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Case Report #1: Rattlesnake Envenomation of a Dog

INTRODUCTION

This case report describes a 12-year-old male Siberian husky dog that suffered from multiple rattlesnake bite wounds to the face while hiking with his owner in the woods of northern New Jersey. The dog presented to the hospital within 45 minutes of his attack with two full-thickness puncture wounds in his forehead and rapidly progressive facial swelling. He was medically managed in intensive care with crystalloid and colloid fluid therapy, pain medication, antibiotics, corticosteroids and antihistamines, a transfusion of fresh frozen plasma, and antivenom therapy. He responded initially to the antivenom, but was euthanized after 72 hours of hospitalization due to his poor prognosis associated with refractory pain, anxiety, and marked facial swelling. The owner declined necropsy and his body was taken for burial.

Approximately 17% of North American snakes are considered venomous.[1] Two venomous snakes species are native to Bergen County, New Jersey; namely, the timber rattlesnake (*Crotalus horridus*) and the northern copperhead snake (*Agkistrodon contortix mokasen*).[a] Experts also believe that the Eastern diamondback can be found as far north as New York.[a] These species are members of the pit viper family, Crotalidae, and are characterized by the presence of heat-sensing facial pits that allow them to locate prey.[1] Pit vipers are also easy to recognize by their elliptical pupils and broad, triangular heads. The timber rattlesnake is a close relative to its more dangerous cousin, the eastern diamondback rattlesnake (*Crotalus adamanteus*), which is the largest North American pit viper capable of delivering up to 700 mg of venom with a single bite.[2] In contrast, the copperhead is commonly implicated in snakebite wounds due to its widespread distribution, but is considered the least potent of the American

vipers.[2] The northern copperhead and timber rattlesnake spend most of the winter months in New Jersey underground in burrows. Like most North American crotalids, they are active during the months of May-October and live largely under brush and on rocky terrain, as they are not skilled at climbing trees.[a] Dogs typically receive a defensive strike from a startled rattlesnake as it is basking in the late morning or early afternoon sun, but usually not without an audible warning. "Dry bites," where there is no expulsion of venom, make up approximately 25-35% of all venomous snakebites.[1-4] The purpose of this mechanism is not completely understood. An investigation[4] of western diamondback (*Crotalus atrox*) venom flow showed that not only do snakes have control over venom injection, but also injection is heavily influenced by the context of the strike. A far greater amount of venom was deposited after a defensive strike when compared to predatory strikes.[4]

The composition of Crotalid venom varies greatly between species, depending on the age and size of the individual snake, the geographic location, and the time of year of the bite.[3] It is composed of various sizes of proteins designed to immobilize and kill prey, many of which have enzymatic properties.[1,3] Symptoms in victims of envenomation are commonly divided into three categories: local, systemic, and coagulative.[3]

Local effects begin with enzymes causing proteolytic damage to endothelial walls, leading to acute vasculitis with protein loss into the interstitium.[1,3] Certain enzymes found in venom, such as hyaluronidase and collagenase, worsen clinical signs by assisting the spread of venom through interstitial spaces.[1] Other potent enzymes, like that of zinc-based metalloproteinases, initiate an inflammatory cascade through the release of tumor necrosis

factor-alpha, which mediates macrophage differentiation, neutrophil degranulation, leukocyte migration, and the release of interleukins.[1] Phospholipase A2 in snake venom causes muscle fiber dissolution, the blockade of synaptic transmissions, increased capillary permeability, red cell fragility, and the release of prostaglandins, which can lead to inflammation and cell death.[1,5] The end result is swelling, pain, redness, echymoses, and possible necrosis at the site of the puncture wounds. Extensive local damage can complicate treatment significantly. Edema or circulatory injury at the site of envenomation could limit delivery of antivenom, by preventing or delaying neutralization.[6] Extensive tissue damage in a stabilized patient may require surgical debridement.[6]

Current theory supports that venom peptides bind to multiple receptor sites within their prey.[3] Snake venom can affect any major organ system. Systemic syndromes diagnosed in people include flaccid paralysis, systemic myolysis, coagulopathy with subsequent hemorrhage, acute renal failure, and cardiotoxicity. Systemic involvement begins with increased vascular permeability and hypovolemic shock.[1]

Rattlesnake envenomations are most commonly associated with hemotoxic effects on the victim. Human and canine patients develop a "pure defibrination" [1,3,7,8] coagulopathy associated with thrombocytopenia that is physiologically distinct from disseminated intravascular coagulation (DIC). Defibrination can occur within 15 minutes of a bite, with circulating fibrinogen-degradation products (FDPs) found in serum up to 14 days in humans.[4,8] In general, hemotoxic components found in venom can be categorized as **fibrinolytics**, **procoagulants, fibrinogen-clotting enzymes, anticoagulants**, proteins that affect **platelet**

function or number, and proteins that affect **vessel walls**.[1,7,8] Although *spontaneous* bleeding is uncommon, primary problems in humans associated with a snakebite coagulopathy include reduced coagulability of blood, a tendency towards frank bleeding secondary to damage of vessel walls, organ dysfunction associated with bleeding (i.e. intracranial or renal hemorrhage), and pathologic thromboses.[8] While emboli to the lungs can occur with some envenomations, this has not been associated with the timber or eastern diamondback rattlesnakes, and is uncommon in dogs.[8]

Fibrinolytics found in snake venom are enzymes that break down fibrinogen via direct or indirect pathways.[1,8] Fibrinogen is an important precursor to a formed clot. It is activated by thrombin to form fibrin, which is stabilized by factor VIII. Plasmin consequently breaks down fibrinogen and fibrin into FDPs during fibrinolysis. FDPs may also act as fibrinolytics during the healing process. The direct pathway for venom fibrinolytics does not need cofactors to cleave fibrinogen directly.[8] The indirect mechanism first converts plasminogen to plasmin, and then cleaves fibrinogen.[8] These plasmin-like proteases found in venom excessively cleave fibrinogen to form fibrinogen-degradation products (FDPs) and ineffective, fragmented fibrinogen, both of which contribute to the overall bleeding tendency.[8]

Procoagulants in venom contribute to hemotoxic effects by causing *in vivo* activation of the coagulation system, causing rapid consumption of factors.[1,8] **Fibrinogen-clotting enzymes**, are thrombin-like enzymes that directly affect fibrinogen. The eastern diamondback venom has a component called "crotalase," which is capable of clotting fibrinogen, leading to secondary activation of plasminogen from endothelial cells. Fibrinogen-clotting enzymes fail to activate

factor VIII.[1] The net result is, therefore, a friable clot that breaks down easily, and although deep vein thrombosis and other thrombotic events have been documented with some human snake envenomations, the thrombotic window is usually short and these complications are not described in dogs.[8] Procoagulants are not common in timber rattlesnakes, but more often associated with elapid snakes.[1,8]

Anticoagulants in snake venom are associated with less severe bleeding abnormalities than procoagulants, but are similar in mechanism. Some venom components with anticoagulopathic characteristics include protein C activators, the phospholipases, antithromboplastic components, and FDPs.[1]

Proteins found in venom that affect **platelet function or number** do so primarily by either inhibiting platelet activity or promoting platelet aggregation by inducing a conformational change in surface glycoproteins to allow fibrinogen binding.[4] Another proposed mechanism is the membrane destruction of platelets by phospholipases.[1,8] Platelets may also be consumed locally at the bite wound.[1] Thrombocytopenia is a key feature in North American rattlesnake envenomations, but the clinical significance is still unclear.[1,8] One study[9] detected thrombocytopenia in 88% of dogs bitten by prairie rattlesnakes, and most of these dogs were discharged from the hospital with platelet counts below reference range regardless of antivenom treatment. All of these dogs survived.[9] A retrospective study of thrombocytopenia[10] in timber rattlesnake envenomations in people showed that antivenom therapy did little to reverse low numbers of platelets, and theorized that a component of timber rattlesnake venom may persist in the blood despite neutralization. Many studies cite the persistence of thrombocytopenia in

patients up to 14 days following envenomation by various *Crotalus* species with unknown clinical significance.[6]

Proteins that affect **vessel walls** are also known as the "hemorrhagins."[8] Hemorrhagins are more common in exotic pit vipers, such as the southeast Asian Russell's viper, and are composed of zinc metalloproteinases that increase vascular permeability or damage the endothelium.[8] Pathologic bleeding into body cavities, kidneys, or the brain is further facilitated if these proteins are combined with procoagulants.[8] Clinical symptoms associated with hemorrhagins include bleeding at the wound site, bleeding from the gums, hematemesis or melena, hematuria, or bleeding into the lungs.[8]

Snakebite coagulopathy is distinct from DIC in many ways. DIC is characterized as a severe coagulopathy accompanied by widespread microvascular thrombosis and a decrease of circulating platelets and procoagulant proteins.[11] Consequently, thromboses and spontaneous bleeding can lead to multi-system organ failure.[11] One underlying mechanism in DIC involves a pathologic activation of thrombin that causes an exaggerated activation of factor VIII, resulting in widespread fibrinogen cleavage into fibrinopeptides A and B.[1,8] DIC patients often have prolonged prothrombin time (PT) and partial thromboplastin time (PTT), low platelet counts, an increase in FDPs, and production of D-dimers.[1,8] Alternatively, snakebite coagulopathies rarely affect intravascular thrombosis and do not result in the production of cross-linked fibrin. Production of fibrinopeptide A or B occurs, but usually not both.[8] There is no depletion of antithrombin, so heparin treatment is not helpful as when treating DIC.[1,8] Laboratory abnormalities can include decreases in fibrinogen and fibrin, an increase in FDPs, prolonged

prothrombin (PT) and partial thromboplastin times (PTT), and thrombocytopenia.[8] Although active bleeding in a snakebite patient is rare, DIC could be a complication observed from massive tissue injury and systemic inflammation secondary to a snakebite, and DIC can cause bleeding.[8,12] Differentiating between the two coagulopathies would be an extreme challenge, and would require careful review of bleeding tendencies and hematologic parameters.

Neurological signs from snake envenomation in North America are usually associated with elapid snakes, such as the coral snakes, or the crotalid Mojave rattlesnake.[1,12] However, neurotoxicity secondary to a compound called "crotoxin" has been described in the South American rattlesnake.[7] Crotoxin combines phospholipase A2 activity with crotapotin, an acid subunit, in order to block transmission at the neuromuscular junction.[7] Effects range from numbness to a flaccid paralysis, muscle fasciculations (called myokymia), respiratory failure, or even death.[7] Myokymia has been rarely associated with timber rattlesnake envenomations.[2] Crotalid or elapid venom can contain myotoxins that increase intracellular calcium, leading to skeletal muscle necrosis and prolonged contraction of muscle fibers.[1,8] This leads to refractory pain and the potential for complications related to myoglobinuria, such as renal failure.[1,13,14]

The overall incidence of renal toxicity resulting from poisonous snakebites is reportedly 1.4-28% in people[14] and is not well documented in dogs. However, it is considered an important global issue, as resources for immediate treatment in some countries can be scarce and delayed therapy increases the risk of renal damage.[8] Ongoing injury to the renal tubules occurs secondary to hypovolemic shock, hemoglobinuria, myoglobinuria, and DIC.[1,14] The histopathologic lesions associated with snakebite induced renal failure include acute tubular

necrosis and patchy or diffuse cortical necrosis.[14] In a report of a 12-year-old boy bitten in the back by a Russell's viper,[14] peritoneal and hemodialysis was implemented and renal function was restored. Since an association between North American crotalid venom and renal toxicity has not been shown,[1] it is unknown if aggressive and early intervention with crystalloid fluids and antivenom therapy would prevent the complication of renal failure.

A diagnosis of snake envenomation is fairly straight forward if the snake was identified at the time of the bite. However, for dogs presenting with puncture wounds or tissue reactions of unknown origin, other types of venomous animal bites should be considered. Spiders, such as the widespread brown recluse or black widow, can cause extensive local injury or even anaphylaxis.[a] Scorpions are an important consideration in the southwestern United States.

Local wound effects, such as swelling and pain, generally begin within 30-60 minutes after a bite.[1,3] Ecchymosis at the site of a bite can begin within 6 hours, primarily due to increased capillary permeability.[1,3,8] Humans complain of intense pain, weakness, swelling, numbness or tingling, rapid pulses, bruising, muscle fasciculations, an unusual metallic taste, vomiting, and/or confusion when bitten by a snake.[12] Clinical findings in dogs include circulatory collapse, hypotension, pallor, prostation, generalized pain, facial paraesthesia, ptosis, exophthalmos, ptyalism, dyspnea, dysphoria, hyperthermia, ventricular arrhythmias, ataxia, bleeding from the punctures and/or gums, or gastrointestinal upset.[1,2,3,8]

When a dog presents with a rattlesnake bite, standard assessment of the patient should include a full physical exam, blood pressure, biochemical profile, complete blood count, a blood

gas analysis, urinalysis, and a coagulation profile that includes partial thromboplastin and prothrombin times, a platelet count, and fibrinogen and D-dimer levels. Additionally, an electrocardiogram and thoracic radiograph are highly recommended, especially in geriatric patients.[1,8] The area of the wound should be clipped and cleaned, and any local swelling should be measured every 15-30 minutes.[1,3] Delayed effects are possible, so careful monitoring for 24 hours in a hospital setting is recommended even for minor envenomations.[3]

Scoring systems are used in human medicine in order to more objectively guide medical practitioners when treating victims of snakebites.[2,4,15] These apply a qualitative index based upon biochemical abnormalities, local wound effects, or effects on the pulmonary, cardiovascular, gastrointestinal, hematologic, or neurologic systems.[2] The Snakebite Severity Score assigns a numeric value to the severity of symptoms experienced per organ system; for example, "0" would be assigned to a patient with a normal heart rate, while "3," would be given to a patient with a tachycardic ventricular arrhythmia.[2] Another method of classification is based upon the overall severity of symptoms.[2,16] In this scoring method, *nonevenomated*, or "dry," bites are defined by the presence of punctures or fang marks without a local or systemic reaction. *Mild envenomation* describes local swelling and pain without systemic reaction. *Moderate envenomation* describes patients with marked systemic signs and symptoms with minimal local effects, or marked local effects with minimal systemic symptoms. Finally, *severe envenomation* describes patients with extensive local effects, systemic signs and symptoms, and marked laboratory abnormalities. To date, there is no snakebite scoring method tailored to canine envenomations.

Biochemical and hematologic abnormalities in the dog may vary based upon the species of snake. Changes largely reflect muscle damage, hemolysis, renal damage, hepatic injury, systemic inflammatory response, and/or a defibrinating coagulopathy.[1,4,7,12,14] Dogs injected with venom from the South American rattlesnake (*Crotalus durissus terrificus*) were found to have a neutrophilic leukocytosis that lasted from two to seven days, and a brief eosinophilia.[7] Transient *eosinopenia* is possible in patients treated with antivenom therapy, due to a physiologic release of histamine.[7] This change usually corrects itself after antivenom therapy is finished. Dogs can also have changes in plasma levels of creatine kinase (CK) and myoglobin secondary to severe muscle damage associated with rhabdomyolysis.[7] Reports of dogs bitten by prairie rattlesnakes in Colorado found thrombocytopenia, echinocytosis, and a mature leukocytosis as common biochemical abnormalities.[9] Other biochemical abnormalities may include changes in plasma alanine transaminase (ALT or GPT), aspartate transaminase (AST or GOT), or alkaline phosphatase (ALP).[7] It is unclear in the literature if these changes are from direct hepatic injury from the venom, or from systemic damage secondary to hemodynamic disturbances associated with circulatory shock, or from antivenom treatment.[1,7] Hypoalbuminemia or hypoproteinemia can occur secondary to vasculitis or through intestinal or renal loss.[1] Changes in blood urea nitrogen (BUN) or plasma levels of creatinine (CREAT), as well as hematuria, myoglobinuria, proteinuria, and hyposthenuria can indicate ongoing renal damage.[1,7,8,14] In addition to analyzing urine components, urine output is also an important monitoring parameter.[14]

Echinocytosis may be the earliest hematologic change consistent with rattlesnake envenomation in dogs.[4] A retrospective study of 28 cases of canine envenomations[17] associated echinocytosis with envenomation in dogs with other systemic signs of a snakebite. Within 48

hours, nearly all of the dogs in this study had mature type III (where 95-100% of mature erythrocytes are affected) echinocytosis.[17] Additionally, approximately 90% of the dogs in the Colorado retrospective study[9] had echinocytosis upon presentation. Another study[18] showed that echinocytosis induced by rattlesnake venom in vitro was directly related to the degree of venom exposure. This correlated clinically with the degree of envenomation. The higher the dose of venom exposed to red blood cells *in vitro*, the more propensity for spheroechinocytic or spherocytic change.[18] Proposed mechanisms for echinocytosis involve the action of phospholipases and ATPase enzymes on red blood cell membranes.[9] Since echinocytosis is self-limiting during the first 48 hours of envenomation, it is unknown if quantification of echinocytes can be used to direct antivenom therapy or predict prognosis.

After the initial assessment, fluid therapy should be used to correct any abnormalities related to shock, lactic acidosis, or electrolyte changes, or fluid loss to the interstitium. There has been concern in the past that the administration of crystalloid or colloid fluids may contribute to the overall incoagulability of envenomated blood;[1] however, current theory supports using balanced crystalloids to maintain overall homeostasis and to preserve kidney function.[2,13] Since many patients experience hypovolemia secondary to vasculitis and/or protein loss, colloids such as hetastarch[b] are helpful when replacing plasma volume because the large molecules do not leave the intravascular space.

The use of donated blood and/or blood components to treat snake envenomation is controversial.[1,8] Since snakebite coagulopathies are due to the presence of toxins in the venom and not disturbances in normal hemostasis, replacement of coagulation factors or platelets with

transfusions may worsen clinical signs by providing substrate for venom procoagulants.[8] Also, platelets are fragile and highly reactive, and therefore difficult to process into a product suitable for transfusion. In addition, it is possible that if a patient's platelets are low due to venom-induced destruction, donated platelets may also be destroyed in peripheral circulation if un-neutralized venom is still present.[10] This phenomenon is seen in patients with immune-mediated thrombocytopenia that receive platelet-rich transfusions.[19]

Fresh frozen plasma (FFP) is a useful blood component for treatment of DIC. It replaces coagulation factors, fibrinogen, antithrombin III, albumin, alpha-macroglobulin, immunoglobulins, and other plasma proteins present in the donor's blood at the time of collection.[20] Replacement of these factors in an envenomated animal, however, will not turn off a venom-induced coagulopathy, and may worsen other mechanisms of pathologic clotting.[8] The administration of fresh frozen plasma may be beneficial after venom has been adequately neutralized in an animal still suffering from inflammation or protein-loss, but there are no studies to support this theory. The use of FFP in canine envenomations has not been shown to improve overall morbidity or mortality; in fact, older reports of rattlesnake defibrination where fibrinogen was given instead of antivenom confirmed negative effects.[8] Ultimately, neutralization of venom appears to be the most effective way of reversing most clinical manifestations of envenomation and preventing progression of signs.[1,2,3,8]

The use of antivenom has significantly reduced overall mortality related to viper envenomations since its conception in 1954.[3,9] A prescription is required to obtain antivenom in the United States, and a permit is required for importation of exotic antivenom treatments.[9]

Veterinarians also can obtain domestic antivenom from nearby human hospitals. Antivenom therapy should be considered in any animal that experiences progressive local effects, or has evidence of moderate or severe systemic change due to venom toxicity.[2] It has been shown to reverse some manifestations of envenomation, such as hypotension and coagulopathy, and to prevent the progression of local tissue damage.[3] However, local tissue necrosis cannot be halted by antivenom treatment, and an irreversible inflammatory reaction from venom can occur 20 minutes after a bite.[1] Antivenom must be given intravenously if venom-induced shock is present, and should be administered within the first 4 hours of a snakebite.[12,13] Administering antivenom after 8-12 hours is of questionable benefit; however, most resources recommend giving antivenom within the first 24 hours if signs of severe envenomation are present.[8,12,13,21] High serum levels of antivenom up to 5 days post treatment have been detected in human patients.[2] Although no current information is available in dogs, levels of antivenom in humans have been shown to gradually decline over 25 days after administration, and low levels have been detected in the blood up to 4 months after treatment.[2]

There are two basic forms of antivenom applicable to veterinary practitioners in the United States: the equine-derived Antivenin (Crotalidae) Polyvalent, or ACP,[c] and the ovine-derived Crotalidae Polyvalent Immune Fab, or FabAV[d].[3,12,21] ACP is a refined and concentrated preparation of serum immunoglobulins obtained from healthy horses immunized with venoms from four species of poisonous snakes: *Crotalus adamanteus* (eastern diamondback rattlesnake), *C. atrox* (western diamondback rattlesnake), *C. durisus terrificus* (South American rattlesnake), and *Bothrops atrox* (Fer-de-lance).[12] The immunoglobulins found in this product are potentially capable of neutralizing the toxic effects of venoms of crotalids native to North, Central, and

South America, including copperheads and water moccasins (*Agkistrodon spp.*).[12] The possibility exists, however, that antivenom produced against venom from snakes in one geographic region could be almost useless when treating bites by the same species from a different region, as seen with the Russell's viper.[8]

A major disadvantage to using ACP is sensitivity to horse serum components and antivenom IgG, and the risk of anaphylaxis.[2,13,21] Antivenom is reported to have a rate of acute reactions in people as high as 20%.[16] However, the severity of allergic reactions to ACP has not been classified in the literature, and some reports claim that acute reactions tend to be mild and characterized only by urticaria.[16] The compound is processed with ammonium sulphate in order to decrease the amount of inert protein present, which aids in reducing the overall immunogenic potential of the product.[21] However, this process also removes much of the albumin from the serum, as well as some of the neutralizing antibody.[21] Consequently, another disadvantage to using ACP is that the final protein level of IgG is only 15-25%, and not all of this binds to venom.[21]

In humans, equine immunoglobulin fixes complement, triggering inflammatory pathways of the complement cascade, leading to circulatory collapse.[2] Two types of hypersensitivity can be seen in both humans and dogs: an immediate type I hypersensitivity that manifests with urticaria, angioedema, laryngeal and bronchial spasm, respiratory distress, tachycardia, hypotension, shock, and cardiac dysrhythmias; and a delayed type III hypersensitivity, or "serum sickness."[2] Serum sickness is considered a self-limiting condition defined by the production of antibodies and t-cell mediated inflammation secondary to the

administration of large foreign proteins.[1,16] Clinical signs can include fever, malaise, lymphadenopathy, joint or generalized pain, and urticaria. Reactions can also progress to glomerulonephritis, vasculitis, and neuritis.[1,16] One report found that 6 of 26 human patients who received ACP had a type I allergic reaction, and serum sickness occurred in 50% of the patients.[16] The incidence of serum sickness in this report was related to the dose of antivenom given, as 5 out of 6 of the afflicted patients had received over 8 vials of antivenom.[16] Another, more recent, report[22] describes a dog bitten by an eastern diamondback rattlesnake. In this dog, fever, chemosis, and limb edema occurred three to six days after receiving antivenom treatment and responded to immunosuppressive (corticosteroid) therapy.[22] Although allergic reactions are potential risk to a patient receiving antivenom therapy, the benefits seem to outweigh the potential threat when used in a patient with life-threatening symptoms.[2]

The ovine Fab antivenom product was approved for use in humans in 2000.[13] It is made from the serum of sheep inoculated with venom from the *Crotalus adamanteus*, *C. atrox*, *C. scutulatus* (Mojave rattlesnake), and *Agkistrodon piscivorus* (cottonmouth) snakes.[3] Unfortunately, its use is limited in both the human and veterinary community due to expense and lack of availability.[13] It is produced by partial enzymatic digestion of IgG, resulting in antibody fragments that retain the ability to bind and inactivate venom, but are smaller and lack the immunogenic potential of the parent IgG.[21] Antibody fragments distribute widely into tissues and possess less risk for anaphylactic complications.[21] However, the smaller fragments are rapidly cleared by renal excretion, and data suggests that Fab may require dosing every few hours or as a continuous rate of infusion in order to bind and inactivate venom; otherwise, large concentrations of unneutralized venom may remain in circulation.[8,21] The ovine Fab has been

used with success in the management of neurotoxicity induced by elapid snakes and some crotalids, a characteristic not seen with ACP administration.[2] It has also been used to treat myokymia associated with timber and western diamondback rattlesnakes.[2]

Older sources advocate the practice of skin testing before administering antivenom. However, recent literature suggests that skin testing does not accurately predict acute side effects and can have a false positive rate as high as 40%.[16] The practice of skin testing delays therapy, and can also cause reactions.[16] Some physicians mandate skin testing in mild to moderate envenomation cases, and others simply premedicate all recipients of antivenom with antihistamines and do not skin test.[16] The vial of ACP horse serum available for skin testing does not have the same amount of protein as the vial presented for intravenous use, which may explain its ineffectiveness in predicting reactions.[16] Skin testing for the ovine Fab product has not been heavily advocated since this product has a much lower incidence of adverse reactions.[21]

Dosing of both ACP and ovine Fab is purely anecdotal, but in humans an initial dose of 5-10 milliliters is given intravenously to test for reactions, and then the rate can be adjusted to give up to 10 vials in the first hour.[13] In dogs, the suggested dose of ACP is 10-50 ml intravenously; this dose can be repeated every 2 hours, as needed.[1] In general, therapy is titrated to clinical improvement of systemic signs. Although the risk of delayed reactions increases with additional vials given, the study of humans treated with ACP[16] showed that the average number of vials given to patients with moderate to severe envenomation averaged 12-18 vials, with a maximum dose of 30 vials given to one individual.[16] A retrospective study of Fab antivenom

administration reported that the total dose of vials administered to an individual patient was from 10 to 47 vials, until the resolution of clinical signs.[23]

Unfortunately, there are no guidelines for "end-points" to antivenom administration for dogs. Some have suggested a daily assessment of echinocytosis as an indicator of improvement.[e] However, since echinocytosis is self-limiting, daily blood smears may not be an appropriate assessment modality. Other sources state that quantifying numbers of platelets is an acceptable measure of improvement,[8] but platelet counts can remain decreased for days to weeks in a stable patient post-envenomation.[3,8] The most important indicator for improvement in patients may be cardiovascular stability, pain control, and *cessation* of swelling and/or changes in hematologic or biochemical parameters instead of persistence of academic coagulopathies.

Neurotoxicities are more difficult to treat, as conventional equine polyvalent antivenin is not usually useful .[13,24] Ovine Fab antivenom has been shown to cause rapid resolution of myokymia or other signs of neurotoxicity.[2] One paper[24] reported a resolution in neurotoxic symptoms in three patients after the immediate administration of the newer ovine polyspecific crotalid antivenom. In addition to antivenom, the use of anticholinesterase drugs such as edrophonium chloride and neostygmine has also been shown to improve side effects in patients bitten by cobras.[2] Since neurotoxicities vary dramatically by species, these drugs should be used judiciously.

Adjunct treatment for snakebites includes the administration of analgesics or anxiolytics, antibiotics, corticosteroids, and antihistamines. Although it is common practice in veterinary

medicine to administer routine prophylactic antibiotic therapy if local tissue damage is present, the incidence of snakebite associated wound infections is surprisingly low.[1,25] Bacteria isolated from crotalid mouths include *Pseudomonas aeruginosa*, *Proteus* spp, coagulase-negative *Staphylococcus* spp, *Clostridium* spp, and *Bacteroides fragilis*.[1] Some believe that snake venom may have antibacterial properties.[1] A prospective study of antibiotic treatment in 114 victims of venomous snakebites in Ecuador reported that there was no statistical difference in wound infection between the group of patients treated with gentomycin and chloramphenicol and patients who did not receive antibiotics.[25] The low incidence of wound infection associated with snakebites was also demonstrated in 54 patients, whereupon only one patient developed evidence of infection during the study period.[26] Therefore, the routine use of antibiotics is not recommended in humans,[25-27] although no studies to confirm or deny wound infection in dogs are available.

Corticosteroid use is routine for some practitioners, although no improvement in morbidity or mortality due to steroid use alone has been demonstrated in either humans or dogs. Corticosteroids are considered reasonable if there is severe tissue inflammation or necrosis, due to its anti-inflammatory and analgesic effects.[1,3,4] However, side effects such as gastrointestinal upset, panting, and polyuria/polydipsia may outweigh the potential benefit of giving the drug. Some specialists believe that steroids may potentiate the toxicity of venom.[4] Corticosteroids are critical, however, when treating type I or type III hypersensitivities secondary to antivenom use.[1,3,21]

Antihistamines are also routinely given to snakebite victims upon presentation or as a premedication to antivenom therapy.[1,3,4,21] There are no controlled studies that support this practice, either.[3] Analgesics should be employed based upon the severity of clinical signs. Extreme pain in humans is associated with envenomation due to subsequent inflammation and necrosis; therefore, the use of opioids may need consideration in animal victims with moderate to severe symptoms.[1,3,4] Careful administration of mind-altering analgesics to patients with neurotoxicities should be employed so as not to mask clinical signs.[1,3]

A final form of treatment in human medicine involves surgical intervention of appendicular compartment syndrome.[13] It is not clear from the literature if compartment syndrome is a common entity in veterinary patients with snakebite wounds. Compartment syndrome in people is diagnosed after direct measurement of compartment pressure within a muscle group secondary to inflammation or hemorrhage.[13] If elevations in pressure exceed 30 mm Hg, surgical fasciotomies may be necessary to relieve tension and pain. Overall, physicians advocate the use of antivenom over surgical intervention except for extreme cases.[1,13]

A vaccine made of western diamondback *(Crotalus atrox)* toxoid (CAT) is currently available[f] for dogs.[27] The vaccine promotes endogenous IgG formation against the venom, and is intended as a prophylactic measure against venom-induced toxicities, such as local necrosis, in the event that antivenom treatment is not available or delayed.[27] Canine antibodies elicited by vaccination with CAT can also bind to proteins found in *C. viridis, C. rubber, C. horridus, C. adamanteus,* and *A. contortix* venom.[27] In murine studies performed by the manufacturer, up to 3 times the lethal dose of *C. atrox* venom was tolerated in vaccinated mice.[27] In addition, no

potential for antigenic cross-reactivity with equine or ovine antivenom exists, and dogs that are vaccinated can still receive antivenom without consequence.[27] Vaccinated dogs that elicit signs of moderate or severe envenomation may still require antivenom therapy.[1,27] The initial vaccines must be administered twice, approximately 4 weeks apart, and boostered biannually for dogs with high risk of exposure to rattlesnakes.[27] Studies on the efficacy or long-term effects of this vaccine in the general dog population have not been performed, so its use is not yet widely recommended.[1]

Prognosis largely depends upon the extent of injury and systemic involvement, as well as availability and response to treatment. An estimate of overall survival in envenomated dogs by one paper was 96.3% with treatment.[1,25] Evidence suggests that the prognosis for dogs bitten by some rattlesnake species is excellent with aggressive supportive care.[2] Furthermore, the overall rate of life-threatening conditions in humans, such as hypotension or shock, occurs in only about 7% of envenomations worldwide. Although renal failure is a common cause of delayed mortality from untreated snakebites in humans living in developing parts of the world,[13,14] the syndrome is a rare complication in dogs. Therefore, the overall risk of death in dogs is estimated to be low, but morbidity due to loss of tissue or limbs is possible.

Clinical Report

A 12-year-old male intact Siberian husky presented on emergency for multiple puncture wounds inflicted by a rattlesnake 45 minutes prior to presentation. The snake was not presented with the dog, but the owner described the snake and rattle. Based upon demographics of local

venomous snakes, the species was assumed to be either a timber rattlesnake, or less likely, an eastern diamondback.

The dog was previously very athletic and hiked daily with his owner. A local veterinarian managed his yearly wellness examinations. He was current on rabies, canine distemper, adenovirus, parainfluenza, parvovirus, and hepatitis vaccinations, and was also screened annually for occult heartworm disease. Other past pertinent medical history included miscellaneous fatty subcutaneous masses and cysts, in addition to a three-centimeter raised and lobulated perianal mass. All had been aspirated by the local veterinarian and determined to be benign. The owner reported that he had no coughing, sneezing, vomiting, diarrhea, or polyuria/polydypsia prior to presentation. He also was not taking any medications prior to presentation.

The dog was triaged as "unstable" at presentation because of his markedly swollen face and brick-red mucous membranes. He was ambulatory but anxious and panting, and therefore moved to an assessment area by gurney to avoid exercise intolerance. His muzzle and periocular tissues were swollen and firm, and two puncture wounds were visible just above his eyes, in the center of his forehead. The punctures were symmetrical and approximately 2 millimeters in diameter, and serosanguinous discharge drained from each hole. His weighed 32 kilograms and had a body condition score of 5/9. His heart rate was elevated at 150 beats per minute (range for his size, 60-120 bpm). His rectal temperature was elevated at 103.5° Fahrenheit (range, 99.0° to 102.5° F). His lung sounds were normal in the cranioventral and dorsocaudal lung fields and his abdomen palpated normally. He had two descended and symmetrical testicles, and an enlarged,

39.7 Deg C (range, 37.2 to 39.2 deg C).

but symmetrical and non-painful prostate. The perianal mass was unchanged per his owner's description.

The dog was neurologically appropriate and all cranial nerves were intact. He was weak and hypotensive, with a blood pressure of 80 mmHg[g] (range, 100-160 mmHg). An assessment of neurological and musculoskeletal strength was complicated by his circulatory collapse; however, motor function in all four legs was present and he did not have defecits in conscious proprioception. No other obvious bite wounds or swellings were apparent at this time.

An 18-gauge intravenous over-the-needle catheter was placed into each cephalic vein. Blood samples for initial "in-house" assessments were obtained and tests included the following: packed cell volume and total solids, a complete blood count[h] and serum chemistry,[i] citrated partial thromboplastin and prothrombin times,[i] and a venous blood gas[i]. Urine was not submitted at this time. These values are shown in Table 1. All results were considered unremarkable, except for the venous blood gas. His pH and anion gap were normal, but his bicarbonate was low and his base excess was significantly elevated. Metabolic acidosis secondary to excessive production of lactate was suspected at this time. A slightly low platelet count was noted, but was considered not yet clinically significant. In addition, his blood was typed[j] and he was DEA 1.1 positive. A macroscopic auto-agglutination saline screen was negative. An in-house blood smear showed marked (>90%) echinocytosis.

Supportive measures performed at the time of presentation included an intravenous injection of 3 mg of hydromorphone[k] (0.1 mg/kg) for pain control and sedation. A dose of

Table 1. In-House Blood Results During the Initial 24 Hours of Hospitalization (5/15/07)

Test	Laboratory Value (at presentation)	Laboratory Value (12 hours post)	Normal Reference
Serum Chemistry			
Phosphorus	3.0 mg/dl		2.5-6.8 mg/dl
Total Bilirubin	0.1 mg/dl		0.0-0.9 mg/dl
Total Protein	6.6 g/dl		5.2-8.2 g/dl
BUN	23 mg/dl		7-27 mg/dl
Calcium	10.5 mg/dl		7.9-12.0 mg/dl
Cholesterol	267 mg/dl		110-320 mg/dl
Creatinine	1.4 mg/dl		0.5-1.8 mg/dl
Glucose	139 mg/dl	112 mg/dl	70-143 mg/dl
Amylase	**489 U/L**		500-1500 U/L
ALT	40 U/L		10-100 U/L
ALP	154 U/L		23-212 U/L
ALB	3.0 g/dl		2.2-3.9 g/dl
Globulin	3.6 g/dl		2.5-4.5 g/dl
Electrolytes			
Sodium	143 mmol/L	147 mmol/L	142-150 mmol/L
Potassium	4.1 mmol/L	4.3 mmol/L	3.4-4.9 mmol/L
Chloride	121 mmol/L	123 mmol/L	106-127 mmol/L
Blood Gas			
Hematocrit %	50	**30**	35-50
Ph	7.395	**7.288**	7.35-7.45
PCO2	**22.3 mmHg**	**30.7 mmHg**	34-40 mmHg
HCO3	**13.7 mmol/L**	**14.7 mmol/L**	20-24 mmol/L
TCO2	**14 mmol/L**	**16 mmol/L**	17-25 mmol/L
Base Excess	**-11 mmol/L**	**-12 mmol/L**	[0]-[+6] mmol/L
Anion Gap	12	14	8-25 mmol/L
Leukocytes			
WBC	9.54 K/mcL		6.0-17.0 K/mcL
NEUT	6.79 K/mcL		3.0-11.8 K/mcL
LYMPH	1.94 K/mcL		1.0-4.8 K/mcL
MONO	0.37 K/mcL		0.2-2.0 K/mcL
EOS	0.42 K/mcL		0.1-1.3 K/mcL
BASO	0.01 K/mcL		0.0-0.5 K/mcL
NRBC	0.0		RARE
NEUT (%)	71.17		60.0-80.0
LYMPH (%)	20.34		12.0-30.0
MONO (%)	3.90		3.0-14.0

Table 1. (continued)

EOS (%)	4.44		2.0-10.0
BASO (%)	0.15		0.0-2.5
Erythrocytes			
NRBC			
RBC	7.66 M/mcL		5.50-8.50 M/mcL
Hb	16.9 g/dl		12.0-18.0 g/dl
MCV	66.6 fL		60.0-74.0 fL
MCH	22.1 pg		19.5-24.5 pg
MCHC	33.1 g/dl		31.0-36.0 g/dl
RDW (%)	15.5		12.0-18.0 %
Thrombocytes			
PLT	**179,000 K/mcL**		200-500,000 K/mcL
MPV	17.8 fL		5.0-15.0 fL
Coagulation			
PT	16 seconds	**18 seconds**	12-17 seconds
PTT	93 seconds	**115 seconds**	71-102 seconds
PCV/TP	50 %/6.9 g/dl	35 %/4.0 g/dl	35-50%/ 6.0-8.0 g/dl
Blood Smear	Severe (>90%)		No echinoccytosis

famotidine[k] (0.5 mg/kg) was administered intravenously. An injection of diphenhydramine[l] (2 mg/kg) was given intramuscularly and 5 mg of dexamethasone sodium phosphate[m] (0.15 mg/kg) was given intravenously. In addition to medications, the dog received an intravenous bolus of hetastarch (5 mg/kg) and lactated ringer's solution (22 ml/kg) simultaneously into each catheter. Circumferential measurement of the dog's facial swelling (taken under the chin, around the face, in front of the ears) was performed with a tape measure. His initial measurement was 68.6 cm.

At this point, lateral and ventrodorsal thoracic radiographs, and a lateral abdominal radiograph were performed to screen this dog for gross concurrent disease. The studies were normal (see Figure 1a-1c). A 6 lead electrocardiogram was also performed, and showed a normal sinus arrhythmia (see Figure 2).

Antivenom[c] therapy was instituted 1 hour after presentation. Antivenom was reconstituted in 10 milliliters of sterile water and swirled until the powder was dissolved (about 20 minutes). It was then diluted in 250 ml of 0.9% sodium chloride solution and administered slowly (1 ml/minute) for the first 10 minutes. No reaction was noted, so the remaining dose was given over four hours.[e] The protocol was repeated for a total of 3 doses in the first 12 hours of hospitalization, given 3 hours apart. His face decreased to 63.5 cm after 5 hours, and then to 62.2 cm 7 hours later.

Figure 1.

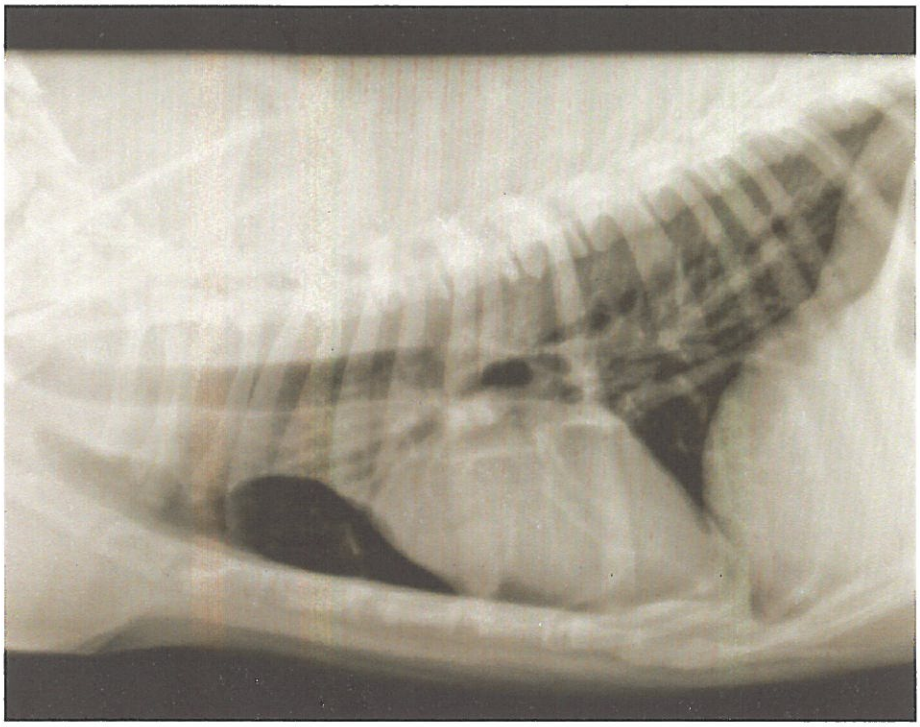


Figure 1a. Right lateral thoracic radiograph

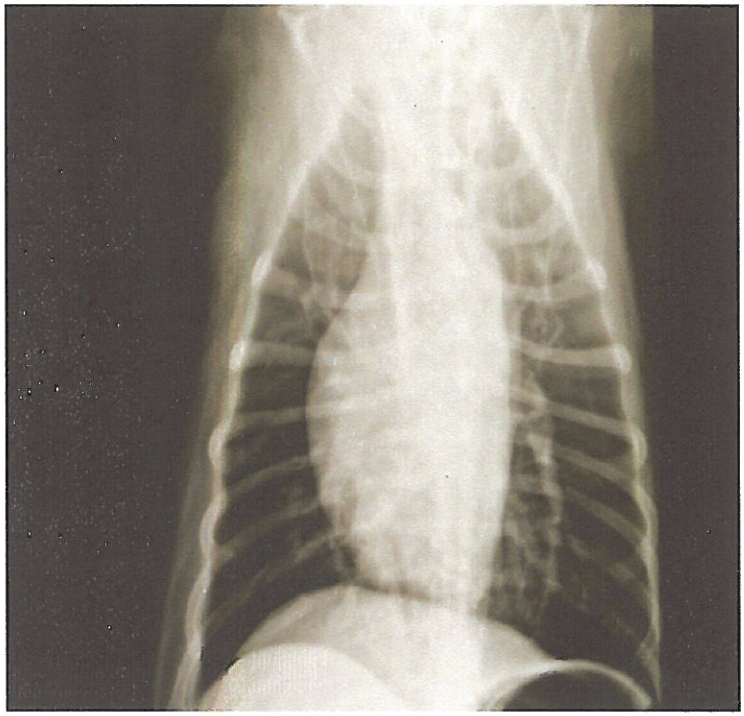


Figure 1b. Ventrodorsal thoracic radiograph

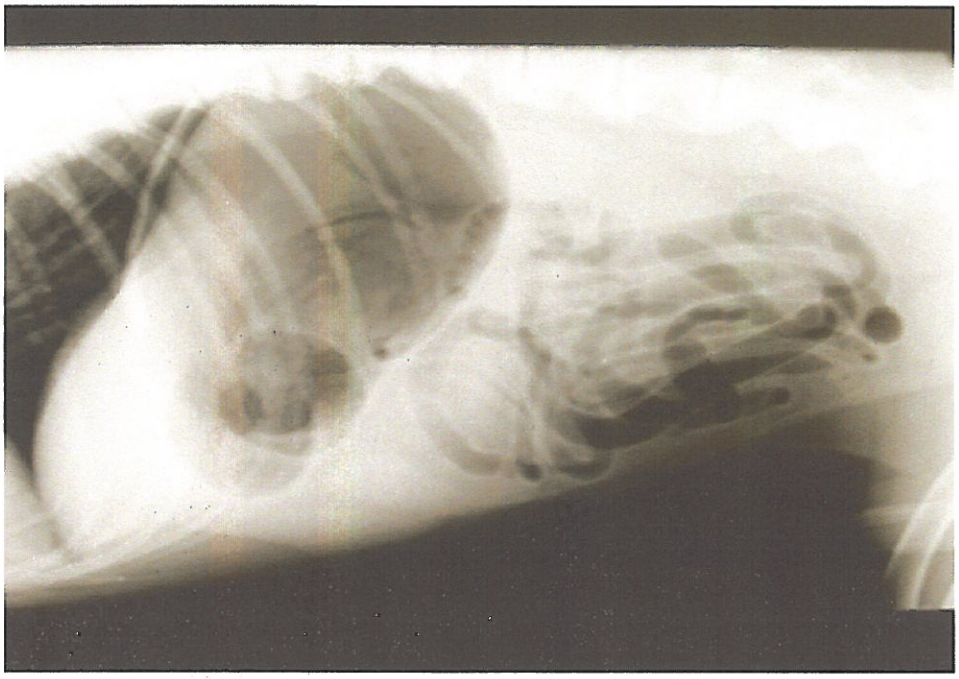
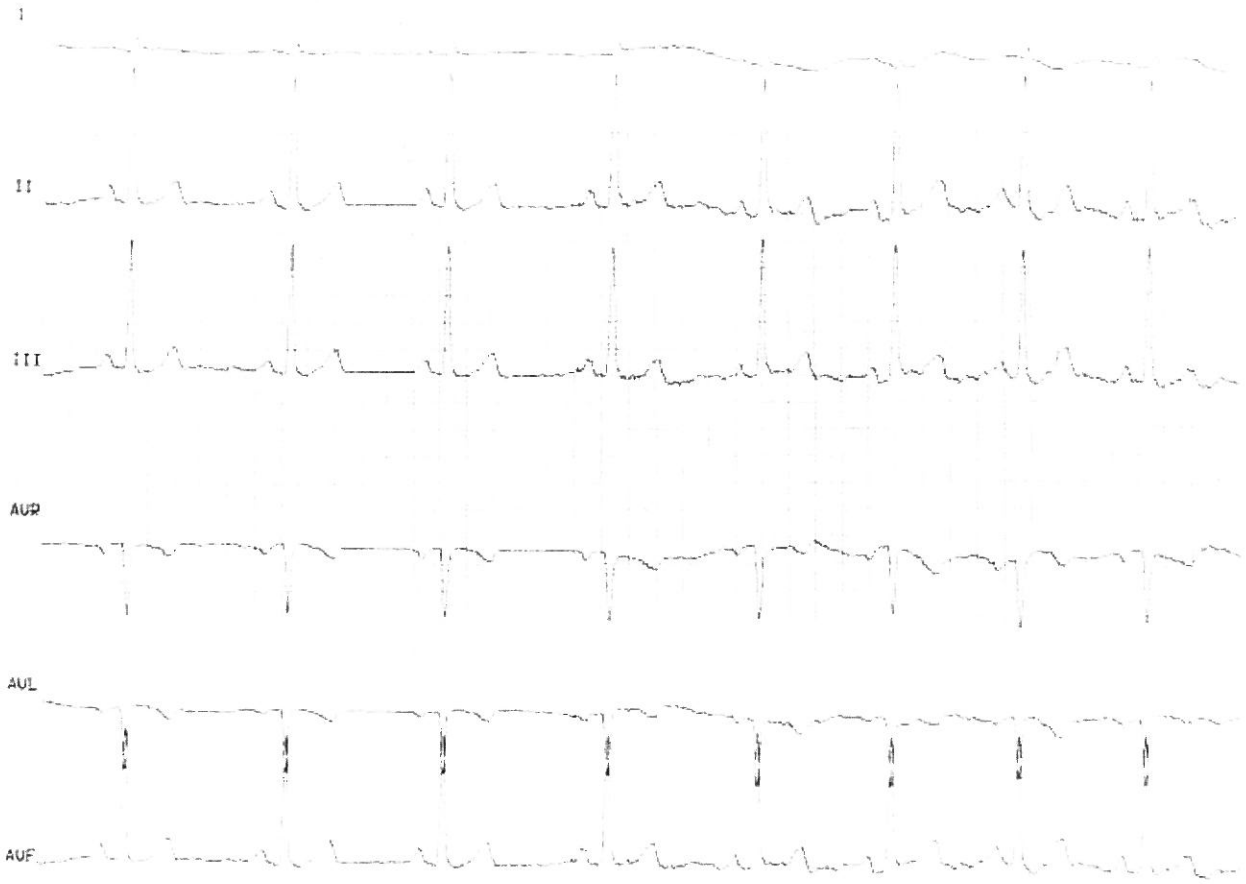


Figure 1c. Right lateral abdominal radiograph

Figure 2. Normal Electrocardiogram



After the dog was stabilized, lactated ringer's solution was administered as a constant rate infusion (CRI). His maintenance dose was 60 ml/kg/day. His rate was doubled for 9 hours (120 ml/kg/day) to correct his initial hypovolemia, and the rates were adjusted throughout his stay based upon his physical and biochemical reassessments. A low dose of hetastarch was also given as a CRI (10 ml/kg/day), to assist with oncotic support without affecting negative feedback mechanisms for protein production by the liver. Intravenous cefazolin[n] (22 mg/kg) was given every 8 hours due to the dramatic facial swelling and suspected tissue damage. After 5 hours of hospitalization, the dog was given a fentanyl[o] bolus (3 micrograms/kg) and then placed on a fentanyl CRI (3 mcg/kg/hr) due to agitation, vocalization, and restlessness.

An indwelling Foley 8 French catheter was placed into the urethra in order to quantify urine production. After initial placement of the urinary catheter, 215 ml of brown-colored urine was evacuated. The dog had received approximately 3295 ml of fluids since admission, or his blood volume multiplied by a factor of 1.14. Blood volume was estimated by multiplying his body weight in kilograms by 90 ml. This fluid load was considered acceptable since the dog's perfusion parameters improved after his initial fluid boluses. Due to concern that urine output was insufficient, the dog was given one dose of furosemide[p] (2 mg/kg) intravenously, and ongoing urine output was then monitored closely.

Biochemical parameters were reassessed 12 hours later. Another sample for a packed cell volume and total solids, PT and PTT, and venous blood gas was obtained (see Table 1). He was anemic, and his PT and PTT were slightly prolonged. His venous blood gas showed an ongoing metabolic acidosis with marked base excess, and a lower pH. His anion gap was still

normal. A nurse checked his perfusion parameters (pulse rate and quality, mucous membrane color, capillary refill time, temperature/pulse/respiration, attitude, and blood pressure) hourly. He was agitated, but his heart rate had begun to decrease to an average of approximately 100 bpm, his temperature decreased to 37.2 deg C 99°F, and he continued to pant. His mucous membranes were pink and his capillary refill time was less than 2 seconds. His pulse quality was improved and his blood pressure was monitored every 4 hours. The average blood pressure was 113 mmHg (ranging from 88-140 mmHg). His crystalloid fluid rate was decreased to 1.5 times (90 ml/kg/day) his maintenance dose.

The dog's facial swelling appeared worse after 12 hours, but measurements were not obtained due to the patient's temperament. He was given a fourth vial of antivenom per protocol. Another 100 mcg bolus of fentanyl was given, and his CRI was increased to 4 mcg/kg/hr. Two hours later, he was still restless and vocalizing, so he was switched to a different analgesic mixture containing fentanyl (4.98 mcg/kg/hr) combined with lidocaine[q] (1500 mcg/kg/hr) and ketamine[r] (120 mcg/kg/hr). He was then able to sleep comfortably with no vocalizing or agitation and his pulse quality and rate was excellent (88-94 bpm), but his oral cavity could no longer be evaluated due to swelling. When he was able to lick small (3-5 ml) portions of A/D diet (Hills® Prescription Diet), his scantly bleeding gumline was visible. Urine output increased 2 hours after the furosemide injection to approximately 300 ml/ hr.

Throughout the dog's hospital stay, standard methods of nursing care included hourly vital parameters, intermittent blood pressure measurements, warm compresses to the face every 4 hours, facial measurements every 1 to 5 hours, hand feeding every 6 hours, body turns to

opposite recumbencies every 6 hours, and an hourly "seizure" watch. The nurses were instructed to give 15 mg of diazepam should any involuntary twitching, muscle fasciculations, or convulsive events occur. In addition, doctor assessments occurred every 4-6 hours.

On the second day, the dog seemed to be comfortable. He was assessed as hydrated based upon his skin turgor and tackiness of his mucous membranes. A photograph of his face is shown in Figure 3. There was serosanguinous discharge coming from his oral cavity. Periocular swelling seemed diminished as his eyeballs were visible, and his facial circumference was 58.4 cm. He was able to ambulate with sling-support. The patient was given crystalloid fluids (60 ml/kg/day) with 16 mEQ of potassium chloride added per liter. He was given famotidine, diphenhydramine, and cefazolin at the previously described doses and intervals. His hetastarch and fentanyl/ lidocaine/ ketamine CRI were continued. Urine output averaged approximately 95 ml/hr, which was considered sufficient because it was between his basal rate of urine production (2 ml/kg/day) and his rate of fluid administration. In-house laboratory testing included: a blood smear to quantify echinocytes, a venous blood gas, a packed cell volume and total solids, a PT/PTT, a urine specific gravity, and a serum albumin. Results are listed in Table 2. He was hypoalbuminemic and anemic. He had severe thrombocytopenia, but his clotting times and echinocytosis had improved. His venous blood gas was similar to the previous day.

After 12 hours on the second day, the technical staff was unable to obtain blood other than a packed cell volume and total solids from a peripheral vein due to the development of severe pitting edema. Since his packed cell volume was decreasing, he was hypoalbuminemic, and at risk for developing DIC, he was given fresh frozen plasma from a DEA 1.1 negative

Figure 3. Photograph of the 12-year-old male castrasted Siberian husky 24 hours post rattlesnake bite to the face.

Table 2. In-House Blood Results During the Second Day of Hospitalization (5/16/07)

Test	Laboratory Value (8 am)	Laboratory Value (8 pm)	Normal Reference
Serum Chemistry			
ALB	**1.3 g/dl**		2.2-3.9 g/dl
Electrolytes			
Sodium	148 mmol/L		142-150 mmol/L
Potassium	3.6 mmol/L		3.4-4.9 mmol/L
Chloride	121 mmol/L		106-127 mmol/L
Blood Gas			
Hematocrit %	**28**		35-50
Ph	7.400		7.35-7.45
PCO2	**22.0 mmHg**		34-40 mmHg
HCO3	**13.6 mmol/L**		20-24 mmol/L
TCO2	**14.0 mmol/L**		17-25 mmol/L
Base Excess	**-11 mmol/L**		[0]-[+6] mmol/L
Anion Gap	16 mmol/L		8-25 mmol/L
Coagulation			
PT	16 seconds		12-17 seconds
PTT	**105 seconds**		71-102 seconds
PCV/TP	**32 %/4.4 g/dl**	**24 %/4.4 g/dl**	35-50%/ 6.0-8.0 g/dl
Urine SG	1.020	1.018	1.017-1.045
Blood Smear	Mod (60%)		No echinocytosis

donor at a total dose of 15 ml/kg given over 4 hours. His hetastarch and lactated ringer's solution were discontinued during this transfusion.

On the third day, the dog was febrile at 103.2°F. (39.6 deg C) His pulse rate and respiratory parameters were considered within normal limits, although his chest excursions were rapid and shallow. He seemed mentally dull and no longer responded to handling. In-house laboratory analysis included a PT/PTT, a packed cell volume and total solids, a venous blood gas, a blood smear for echinocytes, a urine specific gravity, and a serum albumin (Table 3). These results showed that he was more anemic with a mild lymphocytosis and monocytosis, likely due to necrosis and inflammation. His albumin continued to decrease. His blood gas was unchanged. An expanded serum chemistry and complete blood count, as well as a urinalysis and a full coagulation panel was sent to an outside laboratory.[s] His crystalloids, hetastarch, and cefazolin were continued, and was switched to a medetomidine[t] CRI at 1 ml/hr (1 mcg/kg/hr) because he was restless again. His eyes were not visible due to swelling. His antibiotic was switched to ticarcillin (50 mg/kg) to be given every 8 hours. Urine output was approximately 74 ml/hr. The medetomidine CRI afforded him sleep and he was clearly less anxious.

At that point, the patient seemed to be doing poorly overall, and was worsening despite aggressive supportive care. His face felt firmer and the skin was darkening around the puncture wounds. His owner visited and chose euthanasia due to his guarded prognosis, poor daily quality of life during treatment, and the likelihood of future surgical debridement of his face. His body was taken for burial.

Table 3. In-House Blood Results During the Third Day of Hospitalization (5/17/07)

Test	Laboratory Value (8 am)	Normal Reference
Serum Chemistry		
ALB	**1.5 g/dl**	2.2-3.9 g/dl
Electrolytes		
Sodium	149 mmol/L	142-150 mmol/L
Potassium	**3.2 mmol/L**	3.4-4.9 mmol/L
Chloride	124 mmol/L	106-127 mmol/L
Blood Gas		
Hematocrit	**16 %**	35-50 %
Ph	7.377	7.35-7.45
PCO2	25.1 mmHg	34-40 mmHg
HCO3	14.7 mmol/L	20-24 mmol/L
TCO2	15 mmol/L	17-25 mmol/L
Base Excess	**-10 mmol/L**	[0]-[+6] mmol/L
Anion Gap	14 mmol/L	8-25 mmol/L
Coagulation		
PT	14 seconds	12-17 seconds
PTT	105 seconds	71-102 seconds
PCV/TP	**20%/5.6 g/dl**	35-50 %/6.0-8.0 g/dl
Urine SG	1.012	1.017-1.045
Blood Smear	No echinocytes	No echinocytosis
Leukocytes		
WBC	15.96 K/mcL	6.0-17.0 K/mcL
NEUT	5.30 K/mcL	3.0-11.8 K/mcL
LYMPH	**6.91 K/mcL**	1.0-4.8 K/mcL
MONO	**3.70 K/mcL**	0.2-2.0 K/mcL
EOS	0.04 K/mcL	0.1-1.3 K/mcL
BASO	0.00 K/mcL	0.0-0.5 K/mcL
NEUT (%)	**33.20**	60.0-80.0
LYMPH (%)	**43.31**	12.0-30.0
MONO (%)	**23.21**	3.0-14.0
EOS (%)	0.28	2.0-10.0
BASO (%)	0.15	0.0-2.5
Erythrocytes		
NRBC	0	Rare
RBC	3.09 M/mcL	5.50-8.50 M/mcL
Hb	6.4 g/dl	12.0-18.0 g/dl
MCV	63.4 fL	60.0-74.0 fL

Table 3. (continued)

MCH	20.7 pg	19.5-24.5 pg
MCHC	32.7 g/dl	31.0-36.0 g/dl
RDW (%)	14.8	12.0-18.0 %
Thrombocytes		
PLT	**27,000**	200-500,000 K/mcL
MPV	16.8 fL	5.0-15.0 fL

The results of his outside laboratory analyses returned the following day and are reflected in Table 4. Abnormalities of interest on the chemistry profile included the following: moderately elevated ALT and AST, slight hyperbilirubinemia, severe hypoalbuminemia, hypokalemia, hyperchloremia, and hypomagnesemia; and a remarkably high CPK. Differentials for these changes included ongoing muscle and tissue damage, vasculitis, whole body deficits of electrolytes from renal excretion, renal or intestinal loss of protein and electrolytes, hemolysis of the sample, red blood cell damage, and/ or hepatic injury. A less likely possibility for the electrolyte derangements could have been early renal insufficiency. The hemogram showed a marked anemia without evidence of regeneration, a mature neutrophilia, and a slight monocytosis and basophilia. His platelet count was worse. His clotting times were normal but his fibrinogen and D-Dimer levels were elevated. His urinalysis was unremarkable other than gross hematuria.

Discussion

This 12-year-old male castrated Siberian husky is an excellent example of the challenges posed when treating severe symptoms of rattlesnake envenomation in dogs. The exact species of rattlesnake that bit this dog was not identified, but the owner described the snake and rattle. Even though a *snakebite severity score* has not been established for canines, it is reasonable to assume that the dog featured in this report would clearly be defined as "severely envenomated" as judged by his extensive local wounds, hypovolemic shock at presentation, echinocytosis, and thrombocytopenia. Therefore, it was assumed that potent venom was delivered by either a timber rattlesnake or an eastern diamondback.

Table 4. Outside Laboratory Analysis of Blood and Urine (5/17/07)

Test	Laboratory Value	Reference Range
Serum Chemistry		
Glucose	124 mg/dl	70-138 mg/dl
Urea Nitrogen	12 mg/dl	6-25 mg/dl
Creatinine	0.6 mg/dl	0.5-1.6 mg/dl
Total Protein	**3.8 g/dl**	5.0-7.4 g/dl
Albumin	**1.6 g/dl**	2.7-4.4 g/dl
Total Bilirubin	**0.4 mg/dl**	0.1-0.3 mg/dl
ALP	99 U/L	5-131 U/L
*ALT (SGPT)	**134 U/L**	12-118 U/L
*AST (SGOT)	**511 U/L**	15-66 U/L
Cholesterol	149 mg/dl	92-324 mg/dl
Calcium	**7.3 mg/dl**	8.9-11.4 mg/dl
Phosphorus	3.8 mg/dl	2.5-6.0 mg/dl
Sodium	151 mEq/L	139-154 mEq/L
Potassium	**3.4 mEq/L**	3.6-5.5 mEq/L
Chloride	**124 mEq/L**	102-120 mEq/L
Albumin/Globulin	**0.7**	0.8-2.0 RATIO
BUN/Creatinine	20	4-27 RATIO
Globulin	2.2 g/dl	1.6-3.6 g/dl
Lipase	199 U/L	77-695 U/L
Amylase	405 U/L	290-1125 U/L
Triglycerides	113 mg/dl	29-291 mg/dl
CPK	**14,292 U/L**	59-895 U/L
GGTP	<5 U/L	1-12 U/L
Magnesium	**0.8 mEq/L**	1.5-2.5 mEq/L
Corrected Calcium	9.2	
Carbon Dioxide	16 mEq/L	15-25 mEq/L
Anion Gap	14 mEq/L	8-25 mEq/L
CBC		
Hb	**6.2 g/dl**	12.1-20.3 g/dl
HCT	**17.8 %**	36-60 %
WBC	**15.7 x 10^3/mcL**	4.0-15.5 x 10^3/mcL
RBC	**2.54 x 10^6/mcL**	4.8-9.3 x 10^6/mcL
MCV	70 fl	58-79 fl
MCH	24.4 pg	19-28 pg
MCHC	34.8 g/dl	30-38 g/dl
*Platelet Count	**7 x 10^3/mcL**	170-400 x 10^3/mcL
Platelet Estimate	**Decreased**	Adequate
****Differential***		
Neut Absolute	**13,659**	2060-10600

Table 4. (continued)

Bands	0	0-300
Lymphocytes	**628**	690-4500
Monocytes	785	0-840
Eosinophils	471	0-1200
Basophils	**157**	0-150
Reticulocytes	0.9%	0-1 %
Absolute Retics	22,860	<60,000
Corrected Retics	0.3	
Coagulation Profile		
PT	10.2 seconds	6-12 seconds
PTT	14.2 seconds	10-25 seconds
Fibrinogen	**408 mg/dl**	150-400 mg/dl
D-Dimer	**500-1000 ng/ml**	<250 ng/ml
Urinalysis		
pH	7.0	5.5-7.0
Specific Gravity	1.012	1.015-1.050
Appearance	Clear	Clear
Color	Yellow	
Protein	Neg	Neg
Glucose	Neg	Neg
Ketone	Neg	Neg
Bilirubin	1+	Neg to 1+
Blood	**3+**	Neg
WBC	0-3/ HPF	0-3/ HPF
RBC	**4-10/ HPF**	0-3/ HPF
Bacteria	None/ HPF	None/ HPF
Epithelia	Few/ HPF	None-Few/ HPF
Renal Epithelia Cells	None/ HPF	None-Rare/ HPF
Transitional Epithelia Cells	None/ HPF	None-Rare/ HPF
Triple Phosphate Crystals	None/ HPF	None/ HPF
Amorphous Phosphates	None/ HPF	None/ HPF
Calcium Phosphate Crystals	None/ HPF	None/ HPF
Calcium Carbonate Crystals	None/ HPF	None/ HPF
Ammonium Biurate Crystals	None/ HPF	None/ HPF

Table 4. (continued)

Amorphous Urate Crystals	None/ HPF	None/ HPF
Calcium Oxalate Crystals	None/ HPF	None/ HPF
Uric Acid Crystals	None/ HPF	None/ HPF
Mucous	0 Strands/ HPF	0-2+ Strands/ HPF
Hyaline Casts	0/ LPF	0-3/LPF
Granular Casts	0/ LPF	LPF
RBC Casts	None Seen	LPF
Waxy Casts	None Seen	LPF
WBC Casts	None Seen	LPF
Budding Yeast	None	None/ HPF
Oval Fat Body	None	None/ HPF

**Notes from Antech: fibrin clots, hemolysis 1+ noted in samples. This may affect absolute platelet numbers and increase ALT by 15-20% and AST by 10%.*

***Howell-Jolly Bodies, slight hypochromasia, slight anisocytosis, and slight polychromasia were noted on the differential blood evaluation. No spherocytes, echinocytes, or blood parasites were seen.*

During the 72 hours of his hospitalization, this dog suffered from pain, swelling, and the development of necrosis, vasculitis and loss of albumin, anemia, and thrombocytopenia. His temperament during hospitalization added to the challenge, as his level of anxiety was not only difficult to control, but was distressing for his owners to observe. In humans, the most common reaction to snakebite envenomation is terror; disorientation is also possible.[2,3,8] This patient was aware of his environment and even wagged his tail when his owners were visiting, so it seemed more likely that he was anxious from hospitalization or pain rather than from a toxin. His mental dullness on the last day was more likely due to his worsening clinical state, rather than delayed effects of a toxin. Another differential for his mental change was cerebral damage from hypoxia secondary to blood loss or hemolysis. The analgesic protocol for this patient ultimately did require a drug that could also control anxiety, and the case illustrates that careful monitoring of a severe envenomation should include a pain score assessment and routine evaluations of mentation.

The famotidine, dexamethasone sodium phosphate, and diphenhydramine were given to this patient in an attempt to prevent any ongoing gastric upset, pain, or swelling because the onset of his clinical signs was so rapid. There are no studies in the veterinary or human literature that show significant improvements in morbidity or mortality with the use of these medications, however, the potential risk of side effects seemed low enough to warrant their use. Arguments against the use of these drugs may include higher costs due to repeated injections, potential for sedation and/or hypotension with diphenhydramine, potential for gastrointestinal irritation or ulceration as well as electrolyte and fluid shifts with steroids, and gastrointestinal irritation associated with famotidine. None of these side effects was observed in this dog.

The use of antibiotics in this dog could also be questioned. Although most rattlesnake bites are not associated with abscessation,[25] the dramatic loss of integrity in this patient's face, as well as ongoing changes in the character of the tissue (firmness, color), raised concern that concurrent infection may have been possible. On the third day, the dog's wounds had begun to harden and darken, and he developed a slightly elevated temperature and was more depressed. His antibiotic was switched to ticarcillin to improve anaerobic coverage and to protect against *Pseudomonas spp.* in the event that he was becoming septic. His depression and worsened clinical state may have been due to inflammation, weakness associated with his anemia, or pain from his wounds and/or peripheral edema. It was not possible to aspirate or lance his wounds to check for exudates without deep sedation or general anesthesia on this dog, which did not seem appropriate given the unstable nature of the case. Unfortunately, there is not enough information in the veterinary literature to justify not giving antibiotics to an animal with this degree of trauma after a snakebite.

This dog was given fresh frozen plasma on the second day because there was concern that his decreasing packed cell volume and platelet count may have been associated with DIC. It is unclear whether or not plasma may have caused this animal to decompensate; on the contrary, the plasma did not seem to provide any effect at all. He did not have changes in his PT and PTT the morning of his transfusion, but these values could not be assessed again that night due to technical difficulties with phlebotomy. The clotting times were normal on his final coagulation profile that was sent out. The use of plasma may have helped with oncotic support and albumin replacement, but the product was not enough to achieve either of these goals on its own. More

controlled studies on the use of fresh frozen plasma in animals bitten by timber rattlesnakes would be necessary to determine if it is truly harmful or beneficial.

The dog's final coagulation profile showed that he had high levels of fibrinogen consistent with a defibrinating coagulopathy; as well as an extremely low number of platelets, and normal clotting times. He had a high D-dimer level, however, which may indicate that he was in the early stages of DIC. D-dimer is a test for protein fragments that are formed from the degradation of cross-linked fibrin. Since fibrin is not properly cross-linked in patients with fibrinolytic or fibrinogen-clotting components of snake venom, D-dimer concentrations are typically low.[1]

A source for his low red blood cell count was never found. It was unclear if he was becoming anemic secondary to blood loss into his wounds, body cavities, or into the gastrointestinal or urogenital tract, even though he did not have bloody discharge from his rectum or penis and his digital rectal exams were normal. The only sign of active bleeding in this dog was scant hemorrhage from his gumline and mild hematuria. The hematuria may have actually been myoglobinuria, but this was not investigated. It is possible that he was experiencing some degree of hemolysis, although no spherocytes were detected on his complete blood counts. Bone marrow effects of snake venom were not noted in the literature, and it was not possible to know if he had bone marrow insufficiency, as there was not enough time for regeneration before he died.

The dog also had a low albumin. It was assumed that this was from a vasculitis causing protein loss to the interstitium, but a dilutional effect on both his packed cell volume and albumin is possible. Concurrent blood loss seems more likely. Other remarkable changes in his bloodwork included increased liver enzymes, which could have been due to hepatic injury secondary to shock, toxins, or antivenom, or perhaps partially induced by steroid administration. He had a dramatic elevation in his creatine kinase, likely secondary to massive rhabdomyelysis associated with either the snake venom or with muscle necrosis. His hemogram showed a mild neutrophilia with a monocytosis and lymphocytosis, which is consistent with inflammation and is supported by other dogs represented in the literature.[1]

During the first 24 hours of this patient's hospitalization, there was some concern that he may have had oliguric renal failure because he had not produced any urine in his cage. After catheterization, it was clear that he was not making adequate amounts of urine, but a urine specific gravity to assess renal concentrating ability was not measured at this time, and he was severely hypovolemic at presentation. Although the single dose of furosemide was likely not harmful, it probably was not necessary. The patient did begin to produce adequate amounts of urine from that point forward, and was never azotemic.

Venous blood gas testing was used to evaluate metabolic status and early indications of renal failure in this dog. His tests showed that he had a metabolic acidosis defined by a loss of bicarbonate and a normal anion gap. A lactic acidosis was suspected based upon his degree of tissue damage, but in-house testing did not allow for the measurement of lactate. Typically, lactic acidosis causes an elevated anion gap. In this case, concurrent

hypoalbuminemia may have affected the anion gap by decreasing the concentration of net negative charge.

Antivenom administration in this dog was taxing. Since severe envenomations are uncommon in Bergen County, a rush to find adequate amounts antivenin at local human hospitals caused a disturbance in the flow of treatment, and contributed to the overall cost of hospitalization. The "end-points" of antivenom treatment were unclear since dosing is purely anecdotal in dogs. Also, even though an established protocol for reconstitution of the drug is on the label, a protocol for administration has not been established in dogs. The protocol used in this case came from discussions between critical care specialists across the United States. Ultimately, this dog seemed to suffer from his vasculitis, necrosis, and potentially DIC. These complications of rattlesnake bites are not prevented with antivenom treatment, so administering more vials in this case may not have made a difference.

Summary

A 12-year-old male castrated Siberian husky presented one hour after being bitten by a rattlesnake in Bergen County, New Jersey. The dog rapidly suffered from hypovolemic shock and severe swelling around the puncture sites in his face. He was hospitalized for 3 days, whereupon he received repeated doses of antivenom, crystalloid and colloid fluid therapy, fresh frozen plasma, pain medicine, antibiotics, corticosteroids, and antihistamines. Daily assessments included a constant seizure watch, evaluations of packed cell volume and total solids, venous blood gas evaluations, prothrombin and partial thromboplastin times, quantification of echinocytes, and blood pressure evaluations. He also received basic wound care and physical therapy. Despite aggressive supportive care, the patient began to decline and exhibited changes consistent with marked vasculitis and probable necrosis of his face, as well as possible DIC. He was euthanized due to his poor prognosis and quality of life.

Endnotes

[a]New Jersey Department of Parks and Wildlife, personal communication.

[b]Hespan®, Jorgensen Laboratories, Inc., Loveland, CO.

[c]Antivenin [Crotalidae] Polyvalent, Fort Dodge Laboratories, Fort Dodge, Iowa.

[d]FabAV, Protherics, Nashville, TN.

[e]Dr. Yonaira Cortes, Department of Critical Care/ OAH, personal communication.

[f]Red Rocks Biologics, Woodland, CA.

[g]Ultrasonic Doppler Flow Detector, 8.3 MHz Probe, Parks Medical Electronics, Inc., Aloha, OR.

[h]HEMAvet®, HV950FS, Drew Scientific, Oxford, CT.

[i]IDEXX Laboratories, Westbrook, ME.

[j]Canine DEA 1.1 agglutination card, RapidVet-H, dmslaboratories, Flemington, NJ.

[k]Baxter Health Care Corp., Deerfield, IL.

[l]Abraxis Pharmaceutical Products, Schaumburg, IL.

[m]Phoenix Scientific Inc., St. Joseph, MO.

[n]Ranbaxy Pharmaceuticals Inc., Jacksonville, FL.

[o]Hospira, Inc., Lake Forest, IL.

[p]Salix®, Patheon, Inc., Toronto, Ontario.

[q]Phoenix Pharmaceutical Inc., St. Joseph, MO.

[r]Ketaset®, Fort Dodge Animal Health, Fort Dodge, IA.

[s]Antech Diagnostics, Lake Success, NY.

[t]Domitor®, Pfizer Animal Health, Exton, PA.

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