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Emergency Department Management of North American Snake Envenomations

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Abstract

There are approximately 10,000 emergency department visits in the United States for snakebites every year, and one-third of those involve venomous species. Venomous North American indigenous snakes include species from the Crotalinae (pit vipers) and Elapidae (coral snakes) subfamilies. Treatment relies on supportive care, plus antivenom for select cases. While certain principles of management are widely accepted, controversies exist with regard to prehospital use of pressure immobilization, antivenom use, coagulation testing after copperhead envenomation, and fasciotomy. An evidence-based approach to management of North American venomous snakes will be discussed, along with a review of the current controversies.

Case Presentations

A 4-year-old boy is brought to your ED by his distraught parents. An hour ago, he was in the backyard by the pool, playing with what they thought was a toy. He started screaming, and when the mother moved closer, she saw a foot-long black, yellow, and red snake in his hand. She frantically pulled it off him and threw it into the bushes. She reports that she had to pull quite hard before it would release. The child has several small marks on the palm of his left hand. There is minimal redness, and no swelling is apparent. The dad took a picture of the snake with his phone and you can tell quickly that it was a coral snake. The child is asymptomatic currently, but the nearest pediatric ICU is over an hour away. You wonder: should you transfer this patient to the ICU or can you observe him in the ED—and should you start antivenom?

A 26-year-old man arrives to the ED via private vehicle with his arm in a makeshift sling. He reports that his pet rattlesnake bit him on his right index finger about 45 minutes ago. His hand and wrist are swollen. He reports that he has no past medical history besides his 3 previous visits for snakebites. He reports having a "reaction" to the snakebite antidote during his last visit. You wonder whether the patient is immune . . . or should you give antivenom again?

A 51-year-old man with a history of a rattlesnake bite approximately 4 days ago presents from his primary care physician's office for abnormal lab test results. He reports easy bruising and some bleeding when he brushes his teeth, but is otherwise asymptomatic. You wonder how you should manage this patient.

Introduction

According to the American Association of Poison Control Centers (AAPCC) 2006-2015 annual reports, there were 65,695 reported exposures and 31 deaths from snakes in the United States in that time period.[1] There are 2 subfamilies of venomous snakes that are native to the United States: (1) the Crotalinae (pit vipers, subfamily of family Viperidae), which includes rattlesnakes, copperheads, and water moccasins (also called cottonmouths), and (2) the subfamily Elapidae (subfamily of family Colubridae) of which only the coral snake is native to the United States. Bites from snakes from these native subfamilies can produce significant morbidity and, rarely, death, so prompt clinical evaluation and management is essential. In addition, exotic snakes are popular as pets, and bites from these snakes may cause rapid death, depending on the species, so expertise is required to manage them expeditiously.

Patients with snake envenomations generally access healthcare either through the emergency department (ED) or through first-aid providers who generally turn to the emergency clinician for direction. Management of envenomations is considered a core competency of emergency clinicians, and along with Poison Control Centers, they often serve as community resources for snakebite emergencies. Not all envenomations require antivenom; however, delayed administration may lead to significant morbidity and even death, in some cases. This issue of *Emergency Medicine Practice* provides a comprehensive update on the principles of clinical evaluation of envenomations from pit vipers and coral snakes native to the United States as well as current management recommendations and controversies. Resources are also provided to assist in the management of envenomation from exotic species.

Critical Appraisal of the Literature

A literature search was performed on PubMed using the search terms *snake bites, snake envenomation, Agkistrodon, cottonmouth, copperhead, rattlesnake, Crotalinae, Elapidae, Colubridae, water moccasin, coral snake*, and *pit viper.* A total of 120 relevant articles from 2006 to 2017 were reviewed.

A search of literature published from 2006 to 2017 using key terms *snake bite* or *snake envenomation* of the Cochrane Database of Systematic Reviews, Evidence Based Medicine Reviews: Best Evidence (ACP), Database of Abstracts of Reviews of Effectiveness (DARE), and Evidence-Based Medicine Reviews Multifile (EBMZ) identified 11 articles. Of these, 3 were not relevant to indigenous North American snakes, 3 were randomized controlled trials, 1 was a poststudy subanalysis, and 2 were reviews (Cochrane and DARE).

As is the case with most of the toxicology literature, evidence on the management of snake envenomations from high-quality prospective randomized controlled trials is limited. The few published studies in the past 10 years are mostly from other countries where the snake species, the level of supportive care, and antivenom availability and effectiveness are different from that in North America. The literature is comprised primarily of case reports/series, retrospective chart reviews, animal model studies, expert consensus panels, and review articles.

The current relevant literature is comprised of case reports/series describing novel or known but not well-characterized clinical effects after a snake envenomation; observational studies using data from hospital charts, Internet search, Poison Control Centers, and national databases; animal model studies; in vitro venom and antivenom studies; conclusions from expert consensus panels; a position statement; and 3 randomized controlled trials. Many of the retrospective observation studies utilized Poison Control Center data (Texas Poison Control Center Network, Florida Poison Information Center Network, AAPCC database, and the American College of Medical Toxicology ToxIC North American

Snakebite Registry). Poison Control Centers collect self-reported, unverified information provided by the public or healthcare workers on potential or actual exposures, but they may not be true envenomations and may not reflect the true incidence of snakebites. Furthermore, reported clinical effects and outcomes may be incomplete or inaccurate. For example, according to a compilation of data reported to United States Poison Control Centers, there were no deaths from coral snakes from 2006 to 2015; however, a confirmed death after a coral snake envenomation was published in 2009 (the first and only confirmed death in the literature).[2] The ToxIC Registry contains prospectively collected verified clinical information, and it also relies on voluntary reporting.

Most of the management recommendations discussed in this article are based on expert opinion supported by low- to moderate-quality evidence. Expert consensus panel recommendations for the surgical management of snake envenomation were published in 2013.[3] Clinical questions were structured in the "Patient, Intervention, Comparison, Outcome" format, and recommendations were developed using Grading of Recommendations, Assessment, Development, and Evaluation. A unified treatment algorithm for the management of Crotalinae envenomations was published in 2011.[4] Experts utilized a modified Delphi methodology to develop evidence-informed recommendations. Standard evidence-level scales were not used, as only 1 randomized clinical trial involving the treatment of Crotalinae envenomation with antivenom had been published at the time.[5] Since then, a randomized clinical trial comparing Crotalidae Polyvalent Immune Fab (Ovine) (FabAV, CroFab®) to F(ab')2 immunoglobulin derivatives was published in 2015.[6] Additionally, a post hoc analysis of data from this trial comparing copperhead coagulation parameters was also published.[7] A position statement from leading national and international clinical toxicology associations regarding use of pressure immobilization after a North American Crotalinae snake envenomation was published in 2011.[8]

Epidemiology and Pathophysiology

Table 1 shows the number of snake exposures and fatalities reported to Poison Control Centers in the United States from 2006 to 2015, by type of snake. The number of reported snake exposures and fatalities have increased over the past 10 years.

Venomous snake bites tend to occur most frequently in men aged 18 to 49 years during warmer months (84%), peaking in July.[9-12] Provoked bites or intentional snake interactions tend to occur on the upper extremities, particularly the hands and fingers. Unprovoked bites or unintentional snake interactions frequently occur on the lower extremities.[12-14] According to the National Electronic Injury Surveillance System-All Injury Program data from 2001 to 2004, there were nearly 10,000 annual ED visits for snakebites; 32% were from venomous snakes, and 59% of these bites resulted in admission.[15] Reported admission rates are particularly high (85%) following rattlesnake envenomations, with an average length of stay of 2 to 3 days.[12,16]

Snakebite Severity

Snakebite severity depends on several factors, including the amount of venom injected and the composition of the venom. Human factors that can also affect snakebite severity include the body size of the bite victim, the clothing worn, the site of the bite, comorbid conditions (such as asthma), the circumstances surrounding the snake-human interaction, and the timing and quality of medical care after the bite.[17] One study demonstrated reduced venom injection in denim-clothed human limb models.[18]

The amount of venom injected is influenced by the snake's size and maturity, the kinematics of the bite, and the time of the year.[17] A retrospective study of 145 patients showed a positive correlation between rattlesnake size and the bite severity, the number of antivenom vials used, and the hospital length of stay.[19] The amount of venom injected during a bite can vary, based on the species of the venomous snake. In addition, snakes can change the quantity of venom released during a bite based on threat risk, such as biting in defense versus striking prey.[20] An estimated 10% to 25% of pit viper bites are "dry," meaning a bite resulting in no venom release.[12,21]

There is a wide variation in venom composition between snake species and even within the same species.[21,22] The venom composition of pit vipers and coral snakes is described in **Table 2, page 4**. The venom from pit vipers is predominantly hemo-

Table 1. Number of Reported Snake Exposures and Fatalities in the United States, 2006-2015[1]

Type of Snake	Exposures	Fatalities
Crotalinae (Pit Vipers)		
Copperhead	15,107	2
Rattlesnake	11,530	19
Cottonmouth/water moccasin	2300	1
Unidentified Crotalinae	6431	6
Elapidae (Coral Snakes)		
Coral	866	0
Other		
Exotic	1168	1
Unknown type	26,293	2
Total	**63,695**	**31**

toxic. Both localized and systemic effects (such as tachycardia, tachypnea, hypotension, nausea, vomiting, weakness, and diaphoresis) can occur with exposure. Neurotoxicity is not typically associated with pit vipers; however, cases of neurotoxicity (fasciculations, weakness, and paresthesias) have been reported after envenomation by certain crotaline snakes, particularly the Mojave rattlesnake (*Crotalus scutulatus*) and the western rattlesnake (*Crotalus viridis*).[23,24] Rare cases of neurotoxicity have been reported after bites from the timber rattlesnake (*Crotalus horridus*), western diamondback rattlesnake (*Crotalus atrox*), and the sidewinder rattlesnake (*Crotalus cerastes*).[22,25-27] These atypical findings are likely due to interbreeding between species in certain regions of the country. Residual disability after envenomation is common but typically transient.[28]

Copperheads are responsible for most of the snakebites reported to United States Poison Control Centers, but rattlesnake bites produce higher morbidity and mortality and are more likely to be treated with antivenom.[1,9,29] Copperhead bites typically result in only local tissue effects without systemic findings; however, limb-threatening injuries can occur. There are reports describing unusual presentations of shock, syncope, respiratory failure, and significant coagulopathy after intravenous copperhead envenomation.[30,31] Residual venom effects after copperhead envenomations reportedly persist between 7 and 14 days, but can last for months.[32,33]

Crotalinae Family: The Pit Vipers

The Crotalinae family includes rattlesnakes (*Crotalus* and *Sistrurus* genus), cottonmouths (also known as water moccasins) (*Agkistrodon piscivorus*), and copperheads (*Agkistrodon contortrix*). These snakes were responsible for 98% of exposures (total: 35,368) reported to Poison Control Centers in the United States from 2006 to 2015 (among exposures where the type of snake responsible was identified).[1] These snakes are commonly referred to as *pit vipers*, due to the heat-sensing pit located behind their nostrils. **Figure 1** depicts some of the physical characteristics and identifying features for indigenous venomous pit vipers. In general, venomous snakes have a triangular or spade-like head, elliptical pupils, and hollow retractable fangs. Nonvenomous pit vipers have rounded heads, round pupils, a double row of vertical scales on the tail, and lack fangs.

Pit vipers inhabit a wide geographical range. **(See Figure 2, page 5.)** Rattlesnakes have been found in all states except Hawaii. Cottonmouths/water moccasins are distributed throughout the Southern and Southeastern states (Virginia to Texas). Copperheads have a similar range, but have been found as far north as Massachusetts. However, bites from non–native snakes can involve snakes from private collections, zoos, or research centers.[9] Approximately 7% of all bites are from snakes in these types of settings.[13]

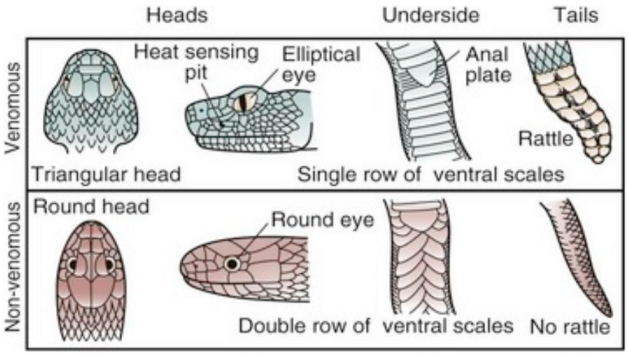
Elapidae Family: The Coral Snakes

There are 3 species of coral snakes in North America, but only *Micrurus fulvius fulvius* (eastern coral snake) and *Micrurus tener* (Texas coral snake) are clinically relevant, with the eastern coral snake producing more-potent venom. Bites from *Micruroides euryxanthus* (Arizona, western, or Sonoran coral snake) are not associated with significant morbidity. The eastern coral snake is found in Southeastern states east of the Mississippi River. The Texas coral snake lives west of the Mississippi River (Arkansas, Texas,

Table 2. Snake Venom Components and Their Clinical Effects

Venom Components	Clinical Effects
Crotalinae Family	
Low-molecular-weight polypeptides	Capillary leak, leading to third-spacing and shock
Metalloproteinases	Hemorrhage
Thrombin-like glycoproteins, fibrinolysins	Coagulopathy, thrombocytopenia, and hypofibrinogenemia
Digestive enzymes	Tissue damage leading to edema and bleeding
Myotoxins	Muscle necrosis
Elapidae Family	
Alpha-neurotoxins	Neurologic effects
Phospholipase A2	Soft-tissue injury
Myotoxins	Muscle necrosis

Figure 1. Comparison of Pit Viper and Nonvenomous Snake Characteristics



and Louisiana). **(See Figure 3.)** Coral snakes are small, with brightly colored circumferential bands of red, yellow, and black around their bodies. In North American coral snakes, the red and yellow bands are adjacent. Snakes with a black band between the red and yellow bands are typically nonvenomous; however, this color-banding pattern for distinguishing venomous coral snakes from nonvenomous mimics is true only for United States species. Regional variation makes this a guideline rather than a rule.

Coral snakes lack the heat-sensing pit present on pit vipers, and they have short, fixed, hollow fangs that are not efficient in breaking human skin. However, these physical characteristics should not be relied upon for definitive coral snake identification, as exceptions have been reported.[34] Coral snakes tend to chew rather than bite, and they can be difficult to remove once they have latched on. Most bites occur on the fingers and hands, with minor local effects (pain, swelling, and paresthesia).[10,11] Systemic symptoms include nausea, vomiting, abdominal pain, or dizziness. Coral snake venom contains potent neurotoxins that bind the muscarinic acetylcholine receptors at the neuromuscular junction. Neurotoxic symptoms include diplopia, difficulty swallowing or speaking, or generalized weakness. Symptoms can be delayed for several hours. Significant systemic neurological effects can develop, including paralysis and respiratory failure.[10,11] Coral snake venom also contains a myotoxin that can lead to significant muscle destruction.[2] Deaths from coral snake envenomation are extremely rare, with only 1 case in the published literature.[2]

Figure 2. Crotalinae (Pit Viper) Distribution in North America

Map shows the distribution of: (A) *Crotalus* (rattlesnakes), (B) *Agkistrodon* (copperheads, water moccasins/cottonmouths), and (C) *Sistrurus* (rattlesnakes).

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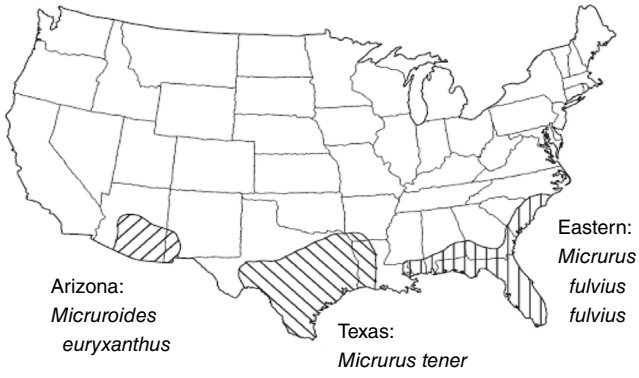
Differential Diagnosis

Differentiating venomous bites from nonvenomous and dry bites can be difficult. A description of the snake and the geographic location of where the bite occurred may provide some guidance; however, misidentification can occur, and snakes may not always be found within their natural geographic region if they are kept as pets. Diagnostic testing may be helpful, as coagulopathy—particularly early hypofibrinogenemia—suggests envenomation by a pit viper snake.

Prehospital Care

Evidence-based approaches for prehospital management of snakebites are lacking, and expert consensus guides current practice. Recommendations for prehospital care have changed over the decades, as research on practices such as incision/excision, venom extraction devices, tourniquets, chill methods, and electroshock therapy have shown potential to worsen patient outcomes. Since no currently recommended prehospital treatment has proven to alter outcome, treatment provided in the field should not delay transport. Correct identification of the snake can help guide management but should only be done if it will not cause further harm. Using a smartphone to take photographs from a safe distance can be useful for identification purposes. Attempts to capture a snake are ill-advised even if the snake is dead, as the bite reflex is often intact and capable of producing envenomation. **Table 3, page 6** lists the basic prehospital care for North American pit viper envenomations.

Figure 3. Elapidae (Coral Snake) Distribution in North America



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Pressure Immobilization

Pressure immobilization is a technique used to slow the lymphatic spread of venom by applying external pressure. To initiate pressure immobilization, bandages are applied at the bite site to compress lymphatic vessels, while preserving circulation. The bandages are then extended proximally up the limb. The bitten extremity is then splinted to further impede lymphatic flow.

Pressure immobilization is employed frequently in Australia due to the prevalence of highly neurotoxic indigenous snakes as well as the often-long transport times, which contribute to mortality rates that are higher than in the United States. In the United States, transport times are usually short, and native snake venom composition is predominantly hemotoxic, producing high morbidity (eg, limb-threatening), but low mortality. A porcine model demonstrated that pressure immobilization prevented death after severe envenomation by the western diamondback rattlesnake.[35] However, because United States pit viper envenomations are rarely fatal, many experts argue that potentially sacrificing the extremity by sequestering hemotoxic venom in the limbs is not justified.[8,36]

In 2010, the American Heart Association and the American Red Cross published first-aid guidelines endorsing the use of pressure immobilization for North American pit vipers.[37] In 2012, these guidelines were corrected twice to statements showing less definitive support for pressure immobilization. Despite the limited literature and statements from the American Red Cross favoring pressure immobilization for bites from North American pit vipers, the American College of Medical Toxicology and other experts do not recommend using this technique for North American pit viper envenomations. We also do not recommend pressure immobilization for these snakebites.

Many of the prehospital recommendations for envenomations from pit vipers are true for coral snakes as well; however, though the use of pressure immobilization is universally not recommended for North American pit vipers, its use after coral snake envenomation is controversial. Pressure immobilization has been used for decades in countries where Elapidae envenomations are common to decrease lymphatic absorption of venom and thereby limit potential systemic effects. A few animal model studies have looked at this technique in the eastern coral snake and showed pressure immobilization to successfully delay severe systemic symptoms.[38,39] Nonetheless, application of pressure immobilization by lay-people and physicians during simulations, even after intense training, proved to be technically difficult, raising concerns for delays in transport to medical facilities for definitive treatment that could ultimately prove fatal for the patient.[40,41]

Table 3. Prehospital Management of North American Pit Viper Envenomations[3,4,8]

DO:

- Keep the patient calm, warm, and at rest to decrease cardiac output and slow potential spread of venom.
- Remove constricting clothing and jewelry.
- Clean the wound.
- Immobilize the bitten body part and maintain a functional or extended position at the level of the heart or in elevation, when possible.
- Pad pressure points to prevent skin breakdown.
- Keep major joints in the bitten extremity (eg, the elbow) in extension (≤ 45° of flexion) to prevent blister formation, improve lymphatic outflow, and decrease dependent edema.
- Transport patient quickly to nearest medical facility. Discuss premixing of antivenom with receiving facility in cases of prolonged transport times and in patients exhibiting rapidly progressing local venom effects or significant systemic symptoms.
- Monitor vital signs and mental status, and observe for signs of hypersensitivity to venom components:
  - Initiate intravenous isotonic fluids if hypotension develops.
  - Treat hypersensitivity with epinephrine and antihistamines.
- Establish intravenous access in an unaffected extremity.
- Mark the leading edge of edema/erythema and repeat every 15 minutes; if splint is present, perform frequent neurovascular checks.

DO NOT:

- Apply pressure immobilization, constrictive dressings, or tourniquets.
- Incise; attempt to suction wound by mouth; or apply suction, tourniquets, ice, electricity, or heat to wound.
- Remove previously paced devices or venous tourniquets if limb ischemia is not present.
- Attempt to catch, kill, or handle live snakes.
- Handle dead snakes, as the bite reflex may remain intact and can still produce envenomation.

Adapted from: Melissa Costello, Alan Heins, Daniel Zirkin. Diagnosis and management of North American snake and scorpion envenomations. *Emergency Medicine Practice.* 2006;8(9):1-28. ©2006 www.ebmedicine.net

Emergency Department Evaluation

Initial Assessment and Stabilization

Evaluation of a patient with a snakebite should follow standard emergency care, prioritizing airway, breathing, and circulation. The patient should be placed on continuous monitoring of blood pressure, cardiac function, and pulse oximetry, using an unbitten extremity. End-tidal capnometry may be useful after envenomation by a neurotoxic or exotic snake. A full set of vital signs should be obtained. Intravenous (IV) access should be established using large-bore catheters. If not already done, recommended prehospital procedures should be initiated, such as removal of constrictive clothing and jewelry, and marking and timing the leading edge of pain, edema, or erythema

with circumferential measurements above and below the bite. Any constrictive devices/bandaging already placed in the field that is not causing ischemia should be left in place until resuscitative equipment and, ideally, antivenom is available and mixed, if indicated. Poison Control Center (1-800-222-1222) or medical toxicology service should be consulted for all suspected snakebites.[4]

If the patient is showing signs of respiratory failure, the airway should be secured. Hypotension should be treated with isotonic IV fluids and, if severe, epinephrine infusion, as it may indicate anaphylaxis. If signs of hypersensitivity are present (hypotension, wheezing, pruritus, urticaria) treat with intramuscular (IM) epinephrine and IV antihistamines. Antivenom will not reverse anaphylaxis. After stabilization, a thorough history and physical examination should be performed to determine whether envenomation has occurred and its severity.

History

A standard history should be obtained on every patient. When a snakebite is suspected, key historical questions include the following:[42]

- Time and location of bite(s).
- Tetanus status.
- Comorbid medical conditions (particularly those requiring use of anticoagulant drugs).
- Medications and allergies, especially to papain or papain-containing products, latex, or sheep or horse-based products.
- The prehospital clinical course and treatment.
- Presence of subjective systemic and neurological symptoms such as dizziness, nausea, numbness, paresthesia, dyspnea, or diplopia.
- Presence of muscle cramps or perioral tingling or numbness.
- Metallic taste.
- History of previous snakebite (as it may predispose the patient to potential anaphylactic reaction via immunoglobulin E antibodies to venom from previous exposure).
- Hypersensitivity to previous envenomation or to antivenom treatment. Sensitization typically occurs after snake envenomation; however, reports of sensitization from consumption, dermal contact, or inhalation of snake proteins in snake handlers has been reported.[43,44]
- A description of the snake may be helpful, but may not be reliable. If the patient or prehospital personnel have taken pictures of the offending snake, it may help in identification.

Physical Examination

A standard physical examination should be performed, with particular attention paid to the cardiovascular, respiratory, neurologic, hematologic, dermal, and musculoskeletal systems. Nonspecific constitutional symptoms, usually mild, can occur with both pit viper and coral snake envenomations, and may include nausea, generalized weakness, paresthesia, pain, restlessness, anxiety, tachycardia, and abdominal pain. Serious systemic symptoms such as syncope, shock, and respiratory failure can occur after significant pit viper or coral snake envenomation.[45] Local tissue effects occur in > 90% of patients after pit viper envenomations and are characterized as pain, erythema, swelling, tenderness, and myonecrosis.[46] These symptoms begin at the bite site and can progress as the venom moves through the lymphatic system.

Cardiovascular Effects

Pit viper venom can produce direct cardiovascular effects and tissue destruction through increased cell permeability. Accumulation of blood and third-spacing of fluid leads to wound swelling. Hypotension may indicate envenomation and/or anaphylaxis. Epinephrine is the vasopressor of choice in snake venom-induced shock. Swelling of a bitten extremity may develop rapidly after a envenomation. Frequent neurovascular examinations should be performed to monitor for the development of possible compartment syndrome.

Pit viper envenomation produces ecchymosis, paresthesia, pain, and even decreased pulses, simulating early compartment syndrome; however, there is typically only subcutaneous hypertension, with preservation of normal compartment pressures. True elevation in compartment pressures, producing vascular compromise, is rare. Consensus recommendations based on moderate-quality evidence strongly recommend diagnosing compartment syndrome based on actual compartment measurements, as the clinical picture may be unreliable. If a bite is in a location where pressure measurements may not be possible (eg, digits, hands, or feet), the presence of neurovascular compromise should be used to determine the presence or absence of compartment syndrome.[3,47] Elevated compartment pressures may be measured if taken from necrotic muscle. Cited risk factors for increased intracompartmental pressures include envenomations in small children, involvement of digits, application of ice or cold packs, and delayed or inadequate antivenom administration.[48]

Respiratory Effects

Rarely, patients may develop respiratory compromise after envenomations, bites to the face or neck, or after envenomation from a neurotoxin-producing snake. Bites to the neck or head (1% of all snakebites) put patients at high risk for airway compromise, and early intubation should be considered.[4] Alternative airway maneuvers, such as nasotracheal intubation or cricothyroidotomy due to airway obstruction, may be necessary. Antivenom will not reverse respiratory failure.

Neurologic Effects

A complete neurologic examination should be performed upon initial assessment to assess for signs of neurotoxicity. Frequent repeat examinations should be performed to monitor for progression or development of new symptoms, particularly in cases of confirmed or suspected bites from neurotoxin-producing snakes. Signs of neurotoxicity may be delayed up to 12 hours after an eastern coral snake bite; delay of symptom onset more than 6 hours after a Texas coral snake bite is rare.[10,49,50] According to a review of 387 eastern coral snake exposures, onset of systemic symptoms occurred, on average, 5.6 hours after the bite, with 3.3% of patients developing respiratory depression.[10]

Coral snake envenomations are uncommon, and there are few studies characterizing the clinical effects.[10] Coral snake venom produces a descending flaccid paralysis characterized by motor weakness, particularly of the cranial nerves.[10,51] Symptoms such as ptosis, dysphagia, paresthesias, diplopia, paralysis, and fasciculation have all been described, with paresthesia and weakness being the most common systemic symptoms. Pain was the most commonly reported local effect. Texas coral snake envenomation typically produces local effects such as pain, swelling, erythema, or local paresthesia, without neurological impairment.[11]

Pit vipers have been reported to cause neurotoxicity as well. The Mojave rattlesnake has been associated with muscular weakness of the cranial nerves and respiratory insufficiency, as well as causing myokymia (repetitive small-muscle fasciculations), sometimes despite antivenom administration. Myokymia in the shoulders, chest wall, or torso can lead to respiratory distress requiring intubation.[52]

Hematologic Effects

Pit viper venom causes decreased fibrinogen and thrombocytopenia from fibrinolysis and increased platelet consumption at the bite site. The result is an uncrosslinked fibrin clot that rapidly breaks down into fibrin degradation products. Venom does not affect other clotting factors.[49] Rarely, severe venom-induced coagulopathy can create a syndrome similar to disseminated intravascular coagulation. Ecchymosis is a common finding. Bleeding can develop beyond the bite site and should be considered a sign of systemic toxicity. Other systemic bleeding signs include bleeding gums, epistaxis, gastrointestinal bleeding, and intracranial bleeding. Severe envenomation can lead to hemorrhage and shock. Patients taking anticoagulant or antiplatelet medications have been found to have an increased risk of bleeding after rattlesnake envenomations.[53]

Dermal Effects

In nearly 50% of patients, bites from coral snakes do not produce any visible skin findings. The number of asymptomatic patients in the literature ranges from 14% to 56%.[10,54] Bite wounds should be evaluated for local effects such as edema, ecchymosis, bullae, and uncontrolled bleeding. Serial skin and neurovascular measurements should be obtained every 15 to 30 minutes to monitor proximal progression of swelling and pain.

Musculoskeletal Effects

Rhabdomyolysis can occur after significant envenomations such as from the *Crotalus horridus atricaudatus* (known as the canebrake rattlesnake, timber rattlesnake, or banded rattlesnake), whose venom is directly myotoxic. Significant rhabdomyolysis has occurred after coral snake envenomation as well.[2] Severe diffuse fasciculation may also lead to muscle breakdown.

Rare Reported Effects

Rare clinical effects have also been reported, such as digital chondrolysis and epiphysiolysis, distal tracheal myonecrosis, osteonecrosis, ischemic stroke, stenosing flexor tenosynovitis, massive pulmonary thromboembolism, and septic shock.[55-62]

Diagnostic Studies

General Recommendations

Recommendations for initial diagnostic testing vary in the literature. Most patients require a baseline complete blood cell count for platelets and hemoglobin, a prothrombin time (PT) test, and a fibrinogen concentration test.[4] Patients with systemic toxicity should also have their electrolytes, creatinine phosphokinase, creatinine, glucose, and urine tested. An electrocardiogram, chest radiograph, and blood gas may also be indicated in patients with cardiac or respiratory symptoms. Consider obtaining a urine pregnancy test in all female patients of reproductive age.

Coagulation Studies

In a retrospective chart review of 131 patients, limiting coagulation testing to only patients who had either a severe envenomation or a rattlesnake envenomation resulted in failure to identify a coagulation abnormality in a large majority of patients (89% were missed when testing was limited to a severe envenomation; 77% when limited to rattlesnake envenomation). Patients with moderate-to-severe envenomation were more likely to have an abnormal PT. Additionally, antivenom administration was associated with an abnormal PT. The study concluded that all patients presenting with pit viper envenomation should undergo coagulation testing.[63] In contrast, another study concluded serial coagulation testing may not be indicated after copperhead envenomation in the absence of bleeding.[64] In cases

of confirmed coral snake envenomation, laboratory testing is likely not useful, as hematologic abnormalities are not expected.

Imaging

A small study used bedside ultrasound to assess snakebite severity. Ultrasound could visualize subcutaneous tissue edema, localized fluid collections, and tendon involvement. The study also suggested future application of ultrasound imaging for suspected compartment syndrome, as the authors could visualize and assess deep muscle compartments, muscle integrity, and vascular flow. Additional study is needed to determine the feasibility of this potential use.[65]

Monitoring/Observation

All patients with suspected pit viper envenomation should be observed for 8 to 12 hours to monitor for the development of venom-induced clinical effects. Upon initial presentation, the leading edge of any edema or erythema surrounding the envenomated area should be marked and timed, with circumferential measurements above and below the bite, and repeated every 15 to 30 minutes. Serial examinations and indicated diagnostic tests for the development and progression of local, hematologic, and systemic venom effects should be performed, with treatment given, based on the observed clinical symptoms. **(See Table 4.)** After an uneventful observation period of 8 to 12 hours, asymptomatic patients may not need laboratory testing again until just prior to discharge. Symptomatic patients will need repeat laboratory testing every 4 to 6 hours and prior to discharge. Patients with no venom effects after the observation period are likely to have received a bite that did not result in venom injection. Patients who show progression of local venom effects, evidence of coagulopathy, or systemic venom effects should be treated with antivenom.

Treatment

In treating snake envenomation, the emergency clinician has 3 primary objectives:

1. Determine whether envenomation has occurred.
2. Offer antivenom treatment if indicated by the history, the patient's clinical condition, and laboratory test results.
3. Disposition the patient according to response to therapy and predicted clinical course.

Grading of Envenomation Severity to Guide Treatment With Antivenom

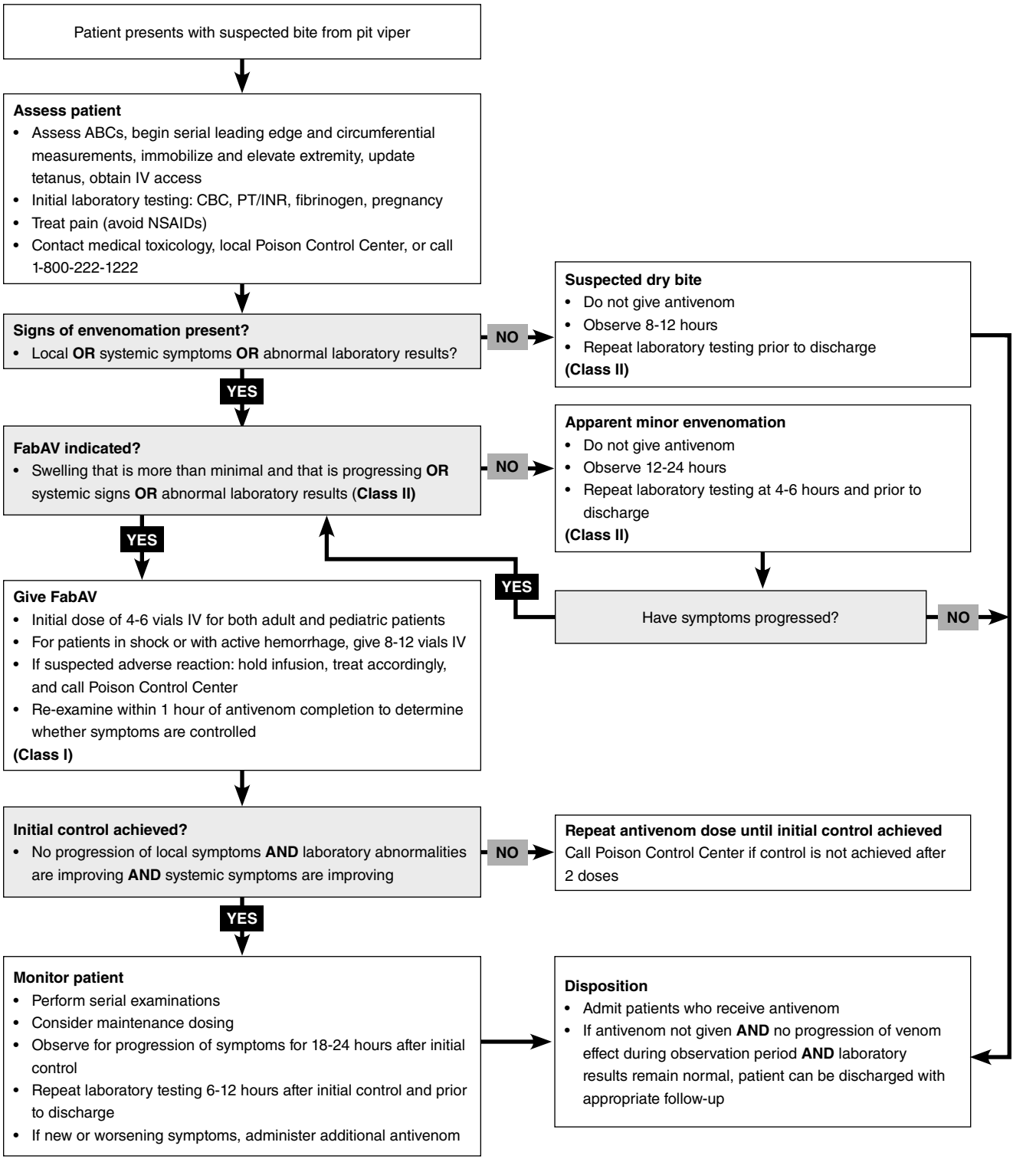
There is no universal grading system for measuring the severity of a snake envenomation. Several grading (or classification) scales are available to help guide management and the administration of antivenom after envenomation from a pit viper. Examples include the Snakebite Severity score,[66] the Minimum-Moderate-Severe score, and the Grade I-IV score.[51,67,68] These scales use patient symptoms, physical examination signs, and laboratory abnormalities to determine envenomation grading or classification (mild, moderate, or severe). Symptoms, signs, or laboratory abnormalities that place the

Table 4. Venom-Induced Clinical Effects and Their Treatment

Clinical Effect	Treatment
• Pain	• Opioids • Acetaminophen • Avoid NSAIDs
• Wound care	• Clean the wound • Update tetanus status • Prophylactic antibiotics are not indicated
• Progressive local effects (swelling, erythema, ecchymosis) • Systemic effects (coagulopathy, neurotoxicity, etc)	• Administer supportive measures and antivenom • Avoid blood products • Antivenom may not reverse neurotoxicity once it develops
• Anaphylaxis	• Administer IV fluids, corticosteroids, antihistamines, vasopressors, and IM epinephrine (standard management) • If there is a known allergy to antivenom and the benefits outweigh the risks, pretreat and administer antivenom by slow infusion
• Compartment syndrome	• Give initial control dose or increased dose of antivenom • Perform fasciotomy only as a last resort if ischemia is present and is refractory to antivenom • Perform fasciotomy only in conjunction with toxicology consult and compartment pressure measurement
• Antivenom-induced serum sickness	• Administer IV antihistamines and corticosteroids

Abbreviations: IM, intramuscular; IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs.

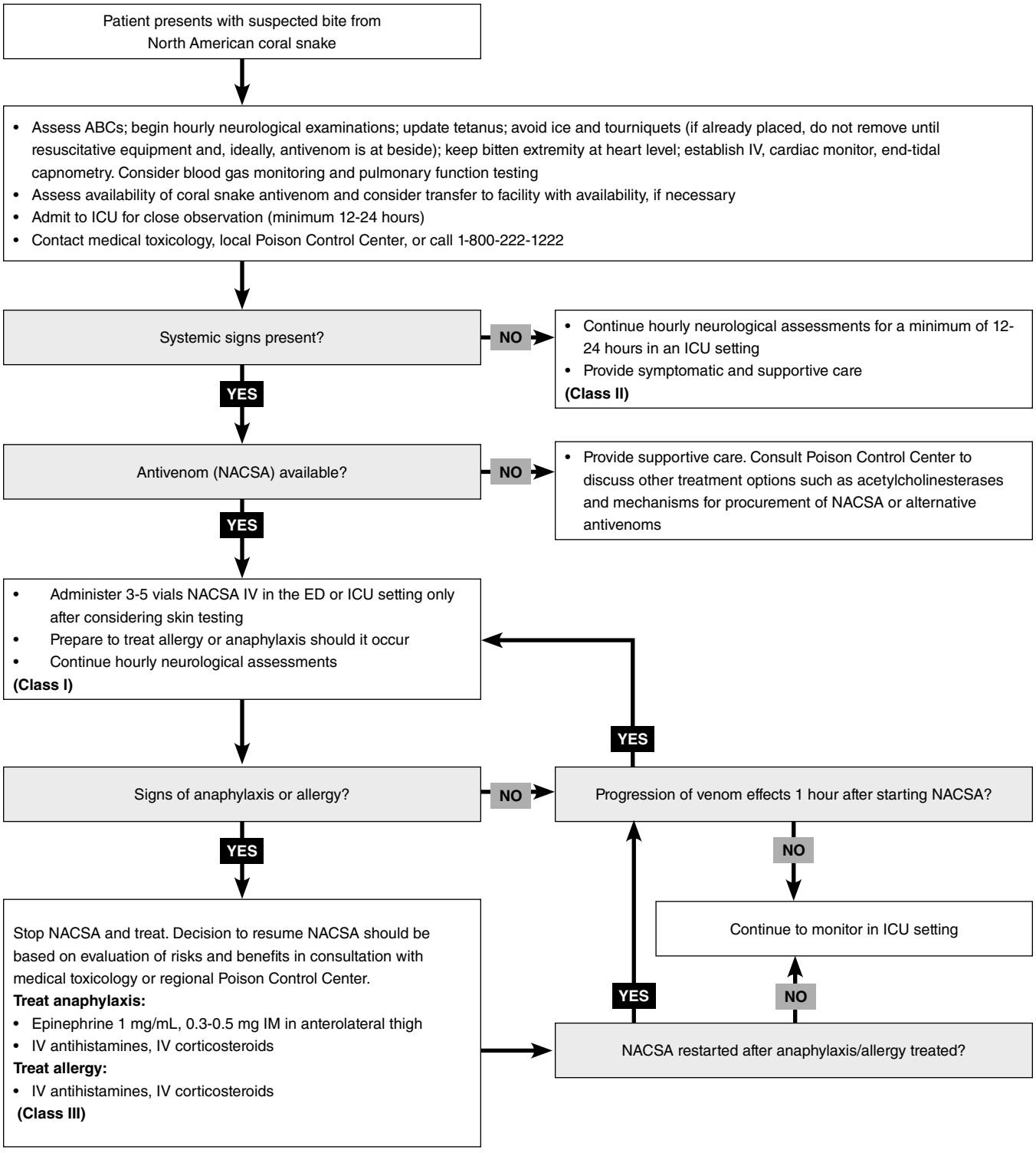
Clinical Pathway for Management of Patients With North American Pit Viper Bite



Abbreviations: ABCs, airway, breathing, circulation; CBC, complete blood cell count; INR, international normalized ratio; IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs; PT, prothrombin time.

For Class of Evidence definitions, see page 12.

Clinical Pathway for Management of Patients With North American Coral Snake Bite



Abbreviations: ABCs, airway, breathing, circulation; ED, emergency department; ICU, intensive care unit; IM, intramuscular; IV, intravenous; NACSA, North American Coral Snake Antivenin (Equine).

For Class of Evidence definitions, see page 12.

patient in the highest category should be used when grading.

There are several important limitations to keep in mind when using these scales. First, these scales capture envenomation severity at a single point in time and do not account for changes that may occur over time.[66,69] Second, these scales include the use of subjective measures that may not fully capture all aspects of the envenomation syndrome. Third, there is a lack of validation in the clinical setting. Fourth, there is a lack of specificity in patients' symptoms, combined with the difficulty of distinguishing symptoms due to envenomation from symptoms due to patient fear and anxiety.[66,69] We recommend that, rather than relying on a grading scale, antivenom treatment should be based on the severity and progression of the presenting symptoms.[42]

Antivenom Treatment of Pit Viper Envenomation

Antivenom administration, along with supportive care, is critical when successfully managing patients who meet treatment indications following envenomation from a pit viper.

FabAV (CroFab®)

FabAV (CroFab®) antivenom is made by injecting sheep with venom from the western diamondback and eastern diamondback rattlesnakes, the Mojave rattlesnake, and the cottonmouth/water moccasin, and then extracting the resulting venom antibodies from the animal's blood. The antibodies are processed using papain, an enzyme derived from papaya, to separate the fraction antigen binding (Fab) from the fraction crystallizable (Fc), which is the part of the antibody that contributes most to the development of allergic reactions. FabAV is effective against the venom from these snakes and has cross-reactivity to other snakes that are immunogenically similar.[30,70]

There are several indications for FabAV:[4,42,46]

- More than minimal local swelling, rapid progression of local swelling, or swelling crossing a major joint
- Evidence of hemotoxicity (elevated PT, low fibrinogen, thrombocytopenia)
- Systemic signs of toxicity (hemodynamic compromise, neuromuscular toxicity)
- Late or recurrent new-onset coagulopathy

An online tool for antivenom dosing is available from MDCalc: www.mdcalc.com/antivenom-dosing-algorithm

Dosing of FabAV

Once the decision to administer FabAV has been made, a bolus dose of 4 to 6 vials IV is recommended to gain control of initial symptoms. Control is defined as arresting progression of local tissue effects (swelling and pain), improvement in coagulation or platelet abnormalities, and resolution of systemic symptoms (except for myokymia, which may be refractory to antivenom). It is recommended that patients with life-threatening envenomation or those in cardiovascular collapse be treated with a starting dose of 8 to 12 vials IV of FabAV.[4,46] Dosing is the same regardless of age.

FabAV can reduce the duration and severity of coagulopathy and thrombocytopenia and prevents progression of swelling; however, it will not reverse tissue necrosis and may not reverse neurological effects.[24] Once initial control of symptoms has been achieved, maintenance dosing (typically 2 vials IV every 6 hours for 3 doses) is recommended to prevent recurrence of symptoms, as the half-life of venom is longer than that of FabAV. If control of symptoms does not occur after the first dose of FabAV, then subsequent bolus doses of 4 to 6 vials IV may be given. The presence of neurologic effects and thrombocytopenia prior to initiation of FabAV were shown to be associated with difficulty achieving initial control, according to results of a multicenter retrospective study of 247 patients.[71]

Class of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Nonrandomized or retrospective studies: historic, cohort, or case control studies
- Less robust randomized controlled trials
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

Contraindications for FabAV

There are no true contraindications for receiving antivenom, as benefits of the treatment outweigh the risks, and patients with known risk factors for allergy can be pretreated.[46] Acute hypersensitivity reactions to the ovine FabAV are uncommon and occur at a much lower incidence rate than with the older equine-derived whole immunoglobulin G products. Serum sickness is characterized by fever, rash, myalgias, and arthralgias, and is a type III hypersensitivity reaction that is a well-known complication of both FabAV and North American coral snake antivenom. A meta-analysis found the incidence of acute hypersensitivity reactions and serum sickness due to FabAV to be 8% and 13%, respectively.[72] Earlier studies reported higher rates, likely due to contamination of FabAV with Fc portions of antivenom.[73,74] Most reactions are mild, can be treated with supportive measures, and do not preclude further dosing. Skin testing is not recommended. Risk factors for allergic reaction to FabAV include known allergy to papaya, papain, chymopapain, pineapple enzyme bromelain, and previous allergic reaction to FabAV. Treatment for antivenom-induced anaphylactoid reactions/anaphylaxis is the same as other causes of severe reactions. Antivenom should be stopped, and IV corticosteroids, IV antihistamines, IV fluids, and IM epinephrine (if severe) should be given. As soon as it is safe to do so, FabAV should be restarted to limit venom effects and spread. Consult your medical toxicology services, regional Poison Control Center, or local expert at 1-800-222-1222 for guidance.

Use of FabAV for Copperhead Envenomation

Copperhead venom is not used in the production of FabAV, though FabAV may be effective for severe envenomations due to immunogenic similarity with the other pit vipers' venom. The use of FabAV for copperhead envenomation has been debated, due to the low morbidity and mortality rate associated with these bites.[31,75] However, limb-threatening injury can still occur after a significant envenomation, and FabAV may be indicated. A randomized controlled clinical trial looking at FabAV compared to placebo for mild-to-moderate copperhead envenomations (ie, swelling crossing 0 to 2 major joints) found FabAV reduced limb disability 14 days after envenomation, compared to placebo. Patients also required less opioid pain control.[76] Another study found no significant difference between the coagulation studies of envenomations from copperheads and other pit vipers and concluded that the patient's clinical picture and individual factors (ie, age, comorbidities, and size) rather than snake species alone should determine whether coagulation studies or FabAV are needed.[7]

Use of FabAV in Compartment Syndrome

Compartment syndrome should be treated with initial control-dose (4-6 vials) or elevated-dose (8-12 vials) antivenom. Antivenom reduces tissue pressures and myonecrosis, potentially eliminating the need for fasciotomy.[46,77] Animal and human studies have shown that antivenom treatment decreases elevated compartmental pressures;[66,78,79] moreover, the utility of fasciotomy is questionable in the setting of snakebite, as removal of surrounding fascia does not affect the muscle necrosis caused by the venom. Fasciotomy should not be used as first-line therapy, as it has not been shown to improve outcomes, but should be reserved for patients who do not improve after appropriate doses of antivenom. (Strong recommendation based on moderate-quality evidence.) In select patients with compartment syndrome with a delayed presentation, it may be appropriate to administer antivenom while preparing for fasciotomy, with reassessment just prior to incision to determine whether improvement has occurred, negating the need for fasciotomy. (Weak recommendation based on low-quality evidence.)

Use of FabAV in Coagulopathy

Antivenom is first-line treatment for coagulopathy, with blood products reserved for actively bleeding or severely anemic patients. Blood products in the presence of nonneutralized venom may be ineffective, as the venom will treat exogenous and endogenous blood products similarly.[46] In a case report of a rattlesnake envenomation, recombinant factor VIIa was effective at stopping life-threatening hemorrhage that failed supportive measures and antivenom therapy.[80]

Recurrent and late new-onset coagulopathy after FabAV treatment have been described in patients with and without laboratory abnormalities during index treatment and in patients with normal follow-up testing.[26,81-85] Several etiologies for recurrent coagulopathy have been proposed, including the shorter half-life of FabAV to that of venom; the possibility that venom stored in soft-tissue deposits release slowly into systemic circulation (a process that can occur over 2 weeks after a bite); that some types of venom have components with late-onset effects; that there may be dissociation of venom-antivenom complexes after initial control; and the existence of variable patient immune responses to the antivenom.[26,86-88]

In a study of 3 patients, recurrent coagulopathy was noted to be more likely to occur in patients with the triad of international normalized ratio (INR) > 6, fibrinogen < 60 mg/dL, and platelet count $< 100{,}000$ cells/mcL.[85] Another study of 60 patients looked at risk factors for the development of late, new-onset coagulopathy (developing 4 or more days after rattlesnake envenomation). Patients with hypofibri-

nogenemia, elevated D-dimer, thrombocytopenia, or elevated INR/partial thromboplastin time (PTT) during the first 48 hours after envenomation or a 20% increase in platelet count within 4 hours post-treatment were at risk for late hematologic abnormality. Patients without these risk factors were found to be at low risk and could forego ongoing hematologic surveillance after discharge.[82,89] A review of 66 rattlesnake envenomations treated with FabAV found recurrent and late-onset hematologic toxicity to be common. Nonetheless, most patients do not develop significant bleeding despite their coagulopathy. A systematic review of 19 cohort studies found the incidence of late-onset medically significant bleeding extremely low, although it is likely underreported.[83] Recurrent and delayed coagulopathy have been successfully treated with FabAV.[84,85]

Antivenom Treatment of Coral Snake Envenomation

Early administration of North American Coral Snake Antivenin (Equine) (NACSA) may halt or limit the progression of muscle paralysis, shortening its course and potentially avoiding intubation. NACSA was produced solely by Pfizer/Wyeth, and until recently, new product was not available. During the shortage, the United States Food and Drug Administration (FDA) extended the expiration date of the existing coral snake antivenom (lot L67530) after performing safety and potency studies.[90] Due to the shortage, many experts took a wait-and-see approach, recommending NACSA treatment at the first signs of systemic toxicity.[10] This approach was supported by the literature, which described a low incidence of major outcomes after coral snake envenomation.[9,91]

An observational study compared patients who were empirically treated with NACSA (134 patients) to those who received treatment after development of systemic signs (withhold group, 106 patients). Patients in the withhold group seemed to have more favorable outcomes; however, the rate of intubation between the 2 groups was not statistically significant.[10] This suggests that NACSA will likely not reverse neuromuscular weakness of the respiratory muscles, and antivenom should be given at the first sign of systemic toxicity to prevent progression.

An observational study of 82 patients found predominantly local effects and, rarely, systemic findings (such as neuromuscular weakness) after envenomation by coral snakes. NACSA was rarely indicated. According to the study findings, treatment for Texas coral snake envenomation should focus on wound care, pain control, and an 8-hour observation period for development of systemic effects or allergy.[11] However, other authorities do not differentiate between the 2 venomous coral snake species when it comes to management. More evidence is needed to support the suggested change from 12- to 24-hour observation for all coral snake bites, as it is common practice to observe for 8 hours after a Texas coral snake bite. Caution should always be used when managing coral snake envenomations, as the geographic range of coral snakes may overlap.

Dosage of North American Coral Snake Antivenin (Equine)

For coral snake envenomation, the initial dose of NACSA is 3 to 5 vials IV for both adult and pediatric patients. The dose can be repeated if symptoms do not improve. Skin testing is controversial. Some reference materials argue against skin testing, as it may not always predict allergy and could sensitize the patient, increasing the risk for allergy during antivenom administration.[92] More than 10 vials may be necessary for severe envenomations. If NACSA is unavailable, then treatment is supportive. Consulting your regional Poison Control Center for guidance is highly recommended.

NACSA is an equine-derived whole IgG product and is thus associated with a higher immune response reaction. Published rates for adverse reactions are high, ranging from 11% to 18%.[10,11] Dermal reactions are the most commonly reported. Treatment is supportive, following standard allergy/anaphylaxis regimens (IV antihistamines, IV corticosteroids, and IM epinephrine).

Experimental Coral Snake Antivenoms and Treatments

The effectiveness of lot L67530 of NACSA (whose expiration date has been extended multiple times) is unknown. Use of expired medications in the United States is prohibited by the FDA and requires preapproval from the FDA and informed consent by the patient.

Coralmyn®, a polyclonal antivenom F(ab')2 coral snake antivenom, produced in Mexico, is an investigational antivenom used to treat North American coral snake envenomations. In mice, Coralmyn® effectively neutralized North American coral snake venom.[93] There is a phase 3 trial studying Coralmyn® antivenom for treatment of coral snake bites, and results are pending.[94]

Acetylcholinesterase inhibitors have been used in other countries to treat neuromuscular weakness from South American coral snakes.[54] An animal model study found decreased toxicity and increased survival after injection of trypsin at the bite site.[95] However, these treatments have limited supportive evidence and are experimental.

Treatment of Non–Native Snake Envenomation

Venomous non–native (exotic) snakes are responsible for higher morbidity and mortality compared

to native species. This, combined with clinician unfamiliarity, leads to more conservative approaches when treating victims of exotic snake bites. Management of exotic snake bites should include identification of the snake, when possible, and consultation with a Poison Control Center or local expert for guidance on treatment, including procurement of the correct antivenom. At times, antivenoms may not be readily available locally and may require checking with a variety of sources, such as zoos and aquariums. Observation in a monitored setting (such as the intensive care unit) for 24 hours is suggested to monitor for development of neurotoxicity, which can be delayed up to 20 hours for some species.[96]

The process of snake identification is a difficult proposition in the ED, but there are many resources available. An emergency clinician is likely to rely on the patient's information and description, a picture taken in haste, or a portion of the snake's body to examine after it has been killed. Additionally, regional variation in coloration, size, and diet can affect the appearance of all wildlife, including snakes. With a simple Internet search, many websites can be found that claim expertise in snake identification. This information can be helpful, but should be viewed with skepticism. It is advisable for emergency clinicians to reach out to regional experts in this field to consult, if needed. The most likely places to find these individuals would be the local zoo or a state university Cooperative Extension Services office. Even then, a large portion of snakebite cases must be managed without identification of the species and its venom potential. Each case should be analyzed on an individual basis, and the risks should be weighed against the benefits.

Special Populations

Pregnant Patients

The incidence of reported snakebites in pregnant patients is low (1.4%).[97] FabAV and F(ab')2 are pregnancy category C drugs. The same general principles for prehospital and ED evaluation and management after a snakebite should be performed for a pregnant snakebite victim. Patients should be transported to a facility with obstetrical coverage, whenever possible. Both maternal and fetal monitoring should be performed, and maternal tissue perfusion should be maintained to prevent fetal distress and hypoxia. Hypotension should be treated with isotonic or crystalloid IV fluids, avoiding vasopressors when possible, to protect blood flow to the fetus. Indications for antivenom treatment are the same, regardless of pregnancy status of the patient. There are conflicting data on the risk of envenomation to the developing fetus and pregnant patient. Fetal demise rates as high as 30% after envenomation have been reported; however, these cases involved venomous snakes that are more potent than those native to North America.[97] Maternal fatality rates of 0% to 10% have been cited.[98,99] The safety of antivenom in pregnant patients has not been studied, as these patients were excluded from trials. CroFab® contains ethylmercury, an organic mercury known to cross the placenta, capable of producing severe fetal cognitive and physical deformities. However, there is no direct evidence that thimerosal preservative in vaccines and antivenom causes fetal defects.[100] For this reason, antivenom treatment is generally recommended to be given if the mother has indications for treatment, as poor fetal outcome is tied directly to the severity of envenomation in the mother.[46,100,101] An increased risk of poor fetal outcome in first-trimester envenomations compared to third-trimester envenomations has been observed.[98,102]

Pediatric Patients

Studies have shown safety and efficacy of antivenom in pediatric populations.[88,103,104] Pediatric and adult dosing is the same, since the amount of venom delivered by a snake is not based on the age of the patient.[46] However, age can be taken into account when reconstituting venom, so that the same dose with less volume is administered. Pediatric patients may be at higher risk for recurrent coagulopathy, given their higher renal blood flow and higher rates of clearance of unbound FabAV complex.[84]

Anticoagulated Patients

Patients on antiplatelet or anticoagulant medications have been found to be at an increased risk of bleeding after pit viper envenomation. Risk is greatest early after envenomation during the index visit; however, there is also a risk of late major bleeding after discharge. Study authors suggested close follow-up with repeat platelet and coagulation studies every 2 days during the first week after envenomation, following the last dose of FabAV.[53]

Controversies and Cutting Edge

Controversies

- Incision and suction of snakebites is nearly universally not recommended. However, the American College of Surgeons Committee on Trauma-Management of Poisonous Snakebites 2004 report states "Most physicians would agree that some form of incision and suction of the fang marks may be beneficial if performed within 15 to 30 minutes from the time of bite."[105] We do not recommend incision and suction, as it may introduce infection into the wound.
- In the absence of ischemia, fasciotomy for snakebite is not recommended, even if compartment pressures are elevated. Multiple studies show

increased morbidity and unnecessary healthcare costs associated with fasciotomy.[106,107] Animal model studies have also shown a reduction in compartment pressures with antivenom treatment without fasciotomy.[79,107] Despite the evidence, some authorities recommend fasciotomy for compartment pressures > 30 mm Hg, with or without evidence of neurovascular compromise.[105] Compartment syndrome—confirmed or suspected—should be treated with initial control doses of antivenom. We recommend fasciotomy only in cases of true limb ischemia that is not responsive to antivenom.

- Experimental studies have shown a potential role for mannitol in postischemic compartment syndrome models.[108-111] A single case report demonstrated resolution of rattlesnake-induced compartment syndrome after combined use of antivenom, mannitol, and hyperbaric oxygen. However, it is unclear whether mannitol and hyperbaric oxygen in the absence of antivenom would have significantly contributed to the successful outcome in this case.[112]
- The shortage of NACSA and recent studies illustrating the paucity of severe outcomes after coral snake envenomation has led to a change in treatment indications. Historically, NACSA was given in cases of known or suspected coral envenomation, regardless of symptoms. Now, most recommend waiting to treat until systemic signs occur. This may be problematic for patients who are initially asymptomatic but manifest delayed systemic toxicity.
- Several studies suggest that mild-to-moderate copperhead envenomations can be managed with observation without antivenom use and that serial coagulation testing may not be needed in the absence of clinical bleeding.[34,64,75,113] Other studies present data to the contrary.[7,63,76] Given the lack of definitive evidence, we recommend copperhead envenomations be managed following the same procedure outlined for other pit vipers.
- Routine maintenance FabAV therapy is recommended by the Crofab® manufacturer and some Poison Control Centers. Maintenance dosing is additional antivenom given to a patient after initial control of symptoms has been achieved to prevent recurrence of symptoms. Most authorities advocate for 2 vials every 6 hours for 3 doses after initial control.[4] However, other experts do not think maintenance dosing is needed in certain circumstances, such as after a copperhead envenomation, for minor envenomations, or when close observation by a physician/expert is available. Due to this practice variation, it is best to consult your regional Poison Control Center.[4]

Cutting Edge

F(ab')2 (Anavip®)

Crotalidae Immune F(ab')2 (Equine) antivenom (Anavip®, Instituto Bioclon SA de CV, Mexico City, Mexico) is developed using *Bothrops asper* and *Crotalus simus* venoms. Despite its production from Latin American snake species, Anavip® is an effective treatment for envenomation from North American Crotalinae.[6,114] The United States Food and Drug Administration (FDA) granted Anavip® marketing approval in 2015, and it is expected to be available in the United States in October 2018. The initial dose of F(ab')2 is 10 vials infused IV over 60 minutes. Additional doses of 10 vials can be given to achieve initial control. Following administration of antivenom, patients should be observed and monitored for a minimum of 18 hours following initial control of symptoms. If symptoms recur, additional dosing with 4 vials may be given.[115]

F(ab')2 is structurally different from FabAV, as it is cleaved on the Fc portion so that a small portion remains linking the 2 Fab arms (unlike FabAV, which has no Fc portion). This structural difference is believed to provide F(ab')2 important advantages over FabAV: (1) a longer half-life, and (2) reduced rates of late coagulopathy.[6,116] The limited available evidence indicates that F(ab')2 may reduce late coagulopathy incidence after envenomation and the need for maintenance dosing, follow-up, and repeat coagulation testing. In addition, F(ab')2 appears to be safe, with adverse event and immune reaction rates similar to FabAV, despite its equine derivation.[6,114,116]

Other promising treatments include:

- Injection of trypsin at the bite site may be a potential alternative treatment or a bridge to antivenom, as it was shown to decrease coral snake venom toxicity in an animal model.[95]
- Limited studies have shown success using continuous IV FabAV, 2 to 4 vials/day, titrated to effect, to treat recurrent and late-onset coagulopathy.[117,118]
- An in vitro study published in 2017 found that iron and carbon monoxide could attenuate *Agkistrodon* venom-mediated degradation of fibrinogen-dependent coagulation. This may potentially serve as a bridge to antivenom in prehospital settings with prolonged transport times and/or as an adjunct to antivenom therapy.[119]

Disposition

Observation

Patients with no symptoms and normal baseline laboratory testing after a bite from a pit viper should be monitored for development of symptoms for 8 to 12 hours from the time of the bite. At the end of the observation period, if there is no progression of symptoms and repeat testing remains normal, then

the patient may be discharged.[46]

Patients with a bite from a coral snake should be admitted and observed for 12 to 24 hours, as delayed toxicity can occur. Traditionally, bites from eastern and Texas coral snakes are managed the same; however, an observational study found low rates of significant symptoms after envenomation from the Texas coral snake. The authors concluded that envenomation from a Texas coral snake without systemic signs of toxicity can be observed for 8 hours to ensure no progression of symptoms.[11] Since coral snake bites are rare, no other studies are available to either confirm or refute these findings. Discussion with your regional Poison Center is recommended in these cases.

Admission

Patients with mild symptoms (nonprogressing swelling, pain, or ecchymosis) after a pit viper envenomation do not need antivenom but should be monitored in an inpatient setting for 12 to 24 hours and given antivenom only if symptoms progress. These patients should have baseline laboratory testing, repeat testing every 4 to 6 hours, and repeated again prior to discharge.[4] Patients with progressive local effects and/ or systemic venom effects should receive antivenom and will require admission. Patients with bites from a coral or exotic snake require admission for 12 to 24 hours regardless of whether symptoms are present.[46]

Follow-Up

Patients with rattlesnake envenomation and those who develop hematologic abnormalities treated with FabAV should undergo repeat coagulation testing in 2 to 4 days and again in 5 to 7 days, as they are at high risk for late hemotoxic effects that often occur 2 to 7 days after antivenom.[82,89,120] Patients with copperhead envenomation without hemotoxic effects during hospitalization and those with mild envenomations that did not require antivenom do not typically require follow-up testing for recurrence.[4] Patients should be instructed to watch for signs of serum sickness (fever, rash, muscle pain, arthralgia, or arthritis) and return for worsening swelling not relieved with elevation, abnormal bleeding, or easy bruising. Wound follow-up should be arranged to monitor progression of wounds and ensure extremity function is returning. Some patients may have long-term disfigurement, disability, pain, numbness, tingling, or neurological issues. Others may require physical therapy and/or occupational therapy due to limited use of the affected extremity that interferes with school and work activities. Patients who use antiplatelet or anticoagulant medications should be continued on these medications only after a careful risk-benefit analysis. Whenever possible, the medications should be discontinued until the risk of recurrent or late hematologic toxicity passes. Patients should be warned to not undergo dental or surgical procedures for up to 3 weeks unless platelet and coagulation studies are documented to be normal immediately prior to the procedure. High-risk activities, such as contact sports, should be avoided.

Summary

Most snake envenomations in the United States result from bites by pit vipers, whose venom commonly produces local tissue swelling and hematologic toxicity that may be debilitating. However, a few pit vipers can produce neurological symptoms as well. Bites from coral snakes represent a small percentage of envenomations, and they predominantly produce neurotoxicity without local tissue effects. Management of patients with pit viper and coral snake envenomation should focus on supportive care, pain control, and specific antivenom, when indicated. Not all envenomations require treatment with antivenom. Monitoring of local and systemic symptoms is crucial to assessing whether antivenom is indicated. All patients requiring antivenom or with a suspected envenomation from a coral snake should be admitted. Consultation with a regional Poison Control Center may be extremely helpful.

Case Conclusions

The 4-year-old child bitten by the coral snake has no signs or symptoms of envenomation at this time, but he is at risk for neurological decline and respiratory arrest. His laboratory workup was unremarkable. Because he did not display any symptoms, you decided to withhold the antivenom while in the ED. You transferred him to the pediatric ICU for hourly neurological assessments and potential administration of antivenom. The patient remained asymptomatic after an observation period of 24 hours and was discharged home.

The 26-year-old man with 3 prior rattlesnake bites was at risk for significant morbidity related to this fourth snakebite, including impaired use of his dominant hand. Additionally, his initial lab values showed a developing coagulopathy. You decided to administer 6 vials of antivenom, but you ordered pretreatment with IV corticosteroids and antihistamines. You moved the patient to your resuscitation area for administration of antivenom and admitted him to the ICU for continued monitoring; fortunately, there were no side effects with the initial dose of antivenom.

You determined that the 51-year-old patient bitten by a rattlesnake who was experiencing bruising and bleeding gums had a recurrent coagulopathy. You gave him a loading dose of 6 vials of antivenom in the ED and admitted him to the floor for subsequent doses and monitoring. After 2 days in the hospital, his coagulopathy resolved, and he was discharged home without incident.

Risk Management Pitfalls for Managing Patients With Snakebites in the Emergency Department

1. **"The patient had some minor abrasions, but no visible fang marks, pain, or swelling at the bite site, so I discharged him."**
   Patients can develop a coagulopathy and covert bleeding from pit viper bites without having visible tissue damage. The patient should be observed for a minimum of 8 hours, and coagulation studies repeated before discharge home. Coral snake bites may not produce any visible signs on examination. If a coral snake is the suspected culprit, the patient should be monitored for 24 hours to ensure delayed symptoms do not develop.

2. **"She was in a lot of pain and the swelling was severe, so I performed a bedside fasciotomy."**
   The true incidence of compartment syndrome secondary to pit viper envenomation is very small. Compartment pressures should be confirmed to be elevated or evidence of ischemia should be present before performing a fasciotomy.

3. **"I thought that I could wait until signs of respiratory distress developed, because the antivenom would quickly reverse the paralysis."**
   Administration of antivenom does not reverse symptoms; it merely halts progression of symptoms. Patients with coral snake bites should be treated with antivenom at the first signs of neurological impairment.

4. **"The child bitten by a coral snake was asymptomatic, so I admitted him to the floor to make sure that he didn't develop symptoms."**
   All patients with suspected bites from a coral snake should be admitted to an intensive care unit, as hourly neurological examinations are necessary.

5. **"I didn't know whether snake antivenom was safe during pregnancy, so I opted to observe the patient, since the swelling was confined to her foot."**
   The true risk of antivenom during pregnancy is unknown; however, the potential morbidity and mortality due to snakebites is well known and avoidable with proper treatment with antivenom.

6. **"I figured the snake's mouth probably isn't clean, so I started prophylactic antibiotics."**
   Secondary infection due to snakebites is rare, and prophylactic antibiotics are likely not needed. Monitor patients closely for signs and symptoms of infection and treat if an infection is clinically suspected.

7. **"The patient had urticaria and wheezing that developed soon after I started administering antivenom, so I stopped the infusion. The patient continued to worsen, even though I stopped it."**
   Allergic reaction to antivenom is a serious adverse effect; however, patients can also develop anaphylaxis and other allergic symptoms to snake venom. For each case, consider this possibility and weigh the risks of not treating a snakebite. Consultation with a regional Poison Control Center is recommended.

8. **"The site where the patient was bitten by the snake was clean, so I didn't think any vaccines were necessary."**
   The incidence of tetanus secondary to a snakebite is unknown. However, with any wound, it is standard practice to ensure a patient's vaccine status is current.

9. **"It was pretty obvious that the patient's arm was swollen, so I didn't think it was necessary to continue to measure it."**
   Serial circumferential measurements and marking the leading edge of swelling are important to determine whether antivenom therapy has halted progression. In addition, objective measurements and markings allow for continuity of care between providers.

10. **"The patient had thrombocytopenia, so I ordered platelets to be given immediately."**
    Blood products may be necessary in an unstable patient with signs or symptoms of hemorrhage; however, blood products alone in a snakebite victim will be only temporizing, as the snake venom will damage or destroy the blood products given. Antivenom must be given in conjunction with blood products to neutralize the snake venom.

Time- and Cost-Effective Strategies

- Mild copperhead envenomations without hemotoxic effects and not requiring antivenom may not need serial laboratory testing or outpatient retesting. Discuss current regional practice patterns with your regional Poison Control Center.
- For most patients, initial laboratory testing should include only baseline complete blood cell count, PT, and fibrinogen concentration. Other testing can be added, depending on the severity of the bite and clinical picture of the patient.
- Consultation with a regional Poison Control Center will help streamline testing, reduce unnecessary antivenom use, and avoid unnecessary hospitalization.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study is included in bold type following the references, where available. The most informative references cited in this paper, as determined by the author, are noted by an asterisk (*) next to the number of the reference.

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CME Questions

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1. What percentage of snakebites are estimated to be "dry" or do not involve venom release?
   a. 0% to 10%
   b. 10% to 25%
   c. 25% to 50%
   d. 50% to 60%

2. Which of the following species of coral snake native to the United States produces the most potent venom?
   a. Sonoran coral snake (*Micruroides euryxanthus*)
   b. Texas coral snake (*Micrurus tener*)
   c. Eastern coral snake (*Micrurus fulvius fulvius*)

3. With regard to prehospital management of pit viper bites, which of the following is recommended?
   a. Making an incision at bite site to drain venom
   b. Using a suction device or mouth to remove venom from bite site
   c. Icing the affected area if swelling occurs
   d. Rapid transport to closest medical facility

4. **Regarding compartment syndrome after snake envenomation, which of the following is true?**
   a. Risk factors include envenomations in small children, involvement of small digits, ice on bite site, and inappropriate or inadequate antivenom treatment.
   b. The clinical picture without compartment pressures is reliable for diagnosis.
   c. Pit viper envenomation commonly produces compartment syndrome.
   d. Antivenom should be used cautiously until a compartment pressure is measured so as not to interfere with the measurement.

5. **Regarding venom-induced neurotoxicity, which of the following is true?**
   a. Myokymia (fine fasciculations) can occur after copperhead envenomations.
   b. Myokymia may not reverse with antivenom treatment.
   c. Neurotoxicity occurs only with coral snake envenomations
   d. Neurotoxicity does not occur with pit viper envenomations

6. **After an appropriate risk-benefit analysis, during which of the following scenarios would administration of FabAV antivenom be potentially withheld?**
   a. Rapid progression of local symptoms in an otherwise healthy individual
   b. Anaphylaxis to papaya or pineapple
   c. History of receiving antivenom previously with no issue
   d. The patient is pregnant

7. **Regarding allergic reactions to FabAV, which of the following is true?**
   a. An allergy to papaya (papain) precludes treatment with antivenom.
   b. Hypotension can be a symptom of both severe snake envenomation and anaphylaxis.
   c. Allergic reaction to any previous antivenom is a contraindication to administration.
   d. Treatment of antivenom-induced allergic reaction with IM epinephrine, IV corticosteroids, and IV diphenhydramine is unlikely to be beneficial.

8. **When are blood products indicated for treatment of a snakebite?**
   a. For all snakebites with resultant coagulopathy
   b. Whenever antivenom is being administered
   c. When a snakebite victim is actively bleeding or severely anemic, in conjunction with antivenom
   d. In lieu of antivenom when it is not available

9. **Regarding recurrent or late coagulopathies, which of the following is true?**
   a. Treatment with antivenom is not necessary.
   b. Recurrence is thought to occur because the half-life of FabAV is shorter than that of venom.
   c. An increase in platelet count of ≥ 20% within 4 hours after FabAV treatment was associated with late new-onset coagulopathy.
   d. Medically significant bleeding is common in recurrent or late coagulopathies.

10. **Regarding envenomations during pregnancy, which of the following is true?**
    a. Antivenom should not be given, regardless of symptoms.
    b. The presence of ethylmercury in antivenom precludes its use in a pregnant patient due to risk to the fetus.
    c. Management of pregnant patients is the same as for nonpregnant patients.
    d. FabAV is pregnancy category A.

In upcoming issues of *Emergency Medicine Practice....*

- Sepsis and Septic Shock
- First-Trimester Emergencies
- Electrical Injuries
- Managing Influenza in the ED

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Target Audience: This enduring material is designed for emergency medicine physicians, physician assistants, nurse practitioners, and residents.

Goals: Upon completion of this activity, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical presentations; and (3) describe the most common medicolegal pitfalls for each topic covered.

Objectives: Upon completion of this activity, you should be able to: (1) describe the evaluation, management, and disposition of patients presenting with envenomations from North American pit vipers and coral snakes, (2) list the indications, contraindications, and dosing for antivenom products for snakebites, (3) manage anaphylactic and anaphylactoid reactions from venom and antivenom, and (4) identify and manage late or recurrent coagulopathy.

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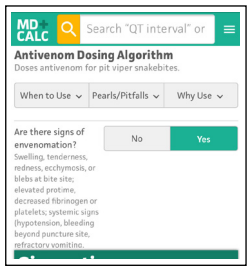

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Antivenom Dosing Algorithm

Introduction: The Antivenom Dosing Algorithm specifies the manifestations of Crotalinae (pit viper, formerly known as Crotalidae) snake envenomation that necessitate aggressive management.

Points & Pearls

- The Antivenom Dosing Algorithm is a unified treatment algorithm that was developed with the goal of quick identification and management of patients who may benefit from treatment with Crotalidae Polyvalent Immune Fab (CroFab®).
- There is significant variability among patients with snake envenomations, and this algorithm does not represent a standard of care.
- All cases of suspected or confirmed snake envenomation should be reported to Poison Control (1-800-222-1222).

Advice

The leading edge of swelling and tenderness surrounding the envenomated area should be marked every 15 to 30 minutes. Elevate and immobilize the affected extremity, treat pain aggressively with intravenous opioids, and update the patient's tetanus status as needed.

Critical Actions

The following should be avoided:

- Cutting or suctioning the wound
- Ice
- Nonsteroidal anti-inflammatory drugs
- Prophylactic antibiotics
- Prophylactic fasciotomy
- Routine use of blood products
- Electrical shock therapy
- Steroids, unless allergic phenomena are observed
- Tourniquets

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Why to Use

The Antivenom Dosing Algorithm is an antivenom dosing tool for Crotalinae (pit viper, formerly known as Crotalidae) snake envenomations.

Antivenom is an extremely expensive resource that carries a risk of adverse events. Emergency clinicians should be aware of the indications for its use, as well as other steps to take in the management of patients with pit viper bites.

When to Use

- Use the Antivenom Dosing Algorithm for patients with known or suspected Crotalinae envenomation.
- This algorithm is not valid for snakebites on the head or neck, snakebites causing rhabdomyolysis, or in cases of anaphylaxis/anaphylactoid reactions to venom.
- This algorithm does not apply to envenomation by coral snakes or any snakes that are not indigenous to the United States.

Next Steps

Maintenance therapy

- Administer maintenance dosing of 2 vials of antivenom every 6 hours for 3 doses, at 6, 12, and 18 hours after initial control of symptoms is achieved.
- Maintenance therapy may not be needed if close observation by a physician-expert is available.

Follow-up planning

- The patient should return if swelling worsens and is not relieved by elevation; if abnormal bleeding occurs (eg, melena, gum bleeding, easy bruising); or if fever, rash, or muscle or joint pains occur (ie, symptoms suggesting serum sickness).
- The patient should be given bleeding precautions: no contact sports, elective surgery, or dental work for 2 weeks.
- The patient should be advised to follow up for repeat laboratory testing twice (at 2-3 days and 5-7 days after discharge), and then as needed.
- Follow up as needed for cases in which antivenom was not administered or antivenom was administered for copperhead envenomation.

Evidence Appraisal

Lavonas et al analyzed the medical literature regarding use of Crotalidae Polyvalent Immune Fab for pit viper envenomations. After analysis of 42 original articles, this panel of experts met and held a consensus-building meeting, which resulted in a unified treatment algorithm.

Use the Calculator Now

Click here to access the calculator.

Calculator Creator

Eric J. Lavonas, MD
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Reference

Original/Primary Reference

- 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.
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