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Crotalinae Snake Envenomation

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Introduction

Snake envenomation is a clinically significant cause of presentation to veterinary hospitals for small animal patients. Approximately 162 snake taxa are native to the United States, about 27 of which are front-fanged venomous taxa, with the majority of these belonging to the family Viperidae, subfamily Crotalinae. Pit vipers (Crotalinae), including rattlesnakes (*Crotalus* spp), copperheads and water moccasins (*Agkistrodon* spp), and pygmy rattlesnakes and massasaugas (*Sistrurus* spp), are responsible for approximately 99% of the venomous bites sustained in the US [1]. Crotalinae envenomation in the United States will be discussed, but general concepts of treatment and disease can be applied to victims in any region. Practicing veterinarians should orient themselves to the venomous snakes indigenous to the region in which their patients may have exposure.

A good deal of dogma surrounds snake behavior, characteristics of envenomation, and resultant clinical signs in victims. A common misconception is that young pit vipers cannot control the amount of venom injected with a bite, therefore resulting in a larger dose of venom. All pit vipers control the amount of venom injected during a bite, with the volume injected dependent upon the size of the snake's venom glands and the nature of the bite. Studies evaluating the flow and volume of venom injected with various types of bites (predatory or defensive) have confirmed that there is a percentage of bites without measureable venom delivery, and there may be a trend toward lower volumes injected with defensive bites [2].

While the mechanics of pit viper venom delivery is fascinating, the clinical reality is that most veterinary patients will present with clinical signs of envenomation. The decision to treat these symptoms will be directed by the severity of clinical signs and available resources.

Snake envenomation can occur at any time of year, depending upon the activity of the snakes and exposure of veterinary patients. In very warm climates, such as the Sonoran Desert, crotalinae envenomation occurs year round [3].

Crotalinae Envenomation

There is relatively more information available on Crotalinae envenomation in dogs compared to cats. The published mortality rates for Crotalinae envenomation are low, ranging from 1.8% to 24% in dogs and 6% to 18% in cats [3–14]. Non-survivors typically suffer envenomations to the head, including the eye and tongue, which may provide a more direct route to the central nervous system or predispose to asphyxiation. Dogs that have suffered distal limb envenomations and acutely died are suspected to have experienced intra-arterial envenomation. Envenomations to the trunk may lead to profound clinical signs, including hemoperitoneum and acute respiratory muscle paralysis [6,15]. Relatively speaking, cats appear more susceptible to profound muscle weakness [6,14]. Dogs with advanced age and increased time from envenomation to treatment are risk factors for death [3]. It is well accepted that Crotalinae envenomation has an overall low mortality rate, but patient suffering and morbidity may be profound, requiring significant and costly therapies. Nearly any body system may be affected following envenomation.

Crotalinae venom is a complex mixture of water, proteins, and peptides. Most of the proteins are enzymatic, while the peptides exert organ toxicity [4,5,16]. The classically described enzymes include hyaluronidase, which facilitates rapid spread of the venom by breakdown of the connective tissues; phospholipase A2, which leads to cytotoxicity, including the characteristic echinocytosis

and spherocytosis observed as well as anticoagulation via anti-Xa activity; thromboxane, which is at least partially responsible for the thrombocytopenia often observed; as well as snake venom metalloproteinases (SMVPs) which contribute to platelet dysfunction, leading to clinical hemorrhage [16–18].

Crotalinae venoms can cause profound and complicated alterations in the coagulation system, leading to both thrombosis and hemorrhage. These proteins can be broadly classified as FV and FX activators, activators of prothrombin, thrombin-like enzymes, anticoagulant factor IX/X binding proteins, activators of protein C, thrombin inhibitors, fibrinolytic enzymes as well as plasminogen activator (see Chapter 70) [19]. Some venoms contain potent neurotoxins, such as the Mojave venom that causes presynaptic inhibition and may lead to progressive paralysis. These toxins have been identified in the venoms of the Mojave rattlesnake (*C. scutulatus*), western diamondback (*C. atrox*), prairie rattlesnake (*C. viridis*) and southern pacific rattlesnake (*C. helleri*) and pose a significant risk of life-threatening neurological complications associated with envenomation [6]. Myotoxins have been identified in a number of venoms, placing patients at risk for widespread myonecrosis and profound neuromuscular weakness. The most salient point is that nearly any body system may be affected.

Clinical Signs of Envenomation

The classic clinical signs of Crotalinae envenomation involve pain, swelling, regional ecchymosis, and one to two small puncture wounds. It is reported that the Mojave rattlesnake may have pure neurotoxins, therefore making identification of a wound difficult.

Most animals presenting for evaluation following envenomation will exhibit local disease at the bite site, in addition to systemic clinical signs. Dogs often suffer bites to their muzzle, with extremity as the next most common site. Cats will often suffer bites to multiple regions of their body. These patients may present anywhere along the spectrum of compensatory to decompensatory shock (see Chapter 152). Bites to the tongue or mouth may swell rapidly, leading to upper airway obstruction. Hyperglycemia and hypokalemia may be appreciated as a consequence of catecholamine surge. Cardiac arrhythmias are common and should be monitored for (see Chapter 53). Pigmenturia may occur due to hemolysis, rhabdomyolysis or both (see Chapter 66). Anemia may occur due to hemorrhage, hemolysis or both. Thrombocytopenia may be observed, with or without prolonged bedside coagulation times (PT, aPTT) (see Chapter 67). Hyperlactatemia is common,

and likely due to both tissue damage and hypoperfusion. Widespread hemorrhage may occur, leading to hematemesis, hematuria, melena, epistaxis, pulmonary infiltrates or any combination thereof. Neurotoxicity may lead to seizures, nystagmus, or paralysis. Hypoventilation is a risk factor for patients with profound weakness and/or central nervous system involvement. Patients may exhibit any combination or degree of severity of these clinical signs.

Patient Evaluation and Stabilization

An extensive human snake bite severity score has been proposed for use in applying objective assessment to veterinary envenomations [20]. Computation of this score requires measurement of coagulation times and platelet count, so it may not be a practical tool for widespread application in veterinary medicine.

A practical approach to assessment of envenomation is to complete a thorough physical examination. Further measurements may be directed based upon abnormalities noted during physical examination. Additional monitoring to consider includes measurement of systolic blood pressure, electrocardiogram, venous blood gas and electrolytes, a complete blood count with blood smear for evaluation of manual platelet count, echinocyte and spherocyte assessment, chemistry panel to assess renal and hepatic function, urinalysis to assess for pigmenturia, and coagulation times. If client or hospital resources are limited, then an abbreviated laboratory evaluation may consist of a blood smear to evaluate for red blood cell abnormalities and platelet count, venous blood gas and electrolytes, packed cell volume and total protein, measurement of blood urea nitrogen and/or creatinine, and a urine specific gravity with visual inspection for pigmenturia. Cystocentesis is contraindicated due to risk of hemorrhage. Circumferential measurement of the bite site is painful and unlikely to confer any significant advantage to the patient, and is not routinely performed by the author.

Patients should receive a triage assessment immediately upon arrival to the hospital (see Chapter 2). If clinical signs of pain, any form of shock or any other abnormalities are noted, rapid venous access should be obtained while the remaining baseline evaluation of perfusion parameters is assessed. Hypovolemic shock should be treated with isotonic balanced electrolyte fluids, in titrated aliquots of blood volume (see Chapter 153). Analgesia should be provided, ideally with a reversible opioid agonist such as hydromorphone or fentanyl (see Chapter 193). Opioid administration is safe and should not be withheld for fear of exacerbating neurological symptoms.

Finally, neutralization of the circulating venom with antivenom is the ideal treatment for patients with clinical signs of Crotalinae snake envenomation. Advances in antivenom manufacturing have occurred in recent years, providing the clinician with safer and more effective options. Veterinarians must familiarize themselves with the venoms in their region, evaluate their patient's clinical signs and then decide if antivenom administration is necessary. It is important, however, to remember that neutralization of circulating venom is the most direct method to reverse or halt progression of clinical signs and minimize patient suffering.

Antivenoms

There are currently two Crotalinae antivenoms approved by the United States Department of Agriculture (USDA) for use in veterinary medicine: Antivenin (Crotalidae) Polyvalent (ACP) and Venom Vet™. Other antivenoms that have been demonstrated safe and effective in the peer review literature include CroFab™ and an F(ab')₂ polyvalent Crotalinae antivenom produced by Veteria Labs, in Mexico (Table 141.1) [3,10,11,14,21].

One antivenom product has predominated veterinary medicine for years: Antivenin (Crotalidae) Polyvalent (ACP), an equine origin antivenom comprised of whole immunoglobulin G (IgG) molecules. Newer antivenoms have been developed from enzymatic digestion of the whole IgG to cleave off the antigen (venom) binding region, termed fragment antigen binding (Fab) region, from the fragment crystallizable (Fc) portion. The creation of a smaller product lacking the Fc portion is believed to increase the volume of distribution and possibly result in a less antigenic product [22–25]. These Fab-based antivenoms include Crotalinae Polyvalent Immune Fab (CroFab™), an ovine origin single Fab-based molecule antivenom, and Fab dimer (F(ab')₂) equine origin antibody-derived antivenoms (Table 141.1). The Fab-based antivenoms tend to have a relatively short half-life and move outside of the intravascular compartment faster than other antivenoms and may necessitate re-administration if re-envenomation occurs. Compared to the Fab monomer, F(ab')₂ antivenoms have a longer half-life and remain in the vascular compartment longer. They also have 2 antigen binding sites per molecule, compared to 1 antigen-binding site on the Fab monomer.

Table 141.1 Commonly available Crotalinae antivenom formulations.

Immunoglobulin type	Formulation	Supplied as	Venoms used in production	Approval status as of March 2018
IgG – equine	Antivenom	Lyophilized powder	<i>Crotalus atrox</i> , <i>C. adamanteus</i> , <i>C. terrificus</i> , <i>Bothrops asper</i>	USDA approved for use in veterinary medicine
Longest T _{1/2} 150kDa 2 venom-binding sites	Crotalinae Polyvalent (ACP) Distributed by Boehringer Ingelheim Vetmedica	Slow reconstitution Room temperature storage		
Fab – ovine	CroFab®	Lyophilized powder	<i>Crotalus atrox</i> , <i>C. adamanteus</i> , <i>C. scutulatus</i> , <i>Agkistrodon piscovorus</i>	FDA approved for use in human medicine Off-label use in veterinary medicine
Shortest T _{1/2} 50kDa 1 venom-binding site	Distributed by Protherics	Fast reconstitution Room temperature storage		
F(ab')₂ – equine	Venom Vet™	Liquid	<i>C. durissus</i> , <i>C. simus</i> , <i>Lachesis muta</i> , <i>Bothrops asper</i> , <i>B. alternatus</i> , <i>B. diporus</i>	USDA approved for use in dogs
Longer T _{1/2} than Fab, shorter than IgG 110kDa 2 venom-binding sites	Produced by Instituto Biologico, Argentino S.A.I.C.	No reconstitution necessary Refrigeration necessary		
F(ab')₂ – equine	Antivenom – <i>Bothrops asper</i> and <i>Crotalus durissus</i>	Lyophilized powder	<i>C. durissus</i> , <i>C. oreganus</i> , <i>C. o. helleri</i> , <i>C. adamanteus</i> , <i>C. scutulatus</i> , <i>C. atrox</i> , <i>C. horridus</i> , <i>Agkistrodon contortix</i> , <i>A. piscivorus</i> , <i>Bothrops asper</i>	Pending USDA approval for use in veterinary medicine Import permits required for experimental use
Longer T _{1/2} than Fab, shorter than IgG 110kDa 2 venom-binding sites	Produced by Veteria Labs, S.A. de C.V.	Slow reconstitution Room temperature storage		

There is one USDA approved F(ab')₂ antivenom available at the time of writing, Venom Vet™. This product is labeled to neutralize the venom of all North American Crotalinae snakes, and is a collection of purified pooled immunoglobulins from healthy horses immunized against multiple species (Table 141.1). There are no peer-review publications describing the clinical efficacy or use of this antivenom. Another widely used F(ab')₂ antivenom is Antivenom Bothrops asper & Crotalus durissus, imported from Mexico and distributed by Veteria Labs. This antivenom has been described in multiple peer review publications, and appears to be safe and effective [3,6,9,10,13,14]. The author finds this antivenom to be effective at clinical improvement with neurotoxins and myotoxins. One vial has been shown to be sufficient to neutralize clinical signs of rattlesnake envenomation in most dogs. Dogs with lower body weight and increased time from bite to presentation require more antivenom [3]. A safety study reported that up to 6 vials could be administered intravenously within one hour safely to healthy dogs [21].

A definitive dose of antivenom has not been established. Each batch of antivenom may have different antigen-binding abilities. It is reasonable to consider starting with two vials of F(ab')₂ antivenom in very small dogs or patients presenting with severe clinical signs such as cardiovascular collapse. Once it has been determined that antivenom is indicated, timely neutralization of venom should be prioritized, so the infusion should be administered as rapidly as possible. Initial infusion rates of 0.25–0.5 mL/kg/h are recommended while monitoring for signs of reaction. If no reaction is appreciated, the rate can be increased to administer the entire dose within 30–60 minutes. Cats may be more likely to experience a reaction to antivenom infusion, so close monitoring and slower infusion rates may be warranted in this species [14].

Some patients experience severe and protracted signs of envenomation, requiring multiple repeat boluses of antivenom. In these instances, it is sometimes advised to administer the antivenom as a constant-rate infusion (CRI). The dosing is empirical, and based upon human CRI protocols for bleeding diathesis [26]. Consider 1–2 vials over 6 hours continuously. Examples include patients with ongoing severe clinical signs such as neuromuscular collapse, profound hemolysis and/or rhabdomyolysis. It is not necessary to perform intradermal testing prior to antivenom administration, nor is it necessary to administer prophylactic diphenhydramine or glucocorticoids [1,3,11].

Endpoints to consider include optimization of perfusion parameters (heart rate, blood lactate, systolic blood pressure, electrocardiogram), resolution of coagulopathy as demonstrated by normalized coagulation times

and/or platelet count, sustained resolution or significant improvement in echinocytosis and spherocytosis if noted at baseline, lack of pigmenturia and/or progressive hemolysis, control of pain, and lack of progressive swelling or tissue damage.

Additional Therapies

There is an equine plasma protein product, RTLR™ (MG Biologics), marketed as snake bite protein support for dogs. This is from horses that have been vaccinated against the Mojave, eastern diamondback, western diamondback, and prairie rattlesnake. The manufacturer recommends administration at about 4 mL/kg. Each bag contains 100 mL of unpurified equine plasma. Peer review literature evaluating safety or efficacy does not exist at this time. The author cautions against offering this therapy to canine and feline patients in lieu of purified antivenom products. Potential complications include volume overload due to relatively larger dose of colloid product compared to antivenom, and risk of acute and delayed hypersensitivity reactions.

Antibiotic prophylaxis has been a controversial topic in the treatment of Crotalinae envenomation. The consensus in human medicine is that antibiotics are not indicated unless evidence of an infection develops [27,28]. Recent veterinary literature evaluating dogs with rattlesnake envenomation does not support routine antibiotic prophylaxis [3,9]. Some wounds will require treatment, likely due to secondary compartment syndrome and opportunistic infections (see Chapter 166). When indicated, single agent with the narrowest spectrum and shortest treatment duration possible, guided by bacterial culture and susceptibility, is recommended.

Routine administration of glucocorticoids is not recommended. No morbidity or mortality benefit has been documented with use of glucocorticoids in dogs envenomated by Crotalinae spp, and potential risks of use outweigh the potential benefit.

Local wound treatment with laser therapy has been promoted by some veterinarians. Peer review evidence of this therapy is lacking. It is a reasonable therapy to offer, should only be used by individuals with proper training, and should not be applied more than every 8 hours. This is an adjunctive therapy and should not be offered in lieu of standard treatments such as neutralizing antivenom, fluid therapy, and analgesia. Non-steroidal anti-inflammatory medications are not recommended, as these patients are at risk for kidney injury due to hypoperfusion, coagulopathy, nephrotoxins in the venom, and pigmenturia. Additionally, gastrointestinal ulceration is possible secondary to hypoperfusion and coagulopathy.

Some patients may require transfusion of red blood cells to treat secondary anemia due to blood loss, hemolysis or both (see Chapter 176). Hemolysis with spherocytosis may be observed, sometimes as late as 72 hours following initial envenomation. It is most likely that these patients are experiencing ongoing envenomation, and treatment with antivenom should be prioritized over immune suppression. In patients experiencing hemorrhagic complications of envenomation, treatment with fresh frozen plasma is not indicated. The mechanism of coagulopathy in most cases is not due to factor deficiency, but rather a complex syndrome of factor inhibition, activation, platelet inhibition, and endothelial dysfunction. As such, neutralization of circulating venom with antivenom is the treatment of choice.

The only reliable means of envenomation prevention is avoidance. Common attempts at envenomation prophylaxis include aversion training and use of a rattlesnake vaccine, *Crotalus atrox* toxoid manufactured by Hygieia Biological Laboratories and distributed by Red Rock Biologics. This vaccine claims efficacy against *C. atrox* venom, and the manufacturer also notes possible protection against venoms of many other Crotalinae snakes. Canine challenge studies evaluating postvaccine antibody titers in dogs or support of clinical efficacy are lacking. A retrospective evaluation of dogs suffering rattlesnake envenomation reported no measurable benefit of vaccination [3]. There is no peer review evidence supporting prophylaxis of snake bite by using avoidance training, behavioral modification, or prophylactic vaccination.

References

- Peterson ME. Snake bite: pit vipers. *Clin Tech Small Anim Pract* 2006;21(4):174–182.
- Young BA, Zahn K. Venom flow in rattlesnakes: mechanics and metering. *J Experiment Biol* 2001;204:4345–4351.
- Witsil AJ, Wells, RJ, Woods C. 272 cases of rattlesnake envenomation in dogs: demographics and treatment including safety of F(ab')₂ antivenom use in 236 patients. *Toxicon* 2015;105:19–26.
- Julius T, Kaelble M, Leech E, et al. Retrospective evaluation of neurotoxic rattlesnake envenomation in dogs and cats: 34 cases (2005–2010). *J Vet Emerg Crit Care* 2012;22(4):460–469.
- McCown J, Cooke K, Hanel R, et al. Effect of antivenin dose on outcome from crotalid envenomations: 218 dogs (1988–2006). *J Vet Emerg Crit Care* 2009;19(6):603–610.
- Willey JR, Schaer M. Eastern diamondback (*Crotalus adamanteus*) envenomation of dogs: 31 cases (1982–2002). *J Am Anim Hosp Assoc* 2005;41:22–33.
- Carr A, Schultz J. Prospective evaluation of the incidence of wound infection in rattlesnake envenomation in dogs. *J Vet Emerg Crit Care* 2015;25(4):546–551.
- Katzenbach J, Foy D. Retrospective evaluation of the effect of antivenom administration on hospitalization duration and treatment cost for dogs envenomated by *Crotalus viridis*: 113 dogs (2004–2012). *J Vet Emerg Crit Care* 2015;25(5):655–659.
- Peterson M, Matz M, Seibold K, et al. A randomized multicenter trial of Crotalidae polyvalent immune Fab antivenom for the treatment of rattlesnake envenomation in dogs. *J Vet Emerg Crit Care* 2011;21(4):335–345.
- Hackett TB, Wingfield WE, Mazzaferro EM, et al. Clinical findings associated with prairie rattlesnake bites in dogs: 100 cases (1989–1998). *J Am Vet Med Assoc* 2002;220(11):1675–1680.
- Hoose J, Carr A. Retrospective analysis of clinical findings and outcome of cats with suspected rattlesnake envenomation in Southern California: 18 cases (2007–2010). *J Vet Emerg Crit Care* 2013;23(3):314–320.
- Pashmakova M, Bishop M, Black D, et al. Multicenter evaluation of the administration of crotalid antivenom in cats: 115 cases (2000–2011). *J Am Vet Med Assoc* 2013;243:520–525.
- Istvan S, Walker J, Hansen B, et al. Presumptive intraperitoneal envenomation resulting in hemoperitoneum and acute abdominal pain in a dog. *J Vet Emerg Crit Care* 2015;25(6):770–777.
- Gopalakrishnakone P, Hawgood BJ, Holbrooke SE, et al. Sites of action of Mojave toxin isolated from the venom of the Mojave rattlesnake. *Br J Pharmacol* 1980;69:421–437.
- Powell RS, Lieb CS, Rael ED. Identification of a neurotoxic venom component in the tiger rattlesnake *Crotalus tigris*. *J Herpetol* 2004;38(1):149–152.
- Gold BS, Dart RC, Barish RA. Bites of venomous snakes. *N Engl J Med* 2002;347(5):347–356.
- Kini RM. Structure-function relationships and mechanism of anticoagulant phospholipase A₂ enzymes from snake venoms. *Toxicon* 2005;45:1147–1161.
- Kamiguti AS. Platelets as targets of snake venom metalloproteinases. *Toxicon* 2005;45:1041–1049.
- Lu Q, Clemetson JM, Clemetson KJ. Snake venoms and hemostasis. *J Thromb Haemost* 2005;3:1791–1799.
- Dart RC, Hurlbut KM, Garcia R. Validation of a severity score for the assessment of crotalid snakebite. *Ann Emerg Med* 1996;27(3):321–326.
- Woods C, Young D. Clinical safety evaluation of F(ab)₂ antivenom (*Crotalus durissus-Bothrops asper*) administration in dogs. *J Vet Emerg Crit Care* 2011;21(5):565–569.

- 22 Gutierrez JM, Leon G, Lomonte B. Pharmacologic-pharmacodynamic relationships of immunoglobulin therapy for envenomation. *Clin Pharmacokinet* 2003;42(8):721–741.
- 23 Lavonas EJ. Antivenoms for snakebite: design, function, and controversies. *Curr Pharm Biotechnol* 2012;13:1980–1986.
- 24 Morais VM, Massaldi H. Snake antivenoms: adverse reactions and production technology. *J Venom Anim Toxins* 2009;15(1):2–18.
- 25 Seifert SA, Boyer LV. Recurrence phenomena after immunoglobulin therapy for snake envenomations: part 1. *Pharmacokinetics and pharmacodynamics of immunoglobulin antivenoms and related antibodies. Ann Emerg Med* 2001;37(2):189–195.
- 26 Bush SP, Seifert SA, Oakes J. Continuous IV Crotalidae polyvalent immune Fab (Ovine) (FabAV) for selected North American Rattlesnake bite patients. *Toxicon* 2013;69:29–37.
- 27 Clark RF, Selden BS, Furbee B. The incidence of wound infection following crotalid envenomation. *J Emerg Med* 1993;11:583–586.
- 28 LoVecchio F, Klemens J, Welch S, Rodriguez R. Antibiotics after rattle-snake envenomation. *J Emerg Med* 2002;23(4):327–328.