REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Snake Envenomation

Steven A. Seifert, M.D., James O. Armitage, M.D., and Elda E. Sanchez, Ph.D.

From the Department of Emergency Medicine and the New Mexico Poison and Drug Information Center, University of New Mexico Health Sciences Center, Albuquerque (S.A.S.); the Department of Internal Medicine, University of Nebraska Medical Center, Omaha (J.O.A.); and the National Natural Toxins Research Center and the Department of Chemistry, Texas A&M University–Kingsville, Kingsville (E.E.S.). Dr. Seifert can be contacted at sseifert@salud.unm.edu or at New Mexico Poison and Drug Information Center, University of New Mexico Health Sciences Center, Albuquerque, NM 87131-0001. Dr. Armitage can be contacted at joarmita@unmc.edu or at Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE 68198-6840. Dr. Sanchez can be contacted at elda.sanchez@tamuk.edu or at National Natural Toxins Research Center, Department of Chemistry, Texas A&M University–Kingsville, Kingsville, TX 78363-8202.

N Engl J Med 2022;386:68-78.
DOI: 10.1056/NEJMra2105228

CME at NEJM.org

Snake envenomation represents an important health problem in much of the world. In 2009, it was recognized by the World Health Organization (WHO) as a neglected tropical disease, and in 2017, it was elevated into Category A of the Neglected Tropical Diseases list, further expanding access to funding for research and antivenoms.[1] However, snake envenomation occurs in both tropical and temperate climates and on all continents except Antarctica. Worldwide, the estimated number of annual deaths due to snake envenomation (80,000 to 130,000) is similar to the estimate for drug-resistant tuberculosis and for multiple myeloma.[2,3] In countries with adequate resources, deaths are infrequent (e.g., <6 deaths per year in the United States, despite the occurrence of 7000 to 8000 bites), but in countries without adequate resources, deaths may number in the tens of thousands. Venomous snakes kept as pets are not rare, and physicians anywhere might be called on to manage envenomation by a nonnative snake. Important advances have occurred in our understanding of the biology of venom and the management of snake envenomation since this topic was last addressed in the *Journal* two decades ago.[4] For the general provider, it is important to understand the spectrum of snake envenomation effects and approaches to management and to obtain specific guidance, when needed.

Epidemiology

Snakes are predators, and with exceptions (e.g., egg-eating snakes), they subdue their prey through constriction, aggressive biting, and chewing or by using venom. The mechanism of venom delivery varies among major groups of snakes (Fig. 1).

Snakes generally avoid human contact by retreating or hiding. Many species have defensive mechanisms (e.g., the rattlesnake's rattle and the cobra's hooding) to ward off an organism perceived as a threat.

A person can be bitten by a snake for several reasons. Accidental causes include reaching or stepping without looking, not being aware of the danger, rolling over onto a snake while sleeping, and being unaware of the presence of a snake because of poor hearing or vision. Handling of a venomous snake by a person who is inexperienced, careless, inattentive, overconfident, or intoxicated can also result in a snakebite. In addition, snake envenomation may occur in an attempt to capture or kill a snake or as part of a religious ceremony. Finally, some cases of envenomation are intentional (e.g., as an attempt to induce tolerance of venom or for pleasure).[5]

Bites most commonly involve the extremities. Unprovoked bites are more likely to involve females and the lower extremities. Provoked bites are more likely to involve males and the upper extremities. The intentionality of the interaction does not appear to be associated with the likelihood or severity of envenomation. The continent with the lowest occurrence of snake envenomation is Europe, and the highest occurrences are in Africa and Asia.[6] In Australia, deaths from envenom-

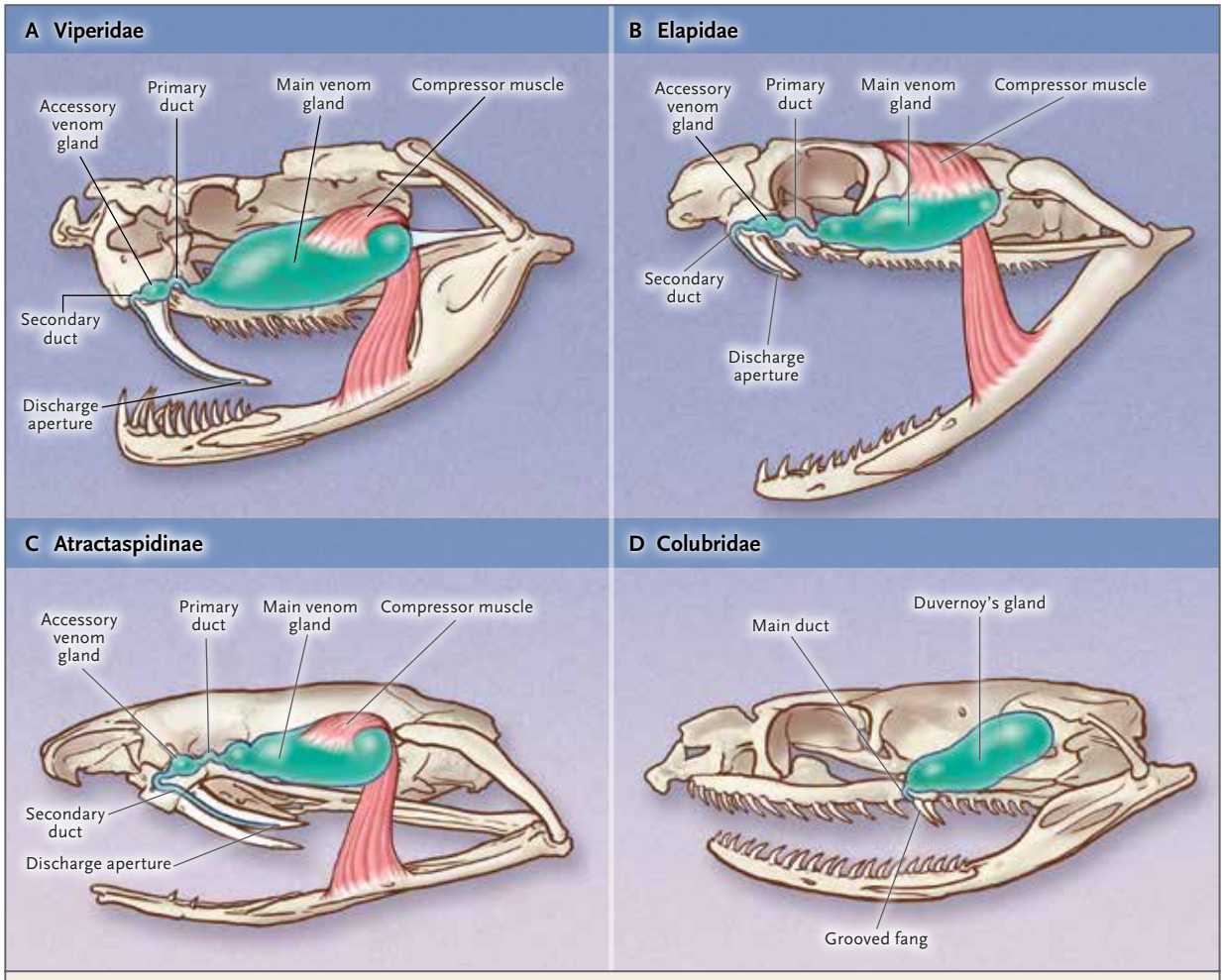

Figure 1. Venom Delivery Systems of Snakes.

All venom delivery systems involve either venom glands or, in the case of colubrids, Duvernoy's glands, which unlike venom glands, do not have a large reservoir of venom. Venom glands are attached to tubular fangs through a duct. In Viperidae, Elapidae, and Atractaspidinae (Panels A, B, and C, respectively), contraction of muscles around the venom glands propels the venom into the fangs and eventually into bitten tissue through openings near the tips. In Colubridae (Panel D), low-pressure channeling of venom into the bite site through grooved fangs occurs. All snakes have teeth on the lower jaw for better tissue purchase.

ation are infrequent, despite the presence of many highly venomous snakes.[7] Snakebites and death from envenomation are most frequent in rural, low-income regions, where health care often cannot be accessed quickly and antivenom and intensive supportive care might not be available. Among patients who survive, delayed or inadequate care can lead to permanent disability (e.g., amputations and blindness).

An understanding of the epidemiology of envenomation is useful in developing preventive and management efforts. In 2019, the WHO established a program to halve the number of snakebite-related deaths and disabilities by 2030, key aspects of which include preventive efforts, improved treatments, and enhanced access to care.[8] That program is currently in a scaling-up phase.

PATHOPHYSIOLOGY OF VENOMOUS SNAKEBITES

Not all bites by venomous snakes involve envenomation; "dry" bites occur in 2 to 50% of cases.[9] When envenomation does occur, the clinical effects depend on the toxins in the venom. Snake

venom contains an array of toxins that can induce clinical effects that can be both local and systemic and range from mild to fatal, as outlined below.

CYTOTOXICITY

Local tissue injury and inflammation are caused by enzymes such as hyaluronidase and collagenase, as well as proteinases and phospholipases. The results are pain and edema; edema can spread from the site of the bite and may also lead to bullae and dermonecrosis. Local ecchymosis may be the result of increased vascular permeability, systemic coagulopathies, or both. The effect of snake venom metalloproteinases on the extracellular matrix results in the release of extracellular matrix–derived peptides that exert diverse actions in the tissue. Some of the peptides cause additional tissue destruction and others are involved in reparative actions. In addition, snake venom metalloproteinases may cause microvascular damage leading to hemorrhage,[10] skeletal-muscle necrosis and lack of muscle restoration,[11] blistering, and dermonecrosis,[12] as well as inflammatory mediators that account for pain, swelling, and leukocyte infiltration.[13] Although elevated compartmental tissue pressure (due to edema in a space bounded by a rigid fascia) or elevated subcutaneous tissue pressure (due to swelling exceeding the elastic limits of the skin) may occur, the direct effects of venom can mimic the symptoms and signs of true compartment syndrome, and pressures may be normal.

LYMPHATIC SYSTEM

In snake envenomation, injury to the lymphatic system plays a role in the development of edema. The lymphatic system is also involved in systemic absorption of venom toxins from tissues. In addition, some venom components are neutralized in the lymphatics, although the process is slow and incomplete.[14]

VENOM-INDUCED CONSUMPTION COAGULOPATHY

Procoagulant toxins in snake venoms promote consumption coagulopathy, which causes the depletion of factors in the clotting cascade and may result in either spontaneous or uncontrolled bleeding. Venoms of different types of snakes vary in the extent to which they affect clotting factors. Toxins in snake venom that promote consumption coagulopathy are categorized according to where they act on the clotting cascade. Some of the most relevant procoagulant toxins, such as metalloproteinases, are activators of prothrombin, factor V, factor X, or thrombinlike enzymes (fibrinogenases).[15] Thrombotic microangiopathy, which may accompany venom-induced consumption coagulopathy, is characterized by thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury.[16]

THROMBOSIS

Snake envenomation can result in myocardial infarction, stroke, or other thrombotic effects. Twenty-two cases of myocardial infarction after snake envenomation have been reported.[17] Proposed mechanisms of myocardial infarction include hypovolemia, anaphylactic shock, coronary thrombosis from procoagulant factors, a direct effect of venom on cardiomyocytes, decreased oxygen-carrying capacity, vasoconstriction, myocardial necrosis and hemorrhage, and microvascular thrombin deposition. Strokes may be either hemorrhagic or ischemic, but ischemic strokes are more prevalent.[18]

THROMBOCYTOPENIA OR ALTERED PLATELET FUNCTION

In severe cases of envenomation from Crotalinae (New World pit vipers), thrombocytopenia is common. It can occur alone or in combination with other coagulopathies, and the consumption of platelets can contribute to the complications associated with venom-induced consumption coagulopathy. Venom-induced thrombocytopenia appears to be associated with the specific venom composition and the quantity of venom introduced with the bite. The mechanisms by which snake envenomation results in thrombocytopenia are unclear; suggested mechanisms include platelet aggregation, platelet sequestration, and decreased platelet production. Profound thrombocytopenia may result in either spontaneous or uncontrolled hemorrhage.[19] In addition, platelets may be inhibited or activated by various venom components (metalloproteinases and lectins), resulting in normal platelet counts but platelet dysfunction.[20]

NEUROTOXICITY

Neuromuscular paralysis is one of the leading clinical disorders due to envenomation from ela-

pids (snakes in the Elapidae family) such as naja, bungarus, and micrurus species[21] and can also be seen with envenomation from other snake families such as Crotalinae in the United States and Hydrophiidae. Neurotoxic snake venoms may contain exclusively postneuromuscular or preneuromuscular synaptic toxins or a mixture of the two types. Postsynaptic neurotoxins bind to and block membrane receptors but remain extracellular. Presynaptic neurotoxins, such as alpha-bungarotoxin, are taken up into the presynaptic membrane and impair the release of neurotransmitters. Either type of neurotoxin may cause a descending, flaccid paralysis (Fig. 2) that progresses to airway compromise and life-threatening respiratory insufficiency.[22] Progressive paralysis from postsynaptic neurotoxins may be reversed because they remain available to neutralization by antivenom. Progression of the paralytic effects of presynaptic toxins may be halted by antivenom, but because the neurotoxins are intracellular and no longer available for neutralization, the effects are not readily reversible. Prolonged respiratory support may be needed once respiratory compromise has occurred.

Figure 2. Neurotoxic Effects of Snake Venom.

Neurotoxins generally cause a progressive, descending paralysis, beginning with bulbar muscles (ptosis and dysarthria) and progressing to respiratory compromise.

MYOTOXICITY, CARDIOTOXICITY, AND HYPOTENSION

Myotoxicity may develop as a result of the direct effect of venom on muscle through myotoxic phospholipase A2, which disrupts the integrity of the plasma membrane and provokes calcium influx. This process initiates a series of degenerative events, pressure-related effects in a muscle compartment, or inflammation overlying muscle and may also directly affect the myocardium.[23] Myokymia of skeletal muscle may result in rhabdomyolysis, respiratory compromise, or both. Hypotension may develop from bradykinin-potentiating peptides, natriuretic peptides, phospholipase A2, proteases, vascular endothelial growth factors, three-finger toxins (a superfamily defined by a common tertiary structure consisting of three beta strand–containing loops projecting from a small hydrophobic core containing four conserved disulfide bonds), and 5′ nucleotidases.[24] Hypotension may reflect hypovolemia due to increased vascular permeability, loss of fluid into soft tissues, myocardial depression, or anaphylaxis.[24]

NEPHROTOXICITY

Snake envenomation can result in acute kidney injury, which may progress to chronic kidney disease or renal failure. A variety of snake venoms — including venom from bothrops species (lancehead pit vipers), crotalus species (e.g., tropical rattlesnakes), and micrurus species (coral snakes) in Central and South America, as well as species in Africa, such as bitis species (puff adders), and daboia species (Russell's vipers) in the Asia–Pacific region — can cause nephrotoxicity through direct venom-related injury mediated by inflammatory cytokines, which results in glomerular degeneration and atrophy, with deposition of proteinaceous material in Bowman's space.[25] Nephrotoxicity as a direct effect of venom is commonly seen with Russell's viper envenomation.[26] Mexican coral snake venom has been shown to induce oxidative stress and decrease renal perfusion and the glomerular filtration rate.[27] Nephrotoxicity may also result from microangiopathy and microangiopathic hemolytic anemia or from rhabdomyolysis, altered clearance of blood degradation products, immune complexes, or from a shock state.

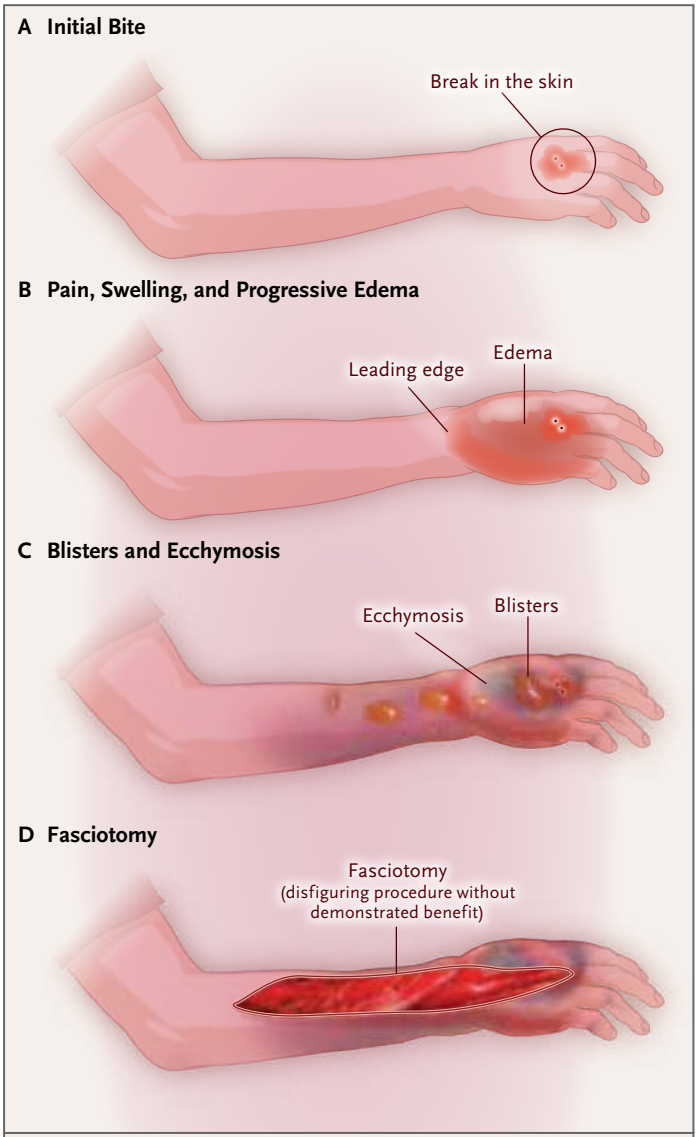

Figure 3. Clinical Appearance, Assessment, and Management of Snakebites.
After a snakebite, a break in the skin is usually seen. This may be a scratch, a single or double puncture, or multiple punctures. Teeth in the lower jaw may also produce multiple, linear punctures (Panel A). Pain, swelling, and progressive edema with a leading edge may be seen with cytotoxic venoms, a finding that may be more tactile than visual (Panel B). Blisters may form at the bite site and elsewhere on the bitten extremity, and ecchymosis and bruising may occur as a result of coagulopathy (Panel C). Fasciotomy is a disfiguring procedure without a demonstrated benefit (Panel D).

OTHER EFFECTS

Other systemic effects of venom can include nausea, vomiting, diarrhea, and diaphoresis. A complex regional pain syndrome may develop, and anaphylaxis may result from prior sensitization to venom components, either from previous envenomation or from the handling of venomous snakes.

DIAGNOSIS

A snakebite or envenomation may not be recognized because of factors pertaining to the patient or the bite. Only one fang may have achieved penetration, the punctures may be obscured by edema, or an abrasion may be the only finding[28] (Fig. 3). Although venom does not cross intact skin or mucous membranes or usually cause injury if swallowed, it may cause ophthalmic injury.[29] The distance between fangs may indicate the size of the snake, with larger snakes potentially containing larger venom loads, but the amount of venom injected can vary. The degree of toxicity also may be related to the specific venom components, which are a function of the genetic and epigenetic factors of the snake. Children pose a particular diagnostic challenge, since they may not be able to relate the relevant history. Context and specific findings may provide clues to the diagnosis. For example, snake envenomation may be the cause of otherwise unexplained coagulopathy, neuropathy, or abdominal pain (e.g., in the case of krait [bungarus species] envenomation).[28]

In Australia, venom detection kits consisting of enzyme immunoassays[30] are available for identifying a snake envenomation and the species of snake. However, in the rest of the world, in the absence of observation of the bite and accurate identification of the biting species, the patient's presentation, the appearance of the wound, and the clinical course may be the basis for diagnosing envenomation and identifying the likely snake species. Species-specific, polyvalent, or paraspecific antivenoms may be needed. In instances in which snake families, genera, or species overlap, identification of the envenomating snake may be difficult, and in cases in which various antivenoms may be available, improper identification sometimes results in incorrect management.[31] Nonnative, captive snakes may pose challenges to species identification and case management. The prehospital application of ineffective and possibly harmful therapies, plus any delay in obtaining competent and definitive care, may also complicate both diagnosis and management.

CLINICAL SYNDROMES

In geographic regions where multiple families, genera, and species overlap, distinguishing among snake taxa may be advantageous for selection of a specific antivenom. However, the division of snake envenomation into distinct syndromes (e.g., neurologic, cytotoxic, and coagulopathic) that are species-specific is simplistic. Envenomation syndromes may vary widely among different species within a geographic region, and identification of a specific snake on the basis of envenomation effects may not be possible. Although venoms can derive from diverse genetic forebears, their effects may have many clinical similarities. Conversely, venoms from within a family, genus, or species may have substantially different clinical effects as a result of snake venomics, variable gene expression, and epigenetic factors.[32] As examples, myotoxicity and neurotoxicity are typically seen in elapid envenomation but also occur in Crotalinae envenomation in Central and South America.[33] Some Mojave rattlesnakes (*Crotalus scutulatus*) contain large amounts of Mojave toxin, a potent neurotoxin, whereas others have none at all.[34] Even in the same snake, different venom effects are the result of ontogenic changes expressed over time, from newborn, to juvenile, to adult.[35] Thus, knowledge of the family, genus, and species of an envenomating snake may not allow accurate prediction of the likelihood of venom-induced toxic effects.[36]

PREHOSPITAL CARE

Because of the wide variety of presentations and management challenges, expert assistance should be sought early. The primary priorities of the prehospital assessment and management of snakebite are, first, to get away from the snake and identify it, if possible; second, to loosely splint the bitten body part, with a default of heart-neutral positioning[37]; third, to anticipate swelling (e.g., remove jewelry); and finally, to obtain transport (with personnel competent in advanced life support) to a capable health care facility. Because the majority of venom enters the circulation through the lymphatics,[38] impairing lymphatic flow may slow the systemic effects of the venom. A compressive bandage, wrapped from distal to proximal extremity (if personnel are trained in its application), or a blood pressure cuff placed proximal to the bite and inflated to sufficient pressure (approximately 50 mm Hg [upper extremity] or 70 mm Hg [lower extremity]) may be considered if there are minimal or no local effects of envenomation and if there is concern about the possibility of a rapid onset of neurotoxicity. Other prehospital interventions, such as the use of arterial or venous tourniquets, incision, suction, heat, cold, electricity, and folk treatments, delay access to definitive treatment and may result in additional trauma.

HOSPITAL CARE

Management of snake envenomation comprises the administration of antivenom (if available), other specific local and systemic treatments, and symptomatic and supportive care. Management approaches generally have poor scientific bases, however, with systematic reviews providing critically low confidence for most interventions and conflicting findings about specific antivenoms.[39,40] In the absence of high-quality data for management decisions, consensus guidelines and expert opinion predominate, sometimes with differing recommendations.[39,41-43]

Once the patient has arrived at a health care facility, vital signs should be obtained and monitored. Restrictive clothing and clothing covering the wound should be removed, the patient examined, and an intravenous catheter placed. Tetanus status should be updated as needed, and the wound (or wounds) should be cleaned and inspected for retained foreign bodies (e.g., fangs or teeth).[41] Ultrasonography may show retained fangs or teeth, as well as the location of edema.[44] If the bite does not appear to contain venom, the patient should be observed for a long enough period to confirm that envenomation has not occurred. The duration of observation varies according to snake taxa and geographic factors, but periods between 6 and 24 hours have been suggested.[41,45]

Studies have shown that antivenoms are a definitive treatment, and these agents are believed to be responsible for reducing the morbidity and mortality associated with envenomation. Early evidence of efficacy was based on an increase in the survival rate or survival time in crude animal models, on retrospective clinical data showing reduced mortality after antivenom

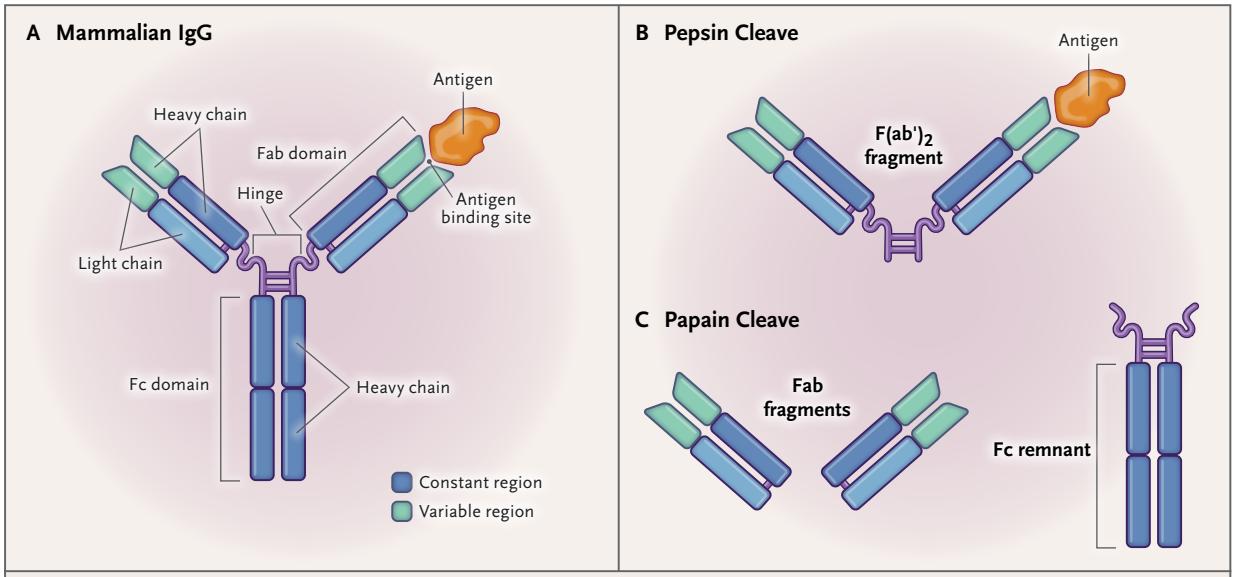

Figure 4. IgG and IgG Fragments Developed against Snake Venom Components.

The mammalian IgG molecule (Panel A) consists of an Fc (heavy) chain, a hinge, and two Fab (light) chains. The light chains have constant and variable regions, which allow the IgG to bind to certain antigens (Ag), such as venom components. When the IgG is treated with pepsin, the IgG molecule is cleaved below the hinge (comprising two disulfide bridges), and an $F(ab')_2$ fragment is produced (Panel B). When the IgG is treated with papain, the cleavage occurs above the hinge, and two Fab fragments are produced (Panel C). The Fc remnant or chain, which is more immunogenic than the Fab chains, can be removed from the remaining solution by means of various purification techniques.

administration, and on suggestive individual case reports and case series.[46] More recently, sophisticated in vitro and animal models, as well as prospective clinical studies, have confirmed a reduction in morbidity and mortality with the use of antivenoms.[46,47]

Antivenom antibodies — IgG, $F(ab')_2$, or Fab fragments — (Fig. 4) that have been developed in a source animal (e.g., horse or sheep) neutralize antigenic components of venom that they encounter in circulation or in tissue, although edema or venom sequestration in lymphatics may limit the presence of venom components in tissue. The efficacy and adverse-effect profiles of antivenoms depend on the source animal, type and degree of purification, specific antibody fraction, host, and other factors. Smaller antibody fragments (e.g., Fab) have larger volumes of distribution and shorter half-lives than larger fragments.[48]

Because the neutralizing power per vial varies, antivenoms are dosed by the vial. Since neither the total venom load nor the load of specific components is known, the initial antivenom dose is selected to arrest or reverse the immediate effects of the venom, with subsequent adjustment according to the response to the initial dose. Because the venom load may be as large in a child as in an adult, children require at least the same amount of antivenom as adults. Children may need larger amounts initially, since their smaller vascular volume can result in an increased concentration of circulating venoms. In addition, children may require more concentrated antivenom to reduce infused fluid volumes.

Pregnant women also constitute a special subgroup of patients with envenomation. Fetal loss may occur, particularly if the bite occurs before 20 weeks of gestation, but most envenomations have minor or no effects and good outcomes. Although no studies have evaluated antivenom safety during pregnancy, antivenom is generally used for the same indications in pregnant patients as in nonpregnant patients, with no reports of adverse reactions.[49]

Since unneutralized venom may remain in tissues and continue to have local and systemic effects, antivenom may need to be readminis-

tered to align venom and antivenom kinetics within the first 24 hours for local effects and in a period of days to weeks for systemic effects.[48,50] Some venom-induced effects may not be easily reversed or may result in long-term or permanent injury. Thus, once envenomation has been confirmed, early administration of antivenom is indicated.

Information regarding antivenoms for specific snakes can most reliably be found at a regional poison center. A WHO database is available online.[51] The Clinical Toxinology Resources website, based at the University of Adelaide, contains detailed information on envenomations and antivenoms worldwide.[52] The online Antivenom Index includes the package inserts of many antivenoms, with their manufacturer-attributed indications and their locations at zoos in the United States.[53] When envenomation from an indigenous snake has occurred, local health care facilities either stock or should know how to obtain an appropriate antivenom. Because of the large crossover of venom constituents across species and genera, an antivenom developed for a small subset of snake species may treat a large variety of regional snakes.[54] For nonnative snakes, different systems exist, including centralized antivenom depots,[55] zoo-based sources,[56] and online resources.[53,56] If a poison center network is available, associated toxicologists will probably know how to source appropriate antivenoms in a timely manner. Package inserts may provide appropriate dosing information. However, since the information may be outdated or may not conform to current practices, expert guidance should be sought.

Antivenoms are not available for bites from certain venomous snakes, such as *Thelotornis capensis* (one of the twig snakes) and the Atractaspidinae (burrowing asps, mole vipers, and stiletto snakes). This lack of availability has resulted in substantial morbidity and mortality. Even when antivenoms do exist, they may be too expensive for local health care use, may not be available in the geographic region where they are needed, or may not be currently available from the manufacturer.[57]

The risk of hypersensitivity reactions to antivenoms ranges from very low to high (type 1, or acute), generally depending on the source animal; whether an IgG, $F(ab')_2$, or Fab fragment is produced; further purification techniques; and host factors. Skin testing before administration is discouraged because the results are insufficiently sensitive to be of value or may be subject to misinterpretation,[58] but pretreatment with epinephrine may be recommended for certain antivenoms with high rates of type 1 hypersensitivity (anaphylactic) reactions.[59] When a choice of antivenom is available, the selection is based on safety, kinetic factors, cost, and whether monovalent or polyvalent antivenom is more appropriate, as well as other considerations.

ORGAN-SYSTEM–BASED ASSESSMENT AND MANAGEMENT

CYTOTOXICITY

Cytotoxicity may serve as an indication for antivenom, and the earliest appropriate use of antivenom is associated with the best outcomes.[60,61] During antivenom infusion, the bitten body part should be elevated. Opioid-level pain control may be needed; however, antivenom treatment of envenomation from a copperhead snake (*Agkistrodon contortrix*) has been shown to reduce the use of opioids.[62] When tissue pressures are suspected to be elevated, appropriate assessments include ultrasonography, magnetic resonance imaging, direct measurement of tissue and compartment pressures, or a combination of these approaches.[44] Increased pressures, either in deep compartments or in subcutaneous tissue, should be considered indications for additional antivenom, elevation of the bitten body part (because most if not all edema is located in the subcutaneous space and is amenable to gravity-assisted lymphatic drainage), and possibly mannitol. Fasciotomy has not been shown to improve outcomes, as compared with antivenom and elevation alone or with fasciotomy plus antivenom.[63] Prophylactic antibiotics to prevent infection have not proved useful. Necrosis is a known risk factor for infection and may be an indication for antibiotic use.[64]

HEMOTOXICITY

In some cases of venom-induced consumption coagulopathy, antivenom has been effective, although the rate and degree of improvement varies. Heparin is ineffective.[15] Either bleeding or thrombosis with infarction may be seen with

venom-induced consumption coagulopathy.[65] Standard testing includes a platelet count, prothrombin time and international normalized ratio, activated partial-thromboplastin time, fibrinogen level, and D-dimer level (as a marker of fibrinogenolysis), as well as the 20-minute whole-blood clotting test.[66] Thromboelastography provides information that is similar to that provided by standard laboratory assays, although it may be useful in anticipation of hypofibrinogenemia.[67] Hematologic effects may persist for several days to more than 2 weeks[68] and may respond less well to late administration of antivenom or may require periodic or continued infusion of antivenom.[69] Blood products can be given, if needed, but should be administered simultaneously with additional antivenom.[41]

MYOTOXICITY

Myokymia may result in rhabdomyolysis, respiratory compromise, or both. Antivenom treatment targets direct myotoxic effects. Rhabdomyolysis is managed according to standard protocols.

NEPHROTOXICITY

It is appropriate to screen for nephrotoxicity in all cases of envenomation. Antivenom against Russell's viper has been shown to reduce renal injury,[26] and appropriate antivenom therapy should be considered in any case of renal injury.

NEUROTOXICITY

Antivenom treatment is most effective against postsynaptic venoms, and early administration is important for presynaptic venoms, while they are still extracellular. Airway management is based on the same principles that guide the management of other conditions involving respiratory compromise.

FUTURE DIRECTIONS

ANTIBODY-BASED ANTIVENOMS

Antivenoms made in horses or sheep are currently the only effective treatment for snake envenomation. IgG-based or incompletely purified antivenoms may be more likely than others to produce type 1 reactions (anaphylaxis), type 3 reactions (serum sickness), or both, with only about 30% of the immunoglobulins directed toward the actual snake toxins.[70] Fab antivenoms are characterized by rapidly falling serum concentrations and are cleared more quickly from the body, conferring a predisposition to recurrent venom effects and making $F(ab')_2$ antivenoms the current standard.[48] However, the price of antivenoms may render their use impossible in many developing countries. Investigations are therefore exploring the efficacy of making antibodies in other animals (e.g., camels, chickens, and sharks) or humanizing animal antibodies.

NATURAL VENOM INHIBITORS

Many animal serums and some plant extracts can neutralize snake venom.[71] For instance, LTNF-11, a peptide derived from the American opossum (*Didelphis virginiana*), inhibits the lethality of hemorrhagic snake venoms.[72] With further development, such inhibitors may be useful as alternative or supplemental treatments.

SYNTHETIC PEPTIDES, PHOSPHOLIPASE A2 INHIBITORS, AND METALLOPROTEINASE INHIBITORS

Some synthetic peptides and secretory phospholipase A2 inhibitors that have the ability to neutralize snake venoms are promising. Varespladib, originally designed to treat acute chest syndrome, has inhibitory effects on secretory phospholipase A2 and may be of value against a broad spectrum of snake venoms. Batimastat and marimastat are matrix metalloproteinase inhibitors that have been shown to inhibit some of the coagulopathies caused by hemorrhagic venoms.[73] Other inhibiting peptides are the nucleotide-based and amino acid–based aptamers and X-aptamers, which can be made toxin-specific, especially against small-molecule venom toxins that may not be immunogenic.[74]

CONCLUSIONS

Snakebite envenomation continues to be a major global health burden. Current technical advances are focused on snake envenomation treatments, including more effective and safer antivenoms. Current efforts aimed at prevention, diagnosis, and increased access to timely and effective treatments are still in early stages of development in much of the world.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Chippaux JP. Snakebite envenomation turns again into a neglected tropical disease! J Venom Anim Toxins Incl Trop Dis 2017;23:38.
2. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1736-88.
3. Longbottom J, Shearer FM, Devine M, et al. Vulnerability to snakebite envenoming: a global mapping of hotspots. Lancet 2018;392:673-84.
4. Warrell DA. Bites of venomous snakes. N Engl J Med 2002;347:1804-5.
5. Senthilkumaran S, Shah S, Balamurugan N, Menezes RG, Thirumalaikolundusubramanian P. Repeated snake bite for recreation: mechanisms and implications. Int J Crit Illn Inj Sci 2013;3:214-6.
6. Chippaux JP. Snake-bites: appraisal of the global situation. Bull World Health Organ 1998;76:515-24.
7. Welton RE, Liew D, Braitberg G. Incidence of fatal snake bite in Australia: a coronial based retrospective study (2000–2016). Toxicon 2017;131:11-5.
8. Minghui R, Malecela MN, Cooke E, Abela-Ridder B. WHO's Snakebite Envenoming Strategy for prevention and control. Lancet Glob Health 2019;7(7):e837-e838.
9. Pucca MB, Knudsen C, S Oliveira I, et al. Current knowledge on snake dry bites. Toxins (Basel) 2020;12:668.
10. Escalante T, Ortiz N, Rucavado A, et al. Role of collagens and perlecan in microvascular stability: exploring the mechanism of capillary vessel damage by snake venom metalloproteinases. PLoS One 2011; 6(12):e28017.
11. Hernández R, Cabalceta C, Saravia-Otten P, Chaves A, Gutiérrez JM, Rucavado A. Poor regenerative outcome after skeletal muscle necrosis induced by Bothrops asper venom: alterations in microvasculature and nerves. PLoS One 2011; 6(5):e19834.
12. Jiménez N, Escalante T, Gutiérrez JM, Rucavado A. Skin pathology induced by snake venom metalloproteinase: acute damage, revascularization, and re-epithelization in a mouse ear model. J Invest Dermatol 2008;128:2421-8.
13. Fernandes CM, Pereira Teixeira CF, Leite AC, Gutiérrez JM, Rocha FA. The snake venom metalloproteinase BaP1 induces joint hypernociception through TNF-alpha and PGE2-dependent mechanisms. Br J Pharmacol 2007;151:1254-61.
14. Paniagua D, Vergara I, Román R, et al. Antivenom effect on lymphatic absorption and pharmacokinetics of coral snake venom using a large animal model. Clin Toxicol (Phila) 2019;57:727-34.
15. Maduwage K, Isbister GK. Current treatment for venom-induced consumption coagulopathy resulting from snakebite. PLoS Negl Trop Dis 2014;8(10):e3220.
16. Isbister GK. Snakebite doesn't cause disseminated intravascular coagulation: coagulopathy and thrombotic microangiopathy in snake envenoming. Semin Thromb Hemost 2010;36:444-51.
17. Kariyanna PT, Jayarangaiah A, Kamran H, et al. Myocardial infarction after snakebite envenomation: a scoping study. Scifed J Cardiol 2018;2:21.
18. Al-Sadawi M, Mohamadpour M, Zhyvotovska A, et al. Cerebrovascular accident and snake envenomation: a scoping study. Int J Clin Res Trials 2019;4:133.
19. Oliveira SS, Alves EC, Santos AS, et al. Bleeding disorders in *Bothrops atrox* envenomations in the Brazilian Amazon: participation of hemostatic factors and the impact of tissue factor. Toxins (Basel) 2020;12:554.
20. Clemetson KJ. Snaclecs (snake C-type lectins) that inhibit or activate platelets by binding to receptors. Toxicon 2010;56: 1236-46.
21. Silva A, Maduwage K, Sedgwick M, et al. Neuromuscular effects of common krait (Bungarus caeruleus) envenoming in Sri Lanka. PLoS Negl Trop Dis 2016;10(2): e0004368.
22. Harris JB, Scott-Davey T. Secreted phospholipases A2 of snake venoms: effects on the peripheral neuromuscular system with comments on the role of phospholipases A2 in disorders of the CNS and their uses in industry. Toxins (Basel) 2013;5:2533-71.
23. Reis LPG, Botelho AFM, Novais CR, et al. Cardiotoxic effects of Micrurus surinamensis (Cuvier, 1817) snake venom. Cardiovasc Toxicol 2021;21:462-71.
24. Péterfi O, Boda F, Szabó Z, Ferencz E, Bába L. Hypotensive snake venom components — a mini-review. Molecules 2019; 24:2778.
25. Marinho AD, Silveira JAM, Chaves Filho AJM, et al. Bothrops pauloensis snake venom-derived Asp-49 and Lys-49 phospholipases A2 mediates acute kidney injury by oxidative stress and release of inflammatory cytokines. Toxicon 2021; 190:31-8.
26. Hung DZ, Yu YJ, Hsu CL, Lin TJ. Antivenom treatment and renal dysfunction in Russell's viper snakebite in Taiwan: a case series. Trans R Soc Trop Med Hyg 2006; 100:489-94.
27. Braga JRM, Jorge ARC, Marinho AD, et al. Renal effects of venoms of Mexican coral snakes Micrurus browni and Micrurus laticollaris. Toxicon 2020;181:45-52.
28. Le Geyt J, Pach S, Gutiérrez JM, et al. Paediatric snakebite envenoming: recognition and management of cases. Arch Dis Child 2021;106:14-9.
29. Tsai TH, Lin CC, Mao YC, et al. Naja atra venom-spit ophthalmia in Taiwan: an epidemiological survey from 1990 to 2016. J Chin Med Assoc 2020;83:77-83.
30. Johnston CI, Ryan NM, Page CB, et al. The Australian Snakebite Project, 2005–2015 (ASP-20). Med J Aust 2017;207:119-25.
31. Bolon I, Durso AM, Botero Mesa S, et al. Identifying the snake: first scoping review on practices of communities and healthcare providers confronted with snakebite across the world. PLoS One 2020;15(3):e0229989.
32. Ali AJ, Horwitz DA, Mullins ME. Lack of coagulopathy after copperhead snakebites. Ann Emerg Med 2015;65:404-9.
33. Keyler DE, Saini V, O'Shea M, Gee J, Smith CF, Mackessy SP. Crotalus oreganus concolor: envenomation case with venom analysis and a diagnostic conundrum of myoneurologic symptoms. Wilderness Environ Med 2020;31:220-5.
34. Massey DJ, Calvete JJ, Sánchez EE, et al. Venom variability and envenoming severity outcomes of the Crotalus scutulatus scutulatus (Mojave rattlesnake) from southern Arizona. J Proteomics 2012;75: 2576-87.
35. Lomonte B, Fernández J, Sanz L, et al. Venomous snakes of Costa Rica: biological and medical implications of their venom proteomic profiles analyzed through the strategy of snake venomics. J Proteomics 2014;105:323-39.
36. Casewell NR, Jackson TNW, Laustsen AH, Sunagar K. Causes and consequences of snake venom variation. Trends Pharmacol Sci 2020;41:570-81.
37. Seifert S, White J, Currie BJ. Pressure bandaging for North American snake bite? No! Clin Toxicol (Phila) 2011;49:883-5.
38. Vergara I, Castillo EY, Romero-Piña ME, et al. Biodistribution and lymphatic tracking of the main neurotoxin of Micrurus fulvius venom by molecular imaging. Toxins (Basel) 2016;8:85.
39. Bhaumik S, Beri D, Lassi ZS, Jagnoor J. Interventions for the management of snakebite envenoming: an overview of systematic reviews. PLoS Negl Trop Dis 2020; 14(10):e0008727.
40. Noutsos T, Currie BJ, Lek RA, Isbister GK. Snakebite associated thrombotic microangiopathy: a systematic review of clinical features, outcomes, and evidence for interventions including plasmapheresis. PLoS Negl Trop Dis 2020;14(12):e0008936.
41. Lavonas EJ, Ruha AM, Banner W, et al. Unified treatment algorithm for the management of crotaline snakebite in the United States: results of an evidence-informed consensus workshop. BMC Emerg Med 2011;11:2.
42. Di Nicola MR, Pontara A, Kass GEN, et al. Vipers of major clinical relevance in Europe: taxonomy, venom composition,

toxicology and clinical management of human bites. Toxicology 2021;453:152724.
43. Turner D, Winter S, Winkel K, MacIsaac C, Padula A, Braitberg G. Review article: let us talk about snakebite management: a discussion on many levels. Emerg Med Australas 2019;31:542-5.
44. Wood D, Sartorius B, Hift R. Ultrasound findings in 42 patients with cytotoxic tissue damage following bites by South African snakes. Emerg Med J 2016; 33:477-81.
45. Hughes A. Observation of snakebite victims: is twelve hours still necessary? Emerg Med (Fremantle) 2003;15:511-7.
46. Dart RC, McNally J. Efficacy, safety, and use of snake antivenoms in the United States. Ann Emerg Med 2001;37: 181-8.
47. Bush SP, Ruha AM, Seifert SA, et al. Comparison of F(ab′)2 versus Fab antivenom for pit viper envenomation: a prospective, blinded, multicenter, randomized clinical trial. Clin Toxicol (Phila) 2015;53:37-45.
48. Seifert SA, Boyer LV. Recurrence phenomena after immunoglobulin therapy for snake envenomations. 1. Pharmacokinetics and pharmacodynamics of immunoglobulin antivenoms and related antibodies. Ann Emerg Med 2001;37:189-95.
49. Ramirez-Cruz MP, Smolinske SC, Warrick BJ, Rayburn WF, Seifert SA. Envenomations during pregnancy reported to the national poison data system, 2009–2018. Toxicon 2020;186:78-82.
50. Seifert SA, Mascarenas DN, Fullerton L, Warrick BJ, Smolinske SC. Unpredicted late-, new-onset thrombocytopenia and hypofibrinogenemia in Fab antivenom-treated rattlesnake envenomation. Toxicon 2020;184:55-6.
51. World Health Organization. Snakebite (https://www.who.int/health-topics/snakebite#tab=tab_1).
52. University of Adelaide. Clinical toxinology resources, 2018 (http://www.toxinology.com).
53. Association of Zoos and Aquariums. Antivenom index. University of Arizona (https://avi.pharmacy.arizona.edu/a/index#top).
54. Pla D, Quesada-Bernat S, Rodríguez Y, et al. Dagestan blunt-nosed viper, *Macrovipera lebetina obtusa* (Dwigubsky, 1832), venom. Venomics, antivenomics, and neutralization assays of the lethal and toxic venom activities by anti-*Macrovipera lebetina turanica* and anti-*Vipera berus berus* antivenoms. Toxicon X 2020;6:100035.
55. de Haro L. Management of snakebites in France. Toxicon 2012;60:712-8.
56. Warrick BJ, Boyer LV, Seifert SA. Nonnative (exotic) snake envenomations in the U.S., 2005–2011. Toxins (Basel) 2014; 6:2899-911.
57. Habib AG, Musa BM, Iliyasu G, Hamza M, Kuznik A, Chippaux JP. Challenges and prospects of snake antivenom supply in sub-Saharan Africa. PLoS Negl Trop Dis 2020;14(8):e0008374.
58. Chuang PC, Chang KW, Cheng FJ, Wu MH, Tsai MT, Li CJ. Risk factors associated with snake antivenom reaction and the role of skin test. Acta Trop 2020;203: 105293.
59. Habib AG. Effect of pre-medication on early adverse reactions following antivenom use in snakebite: a systematic review and meta-analysis. Drug Saf 2011; 34:869-80.
60. Chuang PC, Chang KW, Cheng SY, et al. Benefits of early in-hospital antivenom administration to patients with *Protobothrops mucrosquamatus* envenomation. Am J Trop Med Hyg 2021;104:323-8.
61. Anderson VE, Gerardo CJ, Rapp-Olsson M, et al. Early administration of Fab antivenom resulted in faster limb recovery in copperhead snake envenomation patients. Clin Toxicol (Phila) 2019;57:25-30.
62. Freiermuth CE, Lavonas EJ, Anderson VE, et al. Antivenom treatment is associated with fewer patients using opioids after copperhead envenomation. West J Emerg Med 2019;20:497-505.
63. Cumpston KL. Is there a role for fasciotomy in Crotalinae envenomations in North America? Clin Toxicol (Phila) 2011; 49:351-65.
64. Yeh H, Gao SY, Lin CC. Wound infections from Taiwan cobra (*Naja atra*) bites: determining bacteriology, antibiotic susceptibility, and the use of antibiotics — a cobra BITE study. Toxins (Basel) 2021; 13:183.
65. Zeng X, Hu J, Liang X, et al. Acute cerebral infarction following a Trimeresurus stejnegeri snakebite: a case report. Medicine (Baltimore) 2019;98(23):e15684.
66. Ratnayake I, Shihana F, Dissanayake DM, Buckley NA, Maduwage K, Isbister GK. Performance of the 20-minute whole blood clotting test in detecting venom induced consumption coagulopathy from Russell's viper (Daboia russelii) bites. Thromb Haemost 2017;117:500-7.
67. Leffers P, Ferreira J, Sollee D, Schauben J. Thromboelastography in the management of snakebite-induced coagulopathy: a case series and literature review. Blood Coagul Fibrinolysis 2018;29:656-60.
68. Seifert SA, Kirschner RI, Martin N. Recurrent, persistent, or late, new-onset hematologic abnormalities in Crotaline snakebite. Clin Toxicol (Phila) 2011;49: 324-9.
69. Bush SP, Seifert SA, Oakes J, et al. Continuous IV Crotalidae polyvalent immune Fab (ovine) (FabAV) for selected North American rattlesnake bite patients. Toxicon 2013;69:29-37.
70. Laustsen AH. Guiding recombinant antivenom development by omics technologies. N Biotechnol 2018;45:19-27.
71. Sánchez EE, Rodríguez-Acosta A. Inhibitors of snake venoms and development of new therapeutics. Immunopharmacol Immunotoxicol 2008;30:647-78.
72. Komives CF, Sanchez EE, Rathore AS, et al. Opossum peptide that can neutralize rattlesnake venom is expressed in Escherichia coli. Biotechnol Prog 2017;33:81-6.
73. Arias AS, Rucavado A, Gutiérrez JM. Peptidomimetic hydroxamate metalloproteinase inhibitors abrogate local and systemic toxicity induced by Echis ocellatus (saw-scaled) snake venom. Toxicon 2017; 132:40-9.
74. Lauridsen LH, Shamaileh HA, Edwards SL, Taran E, Veedu RN. Rapid one-step selection method for generating nucleic acid aptamers: development of a DNA aptamer against α-bungarotoxin. PLoS One 2012;7(7):e41702.