

BRIEF REPORTS

Safety and Cost-Effectiveness of a Clinical Protocol Implemented to Standardize the Use of Crotalidae Polyvalent Immune Fab Antivenom at an Academic Medical Center

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Study Objective. To evaluate the safety and cost-effectiveness of a clinical protocol adopted in June 2006 that included a comprehensive, objective assessment of snake bite envenomations and standardized the use of Crotalidae polyvalent immune Fab antivenom (FabAV).

Design. Retrospective medical record review.

Setting. Academic medical center that serves as the regional level I trauma center.

Patients. Seventy-five adults treated with FabAV for snake envenomations in the emergency department between June 1, 2003, and June 1, 2009; 30 patients received treatment according to the protocol (treatment group), and 45 patients received treatment that did not adhere to the protocol (control group).

Measurements and Main Results. Demographic and envenomation characteristics, as well as treatment details, were collected for all patients. In addition, information on quantity of FabAV vials required, length of hospital stay, and length of intensive care unit stay were compared between the treatment and control groups. In the treatment group, significantly fewer vials of FabAV were used (2.5 vs 4.727 vials, $p=0.007$). This decreased in usage correlated to a cost savings of approximately \$2000/patient. Despite no significant difference in the severity of the envenomations between the two groups ($p=0.379$), the treatment group experienced a significantly shorter hospital length of stay (1.933 vs 2.791 days, $p=0.030$). No significant difference in the progression to fasciotomy or the development of allergic reactions was noted between the two groups.

Conclusion. Use of a clinical protocol related to snake envenomations resulted in approximately two fewer vials of FabAV required for each patient. In addition, the treatment group experienced a shorter hospital length of stay without a corresponding increase in adverse events or envenomation progression. Data show that use of the protocol was cost-effective. The development of institution-specific multidisciplinary protocols regarding snake bite envenomations is recommended. Clinical pharmacists can play a vital role in the protocol development to ensure that optimal care is provided for this distinct patient population.

Key Words: snake bite, envenomation, CroFab, FabAV, Crotalidae polyvalent immune Fab, antivenin, clinical pharmacy.

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Introduction

In 2007, the American Association of Poison Control Centers reported 6889 snake bites of which 3669 (53%) were associated with confirmed venomous snakes.¹ Fortunately, snake bite envenomations in North America rarely result in mortality, with an average of only five deaths each year.² However, mortality secondary to envenomations occurs more frequently in high-risk patient populations such as children, the elderly, and those who receive inadequate treatment.³⁻⁵ Despite the low mortality rate, envenomations can be associated with significant morbidity, ranging from severe pain and ecchymosis to more systemic complications, including consumptive coagulopathy, compartment syndrome, and hypovolemic shock.³⁻⁶ Four venomous snakes—the copperhead, timber rattlesnake, cottonmouth, and pigmy rattlesnake—are indigenous to the region served by our institution (Lexington, KY), and they all belong to the Viperidae family.

Pharmacologic therapy targeted at envenomations secondary to Crotalinae snakes, a subfamily of the Viperidae family, has changed in the last decade with the transition between two antivenom treatment options. Previously, patients were treated with antivenin Crotalidae polyvalent (ACP), which is an equine-derived antivenin, but that drug was removed from the market due to its adverse-effect profile; 25% of patients developed anaphylaxis and another 50% experienced serum sickness.^{7, 8} In 2000, ovine Crotalidae polyvalent immune Fab antivenom (FabAV [CroFab; Protherics Inc., Brentwood, TN]) was approved as an alternative to ACP. Fab antivenom is a monospecific antivenin derived from the immunization of sheep with venoms of Crotalinae snakes, and it has been shown to be 5.2 times more effective as ACP in

murine models.^{9, 10} According to the most recent consensus guidelines for stocking antidotes, FabAV is recommended for routine stocking in hospitals.¹¹

The improved safety profile of FabAV comes at a significant cost to health care organizations, as one vial of FabAV has an average wholesale price of approximately \$1000.¹² Based on this information, a treatment course of FabAV as recommended in the package labeling can cost in excess of \$18,000. The use of this drug also poses several other issues, including variations in primary literature recommendations for dosing, length of time required to prepare the agent, and monitoring and treatment of adverse drug reactions, that can be alleviated through the involvement of clinical pharmacists.

Because of an apparent increase in use at our institution, an internal medication use evaluation of FabAV was performed over a 5-month period. The review revealed that dispensing of this agent at our institution had increased by more than 150% from the previous year. Of even more interest was the fact that approximately eight vials of FabAV (representing ~\$8000) were returned to the pharmacy without having been administered to a patient, resulting in financial loss and product waste. In addition, unadministered FabAV was discovered as being due to the occurrence of infusion-related reactions without documented infusion rates. Individual patient case data suggested that much of the increased use could be attributed to ambiguity related to indications for use in the FabAV package insert and to communication barriers among pharmacy staff, physicians, and nurses.¹⁰

To address these issues, a multidisciplinary task force was formed with the goal of developing a standardized protocol for the use of FabAV. This group was composed of clinical pharmacists, pharmacy administrators, pharmacy residents, and emergency medicine physicians who specialized in wilderness medicine. Based on input from the committee, a new clinical reference was adopted to include a more comprehensive, objective assessment of snake bite envenomations (Appendix 1).^{10, 13, 14} This reference includes dosing criteria based on recommendations from the FabAV package insert.¹⁰ In addition, the Snakebite Severity Score criteria were incorporated in an attempt to provide additional objectivity to the initial snake bite assessment.¹³ An algorithm was developed to help address the standardization of FabAV maintenance doses (Appendix 2).^{15, 16} This algorithm

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uses the clinical classifications for snake bite envenomation of minimal, moderate, and severe and is based on the initial assessment of the bite. With feedback from the committee, a staffing decision was made. In addition to emergency medicine clinical pharmacy specialists being involved in the initial management and follow-up of envenomations, a pharmacy resident would participate as part of a 24-hour, in-house, on-call experience. The pharmacy resident is alerted when a new order for FabAV is prescribed by a physician through the computerized provider order entry system. After being alerted, the pharmacy resident is tasked with evaluating the patient and personally communicating with the ordering service to ensure, before reconstitution of FabAV by the pharmacy, that the drug is warranted and is going to be administered. After confirmation, FabAV is delivered by the on-call pharmacist to the patient's bedside to ensure appropriate use and communication with the nursing staff and to determine that appropriate monitoring parameters are assessed. To our knowledge, this was the first comprehensive FabAV protocol to be published in the literature and the first to include clinical pharmacists as major contributors.¹⁷ We subsequently sought to evaluate the safety and cost-effectiveness of this clinical protocol after its implementation.

Methods

Study Design

In this retrospective study, we reviewed the medical records of patients who were treated with FabAV for a snake bite envenomation in the emergency department at our institution between June 1, 2003, and June 1, 2009. The clinical protocol was adopted in June 2006; thus, this study time frame was chosen to provide a relatively equal proportion of patients who were treated with FabAV before the protocol adoption and afterward. The study was conducted in our 409-bed academic medical center that serves as the level I trauma center for the region and was granted institutional review board approval.

We identified all patients aged 18 years or older who had a diagnosis of snake envenomation (*International Classification of Disease, Ninth Revision*, code 989.5). Medical records were reviewed by five trained data extractors with use of a standardized data collection tool. Each data extractor reviewed individual medical records

independently, and all data collection was monitored by two of the authors (S.B. and K.W.). Patients who were treated according to the clinical protocol after its implementation (2006–2009) were considered the treatment group, and those not treated according to the protocol were the control group. The treatment of patients who presented to the emergency department before the implementation of the protocol (2003–2006) was evaluated retrospectively to assess whether the patients' treatments were consistent with the protocol, in which case these patients were included in the treatment group. For patients who received treatment at a different hospital before coming to our institution, that therapy was included in the overall evaluation of their snake bite management. These patients were grouped in the same manner as the others. Group assignment was reviewed by the initial data abstractor and then by two of the authors (S.B. and K.W.) to ensure consistency.

Statistical Analysis

Differences between the treatment group and control group were analyzed with *t* tests, the Mann-Whitney rank sum test, and the Wilcoxon rank sum test, as appropriate. Analyses were conducted using SigmaStat (Aspire Software International, Ashburn, VA) and SPSS (IBM, Somers, NY). A *p* value of less than 0.05 was considered to indicate a statistically significant difference.

Results

Between June 1, 2003, and June 1, 2009, 75 patients met the study criteria. Demographic data, envenomation characteristics, and treatment information for these patients are outlined in Table 1. No significant difference was noted in baseline severity of snake bites, as measured by the Snakebite Severity Score, between the treatment group (mean score 1.7, 95% confidence interval [CI] 1.4–2.0) and the control group (mean score 1.8, 95% CI 1.6–2.0, *p*=0.379). Still, those patients in the treatment group received significantly fewer vials of FabAV (2.5 vials, 95% CI 1.1–3.9) than those in the control group (4.727 vials, 95% CI 3.5–5.9, *p*=0.007) (Figure 1). In addition, patients in the treatment group had a significantly shorter overall hospital length of stay (1.933 days, 95% CI 1.3–2.6) than patients in the control group (2.791 days, 95% CI 2.2–3.4, *p*=0.030), although

intensive care unit length of stay was similar between the groups (0.586 days [95% CI 0.13–1.0] vs 0.341 days [95% CI 0.1–0.6], $p=0.441$). With regard to safety, no significant difference was noted in the progression to fasciotomy or the development of allergic reactions between the two groups.

Discussion

In response to an increase in FabAV usage at our institution and acknowledgment that drug was being wasted, a multidisciplinary team was formed to develop a protocol to ensure consistency in treatment and best practice. To our knowledge, this was the first comprehensive FabAV protocol to be published in the literature and the first to include clinical pharmacists as major contributors.¹⁷ Recently a unified treatment algorithm, similar to ours, for the management of crotaline snake bites was published by nine expert panel members.¹⁸ Our protocol differs in that it represents the cumulative efforts of many practitioners from various disciplines and was developed as an evidence-based protocol to optimize patient care. The data evaluating the safety of our treatment approach demonstrate no significant difference before versus after protocol implementation in progression to fasciotomy or frequency of allergic reactions, the two most feared complications of snake bite envenomation and treatment. However, these

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	Treatment Group (n = 30)	Control Group (n = 45)	p Value
Demographics			
Male, no. (%)	23 (77)	29 (64)	0.327
Mean age (yrs)	33.5	32.2	0.45
Type of snake bite, no. (%)			
Copperhead	17 (57)	35 (78)	0.144
Rattlesnake	6 (20)	7 (16)	0.847
Unknown	7 (23)	3 (7)	0.08
Location of bite, no. (%)			
Hand	15 (50)	28 (62)	0.429
Foot	9 (30)	13 (28)	0.942
Other	6 (20)	4 (8)	0.242
Initial severity of bite, no. (%)			
Minimal	13 (43)	7 (15)	0.212
Moderate	13 (43)	34 (75)	0.08
Severe	4 (13)	4 (9)	0.571
Adverse events, no. (%)			
Progression to fasciotomy	3 (10)	5 (11)	0.806
Allergic reaction, including anaphylaxis	1 (3)	4 (9)	0.637

data do suggest that our protocol is effective at limiting excessive FabAV use and is associated with reductions in overall hospital length of stay. These two end points are likely related because fewer patients who receive scheduled doses of FabAV translates to fewer patients being hospitalized for a set time frame. Similar results—decreased length of hospital stay and subsequent cost savings—have been noted in

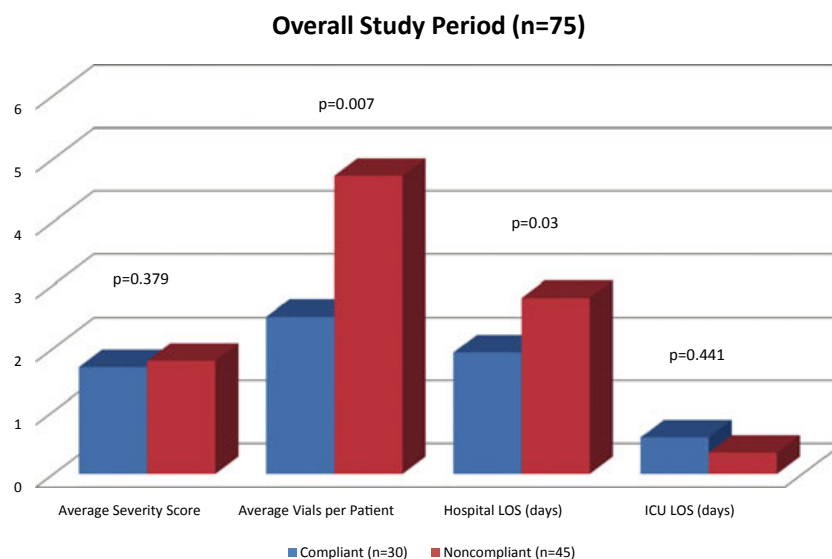


Figure 1. Severity of the envenomation and outcomes assessed in patients who received treatment according to the Crotalidae polyvalent immune Fab antivenom protocol (compliant [treatment group]) compared with those patients who received treatment that did not adhere to the protocol (noncompliant [control group]). The severity of the envenomation was measured using the Snakebite Severity Score. LOS = hospital length of stay; ICU = intensive care unit.

other investigations that examined shortened antidotal regimens.¹⁹ The cost savings from the FabAV therapy alone when administered according to our protocol were approximately \$2000/patient treated, and the actual total cost savings realized were likely in excess of this amount due to the decreased hospital length of stays and thus the reduced use of hospital resources.

The role of the clinical pharmacist in the daily practice of emergency medicine is one that has only recently begun to be defined and expounded upon. The management of North American snake bite envenomations is abundant with opportunities for medication errors, prescriber subjectivity, and drug waste, all resulting in the heightened potential for patient harm. The potential role for the clinical pharmacist in the management of this therapeutic area is extensive and ranges from assisting in the initial evaluation and dosing of the patient, to assisting in the preparation and ensuring the proper administration of the drug, all the way to managing adverse drug reactions and ensuring proper repeat evaluation and retreatment of these individuals.

Our study was limited by its retrospective nature and dependence on accurate documentation by various health care practitioners; both can significantly affect the documentation of envenomation severity and analysis of adverse reactions. However, because both the treatment group and control group were at risk for this error, we believe that this risk was minimized. We also did not assess the cost savings associated with a decrease in hospital length of stay. Because this cost can be variable across institutions, we felt that the reporting of hospital days avoided would allow individuals to calculate their own institution-specific total cost avoidance.

Conclusion

North American snake bite envenomations provide a unique challenge to health care practitioners due to the variety of toxins and the multiple systemic effects. With the development of FabAV, the use of antivenin to treat these bites has become safer and more frequent. However, due to the challenges associated with managing envenomations, significant drug waste can occur, at a high cost to hospitals. Through a multidisciplinary collaboration with many health care providers, a protocol was developed for FabAV usage to help ensure optimal and cost-effective treatment of patients who experience Crotalidae snake bite

envenomations. This protocol was found to be associated with fewer FabAV vials required for each patient and a significant decrease in hospital length of stay. These benefits were noted without a concomitant increase in adverse effects. The development of institution-specific multidisciplinary protocols regarding Crotalidae snake bite envenomations is recommended. Clinical pharmacists can play a vital role in protocol development to ensure that optimal care is provided for this distinct patient population.

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Appendix 1. Indications for Crotalidae Polyvalent Immune Fab Antivenom (FabAV [CroFab])

Description: Sterile, nonpyrogenic, purified, lyophilized preparation of ovine Fab (monovalent) antivenom isolated from sheep flocks with North American venoms.

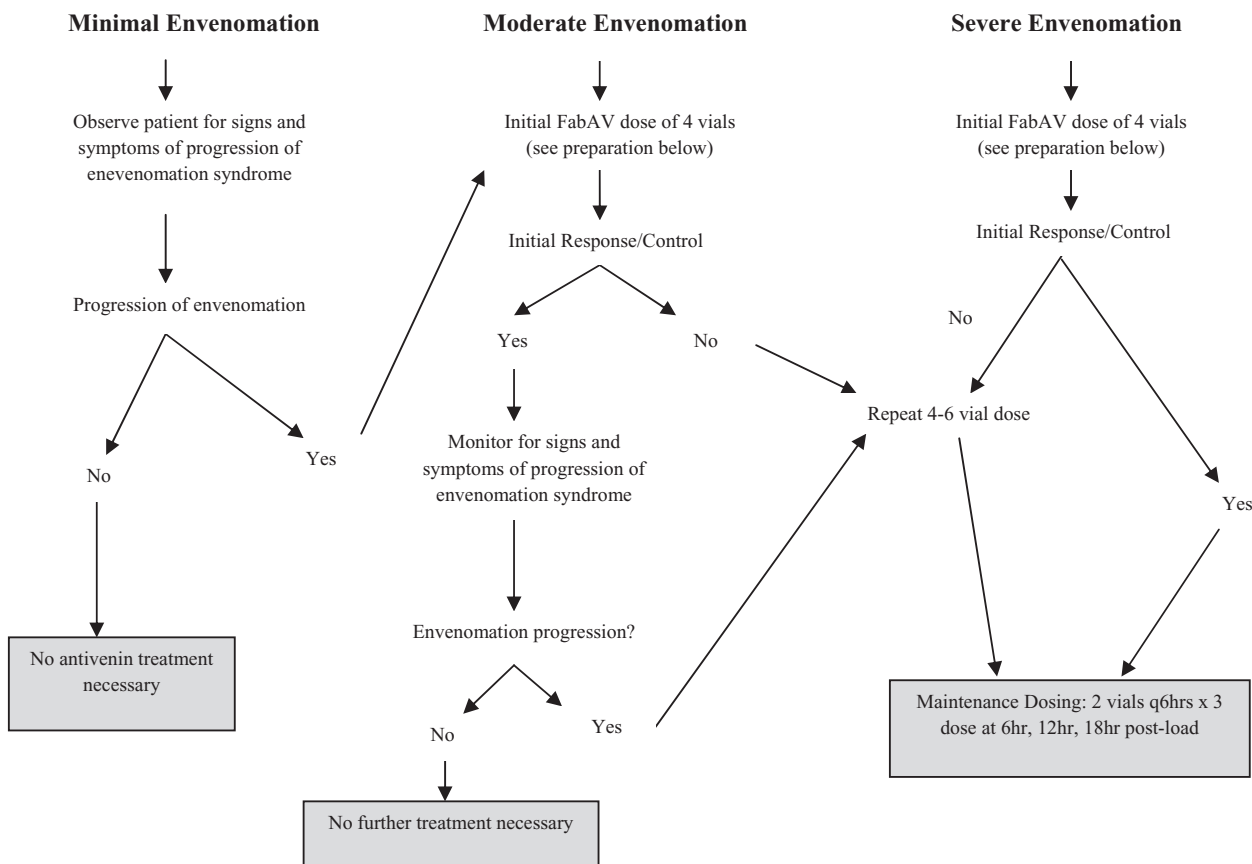
Contraindications and Precautions: Product contains ethyl mercury in the form of thimerosal (mercury 0.11 mg/vial). Use is contraindicated in patients who have a known hypersensitivity to papaya or papain, or prior hypersensitivity to FabAV or any other sheep-derived products. Pregnancy category C.

Initial Evaluation: Patients are eligible for therapy with FabAV if they meet the following criteria:

- Minimal, moderate, or severe envenomation by a North American crotaline snake. Use of FabAV is recommended within 6 hours of envenomation to prevent clinical deterioration and to prevent signs of systemic coagulation abnormalities.
- Progression of envenomation syndrome. Progression is defined by worsening of signs and symptoms of local injury, coagulation abnormalities, and systemic symptoms or signs.
- Pediatric or adult patients. Because the antivenin dose reflects venom size rather than patient size, the United States Food and Drug Administration recommends the same initial dosage and subsequent dosages for pediatric patients.¹⁰ Data show the drug's efficacy and safety for patients as young as 14 months of age.¹⁴

Appendix 2. Treatment Algorithm

A. Initial response or control: cessation of progression of local effects, systemic effects, and



Type of Signs or Symptoms	Severity of Envenomation		
	Minimal	Moderate	Severe
Local	Swelling, erythema, or ecchymosis confined to site of the bite	Progression of swelling, erythema, or ecchymosis beyond 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 such as nausea, vomiting, mild hypotension, perioral paresthesias, and myokymia	Markedly severe signs and symptoms such as hypotension (systolic blood pressure < 80 mm Hg), altered sensorium, tachycardia, tachypnea, and respiratory distress
Coagulation	No coagulation abnormalities or other laboratory abnormalities	Mildly abnormal coagulation profile without significant bleeding	Abnormal coagulation profile with bleeding (↓ international normalized ratio, activated partial thromboplastin time, and fibrinogen level; platelet count < 20 × 10 ³ /mm ³)
Snakebite Severity Score ^a	0–3	4–7	8–20

The Snakebite Severity Score is a validated and objective scale that involves six body categories: local wound, pulmonary, cardiovascular, gastrointestinal, hematologic, and nervous system effects and is used to assess the severity of an envenomation.¹³ The total score ranges from 0–20 and correlated with physician assessment at initial patient presentation ($r=0.63$, $Z=6.52$, $p<0.000001$). Thus, the Snakebite Severity Score could help with interpretation of clinical effects after initial and subsequent doses of CroFab.

coagulopathy from envenomation. Patients should be monitored up to 1 hour after FabAV dosing to assess initial response and control.

- Clinical response: pretreatment signs and symptoms of envenomation were arrested or improved after treatment.
- Partial response: signs and symptoms of envenomation worsened, but at a slower rate than expected after treatment.
- Nonresponse: patient's condition was not favorably affected by treatment.

B. Patients with documented rattlesnake envenomations should be evaluated for scheduled maintenance dosing to prevent recurrence of envenomation.

Preparation and Administration:

- Preparation: if possible, the initial 4–6-vial dose should be prepared in 2-vial increments administered with approximately 100 ml of 0.9% sodium chloride USP. Fluid adjustments may be needed for patients who weigh less than 10 kg. If no acute signs of allergic reaction are evident within the first 10 minutes of the infusion, subsequent doses can be made and delivered to the bedside to be started immediately after the completion of the first 2-vial dose.
- Administration: Begin the infusion of the first 2-vial dose at 25 ml/hour for the first

10 minutes to monitor for signs of acute reaction. If no signs are noted, the rate may be increased to 250 ml/hour until completion. The first 4-vial dose should be cumulatively given over at least 1 hour. Acute reactions to FabAV have been reported in 0–14% of patients. If serious acute reactions occur, the infusion rate should be slowed, and antihistamines, epinephrine, and albuterol should be administered. Subsequent doses can be administered over 30 minutes. Fluid adjustments (i.e., rate of administration and total amount of diluent prepared) may be needed for patients who weigh less than 10 kg.

- Recommended pretreatment: Pretreatment before antivenin therapy is not often required. If pretreatment is considered, histamine₁-receptor antagonists may be used. The recommended dose of diphenhydramine is 0.5–1 mg/kg/dose intravenously for patients aged 6 years or younger, 12.5–25 mg for patients aged 6–12 years, and 25–50 mg for patients older than 12 years.

Subsequent administration of FabAV doses:

- After an initial response, FabAV 2 vials every 6 hours for three doses should be given to limit the chance of recurrence of envenomation. Some investigators noted a significant

risk of recurrence in 8 (50%) of 16 patients ($p=0.002$) when they received as-needed doses of FabAV compared with scheduled maintenance doses after an initial response.¹⁵ However, one group of authors noted that 6 (21%)

of 28 patients had a hematologic recurrence with scheduled maintenance doses.¹⁶ Consequently all patients treated with FabAV may be at risk of a recurrence as evident by bleeding thrombocytopenia and coagulopathy.

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