based on culture and sensitivity results.

Severe rattlesnake envenomations can be associated with increased compartment pressures. The local reaction to envenomation manifesting with marked swelling, tenderness, tenseness, hypesthesia, and pain might mimic true compartment syndrome. In cases of suspected compartment syndrome, clinical diagnosis requires objective evidence of compartment pressure elevations greater than 30 mmHg measured with a Stryker handheld digital monitor (Stryker Corporation, Kalamazoo, Michigan). If compartment pressure is elevated, the authors recommend limb elevation in conjunction with the administration of mannitol, 1 to 2 gm/kg, given IV simultaneously with an additional four to six vials of CroFab over 1 hour [36]. Compartment syndrome in patients who have rattlesnake envenomation is thought to be caused by myonecrosis related to the action of the venom components more so than to increased compartment pressures [37]. The additional antivenom should effectively neutralize the venom components, thereby reducing compartment pressure. If these measures fail to reduce compartment pressure over 4 hours and the patient has circulatory compromise, surgical intervention might be required [37–39]. Surgical intervention primarily uses fasciotomy as a means of lowering elevated compartment pressure. Intense debate flourishes regarding the use of fasciotomy because it does not prevent the progression of the envenomation syndrome, treat coagulopathies, or obviate the need for additional antivenom, yet it is still considered to be routine practice in some areas of the United States. Evidence regarding the efficacy of surgical fasciotomy is sparse [37]. Fasciotomy can lengthen the course of treatment significantly and is associated with nerve damage, disfiguring scars, contractures, and loss of limb function [36].

Serum sickness is a type III hypersensitivity reaction that might be seen 7 to 21 days following treatment with a foreign equine or ovine serum. Serum sickness manifests as fever, rash, arthralgias, and lymphadenopathy. It responds well to a tapering course of prednisone, generally starting at a dose of 60 mg/day with a rapid taper over a 7- to 10-day period.

Assistance in managing venomous snakebites

A regional poison center should be contacted for assistance in managing patients who have been bitten by a native or exotic venomous snake. The

regional centers can be reached through the national hotline at 1-800-222-1222. The centers are staffed by individuals trained in all types of poisonings and maintain a list of consulting physicians throughout the United States who are experienced in management and treatment of venomous snakebite.

The clinical use of antivenoms remains complex. The dynamic and erratic course of the snake envenomation syndrome requires close patient monitoring in an ICU along with prudent clinical decision making. Consultation with a physician experienced in the use of antivenom is recommended.

Summary

Snake venom poisoning constitutes a medical emergency. It is a complex type of poisoning that not only affects the local bite site but can also involve multiple organ systems. In the United States, poisonous snakes account for approximately 8000 bites annually (almost all from pit vipers), resulting in about five or six fatalities [3,5]. The majority of deaths occur in children, the elderly, and untreated or undertreated individuals. Diagnosis and treatment are based on clinical signs and symptoms of envenomation along with identification of the snake. First aid interventions should focus on transport of the victim to the nearest emergency department as soon as possible. Previously advocated measures such as tourniquet, incision and suction, cryotherapy, and electric shock should be avoided [6,21]. The efficacy of treatment is enhanced by prompt administration of sufficient quantities of the appropriate neutralizing antivenom in conjunction with aggressive supportive care in an ICU. Consultation with a physician experienced in the management of envenomated patients is strongly advised.

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