SNAKEBITE / CROTALID ENVENOMATION

SUMMARY

Snakebite / crotalid envenomations are characterized by an erratic and unpredictable clinical course. They should be considered medical emergencies requiring close monitoring. Manifestations of crotalid envenomations may include local tissue injury, coagulopathy, and severe systemic effects. Treatment for venomous snakebites includes aggressive supportive care and prompt administration of antivenom to selected patients. Although prospective data on crotalid antivenoms are limited, use of antivenom in progressive crotalid envenomations should be considered as standard of care.

RECOMMENDATIONS

- **Level 1**
  - **None**
- **Level 2**
  - **Antivenom should be administered within four hours of North American crotalid envenomation to patients showing evidence of progressive or severe venom injury.**
  - **FabAV initial dose is four to six vials IV over 60 minutes, or seven to eight vials depending on the severity of the envenomation.**
    - **An additional dose of four to six vials should be given if initial control is not achieved with the first dose.**
- **Level 3**
  - **Late administration of antivenom (greater than six hours post-envenomation) may be beneficial in patients with coagulopathy and local symptoms.**
  - **NSAIDs are efficacious for analgesia in copperhead snakebites.**
  - **Follow-up evaluation after seven days may be prudent to assess the patient for delayed coagulopathy.**

INTRODUCTION

About 9,000 patients per year are bitten by venomous snakes in the United States, five of which die from their injuries (1). Over 99% of the venomous snake bites in the US are caused by snakes of the subfamily Crotalidae, also known as pit vipers. These snakes include rattlesnakes, cottonmouths/water moccasins, and copperheads (2). Snakebite envenomation is characterized by an erratic and unpredictable clinical course, making assessment and determination of the severity of envenomation difficult. They should be considered medical emergencies that require observation in a hospital setting. Manifestations of crotalid envenomation may include local tissue injury, such as marked tissue swelling, pain with potential soft tissue necrosis and severe coagulopathies characterized by hypofibrinogenemia, prolonged prothrombin time (PT), variable changes to activated partial thromboplastin time (aPTT), and decreased platelet count (3). These coagulopathies have been reported to cause episodes of gingival bleeding, epistaxis,

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

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gastrointestinal hemorrhage, and potential intracranial bleeding. Severe systemic effects including hypotension, cardiovascular toxicity and neurotoxicity may also occur. Treatment for venomous snakebites includes prompt administration of antivenom in the case of progressive symptoms from envenomation (1).

Initial Triage and Management

When a patient arrives to the emergency department after a venomous snake bite, begin by administering tetanus vaccine and/or booster; data suggests that seldom are snake bites associated with *Clostridium tetani*, however, this has become standard practice throughout multiple World Health Organization and local guidelines (1,2,4). The Poison Control center should be notified immediately. Venom metalloproteases cleave cell-cell junctions that weaken vascular walls and increase capillary permeability. There is an increase in vasodilation and third-spacing of fluid and blood. Intravenous fluid should be administered to these patients. Blood should be drawn from an unaffected extremity and a CBC, aPTT, PT/INR, fibrinogen and fibrinogen split-products should be obtained (2). The presence of fibrinogen split-products in the first 12 hours after envenomization is 87% sensitive and 69% specific for the presence of coagulopathy (1).

Applying a tourniquet or constrictive band to the affected extremity above the snake bite has been advocated in the past, but there is no evidence to support this therapy. In fact, applying a tourniquet may precipitate additional local tissue destruction and necrosis. Tourniquets are therefore not recommended. Ice application and wound incisions have also been debunked as beneficial therapies after venomous snake bites (2). Though mostly supported by anecdotal evidence, immobilization of the affected extremity has been theoretically proposed to prevent the spread of venom. Immobilization, elevation, and use of a wide block of compression on an affected extremity (applying up to 20 mmHg of pressure) to assist in compressing superficial veins and lymphatics, have been advocated to be safe initial measures after snake bites with little deleterious effects to the patient. However, the benefit of these therapies is without quality evidence (1,2).

For patients that are asymptomatic after snake bite, they may be safely observed without administration of antivenom. If there is swelling of an extremity, the borders should be marked and re-marked every 30 minutes to monitor for progression of edema (2). Previously, prophylactic fasciotomies were debated as standard of care, however, this has fallen out of favor. Venom may cause edema and local tissue destruction, but compartment pressures are rarely elevated. Increasing edema of an extremity after envenomization often resolves with administration of antivenom therapy without need for fasciotomy. Previous reports in the literature suggest measuring creatinine kinase levels to detect potential rhabdomyolysis following venomous bite. There is poor clinical evidence that snake bites cause rhabdomyolysis however. Clinical judgement should support laboratory studies, but creatinine kinase is no longer recommended as an initial laboratory marker (1).

Pain control should include narcotics. From a theoretical perspective, NSAIDs have been historically avoided for pain control after snakebite due to concern for possible increased bleeding risk. However, in a retrospective chart review of patients at St. Louis Children's Hospital between 1998 to 2016 and from Barnes Jewish Hospital from 2001 to 2016, 147 copperhead snake bite victims were identified (5). Of those, 52% received NSAIDs in the form of IV ketorolac, IV ibuprofen or oral naproxen. The authors concluded that there was no significant association between treatment with NSAIDs and bleeding in patient who sustained copperhead bites (Class III). It should be mentioned that, of all the crotalid snakes, copperheads have the mildest and least-coagulopathic venom. Further investigation should be undertaken to fully elucidate whether NSAID use is safe in all crotalid snake bites.

Some case reports have detailed nerve blocks as effective analgesia after extremity snake bites; this information has only been taken from anecdotal case reports and will require further investigation to detail efficacy in a larger patient population (6).

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Antivenom Therapy

Antivenom therapy is derived from IgG fragments from horses, mules, donkeys or sheep. Due to its immunologic nature, there is potential for severe anaphylactoid reactions and guidelines recommend only administering antivenom in cases of progressive venom injury, defined as worsening local injury (e.g., swelling, ecchymosis), development of a clinically important coagulation abnormality, or systemic effects (e.g., hypotension, altered mental status). Therapy may be held in cases of only localized pain and swelling (1,7). In fact, 20-25% of venomous snake bites are "dry" and provide no venom to the victim; antivenom in these cases will provide no benefit. The severity of envenomation by North American pit vipers can be assessed by using the guidelines provided below.

Guidelines for Assessing the Severity of North American Pit-Viper Envenomations (8)			
Signs and Symptoms	**Severity of Envenomation***		
	Minimal	**Moderate**	**Severe**
Local	Swelling, erythema, or ecchymosis confined to the site of the bite	Progression of swelling, erythema, or ecchymosis beyond the site of the bite	Rapid swelling, erythema, or ecchymosis involving the entire body part
Systemic	No systemic signs or symptoms	Non-life-threatening signs and symptoms (nausea, vomiting, perioral paresthesias, and mild hypotension)	Markedly severe signs and symptoms (hypotension [systolic blood pressure <80 mm Hg], altered sensorium, tachycardia, tachypnea, and respiratory distress)
Coagulation	No coagulation abnormalities or other important laboratory abnormalities	Mildly abnormal coagulation profile without clinically significant bleeding; mild abnormalities on other laboratory tests	Markedly abnormal coagulation profile with evidence of bleeding or threat of spontaneous hemorrhage (unmeasurable INR, APTT, and fibrinogen; severe thrombocytopenia with platelet count <20,000 per mm_3); results of other laboratory tests may be severely abnormal
* The ultimate grade of severity of any envenomation is determined based on the most severe sign, symptom, or laboratory abnormality.			

Antivenom treatment was first introduced by Albert Calmette in the 1890s as an immunoglobulin fragment derived from horse (equine) or sheep (ovine) (4). One of the first commercially available antivenoms was Antivenom (Crotalidae) Polyvalent (ACP), which was introduced in the early 1950's by Wyeth Laboratories. Although the equine-derived antivenom was used clinically for many years and resulted in a marked decrease in mortality rate, there are no prospective data available regarding its efficacy (3,7). In addition, the use of ACP is limited by the frequency of adverse effects, including acute reactions, ranging from minor rashes to anaphylaxis, in 23-56% of patients and serum sickness, a delayed type III hypersensitivity reaction causing fever, chills, malaise, and arthralgia, in 50 to 75% of patients (2,9). Due to the high incidence of hypersensitivity reactions, the manufacture of ACP was discontinued in April 2007.

Approved by the FDA in October 2000, Crotalidae Polyvalent Immune Fab (FabAV) or CroFab™ is the first crotalid snake antivenom approved in almost 50 years. FabAV is the Fab fragment of antibodies derived from ovine sources immunized with venom from Crotalus atrox (Western Diamondback rattlesnake), Crotalus adamanteus (Eastern Diamondback rattlesnake), Crotalus scutulatus (Mojave rattlesnake), and Agkistrodon piscivorus (Cottonmouth or Water Moccasin), in which the immunogenic Fc portions of the antibody and the non-neutralizing components of the serum are eliminated during purification. As such, FabAV may be associated with a lower risk of allergic and serum sickness type reactions. FabAV is associated with an improved reconstitution profile and animal studies indicate that FabAV is up to 5 times

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more potent than ACP (9). Anaphylactoid reactions have been reported in up to 6% of patients but have been reported as mild in nature (1).

Therapy is most effective if started within 4 hours after insult. The premarketing trial of FabAV advocated four to six vials of antivenom as an initial dose for progressive venom injury and this has become the standard initial treatment. Antivenom infusion has been associated with histamine release and this, along with the vasodilatory effects of venom, has required antivenom to be administered with IV fluid. Four to six vials of FabAV should be diluted in 250 mL of normal saline and administered over 1 hour. Previous reports suggest infusing the initial dose slowly over 10 minutes at a rate of 25-50 mL/hr to observe for allergic reaction, however, this slow infusion is controversial and expert consensus data suggests no standard infusion rate for initial administration (1,10). All patients receiving initial antivenom therapy should be observed in the ICU. Epinephrine, H_1 and H_2 blockers and instruments for intubation should be bedside in the case of an anaphylactic reaction. There is no evidence that pre-treatment with antihistamines is beneficial to prevent potential anaphylactic reactions. If a patient tolerates initial antivenom infusion, it is safe to observe the patient in the ward versus the intensive care unit (1).

Laboratory data should be repeated within one hour of initial infusion of antivenom to assess response. There is no evidence for following fibrin split-products after treatment; instead, fibrinogen is a more specific marker of response (1). There is some evidence to suggest thromboelastometry may help drive treatment. Although initial treatment should be antivenom, blood products may aid in resuscitation in the case of continued coagulopathy despite antivenom infusion (11). If labs do not reveal a response to antivenom therapy, dosing should be repeated with an additional four to six vials of FabAV until response is achieved. Reportedly, few patients fail to respond after 18 vials of therapy (1,4,10).

Antivenoms work by binding and neutralizing venom toxins, facilitating redistribution away from target tissues and elimination from the body (10). For this reason, pediatric doses of antivenom are similar to adult dosages (1).

Recurrence

An unexpected observation identified during clinical trials was the recurrence of local symptoms or coagulation abnormalities after completion of treatment. Recurrence is defined as the occurrence of any venom effect following resolution of that abnormality. Recurrent coagulopathy was especially noted among patients with coagulopathy at presentation. Multiple explanations have been proposed for the pathophysiology of symptom recurrence, including prolonged venom absorption from the bite site and dissociation of the venom-FabAV complex (9). Recurrence has been documented to have occurred in up to 50% of patients receiving FabAV. To monitor for recurrence, physicians should observe patients with serial labs, although, local tissue recurrence with pain and swelling may become evident six to 36 hours after treatment. Treatment for recurrence includes a dose of antivenom (four to six vials), although response may be attenuated.

Severe Envenomation

Antivenom therapy is associated with clinical improvement in severe crotaline envenomation (12). Up to 13% of snake bite victims get severe envenomation, with symptoms including hypotension, acute renal failure, bleeding, and deadly cardiac arrhythmias. One case report details a disseminated intravascular coagulation (DIC) reaction leading to ischemic bowel requiring total colonic resection (11). In cases of severe envenomation, eight to 12 vials of antivenom should be infused intravenously immediately (1).

Allergic Reactions to Antivenom

There is no absolute contraindication to antivenom treatment. Patients with previous reactions to equine or ovine serum and patients with severe atopic disease may be most susceptible to anaphylactic response after administration (4). Because papain is used to cleave the whole antibody into Fab, FabAV should be administered cautiously to patients with a history of hypersensitivity to papaya. Appropriate management for anaphylactic reactions should be readily available. Patients with allergies to papain, chymopapain, other papaya extracts, or the pineapple enzyme bromelain may also be at risk of an allergic reaction. Because some dust mite and latex allergens share a similar structure with papain, patients with these allergies may also demonstrate hypersensitivity to FabAV (10). Premedication has been described with Benadryl and

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cimetidine. There is poor data to support applying antivenom in a skin test to assess allergenicity as there is a 10-36% false negative rate and this can precipitate anaphylaxis. Awaiting the results of a skin test may also delay treatment (2).

In cases of allergic reaction, stop infusing the antivenom. Promptly administer epinephrine 0.5 mg for adults or 0.01 mg/kg body weight for children; this should be administered at the first sign of urticaria. After initial dosing with epinephrine, antihistamines should be administered (4).

Follow-Up

After sustaining a snake bite from a venomous snake, consensus guidelines suggest a period of 18-24 hours of observation to be sufficient. During this observation period, laboratory studies should be repeated serially every six to eight hours. Some physicians argue that antivenom therapy should be maintained even after resolution of symptoms and normalization of laboratory blood work to prevent recurrence; this is controversial and there is currently no consensus data to support or refute this. After the first 24 hours of observation, patients are often able to be discharged from the hospital with close follow-up as an outpatient (1). There is a 3% risk of wound infection after snake bite and prophylactic antibiotics at discharge are not recommended (2). Patients should be advised to return to the hospital if they have recurrence of pain or swelling or signs of bleeding such as gingival bleeding or epistaxis.

Serum sickness, a type III hypersensitivity reaction, may manifest with fever, rash and arthralgias in 5-10% of patients treated with antivenom. This can occur within one to four weeks after treatment with antivenom. Serum sickness often responds to a five-day course of antihistamines and systemic corticosteroids (1,4).

Coral Snake Envenomation

Coral snakes belong to the Elapidae family and are the only other native venomous snakes in the United States. Due to the reclusive nature and short, fixed fangs of the coral snake, the incidence of coral snakebites is rare in the United States, accounting for only 20 to 25 bites per year (3). Coral snake envenomation produces little or no local effects, but may result in changes in mental status, such as euphoria and drowsiness, and are characterized by their neurotoxic effects. Neurologic manifestations are usually cranial nerve palsies, including ptosis and dysphagia, and left untreated, may progress to respiratory paralysis (8). The onset of neurotoxic effects may be delayed up to 12 hours and once present, may progress rapidly and are difficult to reverse. The definitive treatment for coral snake envenomation is the immediate administration of antivenom. Unfortunately, production of Antivenom Micrurus Fulvius, the only coral snake antivenom currently available in the United States, was discontinued by Wyeth Pharmaceuticals in 2003. The last remaining Antivenom (Lot No. 4030026) was initially dated to expire on October 31, 2008. Wyeth Pharmaceuticals, in conjunction with the U.S. Food and Drug Administration (FDA) extended the expiration date to October 31, 2011 (13). If no other coral snake antivenom is approved when the current supply is exhausted, physicians will have to rely on supportive care or non-FDA approved antivenom. Supportive treatment alone can be effective, as death is due to the failure to initiate ventilatory support when symptoms develop. Mechanical ventilation may be required. Even with treatment, neurotoxic effects can last three to six days (3). Alternatively, Coralmyn, produced by the Mexican company Bioclon has been shown to be effective in neutralizing coral snake venom (14). However, the rarity of bites and expense of required testing for FDA approval make manufacture in the United States financially unlikely.

LITERATURE REVIEW

In a prospective, open-label, multicenter trial, Dart et al. evaluated the efficacy and safety of FabAV in 11 patients age 10 years or older with progression of envenomation syndrome (defined by worsening of local injury, coagulation abnormalities, or systemic symptoms) after mild or moderate crotalid envenomation in the six hours preceding presentation (15). All patients received an initial intravenous dose of four vials. If clinical symptoms continued to worsen, an additional 4 vials were permitted. All patients demonstrated clinical improvement following antivenom administration. At the four-hour assessment, all patients had improved clinically with snakebite severity scores (SSS), a validated measure of limb swelling, coagulation tests, and gastrointestinal, neurologic, and cardiac signs, having remained the same or decreased, indicating a halt to envenomation progression. Five patients received four vials and six patients required eight vials of study antivenom. The mean severity score was 3.9 ± 2.2 before antivenom administration and

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2.6 ± 1.0 twelve hours after administration. Two patients required additional antivenom for recurrent swelling approximately 15 hours after initial improvement from antivenom administration and one patient was found to have recurrent coagulopathy at the one-week follow-up visit, which resolved over several days. No patients experienced anaphylaxis or serum sickness from antivenom administration at follow-up visits seven and 14 days after discharge (Class II).

To suppress recurrence, Dart et al. conducted a prospective, randomized, open-label trial comparing two dosing schedules of FabAV in 31 patients, aged 10 years or older, with minimal or moderate crotaline envenomations within the six hours preceding antivenom administration showing evidence of progression (9). Patients were initially treated with six vials of FabAV and, if necessary, a second dose of six vials was allowed. After initial control was achieved, the scheduled group received an additional two doses every six hours for 18 hours while the PRN group received no planned additional doses. All patients, both in the scheduled and PRN groups, had a decrease in mean total SSS with mean severity score decreasing from 4.35 to 2.39 ($p<0.001$) after antivenom administration in the 12-hour evaluation period; however, half of the patients in the PRN group required unplanned doses of FabAV for recurrence of local wound progression during the first 12 hours. The total amount of antivenom administered was not statistically different between groups, indicating a continued need for antivenom for adequate treatment. Nineteen percent of patients developed an acute reaction during infusion and 23% developed serum sickness. It should be noted, however, that five of the six patients who developed serum sickness were treated with a batch of FabAV that was incompletely purified due to a flawed manufacturing process (Class II).

Although bites by the copperhead snake (Agkistrodon contortrix) were an exclusion criterion in safety and efficacy trials of FabAV, this agent is being used for copperhead envenomation (16,17). In a retrospective chart review of 32 copperhead snake envenomations, primarily moderate in nature, rapid initial response was achieved in 28 cases (17). There were four treatment failures, defined as progression of envenomation or failure to achieve initial control within 12 hours. Recurrent local effects developed in six patients and repeated, planned doses of antivenom did not reduce the incidence of recurrent swelling (Class II).

Case reports demonstrate that delayed administration of antivenom may be beneficial for patients with coagulopathies and local symptoms greater than six hours after envenomation (18,19). A case series by Lavonas et al. reported 28 patients with severe envenomation, all with clinical improvement after receiving FabAV (Class III) (12).

Optimal dosing beyond an 18-hour period has not been established to-date and there are no prospective data evaluating the efficacy of FabAV in patients presenting with severe envenomation. Additionally, no prospective studies have been conducted comparing FabAV to other treatments for snakebite envenomations, such as ACP or observation alone.

Sánchez et al. compared neutralization between the Wyeth coral snake and Coralmyn antivenoms with the North American coral snake venoms. The venom lethal doses (LD50) and antivenom effective doses (ED50) were determined in 18–20 g, female mice. Coralmyn antivenom was able to effectively neutralize three LD50 doses of all venom from both Micrurus tener tener and Micrurus fulvius fulvius (14).

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