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SNAKEBITE / CROTALID ANTIVENOMS

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.

RECOMMENDATIONS

- **Level 1**
 - **None**
- **Level 2**
 - **Antivenom should be administered within 6 hours of North American crotalid envenomation to patients showing evidence of progressive or severe venom injury.**
 - **FabAV initial dose is 4 to 6 vials IV over 60 minutes.**
 - **An additional dose of 4 to 6 vials should be given if initial control is not achieved with the first dose.**
 - **After initial control is achieved, 2 vials may be administered every 6 hours for up to 18 hours (total of 3 additional doses).**
- **Level 3**
 - **Late administration of antivenom (greater than six hours post-envenomation) may be beneficial in patients with coagulopathy and local symptoms.**
 - **Follow-up evaluation after 7 days may be prudent to assess the patient for delayed coagulopathy.**

INTRODUCTION

Although relatively infrequent, approximately 8,000 venomous snakebites resulting in significant morbidity and several deaths occur each year in the United States (1,2). In the United States, the primary snakes of concern belong to the subfamily Crotalinae, also known as the pit vipers: rattlesnakes, cottonmouths, and copperheads. Snakebite envenomations are characterized by an erratic and unpredictable clinical course, making assessment and determination of the severity of envenomation difficult. They should be considered medical emergencies requiring close monitoring in the intensive care unit. Manifestations of crotalid envenomations may include local tissue injury, such as marked tissue swelling, pain, ecchymosis and severe coagulopathies characterized by hypofibrinogenemia, prolonged prothrombin time (PT), variable changes to activated partial thromboplastin time (aPTT), and decreased platelet count (2).

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.

Additionally, severe systemic effects including altered mental status, tachycardia, respiratory distress, and hypotension can occur (2). Treatment for venomous snakebites includes aggressive supportive care and prompt administration of antivenom to selected patients,

Antivenom therapy Administration of antivenom is generally indicated in the presence 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) (3). The severity of envenomations by North American pit vipers can be assessed by using the guidelines provided below. Antivenoms work by binding and neutralizing venom toxins, facilitating redistribution away from target tissues and elimination from the body (4). Use of antivenom may result in increased patient comfort and fewer invasive treatment measures such as incision or excision of the bite site or performance of a fasciotomy (5,6).

Guidelines for Assessing the Severity of North American Pit-Viper Envenomations (1)			
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 on the basis of the most severe sign, symptom, or laboratory abnormality.			

Antivenin (Crotalidae) Polyvalent (ACP), the first commercially available antidote for crotalid snakebites, was introduced in the early 1950's by Wyeth Laboratories. Although the equine-derived antivenin was used clinically for many years and resulted in a marked decrease in mortality rate, there are no prospective data available regarding its efficacy (2,3). In addition, the use of ACP is limited by the frequency of adverse effects, including acute reactions, ranging from minor rashes to anaphylaxis, in 20 to 25% of patients and serum sickness, a delayed type III hypersensitivity reaction causing fever, chills, malaise, and arthralgia, in 50 to 75% of patients (7). Due to the high incidence of hypersensitivity reactions, the manufacture of ACP was discontinued in April 2007.

Released in 2001, Crotalidae Polyvalent Immune Fab (FabAV) or CroFab™ is the first crotalid snake antivenin 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 nonneutralizing 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 more potent than ACP (7).

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 (7).

FabAV is indicated for the management of patients with minimal or moderate North American crotalid envenomations. Early use (within 6 hours of snakebite) is advised to prevent clinical deterioration and the occurrence of systemic coagulation abnormalities. The recommended initial dose is 4 to 6 vials of FabAV infused IV over 60 minutes. The initial dose should be infused slowly over the first 10 minutes at a rate of 25-50mL/hr to observe for any allergic reaction and increased to 250 mL/hr if no reaction occurs. The patient should be observed for up to 1 hour following completion of the first dose to determine if initial control has been achieved. An additional dose of 4 to 6 vials should be given if initial control is not achieved with the first dose. After initial control is achieved, 2 vials may be administered every 6 hours for up to 18 hours (total of 3 additional doses). If necessary, additional 2 vial doses may also be administered as deemed necessary based on patient's clinical course (4).

Since discontinuation of ACP, there is currently no available, approved antivenom for the treatment of severe crotaline snake envenomation in the United States. However, antivenom therapy has been associated with clinical improvement in severe crotaline envenomation (8).

Because papain is used to cleave the whole antibody into Fab, FabAV should not be administered to patients with a history of hypersensitivity to papaya or papain unless the benefits outweigh the risks and appropriate management for anaphylactic reactions is 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 (4).

Cost may be a consideration when deciding on the treatment course of mild envenomations. The cost of Crotalidae Polyvalent Immune Fab (CroFab™) is \$1976.61 per vial.

Coral Snake Envenomations: Coral snakes belong to the Elapidae family and are the only other native venomous snakes. 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 (2). Coral snake envenomations produce 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 (1). 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 envenomations is the immediate administration of antivenom. Unfortunately, production of Antivenin Micrurus Fulvius, the only coral snake antivenom currently available in the United States, was discontinued by Wyeth Pharmaceuticals in 2003. The last remaining Antivenin (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) has currently extended the expiration date to October 31, 2011 (9). The cost of Antivenin Micrurus Fulvius is currently \$1513.63 per vial.

If no other coral snake antivenom is approved when the current supply is exhausted or expires, 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 3 to 6

days (2). Alternatively, Coralmyl, produced by the Mexican company Bioclon has been shown to be effective in neutralizing coral snake venom (10). 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 6 hours preceding presentation (11). All patients received an initial intravenous dose of 4 vials. If clinical symptoms continued to worsen, an additional 4 vials were permitted. All patients demonstrated clinical improvement following antivenom administration. At the 4-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 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 7 and 14 days after discharge (Class II).

In an effort 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 6 hours preceding antivenom administration showing evidence of progression (7). Patients were initially treated with 6 vials of FabAV and, if necessary, a second dose of 6 vials was allowed. After initial control was achieved, the scheduled group received an additional 2 doses every 6 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 antivenin 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 envenomations (12,13). In a retrospective chart review of 32 copperhead snake envenomations, primarily moderate in nature, rapid initial response was achieved in 28 cases (13). 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 (6,14). A case series by Lavonas et al. (8) reported 28 patients with severe envenomation, all with clinical improvement after receiving FabAV (Class III).

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* (10).

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CROTALID ANTIVENOM GUIDELINES

