

Crotalidae Polyvalent Antivenin (CroFab®) Protocol



Description of Protocol/Indications for dosing:

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

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

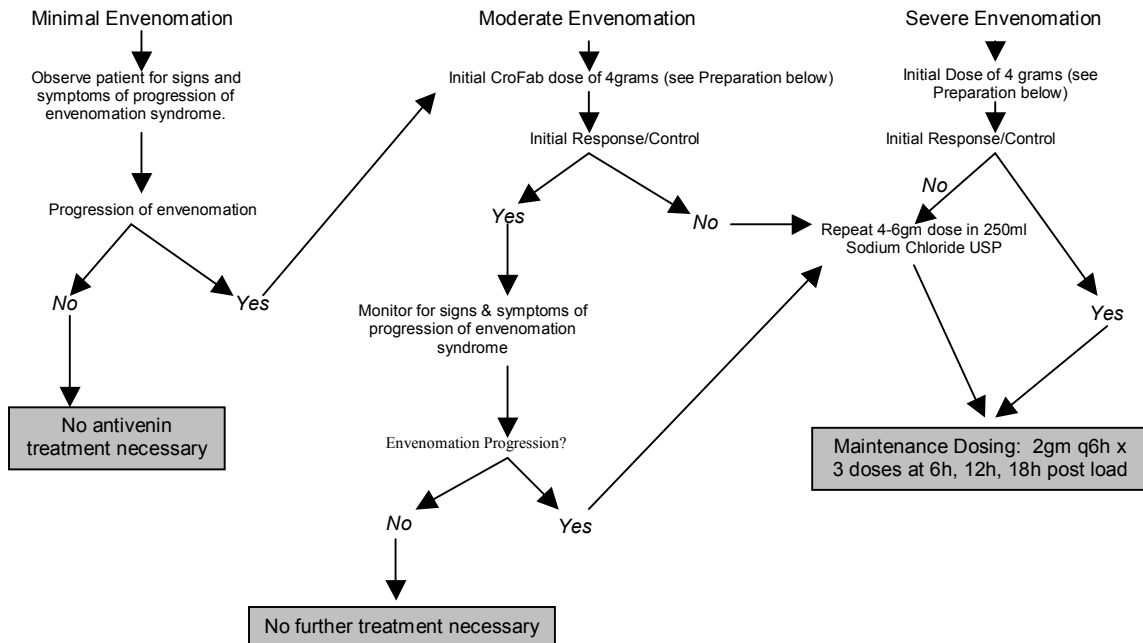
Initial Evaluation: Patients are eligible for therapy with *Crotalidae* polyvalent antivenin if they meet the following criteria:

- *Minimal, moderate, or severe envenomation by a North American crotaline snake.* Early use of *Crotalidae* polyvalent antivenin is recommended within 6 hrs of envenomation to prevent clinical deterioration and to prevent signs of systemic coagulation abnormalities.

Type of Signs or Symptoms	Severity of Envenomation		
	<i>Minimal</i>	<i>Moderate</i>	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 (N/V, mild hypotension, perioral paresthesias, myokymia)	Markedly severe signs and symptoms [hypotension (SBP < 80 mmHg), altered sensorium, tachycardia, tachypnea, and resp distress]*
Coagulation	No coagulation abnormalities or other lab abnormalities	Mild abnl coagulation profile without significant bleeding	Abnl coag profile with bleeding [↓ INR, APTT, fibrinogen; plt count <20,000 per mm ³]
Snakebite Severity Score (SSS)*	0-3	4-7	8-20

- *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.* As the antivenom dose reflects venom size rather than patient size, the FDA recommends the same initial and subsequent doses for pediatric patients. There is data showing efficacy and safety for patients as young as 14 months of age.⁴
 - *The Snakebite Severity Score (SSS) is a validated and objective scale to assess severity of envenomation including six body categories: local wound, pulmonary, cardiovascular, gastrointestinal, hematologic, and nervous system effects (Table 1). The total score ranges from 0-20. The SSS score correlated with physician assessment at initial patient presentation ($r = 0.63$, $Z = 6.52$, $P < 0.000001$).⁹ Thus the SSS score could help with interpretation of clinical effects following initial and subsequent doses of CroFab®.

Treatment Algorithm



^a Initial response or control: Initial control is cessation of progression of local effects, systemic effects, and coagulopathy from envenomation. Patients should be monitored up to one hour following FabAV dosing to assess initial response/control.

Clinical response: Pre-treatment 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.

Non-response: 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/Administration:

- **Preparation:** If possible, the initial 4-6 gram dose should be prepared in 2 gram increments administered with approximately 100 ml of 0.9% Sodium Chloride, USP. Fluid adjustments may be needed for patient <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 gram dose. Doses of 4-6 grams should be diluted into 250ml of 0.9% Sodium Chloride USP unless fluid restrictions are required.
- **Administration:** Begin the infusion of the 1st 2gm dose at 25 ml/hr for the first 10 minutes to monitor for signs of acute reaction. If none noted, the rate may be increase to 250ml/hr till completion. The first 4 grams should infuse over 1 hour total time. Acute reactions to CroFab® have been reported in a range of 0-14% of patients. If serious acute reactions occur, slow the infusion rate, administer antihistamines, epinephrine, and albuterol. 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 patient < 10 kg.
- **Recommended pre-treatment:** Pre-treatment prior to antivenin therapy is not often required.¹⁰⁻¹¹ If pre-treatment is considered, H₁ receptor antagonists may be used. The recommended dose of diphenhydramine is 0.5-1 mg/kg/dose (6.25 mg) IV for pts ≤ 6 YOA, 12.5-25 mg for 6-12 YOA, and 25-50 mg for ≥ 12 YOA.⁸

Subsequent administration of CroFab® doses:

- Following an initial response, additional doses of CroFab® have been suggested at doses of 2 grams q 6hrs x 3 doses (18 hrs) to limit the chance of recurrence of envenomation. Dart and colleagues noted a significant risk of recurrence in 8/16 patients (50%) (P = 0.002) when given PRN doses of CroFab® compared with scheduled maintenance doses following an initial response.² However, Ruha et al. noted that 6/28 pts (21%) had a hematologic recurrence with the scheduled maintenance doses.³ Thus all patients treated with CroFab® may be at risk of a recurrence as evident by bleeding, thrombocytopenia, and coagulopathy.

Appendix/References:

Table 1: Snakebite Severity Score. Adapted from reference 9.
Snakebite Severity Score (SSS)⁹

Criterion	Points
Pulmonary Symptoms	
No symptoms/signs	0
Dyspnea, minimal chest tightness, mild or vague discomfort, or respirations of 20-25 breaths/minute	1
Moderate respiratory distress [tachypnea, 26-40 breaths/minute; accessory muscle use]	2
Cyanosis, air hunger, extreme tachypnea, or respiratory insufficiency/failure	3
Cardiovascular system	
No symptoms/signs	0
Tachycardia [100-125 BPM], palpitations, generalized weakness, benign dysrhythmia, or hypotension	1
Tachycardia [126-175 BPM] or hypotension, with SBP > 100 mmHg	2
Extreme tachycardia [>175 BPM], hypotension with SBP < 100 mmHg, malignant dysrhythmia, or cardiac arrest	3
Local wound	
No symptoms/signs	0
Pain, swelling, or ecchymosis within 5-7.5cm of bite site	1
Pain, swelling or ecchymosis involving less than half the extremity [7.5-50cm from bite site]	2
Pain, swelling or ecchymosis involving half to all of extremity [50-100cm from bite site]	3
Pain, swelling or ecchymosis extending beyond affected extremity [more than 100cm from bite site]	4
Gastrointestinal system	
No symptoms/signs	0
Pain, tenesmus, or nausea	1
Vomiting or diarrhea	2
Repeated vomiting, diarrhea, hematemesis, or hematochezia	3
Hematologic symptoms	
No symptoms/signs	0
Coagulation parameters slightly abnormal: PT < 20 secs; PTT <50 secs; PLTs 100-150K/mL; or fibrinogen 100-150 mcg/mL	1
Coagulation parameters abnormal: PT <20-25 secs; PTT <50-75 secs; PLTs 50-100K/mL; or fibrinogen 50-100 mcg/mL	2
Coagulation parameters abnormal: PT <50-100 secs; PTT <75-100 secs; PLTs 20-50K/mL; or fibrinogen <50 mcg/mL	3
Coagulation parameters markedly abnormal, with serious bleeding or the threat of spontaneous bleeding; unmeasurable PT or PTT; PLTs <20K/mL; or undetectable fibrinogen; severe abnormalities of other laboratory values also fall into this category	4
Central nervous system	
No symptoms/signs	0
Minimal apprehension, headache, weakness, dizziness, chills, or parasthesia	1
Moderate apprehension, headache, weakness, dizziness, chills, parasthesia, confusion, or fasciculation in area of bite site	2
Severe confusion, lethargy, seizures, coma, psychosis, or generalized fasciculation	3

References:

- ¹Dart RC, Seifert SA, Carroll L, et al. *Ann Emerg Med* 1997; 30:33-39.
- ²Dart RC, Seifert SA, Boyer LV, et al. *Arch Intern Med* 2001;161:2030-2036.
- ³Ruha AM, Curry SC, Beuhler M. *Ann Emerg Med* 2002; 39:609-615.
- ⁴Offerman SR, Bush SP, Moynihan JA, Clark RF. *Pediatrics* 2002;110:968-971.
- ⁵Bush SP, Green SM, Moynihan JA, et al. *Ann Emerg Med* 2002;40:619-624.
- ⁶Lavonas EJ, Gerardo CJ, O'Mailey G, et al. *Ann Emerg Med* 2004;43:200-206.
- ⁷Protherics, Inc. *Crotalidae* polyvalent immune fab (ovine) [CroFabTM] package insert. Brentwood, TN: 2002.
- ⁸Taketomo CK, Hodding JH, Kraus DM. *Pediatric Dosage Handbook*. 10th ed. 2003.
- ⁹Dart RC, Hurlbut KM, Garcia R, Boren J. *Ann Emerg Med* 1996;27:321-326.
- ¹⁰Gold BS, Barish RA, Dart RC. *Emerg Med Clin N Am* 2004;22:423-443.
- ¹¹Gold BS, Dart DC, Barish RA. *N Engl J Med* 2002;347:347-356.