Management of Venomous Snakebite Injury to the Extremities

Abstract

Pit vipers (subfamily Crotalinae) are responsible for most venomous snakebites in the United States. The mixture of proteins with cytotoxic, proteolytic, and/or neurotoxic enzymes in snake venom varies by species. Treatment in the field consists of safe identification of the species of snake and rapid transport of the patient to the nearest health care facility. Swelling, bruising, and systemic symptoms are seen following snakebite. Most patients respond to elevation of the affected extremity and observation. Some require the administration of antivenin. Crotalidae Polyvalent Immune Fab (Ovine) (CroFab, BTG International, West Conshohocken, PA) antivenin is safe and effective for the management of local and systemic effects of envenomation. Rarely, compartment syndrome may develop in the affected limb because of edema and tissue necrosis. Close monitoring of the extremity via serial physical examination and measurement of compartment pressure is a reliable method of determining whether surgical intervention is required.

Approximately 45,000 snakebite injuries are reported annually in the United States. Nearly 9,900 patients were treated in emergency departments between 2001 and 2004, and 32% of those patients had confirmed envenomation. In the early 1900s, snakebite mortality was estimated to be 5% to 25%. In 1987, approximately 10 to 15 fatalities were estimated to occur annually, with 95% of those involving diamondback rattlesnakes. More recent estimates have reported five to six snakebite-related fatalities per year in the United States. This decreasing trend in mortality is multifactorial, including advances in antivenin research; increased access to medical care; reduction in rural habitation, leading to reduced human-snake interaction; and changes in snake habitat, with changes in population and in characteristics of indigenous snake populations.

Epidemiology of Snakebites

Seventy percent to 80% of snakebites occur in males. Intentional exposure, whether in a professional context (eg, snake handling) or non-professional context (eg, playing with snakes in the wild) accounts for most snakebites. Historically, snakebites have been classified as legitimate or illegitimate. Legitimate bites include episodes in which persons fail to evade a snake, do not detect a snake before injury, or are unintentionally bitten during professional handling. The most common legitimate scenario involves children who inadvertently step on or near an un-
detected snake and sustain a bite to the lower extremity. Illegitimate bites include instances in which the person recognizes an encounter but does not attempt to avoid contact. Approximately 57% of bites are illegitimate. Alcohol consumption is involved in 57% of illegitimate bites, compared with 17% of legitimate bites. At a tertiary care center in Albuquerque, NM, Downey et al reported hand involvement in 20 of 36 patients with snakebite (56%). The high correlation between alcohol use and hand injury implies that bites occur when the person is involved in risky behavior, not when he or she is attempting to evade the snake.

### Venous Snakes

In North America, snakes from the subfamily Crotalinae (ie, pit vipers) are responsible for 99% of venomous bites. Snakes of this subfamily include rattlesnakes, copperheads, and cottonmouths (ie, water moccasins). The triangular head is the most easily identifiable physical trait of pit vipers. Other physical characteristics include elliptical pupils, prominent fangs, a single row of scales distal to the anal plate, and heat-sensing loreal pits (ie, external orifices of a sensitive infrared detection organ), which are located between the nostrils and the eyes (Figures 1 and 2). The remaining 1% of bites are attributed to coral snakes and other exotic pet snakes (Table 1).

Rattlesnakes are the most diverse class of pit viper in the United States; each of the lower 48 contiguous states is home to at least 1 of the 21 native species. These snakes are differentiated from other pit vipers by the presence of a tail appendage that the animal vibrates to create an audible warning when it is threatened (Figure 3). Natural habitat differs by species, and rattlesnakes can be found in deciduous forests, swamps, sandy coastal regions, and deserts. The highest density is found in the southwestern states. Rattlesnake bites represent 69% of venomous bites.

Although copperhead snakebites account for 20% of all snakebites in the United States, certain areas (eg,
eastern states) report a higher percentage of copperhead envenomations than rattlesnake bites.12-15 The copperhead can be found in the coastal areas of Massachusetts, along the eastern seaboard and through the Appalachian Mountains, as well as in all the southeastern states and as far west as Texas. Copperheads tend to remain motionless on detection or endangerment, and their intricate coloration provides effective camouflage. As a result, they often remain undetected and strike only in the case of inadvertent contact.

The cottonmouth (Agkistrodon piscivorus), or water moccasin, is the only semiaquatic viper. This strong swimmer inhabits swamps and areas surrounding lakes and streams in the southeastern United States. Cottonmouths aggressively protect their nests and have been known to pursue invaders. The snake’s colloquial name stems from its cotton-colored throat, which is visible when it opens its mouth in the defensive stance it assumes when approached.

The coral snake (family, Elapidae) is characterized by red, yellow, and black banding. The three species found in the United States have a distinctive order of coloration with red bands adjacent to yellow bands. All coral snakes indigenous to the United States have this order of coloration. Several nonvenomous species, such as the scarlet king snake (Lampropeltis triangulum elapsoide), have similar banding; however, the red bands are adjacent to the black bands. A colloquial saying is helpful in distinguishing coral snakes from species with similar coloration: “Red on black, venom lack; red on yellow will kill a fellow.” The eastern coral snake (Micrurus fulvius) can be found along the eastern seaboard, from the coastal plains of North Carolina through Florida, as well as westward through southeastern Louisiana. The habitat of the Texas coral snake (Micrurus tener) extends from southwestern Arkansas and Louisiana through southern Texas. The sonoran coral snake (Micruroides euryxanthus) is found in central Arizona, southwestern New Mexico, and northern Mexico.

**Physiology of Venom**

Viper venom contains a complex and variable combination of proteins.

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**Table 1**

<table>
<thead>
<tr>
<th>Family</th>
<th>Subfamily</th>
<th>Genera</th>
<th>General Name</th>
<th>Common Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viperidae</td>
<td>Crotalinae</td>
<td>Crotalus, Sistrurus</td>
<td>Rattlesnake</td>
<td>Banded rock, black-tailed, canebrake, eastern</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>diamondback, western diamondback, eastern</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>massasauga, western massasauga, Mojave,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mottled rock, northern pacific, southern pacific,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>southeastern pigmy, western pigmy, prairie, red</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>diamond, ridgenose, sidewinder, speckled, tiger,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>timber, twin-spotted</td>
</tr>
<tr>
<td>Viperidae</td>
<td>Crotalinae</td>
<td>Agkistrodon</td>
<td>Copperhead</td>
<td>Southern, broad-banded, northern, osage, trans-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>pecos</td>
</tr>
<tr>
<td>Viperidae</td>
<td>Crotalinae</td>
<td>Agkistrodon</td>
<td>Cottonmouth/</td>
<td>Eastern, floridian, western</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>water moccasin</td>
<td></td>
</tr>
<tr>
<td>Elapidae</td>
<td>—</td>
<td>Micrurus, Micruroides, Leptomicrurus</td>
<td>Coral snake</td>
<td>Eastern/common, Texas, Arizona</td>
</tr>
</tbody>
</table>

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Adam W. Anz, MD, et al

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These peptides and polypeptides may act as cytoxins, proteolytic enzymes, and cell-signaling ligands. The action of these proteins can cause cell lysis, capillary leak, hemostatic coagulopathy, and inhibition of presynaptic or postsynaptic activity. These proteins primarily cause injury involving muscle necrosis, tissue edema, and peripheral nerve palsy. Muscle necrosis and edema can result in serious local consequences (e.g., increased compartment pressure, ischemia) and systemic consequences (e.g., acute renal failure).<br><br>Figure 3<br><br>Eastern diamondback snake (Crotalus adamanteus). (Courtesy of Jeff Hall, Partners in Amphibian and Reptile Conservation, North Carolina Wildlife Resources Commission, Raleigh, NC.)<br><br>Envenomation creates a range of injury, the severity of which is deter-
mined by seven major factors: species of snake and its geographic location, which dictate the composition of the venom; size of the snake; venom load delivered; location of the injury; and the size and general health of the victim. Two puncture marks are typically seen in pit viper bites. The bites of coral snakes are often similar to scratches or abrasions. Children often fare worse than adults, given their smaller size and limited reserve. Mock venom studies have demonstrated that lymphatic spread of venom to the central circulation takes a mean of 58 minutes without exercise. However, venom has been reported to spread within 2 minutes.

Common symptoms related to the cytotoxic and proteolytic components of venom include pain, edema, weakness, swelling, and ecchymosis. Neurologic responses also may be seen with the involvement of cell-signaling ligands. Paresthesia, fasciculation, paralysis, dysphagia, sweating, weakness, and cardiac arrhythmia have been documented in patients bitten by snakes with neurotoxic venom.

Most rattlesnakes have venom that is composed mainly of cytotoxins and proteolytic enzymes. Local edema with muscle injury, hematologic abnormalities, and secondary systemic injury are common in patients bitten by these snakes. Upper extremity bites are associated with a higher incidence of complications, and special vigilance and strict elevation are required (Figure 4). In a review of 236 patients treated at a tertiary referral center, the authors reported coagulopathy in 60%, hypofibrinogenemia in 49%, thrombocytopenia in 33%, and bullae formation in 22%. Surgical intervention was required in 3.4% of patients. Local signs and symptoms of rattlesnake bites typically manifest within 1 hour following envenomation. The local reaction involves edema; erythema, which resembles cellulitis; and pain. Ecchymosis may present within the next 6 hours as the venom affects microvasculature permeability, which allows red cells, albumin, and fluid to extravasate into the surrounding tissues. In rare cases, injury progresses to compartment syndrome in the extremities. Careful neurologic examination and monitoring are necessary with any rattlesnake bite, given the potential presence of a neurotoxin in the venom of select snake species.

Coral snakes are nonaggressive and rarely bite. They spend most of their time hidden in cool environments. Their bites may not manifest clinically until 24 hours following injury. Local injury is minimal and often is characterized by abrasion and mild local erythema. Overall vigilance and careful cardiorespiratory monitoring should be

### Table 2

**Enzymatic Composition of Venom**

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Crotalidae</th>
<th>Sistrurus</th>
<th>Agkistrodon</th>
<th>Micrurus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteolytic enzymes</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Arginine ester hydrolase</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Thrombin-like enzyme</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Collagenase</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Hyaluronidase</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Phospholipase A₂</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Phospholipase B</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Phospho-monoesterase</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Phosphodiesterase</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Acetylcholinesterase</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ribonuclease</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Deoxyribonuclease</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5’-nucleotidase</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Nicotinamide adenine dinucleotide-nucleotidase</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>L-amino-acid oxidase</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

\(+ = \text{presence of enzyme, } – = \text{absence of enzyme, } — = \text{unknown}\)

maintained for 24 hours following injury, given the possibility of delayed onset of toxic effects. Neurologic effects may be mild (eg, ptosis, slurred speech) or severe, progressing to obtundation and respiratory failure. Since the development of North American Coral Snake antivenin (Wyeth-Ayerst Laboratories, Philadelphia, PA) in 1967, only one death has been reported. In that case, which occurred in 2009, the patient did not seek medical attention.25

Field Management

Field management of and first aid for snakebites has changed radically in the past few decades with regard to treatment considerations and philosophy. First aid strategies in the field have been replaced by a focus on transporting the patient to a medical facility with the capability of definitive monitoring and treatment. Few of the traditional first aid strategies that were believed to be beneficial following snakebite have proved to be effective. Much of the difficulty in snakebite field management stems from the fact that it is unclear what percentage of snakebites result in envenomation. Seventy-five percent of coral snake bites result in envenomation, but the percentage within the pit viper population has not been described.24 Initial signs and symptoms cannot be relied on to differentiate patients who are envenomated from those who are not. Thus, envenoma-
The first step following snakebite is the safe removal of the patient from the snake’s striking range. If a picture of the snake can safely be taken, it should be acquired to aid in identification and to guide therapy. No attempt should be made to capture the snake. Even if the snake is presumed to be dead, no attempt should be made to touch the animal because of the risk of envenomation by reflex biting. Initial management focuses on the resuscitative cornerstones of airway, breathing, and circulation. Regardless of subsequent treatment, the patient should be kept immobilized to the extent possible.

Traditional therapies implemented in the attempt to prevent the systemic spread of toxin include incision with suction at the bite wound, suction alone, cryotherapy, electrotherapy, tourniquet application, and pressure immobilization (PI). No evidence exists in the literature to support the efficacy of incision with suction and electrotherapy. In fact, these methods may cause additional harm because they may promote infection and damage to deep structures. Extraction of venom through the puncture wound theoretically decreases the total volume load, and commercially available extraction pumps have been developed. Although initial reports appeared promising, clinical studies have shown an insignificant reduction in venom load per patient with the use of extraction pumps. The literature does not support direct suction as first line therapy.

Tourniquet application is often the first treatment method attempted by many first aid providers. It is also the most controversial. Severe damage to the extremity resulting from arterial tourniquet use for >1 to 2 hours has been reported. For this reason, arterial tourniquets should be avoided because of the potential for local damage from limb ischemia. Alternatively, venous tourniquets decrease blood and lymphatic flow from the extremity and can slow the systemic spread of venom. Venous tourniquets should have a goal pressure of 20 to 30 mm Hg and should be loose enough to admit one to two fingers. Animal study has illustrated a decrease in systemic spread of venom with the use of a venous tourniquet; however, these results have not been replicated in human studies. Containing the venom within the extremity and decreasing blood flow from the extremity increases the potential for local damage. Given the potential complications, tourniquet use is not recommended unless obvious, worsening life-threatening neurotoxic effects (e.g., difficulty breathing, cardiac arrhythmia, decreased level of consciousness) are observed.
PI is an alternative method of slowing the spread of venom. A splint is applied, and the affected extremity is wrapped with a bandage from the distal tip of the extremity, over the snakebite, continuing proximally to achieve a pressure of 55 mm Hg. In 1979, the Australian National Health and Medical Research Council endorsed the use of PI for the management of venomous snakebites. Animal trials have demonstrated moderate efficacy following splint application, but prospective studies in humans are lacking. In the animal model, a pressure of 55 mm Hg provided a significant block of lymph and superficial flow without compromising deep venous flow. Bandages that provide pressure measuring >70 mm Hg have been associated with increased permeability, leading to the spread of toxin, possibly because of increased movement resulting from pain or increased interstitial pressure. Promising studies from the Union of Myanmar demonstrated retardation of venom in 13 of 15 patients with the application of a compressive dressing. However, it is difficult to achieve the ideal level of pressure with this modality. In Australia, approximately one fifth of patients with snakebite who present to the hospital undergo appropriate PI application, only to suffer a bolus effect with release. A study of PI published in 2005 reported correct application in only 13 of 100 simulated attempts by emergency physicians and 5 of 100 simulated attempts by laypersons. Concerns associated with PI include the ability to contain venom within the extremity and the possible increased risk of local damage from necrosis, ecchymosis, and edema.

No empiric recommendations can be made regarding a single best field treatment method for all snakebites. In each situation, the risks and benefits of encouraging dissemination of venom versus stasis of venom at the bite site must be considered, taking into account the potential length of transport and availability of care. In situations in which the snake’s venom is known to have potent neurologic effects, stasis of venom at the bite site should be encouraged during patient transport with a gravity-dependent posture and PI. In a patient with severe life-threatening neurologic effects, short-term tourniquet use can be considered. Alternatively, a patient who demonstrates severe local effects and no neurologic or systemic symptoms may be treated with elevation of the extremity en route to decrease the incidence of local injury. Field management of snakebite injury must be individualized, and the clinician should be familiar with the broad categorization of snakes and the potential of local and systemic injury.

**Hospital Evaluation**

Complete patient assessment, including a thorough history and physical examination with hematologic and comprehensive metabolic screening, is essential on arrival at the medical facility. Venom can affect any major organ system; thus, it is crucial to evaluate the patient for pulmonary, cardiovascular, renal, and central nervous system compromise. After the airway, breathing, and circulation have been assessed, the physical examination should focus on the affected extremity. Neurovascular status proximal and distal to the site of injury should be documented, and areas of erythema and edema should be outlined with a permanent marker to help visualize the progression of local injury (Figures 4, B, and 5). All wounds should be thoroughly irrigated.

Envenomation often affects the hematologic system; thus, serial coagulation profiles and blood counts, including prothrombin time, international normalized ratio, partial thromboplastin time, platelet counts, hematocrit levels, and fibrinogen, should be obtained on admission and closely followed thereafter. Patient status determines the frequency of blood screening. Blood tests should be repeated within 2 to 3 hours after admission and again 2 to 3 hours later. Once improvement is shown, serial blood tests may be discontinued. Progression of the local injury in the form of ecchymosis, pain, and soft-tissue edema should be monitored closely. Patients who have been bitten by rattlesnakes and coral snakes should undergo cardiopulmonary monitoring because of the possible neurologic sequelae of these injuries.

**Surgical Intervention**

Historically, incision/débridement and fasciotomy have played a large role in the management of snakebites, but antivenin, which has become an effective medical treatment of both local injury and systemic sequelae, is now the standard of care. The patient with swelling and pain suggestive of compartment syndrome should be monitored with serial examination and treated with strict elevation of the affected limb and antivenin. Despite the effectiveness of antivenin, some patients may not respond to nonsurgical treatment and may require fasciotomy. Surgical intervention for compartment syndrome is required in 2% to 8% of cases. The diagnosis of compartment syndrome begins with physical examination. Symptoms of concern include pain out of proportion to injury, tense compartments, decreased sensation, pain with passive range of motion, and signs of compromised...
distal perfusion. Invasive pressure monitoring can be used to confirm compartment syndrome, but it is not necessary for diagnosis. Pressures within 30 mm Hg of diastolic blood pressure are suggestive of compartment syndrome. The local symptoms of envenomation and compartment syndrome often have similar presentations, which may make it difficult to determine a definitive diagnosis. As a result, compartment pressure measurement is used more frequently in the incidence of snakebite than in the trauma setting. Administration of antivenin has been shown to decrease compartment pressures in animal models, thus, monitoring pressures while administering antivenin in the early stages of compartment syndrome is a viable treatment option. However, some authors advocate early fasciotomy when compartment syndrome is confirmed or suggested on physical examination.

Early diagnosis is the key to successful management. Delay can be devastating for the patient. The medical team must remain vigilant for superimposed infection with snakebite injury. This is especially important with cottonmouth snakebites because of the potential for aerobic and anaerobic bacteria in the snake’s aquatic environment. Necrotizing fasciitis following a cottonmouth bite has been effectively managed with broad-spectrum antibiotics, antivenin, and surgical intervention.

Antivenin Development

In 1954, Wyeth Laboratories introduced Antivenin Crotalidae Polyvalent (ACP; Wyeth-Ayerst Laboratories, Philadelphia, PA), a preparation of serum globulins obtained from horses immunized with Crotalinae venom. This antivenin contains whole immunoglobulin G, including the immunogenic Fc portion, which is responsible for initiating acute hypersensitivity reactions and delayed serum sickness. Common acute side effects of this preparation include urticaria, bronchospasm, and hypotension. In a retrospective study, acute anaphylactic reaction was reported in 23% to 56% of patients. Serum sickness was common, as well, with symptoms including fever, diffuse rash, hematuria, and arthralgia. In addition to a significant side-effect profile, ACP was plagued by therapeutic failures, including the failure to reverse neurotoxic effects and the inability to manage thrombocytopenia. Retrospective case reviews involving ACP reported serum sickness in 11% to 100% of patients, including 75% of those treated with three or more vials and 86% of patients treated with eight or more vials.

In 2001, Crotalidae Polyvalent Immune Fab (CroFab; BTG International, West Conshohocken, PA) was introduced as a promising alternative to ACP. Sheep are immunized with the venom of eastern and western diamondback rattlesnakes, Mojave rattlesnakes, and cottonmouths. The serum obtained from the sheep is then digested with papain, a protease that isolates the Fab and Fc fragments of the immunoglobulin, which are then isolated and removed. Four specific Fab preparations are combined to form the final product. The end result is a highly purified antivenin that lacks the immunogenic Fc fragments and proteins. In clinical trials, the overall rate of serum sickness following administration of CroFab was 16%, and the rate of acute reaction was 14.3%. These rates are substantially lower than those reported with ACP. Anaphylaxis has not been reported with CroFab.

Antivenin Administration

The known side effects of antivenin warrant careful consideration of the associated risks and benefits prior to administration. The general indication is the progression of local injury or the manifestation of substantial systemic injury. Manifestations of systemic injury may include impaired consciousness, cardiac arrhythmia, hypotension, thrombocytopenia, myoglobinemia, rhabdomyolysis, and azotemia. A grading system can be used to classify the injury and determine appropriate management (Table 3). The snakebite severity score is more precise and has proved to be effective.

Observation with antivenin administration is the standard of care in the patient who presents with symptoms of neurotoxicity following coral snake envenomation. The patient should be admitted for 24 hours of observation regardless of the clinical presentation. Currently, North American Coral Snake antivenin (Wyeth-Ayerst Laboratories) is the only commercially available antivenin that is effective in the management of coral snake envenomation in the United States. Production of this antivenin was discontinued, and current stocks were set to expire in October 2010. Management of snakebites without antivenin administration includes endotracheal intubation and respiratory support at the first signs of airway compromise.

Summary

In the United States, venomous snakebites can cause substantial morbidity and even mortality. Rattlesnake bites in particular have the potential for increased injury, and some patients experience severe systemic and neurologic sequelae. The mainstay of treatment in the field includes safe identification of the snake and
Table 3

Classification of Snakebite Severity and Recommended Intervention

<table>
<thead>
<tr>
<th>Degree of Envenomation</th>
<th>Clinical Manifestation</th>
<th>Extremity Treatment</th>
<th>Antivenin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Mild pain at bite site</td>
<td>Local wound care</td>
<td>None</td>
</tr>
<tr>
<td>I</td>
<td>Local edema, ecchymosis</td>
<td>Local wound care, strict elevation</td>
<td>Copperhead or cottonmouth bite and normal blood panel: none</td>
</tr>
<tr>
<td>II</td>
<td>Edema extending proximally from the bite site, mild coagulopathy, mild change in renal/liver profile, nausea, vomiting</td>
<td>Local wound care, strict elevation, evaluation for signs and symptoms of compartment syndrome every 2–4 h</td>
<td>5–15 vials</td>
</tr>
<tr>
<td>III</td>
<td>Swelling of entire extremity, intense pain, severe systemic signs, moderate abnormality in blood tests</td>
<td>Strict elevation, hourly evaluation for signs and symptoms of compartment syndrome</td>
<td>15–20 vials</td>
</tr>
<tr>
<td>IV</td>
<td>Hypotension, obtundation, cardiac arrhythmia, severe abnormality in blood tests (eg, platelet count &lt;20,000/mm³)</td>
<td>Strict elevation, evaluation for signs and symptoms of compartment syndrome, consider measuring compartment pressure</td>
<td>≥20 vials</td>
</tr>
</tbody>
</table>


References

Evidence-based Medicine: Levels of evidence are described in the table of contents. In this article, no level I and II studies are cited. References 7, 26, 29, and 35 are level III studies. References 5, 6, 8-10, 12, 13, 15, 23, 25, 27, 28, 34, 36-40, and 42-44 are level IV case studies. References 11, 14, 16-18, 23, 30, 33, 39, and 41 are level V expert opinion.

Citation numbers printed in bold type indicate references published within the past 5 years.


