North American Poisonous Bites and Stings

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KEYWORDS

• Envenomations • Poisonous bites • Poisonous stings • North America

KEY POINTS

- North American scorpion, arachnid, Hymenoptera, and snake envenomations cause clinically significant problems.
- Critical care management of envenomed patients can be challenging for clinicians.
- Although the animals are located in specific geographic areas, patients envenomed may travel to endemic areas and present to health care facilities remote from the exposure.

This article focuses on the management of the most common North American scorpion, arachnid, Hymenoptera, and snake envenomations that cause clinically significant problems. Water creatures and less common animal envenomations are not covered in this article. Critical care management of envenomed patients can be challenging for clinicians. Although the animals are located in specific geographic areas, patients envenomed on passenger airliners and those who travel to endemic areas may present to health care facilities distant from the exposure.

HYMENOPTERA

This taxonomic order, Hymenoptera, consists of bees, ants, and wasps. These insects have stingers that can cause local reactions and anaphylaxis in susceptible patients. Confusion often exists regarding the differences between bees and wasps. **Table 1** illustrates some of the key differences between relevant Hymenoptera.[1–4]

Wasps are neither bees nor ants and they have hairless, smooth bodies. They can sting multiple times because their stingers are smooth and retractable. Wasps feed on all types of sugary substances whereas bees feed on flower nectar. Bee stingers are barbed so a bee is likely to eviscerate itself after a single sting.

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Table 1
Hymenoptera characteristics

Insect	Envenomation Mechanism	Nest
Bees	Barbed stinger (stings once)	Hives, above or below ground; vertical flat wax honeycomb
Wasps (including hornets and yellow jackets)	Smooth stinger (may sting repeatedly)	Hollowed-out trees or in-ground burrows; paper-like combs, often horizontal
Ants (fire ants)	Modified ovipositor (female)	Ground mounds

Data from Refs.[1–4]

Hybridized bees are often called Africanized bees or killer bees in the lay press. In 1957, European honeybees crossbred with African species in Brazil, South America. Unfortunately the crossbreeding did not improve the aggressive nature of the African species. Gradually the hybridized bees made their way from South America in the mid-1950s through Central America, landing in the Southwestern United States in the 1990s. Their migration continues to spread northward each year. Hybridized bees are more aggressive than their European counterparts and they defend their nests farther.[5]

Ants are social insects that form nests in the ground. The ants with the most significance in North America are the black imported fire ant (*Solenopsis richteri*), the red imported fire ant (*Solenopsis invicta*), and the harvester ant (*Pogonomyrmex* species). Fire ants were introduced into the Southeastern United States port of Mobile, Alabama, in 1939 from Brazil.[6,7] They have spread rapidly throughout the United States. Harvester ants are located primarily in the Southwestern United States. These insects can cause reactions similarly to stings from other hymenoptera species. The mechanism of envenomation is through a stinger much like a bee or wasp. The ant grasps its pray with mandibles and injects them with a stinger located at the tip of the gaster (ie, the caudal end of the abdomen).[8]

Hymenopteran venom can cause varying effects depending on the amount injected, the number of stings, and the host's immune system reaction. These can range from local reactions to significant reactions, such as life-threatening anaphylaxis. Components of the venom include peptides, vasoactive substances, and enzymes causing catecholamine release, mast cell degranulation, and pain (**Table 2**).[4,9–13]

The severity of envenomation reactions cannot be predicted.[14] Allergic reactions from Hymenoptera occur through immunoglobulin E (IgE)-mediated reactions or type I hypersensitivity. These reactions are a consequence of previous exposure to Hymenopteran venom causing antibodies to be produced. On subsequent exposure, a reaction occurs

Table 2
Major hymenopteran venom components and actions

Venom Component	Action
Melittin	Increases cell membrane permeability
Phospholipase A2	Major antigen and allergen; coagulopathy
Hyaluronidase	Increases tissue permeability
Serotonin	Pain
Acetylcholine	Pain

when mast cell degranulation occurs, releasing several substances, including histamine. The reaction may be quick and severe.[15] The most severe reactions can cause tissue edema, erythema, cardiovascular collapse, respiratory distress from bronchospasm, severe urticaria, and death. Treatment of severe reactions includes antihistamines, corticosteroids, inhaled β-adrenergic agonists, and epinephrine.

Cross-reactions between Hymenoptera species may occur. Those with reactions to fire ant stings are likely to have a reaction to bee and wasp stings. The reverse may also be true. Those with bee venom reactions are unlikely to have a significant reaction to wasp stings.[7,16]

Patients with significant envenomation may require ICU admission for frequent monitoring and development of severe systemic symptoms. Otherwise mild to moderately symptomatic patients can be admitted for observation to a monitored bed.

Evaluation of these patients should be tailored as patient specific (**Table 3**). Those with comorbid conditions, such as coronary artery disease, should be scrutinized more closely than healthy individuals without medical problems.

Minor local reactions consist of mild edema, erythema, pain, and pruritus and may be symptomatically treated and carefully monitored. Moderate to severe reactions may occur from large envenomations. These are not mediated through IgE.

Depending on the Hymenoptera species, a significant number of hybridized bee stings is considered approximately 50.[17] Patients with 50 or more stings should be observed for systemic symptoms for up to 24 hours. Delayed systemic problems (renal, hematologic, and neurologic) can occur 8 to 24 hours postenvenomation.[5] The median lethal dose from honeybee envenomation is estimated through animal models to be 19 stings per kilogram body weight.[18]

Removal of stingers should be performed to avoid foreign body reactions from the retained stingers. The technique of scraping or squeezing the stingers was once debated. Theoretically, squeezing the stinger may inject further venom into the wound. The venom apparatus continues to contract, however, propagating venom into the wound even after the bee is disemboweled. Removing stingers quickly by any method results in less venom injected into the wound.[19] In patients with multiple stings, the amount of venom left in the venom sac is minimal so any method would be satisfactory for removal.

Systemic signs and symptoms consist of nausea, vomiting, abdominal pain, rhabdomyolysis, renal injury, coagulopathy, serum transaminase elevations, seizures,

Table 3
Laboratory testing in severe envenomations by Hymenoptera

Test	Potential Findings
Complete blood cell count	Anemia, thrombocytopenia, leukocytosis
Serum urea nitrogen, creatinine, electrolytes	Acute kidney injury
Serum transaminases	Liver involvement
Prothrombin time	Coagulopathy (DIC)
Serum creatine kinase	Rhabdomyolysis
Plasma fibrinogen	DIC
Urinalysis	Hematuria
Cardiac biomarkers	Myocardial infarction
Chest radiograph	Pulmonary edema
Electrocardiogram	Myocardial infarction

headache, disseminated intravascular coagulation (DIC), myocardial infarction, stroke, and edema. Specific treatments should be tailored for each of these issues. It is imperative that patients with allergic and anaphylactic reactions be discharged with a prescription for a subcutaneous epinephrine autoinjector (EpiPen).

Type III hypersensitivity may occur in those patients with significant envenomation. These reactions manifest as joint pain, fever, swelling, and rash approximately 5 to 10 days after envenomation. Often called serum sickness, the treatment includes corticosteroids and supportive care but rarely requires hospitalization.

SPIDERS (ARACHNIDA)

Arachnids have a worldwide distribution but cause a few clinically significant envenomations despite public belief that implicates them as a common cause of cutaneous abscess formation. In North America, there are only a few species of arachnids that can cause significant clinical problems.

Loxosceles reclusa (Brown Recluse)

The brown spider has a characteristic violin-shaped area on its back. The genus, *Loxosceles*, is distributed worldwide. Some species cause significant clinical findings whereas others do not. The spider lives in woodpiles and feeds at night. The female spiders are more likely to envenomate than the male spiders and to bite when provoked. The species that causes clinically significant findings in the United States is *L reclusa*. Distribution of this particular spider is limited to the Southeastern United States (**Fig. 1**).[20]

The venom of *L reclusa* consists of several enzymes that affect human tissue. Important enzymes include sphingomyelinase D and hyaluronidase.[21,22] These enzymes cause a series of reactions, leading to tissue damage by way of inflammatory mediators. Eventually tissue necrosis occurs, with some severe wounds requiring skin grafting. Other spiders can cause necrotic wounds that may be similar in appearance to bites from *L reclusa* but less severe.

Diagnosis of an envenomation caused by *L reclusa* is through identification of the spider, if available. There are no routine laboratory tests to confirm envenomation. Laboratory tests in severe envenomations should include those that detect hemolysis,

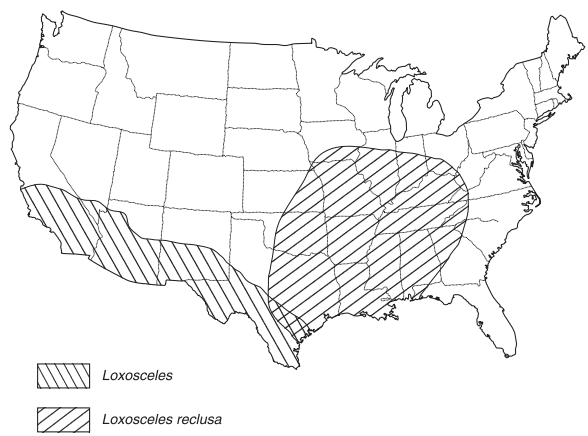

Fig. 1. *Loxosceles* species distribution.

hematuria, and coagulopathy. **Table 4** serves as a guide for testing in severe envenomations by *Loxosceles*.

Clinical symptoms of envenomation may not be immediate because the spider bite may not be initially noticed but often it presents as a stinging pain. As the wound blisters and bleeds over the next 24 to 48 hours, it eventually forms a necrotic lesion during the next 5 to 7 days.[23–25] The wound eschar ulcerates over the next 1 to 2 weeks and may require skin grafting and débridement at a later date.

Typically, bites by *L reclusa* do not require ICU admission except in cases of systemic loxoscelism, which occurs 24 to 72 hours after the bite. This syndrome presents with fever, chills, nausea, vomiting, arthralgias, DIC, rhabdomyolysis, and hemolysis.[24,26–29] Severe cases involve respiratory failure, soft tissue edema, renal failure, and rarely death. Management of systemic symptoms is mainly supportive with standard treatments, such as mechanical ventilation, blood product transfusions, and hemodialysis as necessary.[23]

Antivenom treatment of *Loxosceles* species is not available in the United States but is available in Brazil, Argentina, Peru, and Mexico.[30] Treatment with steroids, antihistamines, and prophylactic antibiotics is not recommended. Antibiotics should be started in patients with signs and symptoms of infection. Dapsone was believed to help with decreasing leukocyte aggregation at the bite site reducing tissue damage.[31–33] Results with dapsone use are mixed. Without a well-designed clinical trial to support its use, it should not be used routinely.[24] Early excision of the bite site is not recommended because scarring is likely to occur.[34] Hyperbaric oxygen therapy has been used with mixed results; its use is not recommended.[33,35–37] On discharge from a hospital, patients should be referred to a specialist who can manage the wound for healing and possible débridement.

Latrodectus Species (Black Widow Spiders)

Black widow spiders (*Latrodectus mactans*) belong to the general category of *Latrodectus* species, which are similar around the world. There are many subspecies, but their venoms and characteristics are similar. The spiders live in woodpiles and garages, particularly in dark places. They feed primarily at night with their meals consisting of insects. Black widow female spiders are much larger than their male counterparts. Because of their size, female spiders are responsible for all significant human bites because their fangs are long enough to penetrate through skin. Often after mating, the female spider eats the male spider, giving this arachnid the name, black widow.

Table 4
Laboratory testing in severe envenomations caused by *L reclusa*

Test	Potential Findings
Complete blood cell count	Anemia, thrombocytopenia, leukocytosis
Serum urea nitrogen, creatinine, electrolytes	Acute kidney injury
Serum transaminase activity	Liver involvement
Prothrombin time	Coagulopathy (DIC)
Serum creatine kinase activity	Rhabdomyolysis
DIC panel	DIC: fibrinogen (↓), fibrin(ogen) split products (↑), D-dimer (↑)
Urinalysis	Hematuria
Coombs test	Hemolysis

The bite of the black widow generally results in the onset of intense pain, with or without evidence of fang marks or the classic target sign. There may be local sweating due to local norepinephrine release at the bite site. The onset of symptoms is generally within 30 to 60 minutes and lasts 24 to 48 hours. The venom contains α-latrotoxin, which causes catecholamine release through neurotransmitter stimulation of norepinephrine and acetylcholine into synaptic terminals.[38,39] The result is severe muscle spasm, tachycardia, high blood pressure, agitation, pain, diaphoresis, and anxiety. The envenomation may cause abdominal muscle spasms and symptoms mimicking acute appendicitis.

Treatment of black widow bites includes pain control with opioids and anxiolytic medications, such as benzodiazepines. Intravenous (IV) fluids may correct dehydration from hyperadrenergic stimulation. Most patients require only pain control without needing admission. Only the most severely symptomatic patients require further care in the hospital. Severely envenomed patients may require high doses of analgesia to control pain. Those with comorbid conditions, such as underlying cardiac or respiratory disease, may require more aggressive supportive care with other agents. Calcium infusions were believed to help the symptoms of black widow bites; however, this intervention has not been proven effective.[40]

Severe black widow envenomation that causes systemic symptoms is known as latrodectism. These symptoms may include facial swelling (latrodectus facies), parvor mortis (feeling of impending doom), tachycardia, chest pain, diaphoresis, conjunctivitis, muscle spasms, nausea, vomiting, abdominal pain, and priapism.[41–45] Rarely, severe hypertension, respiratory depression, compartment syndrome, and gangrene at the bite site have been reported. Death from *Latrodectus* envenomation is rare and has not been reported in decades.

If antivenom is available, the indications are summarized in **Box 1**. Pregnant patients and those with comorbid conditions, such as coronary artery disease or chronic obstructive pulmonary disease, are at high risk and should receive antivenom.[46–49] Merck has manufactured black widow spider antivenin since the 1950s. As of late 2011 this antivenom was still available on a limited basis from the manufacturer. Use of this equine-derived antivenom has been used sparingly in the United States. This may be because of a case report of a death after a patient received this antivenom.[40] The package insert states that either a skin test or conjunctival test should be performed for the possibility of an allergic reaction to antivenom.[50] Skin testing does not exclude the possibility of anaphylaxis to antivenom, and routine skin testing is not recommended.[51] Careful consideration should be performed in those with allergies to horses and horse products as well as patients with asthma because deaths have been reported after antivenom administration.[40,52] The usual dose is one vial, with subsequent administration of additional vials if the symptoms have not resolved. Each vial should be infused over 20 to 30 minutes to avoid anaphylactoid reactions. Time to relief of symptoms after antivenom treatment averages 31 minutes.[41,53] Serum sickness, which manifests as fever, joint pain, and rash, has often occurred with this antivenom.

Box 1
Indications for *Latrodectus mactans* antivenin

Uncontrolled hypertension

Respiratory difficulties

Pregnancy

Intractable pain

SCORPION

Scorpions are located throughout the Southwestern United States. There are many species of scorpions in North America but only one causes clinically relevant symptoms. The *Centruroides sculpturatus*, also known as *Centruroides exilicauda*, is colloquially referred to as the bark scorpion. These scorpions are located in the Southwestern United States, especially in Arizona, California, New Mexico, Texas, and Nevada. Scorpions have been transported to other non-native areas as stowaways, causing surprise and pain.[54,55]

Scorpions have several distinctive anatomic features. These parts are the pinchers, or pedipalps, and grabbers, or chelicerae, which assist moving food to its mouth; the tail or metasomal segments; and the telson, or stinger (venom apparatus). The exoskeleton is made of chitin. The chemical, β-carboline, contained in the exoskeleton causes the scorpion to fluoresce under ultraviolet light.[56]

Scorpion venom is injected into its victim to cause immobilization through neurotoxic effects. The venom contains many components but the effect on humans is centered on the sodium channels. Sodium channels are dual-gated channels that are affected by the inhibited closure of one of these gates, thereby depleting the channel for sodium. This results in repeated action potentials generated stimulating the neuron. Clinically these effects manifest as muscle jerking, opsoclonus (rapid, irregular, and nonrhythmic eye movements), tongue fasciculations, and loss of muscle control. Opsoclonus is often referred to as nystagmus; however, these 2 entities are separate. Nystagmus is a rhythmic oscillation of the eyeballs, with alternating fast-phase and slow-phase movements within a particular plane, whereas opsoclonus is unpredictable in both movement and direction.

Venom effects are especially worrisome in infants, children, and elderly patients. The most severe symptoms occur when there is loss of the airway muscles coupled with increased salivation causing the inability to control secretions, leading to respiratory failure. Pancreatitis is not a common finding in envenomations by *Centruroides* but is associated with those stung by Buthidae, a scorpion indigenous to Trinidad.[57]

Symptom onset may occur immediately to 15 minutes after envenomation.[58] The severity of symptoms may depend on the amount of antivenom injected into the victim. Half-life of the venom ranges from 313 minutes to 515 minutes.[59] Generally, minimal to no local wound effects are seen. There may be erythema and pruritus. Local symptoms include pain and paresthesia at the bite site and may progress proximally in the affected limb. A grading scale has been developed for scorpion envenomations, and a summary of these signs and symptoms is given in **Table 5**.[60]

Table 5
***Centruroides* scorpion severity grade**

Grade I	Pain or paresthesia at the sting site
Grade II	Pain or paresthesia at the sting site and remote areas
Grade III	Cranial nerve and autonomic dysfunction[a] or somatic skeletal neuromuscular dysfunction[b]
Grade IV	Both cranial nerve and somatic skeletal neuromuscular dysfunction

[a] Cranial nerve dysfunction: blurred vision, opsoclonus, hypersalivation, tongue fasciculation, dysphagia, dysphonia, upper airway abnormalities.
[b] Somatic skeletal neuromuscular dysfunction: restlessness, severe involuntary extremity movements (limb jerking).

Poison control center data reveal there were no deaths in 2010 from scorpion envenomations.[61] This may be due to the availability of an F(ab′)2 antivenom that has been used on an investigational basis in areas endemic to scorpions.

The management of most scorpion stings includes pain control with nonsteroidal anti-inflammatory agents, opioid medications, and anxiolytic drugs. Antivenom is reserved for those individuals who have severe systemic symptoms, such as grade III or grade IV findings. As of 2011, *Centruroides* (scorpion) immune F(ab′)2 (equine) injection (Anascorp) was Food and Drug Administration approved for use in severely envenomed patients.[62] **Fig. 2** and **Box 2** outline treatment algorithms for using the antivenom. In a randomized, double-blind study, the severity of symptoms were significantly decreased 2 hours after infusion of the antivenom.[63] The most common adverse reactions occurred in approximately 2% of patients. These were mainly vomiting, pyrexia, rash, nausea, and pruritus.[62] Antivenom treatment may not halt all symptoms of envenomation. This is due to the inability of antivenom to reach venom at the level of affected neurons or certain other tissues. In addition, the amount of venom may exceed the antivenom's neutralizing power (ie, insufficient antivenom). Patients treated with antivenom generally are discharged home. Rarely, patients

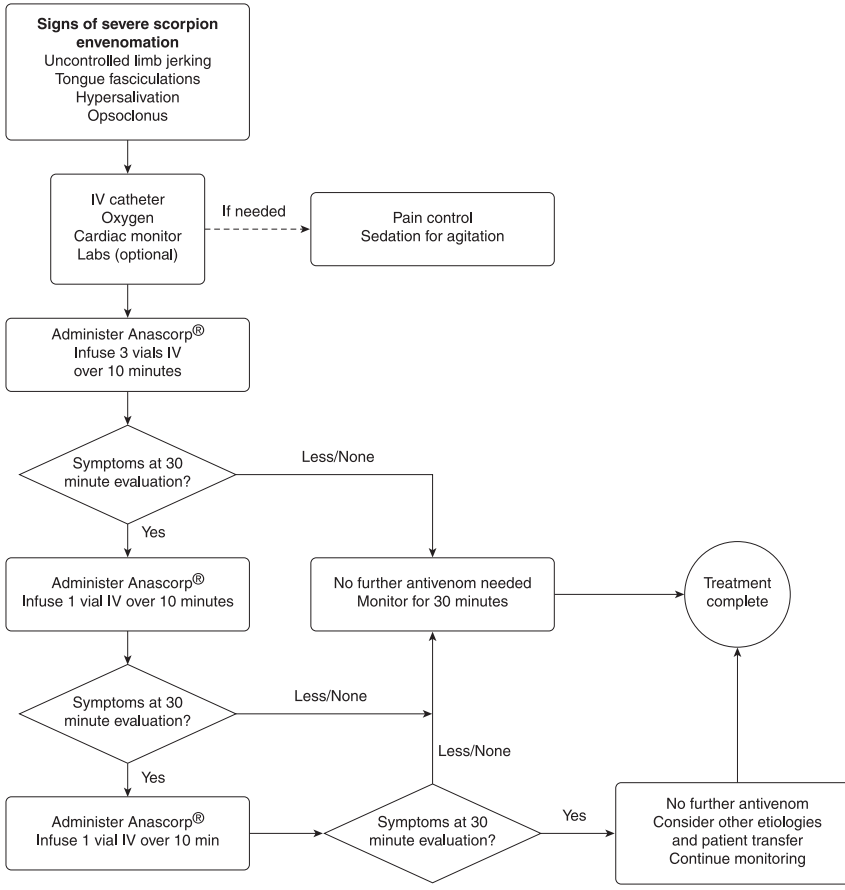

Fig. 2. Anascorp treatment flow diagram.

Box 2
Anascorp dosing

- Give initial dose of 3 vials
  - Reconstitute each vial with 5 mL normal saline
  - Add the contents of the 3 vials to a 50 mL bag of sterile normal saline
  - Infuse IV over 10 minutes minimum
- Monitor patient up to 60 minutes for improvement of signs and symptoms
- Give additional doses, one vial each (up to 2 doses) if symptoms do not improve
  - Reconstitute each vial with 5 mL normal saline
  - Add the contents of the vial to a 50-mL bag of sterile normal saline
  - Infuse IV over 10 minutes minimum
- Monitor patient up to 60 minutes for improvement of signs and symptoms

Data from Anascorp package insert.

who continue to have severe symptoms despite antivenom treatment may be observed for 24 hours and be discharged home after symptoms improve.

Severe envenomations (grade III or IV) may be managed without the use of antivenom. Patients are treated with symptomatic relief and may require airway support with mechanical ventilation along with sedation for severe agitation. Ventilated patients require approximately 24 to 48 hours of mechanical ventilation.[64] Complications associated with severe scorpion envenomation include aspiration pneumonitis, rhabdomyolysis, dehydration, and convulsions. The use of corticosteroids, antihistamines, and antibiotics is not routinely recommended. Antibiotics should be reserved for those patients who have signs and symptoms of bacterial infections. Those envenomed by scorpions may continue to complain of numbness, tingling, paresthesia, and pain that may persist for weeks without permanent sequelae.

SNAKES

Snakes play an important role in nature's ecology by controlling the population of rodents and other small animals. Snakes are often feared by hikers, backpackers, campers, and swimmers, including men, women, and children. Treating snakebite patients can be challenging. The most common poisonous snakes encountered in North America belong to the subfamily Crotalinae (family Viperidae) and the subfamily Elapinae (family Elapidae). The subfamily Crotalinae includes the genera *Crotalus*, *Agkistrodon*, and *Sistrurus*. The subfamily Elapinae includes the genus *Micrurus*. These snakes can cause substantial morbidity and mortality in those who have been bitten and envenomed.

Coral Snakes (Elapidae)

Coral snakes belong to the family Elapidae, which includes species that are distributed around the world. In North America, *Micrurus* species are located primarily on the Gulf Coast states of the United States. The 2 clinically relevant species are *Micrurus fulvius fulvius* (Eastern coral snake) and *Micrurus fulvius tenere* (Texas coral snake). The species *Micruroides euryxanthus euryxanthus* (Sonoran or Arizona coral snake) is not considered significantly venomous because the amount of venom delivered is

much less than the bites of other coral snakes (**Fig. 3**). Several nonvenomous snakes have a similar appearance to the coral snake, including the king snake and milk snake. The mnemonic, "red on yellow, kill a fellow; red on black, venom lack," holds true only for coral snakes north of Mexico City.[65]

Envenomation by the coral snake occurs through grooved fixed fangs where venom flows down into the wound created by the reptile biting through the victim's skin. Effective envenomation occurs when the snake chews and attaches itself as venom enters the wound.

Coral snake venom contains several components that cause systemic neurotoxic effects and local wounds. Neurologic venom effects are caused by α-neurotoxin.[66] Wound effects are caused primarily by phospholipase A2.[67]

The diagnosis of a coral snake bite may not be readily apparent. The bite site may not be seen and local swelling may not occur. Symptoms of coral snake envenomation include nausea, vomiting, headache, abdominal pain, diaphoresis, paresthesias or numbness, dysphonia, dysphagia, or respiratory insufficiency leading to respiratory failure.[68] Symptoms may be delayed up to 12 h or longer.[69] Careful monitoring of a patient's respiratory status should be performed in the ICU setting and mechanical ventilatory respiratory support should not be delayed when signs and symptoms occur. The use of end-tidal capnometry or capnography, pulse oximetry, and arterial blood gases may be helpful in monitoring a patient's respiratory status. Complete resolution of the neurologic effects takes weeks. Envenomed patients suffer neurologic effects causing paralysis for 3 to 5 days if they are untreated with antivenom.[70]

Severe manifestations (described previously) are associated with the Eastern coral snake (*Micrurus fulvius fulvius*). Envenomation with the Texas coral snake (*Micrurus fulvius tenere*) may not require treatment with antivenom and only require pain control. Bites with this coral snake cause local effects (pain, swelling, erythema, or paresthesia) without neurologic impairment. Patients envenomed by a coral snake west of the Mississippi river may be monitored for 8 hours and treatment with antivenom is considered for those with progressively worsening bites and systemic effects.[71]

The decision to treat with coral snake antivenom must be weighed against the availability of antivenom and geographic consideration of the type of coral snake species that caused the bite. Dosing for the Wyeth coral snake antivenom consists of an initial dose of 5 vials with a repeat dose of 5 vials if symptoms do not improve.[72] In significant envenomations, more than 10 vials may be required. Antivenom is likely not effective once neurologic signs and symptoms occur.[69]

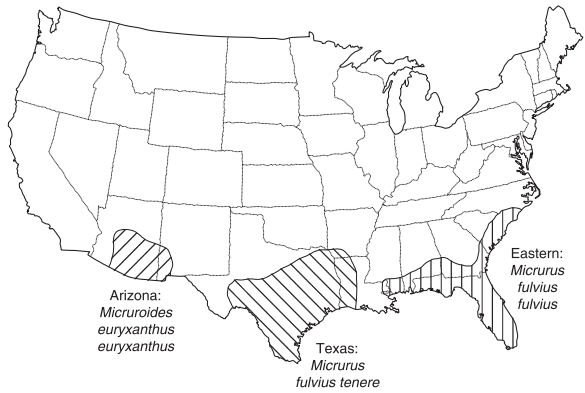

Fig. 3. Coral snake distribution in North America.

Treatment of coral snake envenomations in the United States will be challenging in the coming years because production of the Wyeth North American coral snake antivenom (equine origin) was discontinued in October 2010. The availability of antivenom is limited to stock on hand. Antivenom administration is recommended with significant envenomations, especially east of the Mississippi River, because of the prolonged neurologic effects.

Pit Viper (Crotalinae)

Of all the venomous creatures encountered in North America, bites from Crotalinae, or pit vipers, may be the most deadly. The total number of crotaline exposures reported to US poison control centers in 2010 was 3465 with 1 death reported.[61] **Fig. 4** show the areas where the genera *Crotalus*, *Agkistrodon*, and *Sistrurus* are found. *Crotalus* and *Sistrurus* possess rattles and are called rattlesnakes. *Agkistrodon*, which includes the cottonmouth (*Agkistrodon piscivorus*) and the copperhead (*Agkistrodon contortrix*), lacks rattles.

Pit vipers have poor eyesight, are deaf, and rely on their heat sensing pits as well as their sense of smell to detect prey. Their venom is delivered through sharp, hollow, mobile fangs from venom sacs. The speed and striking distances of the snake can be as fast as 8 feet per second and up to one-half of the snake's body length, respectively.[73]

Venom

Venom composition is complex and unpredictable. Factors that influence the composition vary from species to species, and by geographic location, diet, and time between feedings for the snake.[72] Venom components affect certain body processes.

Fig. 4. Distribution of Crotalinae in North America. (*A*) *Crotalus*, (*B*) *Agkistrodon*, and (*C*) *Sistrurus*.

Each of these is essential to immobilize prey and to initiate the digestive process. Venom contains numerous proteins. **Table 6** summarizes some key components of pit viper venom.[65,72]

Pit viper venom causes tissue damage by increasing cell permeability. Blood and fluid from cell damage contribute to wound swelling. Fluid accumulates under the skin causing blebs filled with a mixture of substances resulting from reactions catalyzed by enzymes in the venom. The blebs are often bluish black in color and may swell impressively. Hemorrhage into the surrounding tissue occurs through the venom's effects on hematologic processes.

Hematologic effects of pit viper venom generally affect prothrombin time, fibrinogen, and platelets through consumptive coagulopathy. These reactions occur through a process that resembles DIC. True DIC is generally caused by sepsis, cancer, and endothelial insults activating the coagulation cascade to cause hemolytic anemia and intravascular clotting. DIC can occur in pit viper envenomations but it is rare. The syndrome caused by this venom's thrombin-like protein and other proteolytic enzymes results in fibrinolysis with decreased fibrinogen and thrombocytopenia from platelet aggregation and consumption at the bite site. A disorganized, uncrosslinked fibrin clot forms and is rapidly degraded into fibrin degradation products. Patients do not have problems with clotting because thrombin and factor XIII are not affected by pit viper venom and cross-linked fibrin clots continue to form. D-dimer assay results generally be in the normal range. **Fig. 5** depicts this process.

Neurologic effects are associated with crotalid envenomation, particularly that of the Mohave rattlesnake (*Crotalus scutulatus scutulatus*) and the Southern Pacific rattlesnake (*Crotalus oreganus helleri*). Geographically these rattlesnakes are located in California and Arizona. Mohave toxin A is a neurotoxin in the venom of these rattlesnakes that immobilizes its prey and causes the described tissue effects. The mechanism of action of this neurotoxin is through the inhibition of acetylcholine at presynaptic neuron terminals. Mohave toxin A may cause respiratory depression, cranial nerve palsies, and generalized weakness.[74] **Table 7** summarizes specific clinical effects for certain pit viper species.[75–77]

Diagnosis

The presentation of patients with pit viper bites depends on the severity. The most common clinical findings are fang marks, edema, weakness, pain, diaphoresis, paresthesia, and abnormal pulse rate.[72,78] Patients may not even realize they have been envenomed and have only pain and minimal swelling at the bite site.

The degree of envenomation varies. A bite is classified as a dry bite if it causes little or no swelling and no laboratory abnormalities. Dry bites are reported to occur in approximately 20% of all pit viper bites.[72] Those patients that present with no

Table 6
Summary of key pit viper venom components

Venom Components	Clinical Effects
Low molecular weight polypeptides	Shock from capillary leakage causing third spacing
Metalloproteinases	Hemorrhage into tissues and shock
Thrombin-like glycoproteins, fibrinolysins	Coagulopathy, thrombocytopenia, and hypofibrinogenemia
Digestive enzymes	Tissue damage, edema, and hemorrhage
Myotoxins	Muscle necrosis

significant evidence of pit viper envenomation can be observed for a minimum of 6 hours. Initial blood work should be obtained (**Table 8**) on arrival and repeat complete blood cell count, prothrombin time, and fibrinogen levels obtained in 6 hours to determine if any hematologic venom effects are occurring. Vigilant observation for swelling, bleeding, systemic symptoms (eg, nausea or vomiting), and increasing pain must be performed during this period. Taking measurements of the extremity every 30 minutes monitors for swelling progression (**Fig. 6**). Asymptomatic patients with no laboratory abnormalities during this observation period may be discharged without further treatment. Exceptions to this recommendation are children and lower extremity wounds. Significant swelling may not be evident and may go unnoticed. Conservative observation in the hospital may be warranted in select patients.[80,81]

A summary of pit viper envenomation severity is contained in **Table 9**. Mild bites cause slight local swelling and pain but without laboratory abnormalities. Moderate to severe envenomations are associated with laboratory abnormalities in platelet count, fibrinogen level, and prothrombin time along with significant swelling and pain. Severe envenomations manifest these plus severe respiratory and cardiovascular problems. Systemic signs and symptoms of envenomation include a metallic taste, nausea, vomiting, hypotension, and bradycardia.

Moderate pit viper bites may develop fluid-filled blebs, or blood blisters. If the skin covering the bleb is removed, the tissue beneath may appear dusky and necrotic. Sensation to this exposed area is a good sign that the tissue may not require significant débridement. Insensate areas indicate the wound is necrotic and amputation or significant débridement may be required at a later time. During the acute phase of pit viper treatment, the wounds do not require immediate débridement, but surgical intervention can be considered once control of venom effects are stabilized with antivenom. Severe swelling and lymphangitis generally occur, which may give the impression that the bite is infected. Bacterial infection is rare, however, and antibiotics are only indicated if there is evidence of infection. Hemorrhage and swelling may occur remote from the bite site. There is no specific treatment other than antivenom.

The spread of pit viper venom is propagated by the lymphatic system except in those rare cases of intravascular envenomation. With each movement of the limbs the lymph system transports venom to the central circulation. Eventually, the venom circulates throughout the body via the bloodstream. There may be lymphatic swelling. Tender inguinal and axillary lymph nodes may indicate advancement of venom.

Management

Consultation with a clinician experienced with pit viper bites is recommended, especially for moderate to severe envenomations. Admission to the hospital is based on the severity of the bite. Mild pit viper bites on the upper extremity may be observed for a period of time in the emergency department with frequent limb measurements to monitor for progression of swelling. Laboratory examination of platelet count, fibrinogen level, and prothrombin time should be made on arrival and at 8 hours postbite to assess whether antivenom treatment is required. Lower extremity bites should be observed for a minimum of 24 hours because those compartments are much larger than the upper extremities and significant swelling may go unnoticed. Moderate and severe envenomations require admission to the ICU because antivenom treatment, wound care, cardiopulmonary, and neurologic monitoring are necessary.

Measure the affected extremity at 3 sites of the extremity (see **Fig. 6**) every 30 minutes initially to assess for worsening swelling and to determine the necessity for antivenom treatment. Once antivenom has started to infuse, hourly measurements

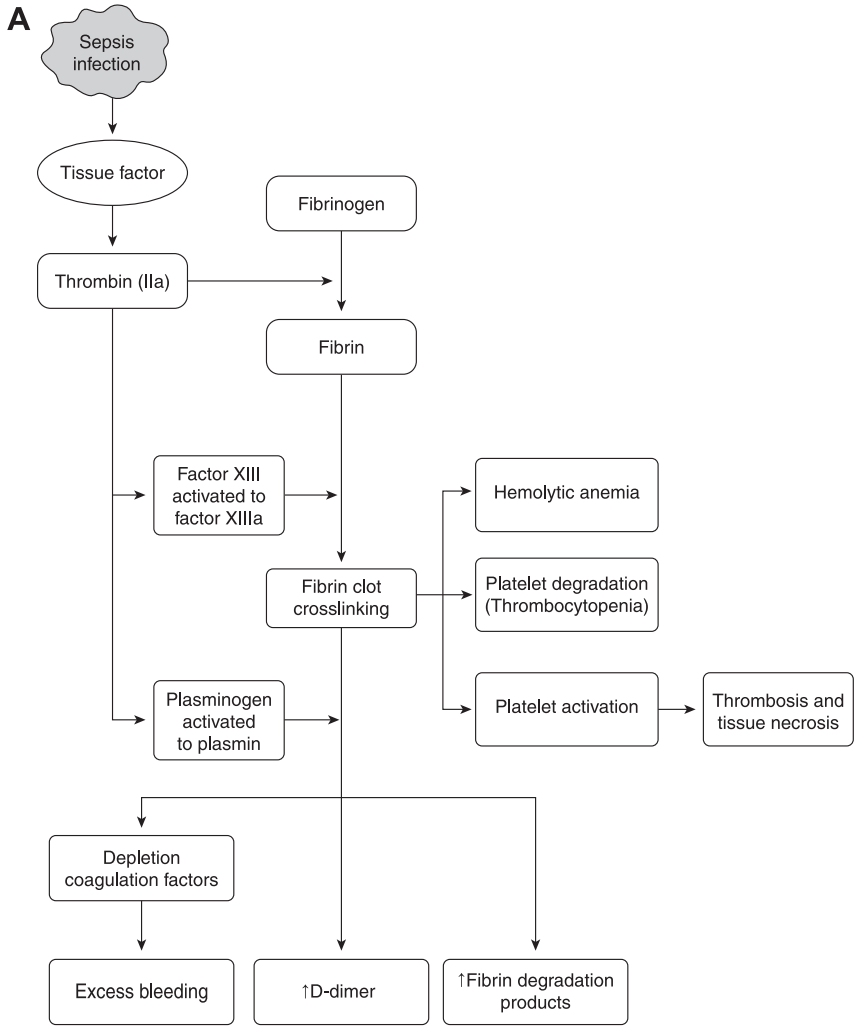

Fig. 5. Hematologic effects of crotaline venom and comparison to DIC. (*A*) DIC and (*B*) pit viper.

should be taken until the swelling has stabilized. Measurements can then be taken every 4 to 6 hours during maintenance antivenom infusions. Recording the measurements on a nursing flow sheet or progress note is essential to monitor for worsening swelling. Uncontrolled pain may be an indication to measure compartment pressures.

Patients should be placed on a cardiac monitor and receive supplemental oxygen. Two large-bore IV catheters should be inserted. Depending on the degree of envenomation, IV fluid boluses of isotonic crystalloid solutions should be instituted, especially in moderate to severe bites. Third spacing of fluids can cause significant swelling in the extremity and deplete intravascular volume leading to hypotension. Decreased urine output may occur in those victims that develop hypotension or rhabdomyolysis, either of which can result in acute kidney injury.

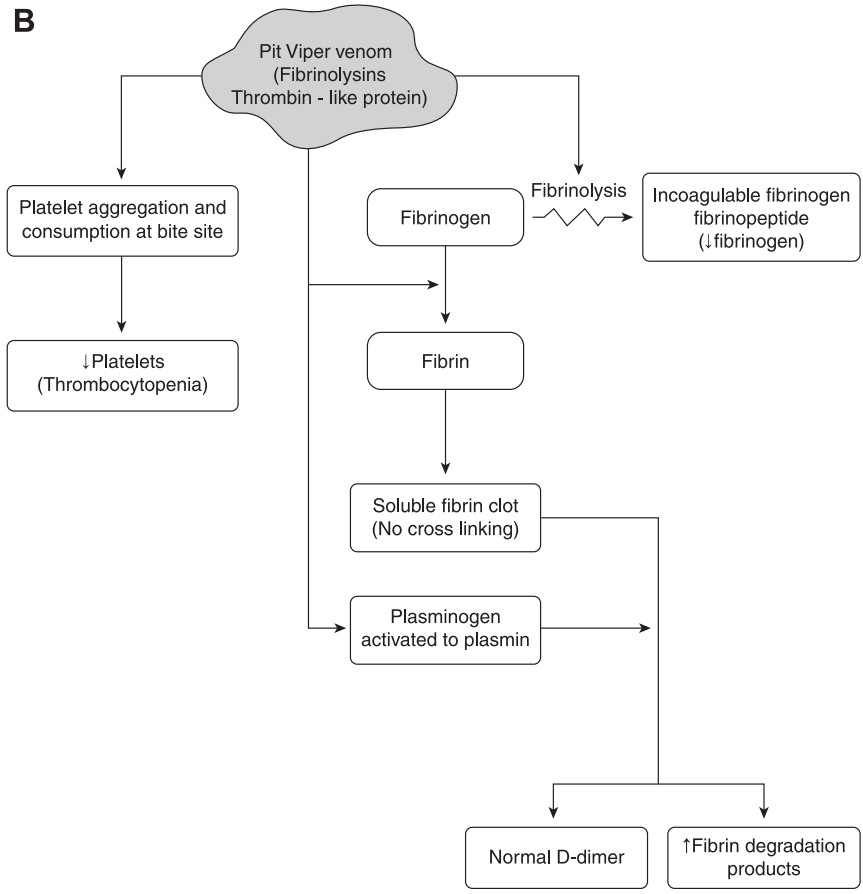

Fig. 5. (*continued*)

Table 7
Summary of clinical effects of certain pit viper species

Species	Effects
Mohave rattlesnake (*Crotalus scutulatus scutulatus*)	Neurologic complications from Mohave toxin A
Southern Pacific rattlesnake (*Crotalus oreganus helleri*)	Severe thrombocytopenia, no significant hypofibrinogenemia; neurologic complications (from Mohave toxin A)
Canebrake rattlesnake (*Crotalus horridus atricaudatus)*	Rhabdomyolysis
Copperhead (*Agkistrodon contortrix contortrix*)	Local swelling and pain, but rarely causing severe hematologic effects (antivenom is rarely indicated)
Water moccasin or cottonmouth (*Agkistrodon piscivorus*)	Causes less severe swelling and hematologic effects
Timber rattlesnake (*Crotalus horridus horridus*)	Severe thrombocytopenia, with or without prothrombin time increase; myokymia

Table 8
Laboratory testing in pit viper envenomation

Laboratory Examination	Indications and Potential Findings
Hemoglobin and hematocrit	Bleeding, hemolysis, anemia
Platelet count	Thrombocytopenia
Serum creatinine concentration	Acute kidney injury
Serum aspartate aminotransferase and alanine aminotransferase activity	Hepatic dysfunction, rhabdomyolysis
Prothrombin time	Venom-induced coagulopathy
Fibrinogen level	Venom-induced hypofibrinogenemia
Serum creatine kinase activity	Rhabdomyolysis
Fibrin(ogen) split products[79]	May predict hypofibrinogenemia

Tetanus status should be ascertained and updated if necessary. Pain control with opioid medications, such as fentanyl or hydromorphone, should be given.[82] Morphine may cause histamine release decreasing blood pressure and thereby complicating the picture of possible anaphylaxis to either crotaline venom or antivenom. Treatments with antibiotics, antihistamines, and corticosteroids has a limited role in the acute management unless there are signs and symptoms of infection or allergic reaction.[83–86]

Elevation of the extremity should be done to decrease the swelling of the affected limb. Limb positioning is controversial and there is no evidence on what position the affected limb should be placed. Theoretically, elevating the limb above the heart can cause venom to move toward the central circulation. Therefore, antivenom should be initiated before elevation.

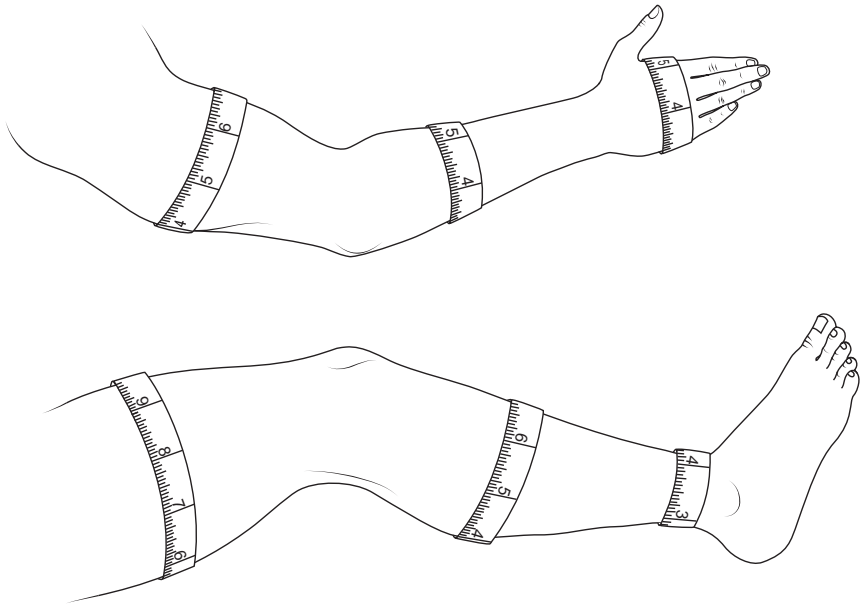

Fig. 6. Measuring the extremity to monitor for swelling.

Table 9
Pit viper envenomation severity

Mild	Moderate	Severe
• Local wound effects at the bite site • No systemic symptoms • No laboratory abnormalities	• Evidence of swelling, erythema, ecchymosis beyond the bite site • Minor systemic symptoms • No significant bleeding or significant laboratory abnormalities	• Swelling, erythema, ecchymosis of the entire body part • Systemic symptoms (significant hypotension, altered mental status, respiratory distress, tachycardia) • Significant bleeding, elevated prothrombin time, decreased fibrinogen level, thrombocytopenia (<20,000 μL^{-1})

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

Initial laboratory orders should focus on obtaining a complete blood cell count, a basic metabolic panel, serum transaminases, prothrombin time, fibrinogen level, and creatine kinase activity (see **Table 8**).

Infusing blood products for thrombocytopenia and hypofibrinogenemia is not necessary for pit viper envenomations unless life-threatening hemorrhage occurs. Circulating venom affects transfused blood products rendering them ineffective. Therefore, antivenom should be given before blood product administration unless a patient's condition warrants otherwise.

Antivenom administration should be initiated if a patient has moderate to severe symptoms, such as progressive swelling, uncontrolled pain, hematologic abnormalities, anaphylaxis, hypotension, and respiratory difficulties. Crotalidae polyvalent immune Fab antivenom (CroFab) is an ovine-derived immunoglobulin G (IgG) fragment made from 4 pit viper venoms: *Crotalus atrox*, *Crotalus adamanteus*, *Crotalus scutulatus*, and *Agkistrodon piscivorus*.[87] Antivenom cross-reactivity between pit viper species allows this antivenom to be used for all North American species. **Fig. 7** is a flow diagram of CroFab antivenom administration. Obtaining control of the swelling, pain, and hematologic effects is done by administering repeat doses of 4 to 6 vials. Control is defined as the end of progressive swelling and pain and improvement of hematologic effects. Maintenance therapy decreases the chance of recrudescence once control is achieved. Laboratory tests should be obtained after each dose of antivenom to monitor for worsening hematologic effects.

It is critical to explain to patients that antivenom does not reverse tissue damage and may not prevent further damage depending on the amount of venom in the tissue. Antivenom treatment helps correct hematologic effects and assist in the removal of circulating venom.

Other Treatment Considerations

Treatments, such as tissue excision, incision, and suction extraction; ice or heat application; electric shock; and so forth, have not proved useful and potentially may cause harm in envenomed patients.[65,88]

Constricting bands, tourniquets, and the Australian pressure immobilization technique are thought to reduce venom travel in the extremity to prevent worsening symptoms. The risk of tissue damage from the constricting band may cause more harm than

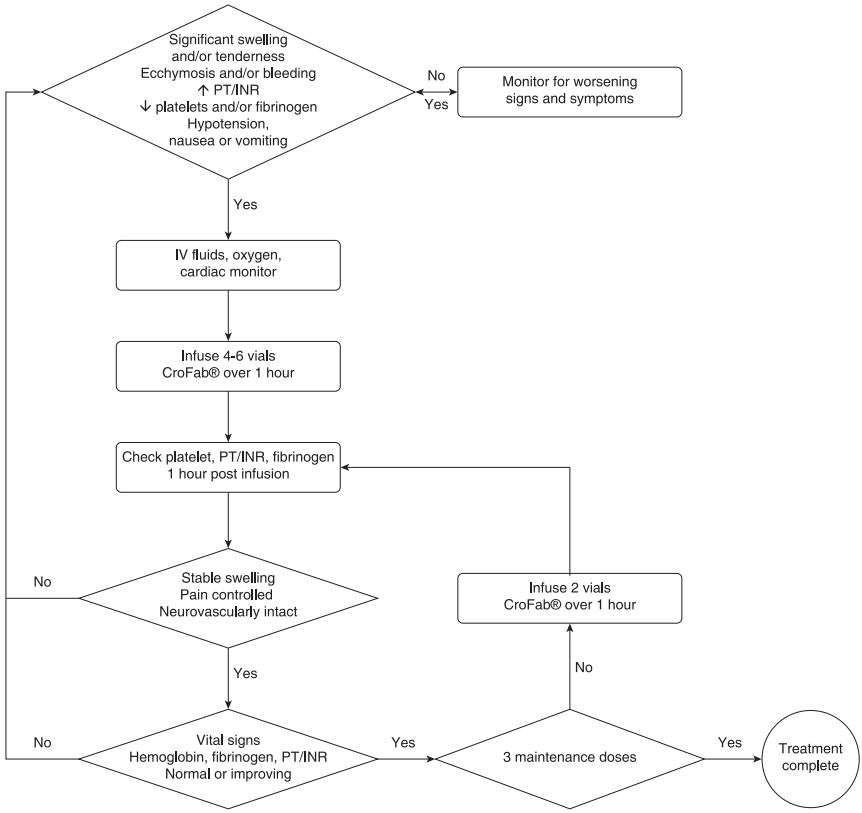

Fig. 7. CroFab antivenom administration flow diagram.

good. The pressure required to halt venom progression coupled with the difficulty to control the amount of pressure in the compartments make this technique dangerous. Because the tissue already has vascular compromise from swelling, it is not recommended in North American rattlesnake bites.[89–91]

Rattlesnake envenomations can cause severe tissue necrosis and impressive swelling. Swelling can lead to elevated compartment pressures and the risk of developing compartment syndrome. It is estimated that 2% to 8% of pit viper bites develop this limb-threatening problem.[92–94] Animal studies have shown that compartment pressures are decreased using antivenom.[95] In a recent review of the literature, Cumpston found no compelling evidence that fasciotomy or dermotomy may be tissue saving.[96] Fasciotomy is performed by making an incision into the skin and fascia to release pressure in the involved compartment. Decompressive dermotomy is an incision made into the skin to release compression made by skin. Until a properly designed study regarding the routine or prophylactic use of fasciotomy or dermotomy in crotaline envenomations occurs, this practice should be reserved only for extreme cases where antivenom therapy fails to decrease swelling and there is evidence of limb ischemia (**Box 3**).[97]

Both venom and antivenom may cause either anaphylaxis or anaphylactoid reactions. Standard measures using IV fluids, corticosteroids, antihistamines, epinephrine, and, if needed, vasopressors are recommended for treating these reactions.

Box 3
Indications for fasciotomy or dermotomy despite antivenom treatment in crotaline envenomations

Pulselessness

Persistently elevated measurements of intracompartamental pressure (>30 mm Hg) despite adequate antivenom treatment

Pallor

Disposition, Follow-up, and Complications

Patients should be expected to improve over the next 2 to 4 weeks after the bite. Disability from pit viper bites may persist for weeks due to pain, swelling, and tissue damage. Function of the extremity may not totally recover depending on the type of wound. Severe wounds requiring amputation, fasciotomy, or dermotomy cause significant disability and reconstructive surgery may be necessary. Physical and occupational therapy may assist patients with performing activities of daily living and arranging for assistance equipment before discharge from the hospital. Pain control should be an integral part of discharge treatment.

Recurrent venom effects or recurrence is a phenomenon that may occur after completion of pit viper antivenom treatment. Circulating antivenom may be eliminated from the body before the venom diffusing into the circulation.[98] Thus, the signs and symptoms of pit viper envenoming can reappear, such as increased swelling, pain, and hematologic effects, such as prothrombin time elevation and falling platelet counts and fibrinogen levels. Patients are encouraged to have laboratory examinations at 2 to 4 days and at 7 days after antivenom treatment.[99] Patients at highest risk of late hematologic abnormalities are those with hypofibrinogenemia, elevated D-dimer levels, thrombocytopenia, or elevated prothrombin or partial thromboplastin times during the first 48 hours after envenomation.[100] Treatment of recurrence with antivenom depends on the clinician and the presentation of the patient. In general, patients with bleeding and severe hematologic abnormalities should be readmitted to the ICU for continued antivenom treatment and possible blood product transfusion. **Box 4** summarizes recommendations regarding recurrence.[101] Serum sickness is a possibility with antivenom administration (discussed later).

ANTIVENOM

Antivenom, also called antivenin, is made by injecting animals with venom obtained from the target animal. The injected animal's serum is later recovered and contains IgG antibodies directed to the venom. That serum is refined and processed to obtain antivenom suitable for human injection. **Table 10** summarizes the antivenoms

Box 4
Consider additional antivenom administration in patients with recurrence and any of the following findings

Fibrinogen concentration <50 mg/dL, platelet count <25,000 μL^{-1}, international normalized ratio >3.0, or partial thromboplastin time >50 seconds

Multicomponent coagulopathy with abnormal laboratory values of a lesser degree

A clear worsening trend at follow-up in patients who had a severe early coagulopathy

High-risk behavior or comorbid condition

Table 10
North American snake, scorpion, and black widow spider antivenom

Venom Source	Antivenom	Origin	Antibody Type	Preservatives and Additives
Agkistrodon piscivorus and *Crotalus atrox*, *Crotalus adamanteus*, and *Crotalus scutulatus* (pit vipers)	Crotalidae polyvalent immune Fab (CroFab, Protherics)	Ovine (sheep)	IgG Fab	Papain (from papaya), used as a cleavage agent[87]
Centruroides (scorpion)	Immune $F(ab')_2$ (Anascorp, Rare Disease Therapeutics)	Equine (horse)	IgG $F(ab')_2$	Thimerosal (mercury)[62]
Micrurus fulvius fulvius (Eastern coral snake) and *Micrurus fulvius tenere* (Texas coral snake)	North American coral snake antivenin (Wyeth, no longer manufactured)	Equine (horse)	Whole IgG	Thimerosal (mercury) and phenol[102]
Latrodectus mactans	Black widow spider antivenin (Merck and Co)	Equine (horse)	Whole IgG	Thimerosal (mercury)[50]

discussed in this article. Clinicians should determine if a patient has any hypersensitivity to the antivenom ingredients before its infusion. When giving antivenom, the risks and benefits of giving these drugs should be explained to patients, as outlined in **Box 5**.

Infusion of antivenom should be initiated slowly and the infusion rate gradually increased while monitoring for anaphylactoid or anaphylactic reactions. Anaphylactoid reactions may resemble anaphylaxis with skin flushing, dyspnea, bronchospasm, hypotension, tachycardia or bradycardia, tongue swelling, nausea, vomiting, and so forth. Cardiac monitoring and preparation with bedside IV medication infusions (epinephrine, antihistamines, and corticosteroids) may be helpful in these emergent situations. Consider having these medications at the bedside for faster administration should the need arise. For patients who are severely allergic to any component of antivenom, pretreatment with corticosteroids and antihistamines is necessary along with slow infusion of antivenom to monitor for adverse effects. The causes of antivenom reactions are thought to be mediated by complement activation against antivenom IgG, total protein concentration, antibody aggregation, additives and processing agents (eg, the cleaving agent papain used in $F[ab']_2$ processing), and previous exposure to the animal from which the antivenom is derived.[98]

Serum sickness is a type III (immune complex) hypersensitivity reaction that may occur with the administration of antivenom. Foreign proteins (antivenom IgG) can cause a delayed reaction due to immune complex formation between the antivenom and human IgG and collect in the joints and blood vessels.[103,104] Patients have fever, headaches, generalized rash, lymphadenopathy, and joint pain approximately 3 to 21 days after receiving antivenom.[105] Severe cases may present with nephritis, bronchospasm, and purpura.[65] Patients with this type of reaction are treated using a tapering course of corticosteroid and antihistamine medications.[104]

Skin testing was once advocated before the administration of some antivenom, especially horse-derived products. This routine practice has fallen out of favor because it did not predict which patients have a reaction to the antivenom.[106–108]

Special populations include pregnant patients and children. Most antivenoms have not been proved safe to give in pregnancy. The risk of fetal effects must be weighed when giving antivenom. The risk includes maternal symptoms that may cause hypoxia, increased circulating catecholamines, the length of illness, and the types of effects on the mother and fetus (eg, the hematologic effects of pit viper venom). The risk and benefits of administering antivenom to these individuals must be discussed with the

Box 5
Risks of antivenom administration

Risks

Anaphylaxis (type I hypersensitivity reactions)

Serum sickness (type III hypersensitivity reactions)

Anaphylactoid reactions

Hypersensitivity to components of the venom or venom processing

Possibility of transplacental passage (pregnant patients)

Unknown long-term effects, especially in children and pregnant patients

Precautions

Renal failure (unable to excrete venom-antivenom complexes)

patient and their families. Antivenom has not proved deleterious to a fetus, children, or pregnancy in the long term. There are few data to support withholding antivenom when it is required.[109–111]

SUMMARY

Care of envenomated patients can be challenging. Consultation with an experienced clinician or a poison control center (800-222-1222) can assist in the diagnosis and management of these bites and stings.

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