Rattlesnake Envenomation

Laura Najman, DVM, DACVECC
Ravi Seshadri, DVM, DACVECC, DAVBP
Advanced Critical Care and Internal Medicine
Tustin, California

**ABSTRACT:** Snake envenomation has been widely reported throughout the human and veterinary literature. The effects of venom include coagulation disorders, neurotoxicity, and tissue effects, such as local swelling and necrosis. Significant progress has been made in understanding the pathophysiology of envenomation, leading to changes in treatment protocols. Recent developments include the production of a new antivenin and a canine rattlesnake vaccine.

Over 120 species of snakes are native to the United States. Of these species, 20 are considered venomous. Human snakebites are most often reported in the southeastern, southwestern, and south central United States. Most bites reportedly occur in the warmer months (i.e., April through September) when snakes are active. North American venomous snakes can be divided into two families: Crotalidae and Elapidae.

In the United States, most reported envenomations in animals and humans are due to Crotalidae (pit vipers; Table 1), including rattlesnakes, copperheads, and cottonmouths (water moccasins). The eastern and western diamondback rattlesnakes (*Crotalus adamanteus* and *Crotalus atrox*, respectively) are responsible for most of the morbidity and mortality from snake envenomation because of their widespread geographic distribution and relatively potent venom. Copperhead snakes have the least potent venom, and their bites rarely require antivenin therapy. Elapidae (i.e., coral snakes) are an infrequent cause of envenomation: they are involved in less than 25 reported cases of venomous snakebites in people each year. Their venom contains a potent neurotoxin that has been previously described in the veterinary literature. This article focuses on Crotalidae envenomation.

Crotalidae are known as pit vipers because they have heat-sensing pits that allow them to locate prey and determine the direction of strike. Three genera of crotalids (i.e., *Crotalus*, *Sistrurus*, and *Agkistrodon* spp) inhabit the United States. Both *Crotalus* and *Sistrurus* spp have rattles.

**ENVENOMATION AND VENOM COMPOSITION**

Twenty percent to 25% of rattlesnake bites are dry: they penetrate the skin without resulting in envenomation. One study that surgically implanted transonic probes to directly measure venom release in western rattlesnakes reported the incidence of dry bites to be as high as 35%. This number may be falsely elevated because the flow probe was implanted in only one of the two fangs.

Crotalid venom consists of 90% water, numerous enzymes, and peptides. Proteins range in size from six to 100 kD. Specific components vary among species and even between different geographic subgroups of the same species, resulting in varied effects of envenomation. Many of these proteins have enzymatic...
Table 1. North American Crotalids

<table>
<thead>
<tr>
<th>Scientific Name</th>
<th>Common Name</th>
<th>Geographic Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agkistrodon contortrix</td>
<td>Copperhead</td>
<td>United States</td>
</tr>
<tr>
<td>Agkistrodon piscivorus</td>
<td>Cottonmouth</td>
<td>United States</td>
</tr>
<tr>
<td>Crotalus adamanteus</td>
<td>Eastern diamondback rattlesnake</td>
<td>United States</td>
</tr>
<tr>
<td>Crotalus atrox</td>
<td>Western diamondback rattlesnake</td>
<td>United States, Mexico</td>
</tr>
<tr>
<td>Crotalus cerastes</td>
<td>Sidewinder rattlesnake</td>
<td>United States, Mexico</td>
</tr>
<tr>
<td>Crotalus horridus atricaudatus</td>
<td>Canebrake rattlesnake</td>
<td>United States</td>
</tr>
<tr>
<td>Crotalus horridus</td>
<td>Timber rattlesnake</td>
<td>United States</td>
</tr>
<tr>
<td>Crotalus lepidus</td>
<td>Rock rattlesnake</td>
<td>United States</td>
</tr>
<tr>
<td>Crotalus michellii</td>
<td>Speckled rattlesnake</td>
<td>United States, Mexico</td>
</tr>
<tr>
<td>Crotalus molossus</td>
<td>Black-tailed rattlesnake</td>
<td>United States, Mexico</td>
</tr>
<tr>
<td>Crotalus oreganus abyssus</td>
<td>Grand Canyon rattlesnake</td>
<td>United States</td>
</tr>
<tr>
<td>Crotalus oreganus cerberus</td>
<td>Arizona black rattlesnake</td>
<td>United States</td>
</tr>
<tr>
<td>Crotalus oreganus concolor</td>
<td>Midget faded rattlesnake</td>
<td>United States</td>
</tr>
<tr>
<td>Crotalus oreganus kentleri</td>
<td>Southern Pacific rattlesnake</td>
<td>United States, Mexico</td>
</tr>
<tr>
<td>Crotalus oreganus lutosus</td>
<td>Great Basin rattlesnake</td>
<td>United States</td>
</tr>
<tr>
<td>Crotalus oreganus nuntius</td>
<td>Hopi rattlesnake</td>
<td>United States</td>
</tr>
<tr>
<td>Crotalus oreganus oreganus</td>
<td>North Pacific rattlesnake</td>
<td>United States, Canada</td>
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<tr>
<td>Crotalus pricei</td>
<td>Twin-spotted rattlesnake</td>
<td>United States, Mexico</td>
</tr>
<tr>
<td>Crotalus ruber</td>
<td>Red diamond rattlesnake</td>
<td>United States, Mexico</td>
</tr>
<tr>
<td>Crotalus scutulatus</td>
<td>Mojave rattlesnake</td>
<td>United States, Mexico</td>
</tr>
<tr>
<td>Crotalus tigris</td>
<td>Tiger rattlesnake</td>
<td>United States, Mexico</td>
</tr>
<tr>
<td>Crotalus viridis viridis</td>
<td>Prairie rattlesnake</td>
<td>United States</td>
</tr>
<tr>
<td>Crotalus willardi</td>
<td>Ridge-nosed rattlesnake</td>
<td>United States, Mexico</td>
</tr>
<tr>
<td>Sistrurus catenatus</td>
<td>Massasauga rattlesnake</td>
<td>United States, Mexico</td>
</tr>
<tr>
<td>Sistrurus miliarius</td>
<td>Pigmy rattlesnake</td>
<td>United States</td>
</tr>
</tbody>
</table>

This is a partial list.

Properties, which aid in immobilization, death, and digestion of prey. Hyaluronidase and collagenase aid in spreading venom through interstitial spaces, proteases are known to lead to coagulopathies and necrosis, and phospholipases cause cytotoxic effects that lead to both endothelial cell damage and resultant inflammation.

**PATHOPHYSIOLOGY**

**Tissue Injury**

Crotalid venom increases the permeability of capillary cell membranes, which allows the venom to spread within the prey. Low-molecular-weight polypeptides cause capillary endothelial cell damage, which leads to endothelial cell swelling and rupture. The resultant gaps in the microvasculature allow third spacing of plasma and erythrocytes, leading to both edema and ecchymosis (Figure 1). This process occurs in any capillary exposed to venom, including in the lungs, kidneys, myocardium, peritoneum, and, occasionally, central nervous system. Zinc-based metalloproteinases in venom are directly involved with release of tumor necrosis factor-α, which induces macrophage differen-
tiation, neutrophil degranulation, leukocyte migration, and the release of mediators of inflammation, such as interleukins. This leads to destruction of vascular basement membranes and perivascular extracellular matrices, resulting in increased vascular permeability with possible hypotension, hypovolemic shock, and lactic acidosis.\(^1,2,7\)

Venom can contain myotoxin a, a component that causes an increase in intracellular calcium, leading to necrosis of skeletal muscle.\(^7\) Increased intracellular calcium activates damaging enzymes and the troponin complex, causing myonecrosis and prolonged contraction of muscle fibers.\(^7\)

### Cardiovascular Effects

Most cardiovascular effects are secondary to the increase in vascular permeability and subsequent third spacing of fluids, often leading to hypotension. Hypotension can also occur secondary to fluid losses from vomiting and hemorrhage.\(^7\)

### Coagulopathy

Snake venom has a complex makeup of proteins and enzymes that frequently result in coagulopathy via multiple mechanisms. These components can be categorized as fibrinolytics, fibrinogen-clotting enzymes, procoagulants, anticoagulants, proteins affecting platelet function, and proteins affecting the vessel wall.\(^10\) Spontaneous bleeding rarely occurs, but significant bleeding can be induced with something as simple as a prick of a needle.\(^11\) Snakebite coagulopathy differs from other forms of coagulopathy. Standard treatments, such as transfusions, are often ineffective and even dangerous in cases of envenomation.\(^11\)

**Fibrinolytics, fibrinogen-clotting enzymes, and resulting defibrination**—The most common mechanism of coagulopathy in North American crotalid envenomation is pure defibrination without disseminated intravascular coagulation (DIC), which results in the depletion of fibrinogen and fibrin.\(^7\) Fibrinogen clotting and fibrinolytic snake venom toxins directly affect the thrombus-forming protein fibrinogen.\(^11\) Although an unstable clot may initially form, the end result is an increased bleeding tendency.\(^11\)

Many types of venom (i.e., of Crotalidae and other genera) contain fibrinolysins, which result in the destruction of fibrinogen and fibrin.\(^7\) In addition, fibrinogen-degrading enzymes (i.e., fibrinogenases) are present in Crotalidae venom. These cause degradation of fibrin by both direct and indirect mechanisms.\(^10\) Direct fibrinogenases do not require cofactors and cleave fibrinogen directly, whereas indirect mechanisms involve converting plasminogen to plasmin, which in turn cleaves fibrinogen.\(^10\) In the natural coagulation process, thrombin hydrolyzes the bonds between fibrinopeptides and the α and β portions of the A\(^α\) and B\(^β\) chains of fibrinogen.\(^12\) The site of cleavage by the venom fibrinogenases differs from the natural process, resulting in cleavage of only one pair rather than both pairs of fibrinopeptides.\(^10,12\) Most crotalid venom cleaves fibroprotein A from fibrinogen, which results in a poorly constructed fibrin clot.\(^7,12\) One exception is Mojave rattlesnake (Crotalus scutulatus) venom, which appears to have no hemorrhagic properties.\(^12\)

Fibrinogen-clotting enzymes are likely the most common form of procoagulant in snake venoms. These are often known as thrombin-like enzymes because they act similarly to thrombin, converting fibrinogen to fibrin.\(^10,11\) Thrombin-like enzymes fail to activate factor XIII, which normally cross-links fibrin chains, resulting in a friable clot.\(^7,10\)

The fibrinolysins and the thrombin-like enzymes result in depletion of fibrinogen and fibrin, decreased

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**Figure 1. Tissue effects of rattlesnake envenomation include swelling, edema, and necrosis.**
ability to form intravascular clots, elevated fibrin degradation products (FDPs), and prolonged clotting tests. Patients develop hemorrhagic defibrination coagulopathy. Pure defibrination differs from true DIC in that it does not cause consumption of platelets or factor VIII and cannot be inhibited by heparin. Unlike true DIC, coagulopathies from rattlesnake envenomation have normal antithrombin, factor XIII, and D-dimer levels (Table 2). Also, most of the thrombin-like enzymes are not inhibited by thrombin inhibitors, such as antithrombin. Because of these differences, treatments for standard coagulopathies, such as heparin and transfusions, are ineffective and often harmful. True DIC is rare in rattlesnake envenomation but can occur through activation of the coagulation cascade from vascular endothelial damage caused by the venom or by proteolytic enzymes and inflammatory mediators.

Other procoagulants—Some snake venoms contain other procoagulants. Venom can activate prothrombin by varying mechanisms. Some venom, such as that from the Russell’s viper (Daboia russelii), activates factor X; venom from some other species activates factor V.

Anticoagulants—Anticoagulant properties in some snake venoms include protein C activators, phospholipases, antithromboplastic components, and FDPs. Protein C is a vitamin K–dependent serine protease that serves to degrade coagulation cofactors VIIIa and Va, thus contributing to the regulation of hemostasis. Once activated, protein C acts as an anticoagulant. Protein C activators have been isolated from the copperhead (Agkistrodon contortrix) and closely related species.

Phospholipases in snake venom have various functions, some of which are anticoagulant in nature. Some phospholipases activate or inhibit platelet aggregation, whereas others can bind to or hydrolyze plasma and platelet phospholipids, hindering their activity. Another venom anticoagulant effect is prevention of the formation of the prothrombinase complex (i.e., the interaction of calcium, factor Xa, factor V, and prothrombin with the platelet phospholipid matrix). The high level of circulating FDPs in snake venom can bind thrombin, inhibit fibrin polymerization, and inhibit platelet activation, all of which act as effective anticoagulants.

Platelet function effects—Snake venom has some

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**Table 2. Comparison of Disseminated Intravascular Coagulation with Coagulopathy from Crotalid Venoms**

<table>
<thead>
<tr>
<th>Manifestations/Therapy</th>
<th>Disseminated Intravascular Coagulation</th>
<th>Crotalid Venom-Induced Coagulopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathologic thrombin production and activity</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Pathologic activation of factor XIII by thrombin</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Thrombin production of both fibrinopeptide A and B</td>
<td>Yes</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Production of either fibrinopeptide A or B, but not both</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Production of cross-linked fibrin</td>
<td>Yes</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Production of fibrin degradation (split) products</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Production of D-dimer</td>
<td>Yes</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Antithrombin depletion</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Almost always</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Active bleeding</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Intravascular thrombosis</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Heparin therapy</td>
<td>Possibly helpful</td>
<td>Not helpful</td>
</tr>
<tr>
<td>Crotalid antivenin therapy</td>
<td>Not helpful</td>
<td>Helpful</td>
</tr>
</tbody>
</table>

components that cause platelet aggregation and others that inhibit it. The net effect of venom on hemostasis is an anticoagulative state that is similar to DIC, with some unique properties.

**Thrombocytopenia**

Thrombocytopenia is common after crotalid envenomation in both humans and dogs. The mechanism is not entirely understood, but in most cases, thrombocytopenia resolves in 72 hours, although it can last longer in some patients. Proposed mechanisms that may act in combination include:

- Phospholipases may damage platelet membranes, triggering their destruction.
- The venom may initiate platelet aggregation.
- Platelets may be consumed at the sites of envenomation and associated inflammation.

Thrombocytopenia often improves after antivenin administration. It is important to note that thrombocytopenia induced by venom components should not be interpreted as a sign that DIC is present. Active bleeding rarely results from thrombocytopenia and coagulopathy associated with envenomation.

**Renal Failure**

Acute renal failure occasionally occurs secondary to rattlesnake envenomation, and causes can be multifactorial. The pathogenesis of renal lesions includes hypertonization membrane. Crotalid venom has not been proven to be directly nephrotoxic. Renal failure is most often reported following bites by members of the Viperidae group (i.e., vipers), which are not native to North America.

**Neurotoxicity**

Most neurologic clinical signs are secondary to Elapidae envenomation, but neurologic signs have also been observed secondary to envenomation by the Mojave rattlesnake (*C. scutulatus*), which is found throughout the American Southwest. Geographic differences exist in the potency of neurotoxin delivered by envenomation within the same species. Clinical signs include weakness and paralysis secondary to noncompetitive calcium channel blockade in presynaptic neurons that prevents the release of acetylcholine at the motor endplate.

**DIAGNOSIS**

The diagnosis of rattlesnake envenomation is often based on both history (i.e., location of the attack and time of day) and clinical signs. Most puncture wounds are found on the head and neck or, less frequently, on an extremity. If there has been little or no envenomation, clinical signs will consist of minimal swelling and a lack of systemic signs. With moderate to severe envenomation, immediate and progressive swelling and pain are noted. Local signs usually start within 30 to 60 minutes after envenomation. Ecchymosis at the site of the bite occurs within 6 hours. These signs are often followed by tissue necrosis. Systemic signs reported include lethargy, weakness, hypotension, hyperthermia, arrhythmias (e.g., ventricular tachycardia, ventricular premature contractions, ventricular fibrillation), ataxia, bleeding, vomiting, diarrhea, respiratory distress, and shock. In humans, three systems are used to measure the degree of envenomation and progression:

- The minimal–moderate–severe scoring method
- The grade 0 through IV scoring method
- The snakebite severity score
To date, there is no established method in veterinary medicine to measure the degree of envenomation.

Laboratory abnormalities following envenomation include echinocytosis, thrombocytopenia, anemia or mild hemoconcentration, hypofibrinogenemia, elevated fibrin split products, leukocytosis, and prolonged clotting times. Serial blood testing should be conducted because the onset of coagulopathies can often be delayed. Chemistry profile changes that occur with rattlesnake envenomation include azoemia, hypoalbuminemia, hypoproteinemia, and elevated levels of creatinine kinase, alanine transaminase, $\gamma$-glutamyl transferase, and aspartate transaminase.

Echinocytosis has been associated with rattlesnake envenomation in humans, cats, and dogs and can be used to aid in the diagnosis. Echinocytes are erythrocytes with uniform, regularly spaced membrane projections (Figure 2). Echinocyte formation is thought to be caused directly by the venom itself, is dose dependent, and is self limiting; morphologic changes resolve within 48 hours.

In one study, canine blood was mixed in vitro with western diamondback rattlesnake venom. The degree of echinocyte formation was proven to be dose dependent, with the lowest doses producing types I and II echinocytes and the highest doses producing type III echinocytes, spherochromeinocytes, and spherocytes. Hemolysis was noted in all samples. Spherocytosis and hemolysis noted after envenomation should be interpreted as signs of severe envenomation rather than as signs of immune-mediated hemolytic anemia. Purified phospholipase A$_2$, a calcium-dependent component of both Crotalidae and Elapidae venom, has induced echinocytosis and hemolysis in vitro and is thought to be the component in venom responsible for these changes in vivo. The mechanism involves incorporation of lysolecithin in the outer erythrocyte membrane, leading to expansions and morphologic changes consistent with echinocytosis and spherocytosis. Two studies have reported the frequency of echinocytosis in snake envenomation to be 89% to 92% in dogs.

**TREATMENT**

The mortality rate of rattlesnake envenomation in dogs has reportedly been as low as 3.7% with treatment. The treatment should initially focus on stabilization of systemic signs and antivenin administration, as needed. A complete physical examination should be performed after standard airway-breathing-circulation assessment and therapeutic intervention. A urinalysis and the following baseline blood work should be conducted: a complete blood count with a direct smear for erythrocyte morphologic analysis and a manual in-house platelet count, a chemistry profile, activated clotting time, prothrombin time, partial thromboplastin time, fibrinogen level, D-dimers, electrolyte levels, and blood gas analysis. An electrocardiogram should be obtained, and thoracic radiography is indicated after the patient has been adequately stabilized.

The area of the puncture should be gently clipped to
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remove fur, lightly cleaned with antiseptic solution, and kept dry (Figure 3). The circumference of the swelling should be measured and recorded every 15 minutes to help determine progression and requirements for antivenin administration. If the wound progresses and local necrosis occurs, the affected area should be treated like an open wound until a healthy granulation bed forms. Surgical debridement may be needed for necrotic tissue after several days. In people, if a puncture is present with no local or systemic signs, at least 12 hours of hospitalized observation is recommended.

**Fluid Therapy**

Because of increased vascular permeability and subsequent third spacing, vomiting, and hemorrhage, many affected patients present with hypovolemia and in shock. Intravenous fluids should be administered at presentation. Administration of either crystalloids or a combination of crystalloids and colloids should be considered. Clinical parameters, such as mucous membrane color and capillary refill time, pulse quality, blood pressure, degree of lactic acidosis, and urine output, can all be used to help guide fluid therapy.

Few studies critically evaluate types of intravenous fluid therapy for snake envenomation. Previously, concern existed that colloids may worsen coagulopathy associated with snake envenomation. In one study, dextran 40 increased coagulopathy associated with snake envenomation in rodents. However, this study did not model most clinical envenomations because the venom was injected intravenously, which rarely occurs clinically, and no antivenin was administered. Both of these factors limit the application of these findings. With the known endothelial damage and the subsequent permeability defects to capillary membranes, colloids appear to be beneficial in maintaining vascular volume and colloid oncotic pressure.

In the past, blood and blood products were recommended to correct coagulopathy associated with rattlesnake envenomation, but this has fallen out of favor. Coagulopathy associated with rattlesnake envenomation is consumptive and unresponsive to either heparin or blood products while unneutralized venom is circulating. Providing coagulation factors and blood products adds substrate for unneutralized venom, which leads to increased FDPs. Current recommendations emphasize neutralization of venom with antivenin.

**Antivenin**

Antivenin administration is recommended for worsening local injury (i.e., ecchymosis, pain, swelling), clinically significant coagulopathy, or systemic signs (e.g., hypotension). The production of antivenin, which began in 1954, contributed to a decrease in human mortality from 25% in the 19th century to less than 0.5% by 2002. Antivenin should ideally be administered within the first 4 hours after envenomation. The benefits of antivenin decrease if administration is delayed, but antivenin can still have clinically positive effects for up to 24 hours after envenomation. When administered early, antivenin binds to the venom itself, subsequently neutralizing it, reversing some clinical manifestations of envenomation, and preventing further progression. Unfortunately, local tissue necrosis cannot be stopped by antivenin administration. Within 20 minutes of envenomation, an irreversible inflammatory cascade begins, leading to tissue necrosis.

Two antivenins are currently available to treat venomous snakebites within the United States. Antivenin (Crotalidae) Polyvalent (ACP; Fort Dodge Animal Health) for animals is reportedly the same as the ACP produced by Wyeth Laboratories for humans. This antivenin can neutralize venom from all North, Central, and South American crotalids. A second, newer antivenin was recently introduced: Crotalidae polyvalent immune Fab (ovine; CroFab, FabAV, Protherics, Nashville, TN) is licensed for use in humans. It is an ovine-derived antivenin that is produced when sheep are inoculated with venom from

Coagulopathy induced by rattlesnake envenomation differs from DIC and should be treated by neutralizing the venom with antivenin.
western and eastern diamondback rattlesnakes, Mojave rattlesnake, and cottonmouth, but it can neutralize venom from many more species.\textsuperscript{33} It is considered five times more potent than ACP\textsuperscript{1} and appears to be effective in treating crotalid-induced neurotoxicity.\textsuperscript{31} Instead of containing the entire IgG molecule, it is pure Fab immunoglobulin and less than 3\% of the Fc fragment.\textsuperscript{32} It has a more rapid reconstitution and thus can be administered earlier to patients.\textsuperscript{33} The smaller size of the Fab molecule allows it to be renally excreted and thus have a more rapid elimination than does ACP.\textsuperscript{34} The half-life of FabAV in humans is less than 12 hours, while the half-life of ACP is 61 to 194 hours.\textsuperscript{35} The faster half-life of the Fab antivenin allows the effects of unneutralized venom to recur. Recurrent coagulopathy and local tissue effects have been documented in patients who received the Fab antivenin after envenomation. This has led to recommendations for repeated dosing for at least 18 hours, if not longer.\textsuperscript{36} Therefore, Fab antivenin has not been financially justifiable in animals at this time. Fab antivenin is more effective than ACP, with fewer cases of both anaphylaxis and serum sickness because it does not contain the immunoglobulin portion that binds to complement.\textsuperscript{35}

ACP is an equine-derived product and is reportedly highly allergenic, with acute signs in humans reportedly as high as 20\%.\textsuperscript{37} Anaphylactic reactions (i.e., type I hypersensitivity), anaphylactoid reactions, and delayed hypersensitivity or serum sickness (i.e., type III hypersensitivity) are potential side effects.\textsuperscript{2} Anaphylactic and anaphylactoid reactions appear identical clinically but differ in their pathogeneses.\textsuperscript{2} Both result in the binding of complement fragments (i.e., C3a, C5a) to mast cells and basophils, resulting in the release of histamine, heparin, serotonin, prostaglandins, leukotrienes, platelet-activating factor, eosinophil chemotactic factor, and other mediators. Anaphylactic reactions are type I hypersensitivity reactions mediated by IgE, with circulating antigen binding to Fc receptors on mast cells and basophils, whereas anaphylactoid reactions do not involve the IgE molecule and are rate and dose dependent.\textsuperscript{2} In anaphylactoid reactions, proteins directly activate the complement cascade and mast cell degranulation rather than indirectly mediate them through IgE.\textsuperscript{2} Clinical signs of both anaphylactic and anaphylactoid reactions include fever, urticaria, pruritus, bradycardia, hypotension, and respiratory distress.\textsuperscript{2} Pretreatment with both H\textsubscript{1} (i.e., diphenhydramine) and H\textsubscript{2} blockers has been recommended before antivenin administration.\textsuperscript{3} There have been no controlled human trials to establish the efficacy of pretreatment.\textsuperscript{1} Once anaphylactic and anaphylactoid reactions occur, they can be treated with histamine blockers, systemic corticosteroids, epinephrine, and slowed or discontinued administration of the antivenin, if indicated.

Skin testing has been recommended before antivenin administration to help predict which patients are predisposed to immediate hypersensitivity reactions. This has been controversial for many reasons. Both false-positive and false-negative skin testing results occur.\textsuperscript{38} False-negative rates have reportedly been as high as 10\% to 36\%, and false-positive rates have reportedly been 33\%.\textsuperscript{3} Skin testing also delays antivenin administration. Delayed hypersensitivity or serum sickness secondary to ACP has been extensively documented in the human literature and recently documented in the veterinary literature. Serum sickness is an immunocomplex disease in which large foreign proteins stimulate the production of antibody and T-cell responses.\textsuperscript{27} Clinical signs (e.g., urticaria, arthralgia, myalgia, fever, malaise, lymphadenopathy, and occasionally vasculitis, glomerulonephritis, and neuritis) usually occur 3 days to 3 weeks after antivenin administration in humans.\textsuperscript{2} The clinical signs commonly have an average onset of 1 week after administration.\textsuperscript{2} Serum sickness is self-limiting, and treatment involves administering a combination of anti-histamines and glucocorticoids.\textsuperscript{27} Plasmapheresis has been used in the most severe cases.\textsuperscript{27}

It is thought that serum sickness secondary to antivenin administration is uncommon in animals because antivenin is administered less frequently and in smaller overall doses to animals compared with administration in humans. A case of canine serum sickness
was recently documented in the veterinary literature. Clinical signs, including fever, anorexia, lethargy, vomiting, and pitting edema, were described in a boxer 3 days after treatment with ACP. The clinical signs resolved with H1- and H2-blocker and corticosteroid administration.

**ACP Administration**

Antivenin should be reconstituted as directed with diluent or sterile water if significant clinical signs are present following envenomation. It should be administered as soon as possible, ideally within the first 4 hours after envenomation. The patient should be closely monitored for urticaria or other signs of allergic reaction. The suggested dose is 10 to 50 ml (i.e., one to five vials) IV, depending on the severity of clinical signs, time since the bite, size of the bite, and size of the patient. Additional doses can be given every 2 hours, as needed. According to the Fort Dodge package insert recommendations, smaller patients may require relatively higher doses. This recommendation is not supported in the human literature. Although the milligram-per-kilogram dose of venom administered is higher in smaller patients, the overall molar dose of venom is the same regardless of the patient’s size. Antivenin is generally dosed to reverse the total molar amount of venom injected. The doses recommended for smaller pediatric patients are the same as those recommended for adults, based on clinical signs and severity score rather than weight or size. With humans, it is not uncommon to administer at least 10 to 20 vials of antivenin.

Dosing in animals is more difficult and is often based on clinical signs and monitoring of coagulation status. Serial physical examinations and measuring of tissue swelling every 15 to 30 minutes should be performed to determine whether swelling continues after antivenin administration. If local swelling continues to worsen, administration of another vial of antivenin should be considered. Administration of additional antivenin should also be considered for persistent, clinically significant coagulopathy. It has been noted in the human literature that normalization of coagulation parameters with antivenin administration does not always occur, but a trend toward normalization should be considered the end point of treatment.

**Antibiotics**

Administration of systemic antibiotics following envenomation has traditionally been advocated in the veterinary literature. The bacteria most commonly isolated from crotalid mouths include *Pseudomonas aeruginosa*, *Proteus* spp, coagulase-negative *Staphylococcus* spp, *Clostridium* spp, and *Bacteroides fragilis*. Previous human studies recommending antibiotics were based on studies on the oral flora from snakes rather than the incidence of wound infection. Although no veterinary research is available on this topic, multiple, prospective, controlled human trials have shown no statistically significant difference in the number of wound infections following snake envenomation between patients who received antibiotics and those who did not. In fact, the incidence of secondary wound infection was quite low in patients who did not receive antibiotics. It is unknown whether data from the human literature apply across species. There is some evidence that venom has antibacterial properties. It may also be easier to keep the wound clean in humans compared with animals. Therefore, although administration of antibiotics may be unnecessary in snake envenomation, these drugs should still be considered until further veterinary data are available.

**Opioids**

Opioid therapy is recommended for the pain associated with snakebite. To avoid masking effects and allow accurate assessment of the patient’s neurologic status, it is recommended that opioids be withheld when neurologic signs are present.

**Other Therapies**

Corticosteroids were previously used to treat snakebites and were considered the standard of care. Current human studies have failed to document any
benefits of corticosteroid administration in treating snakebites, other than for anaphylactic reactions and serum sickness secondary to antivenin administration.\textsuperscript{7,22} In the human literature, corticosteroids are not routinely administered to snakebite patients, and the use of these drugs in veterinary snakebite patients should be questioned.

Compartment syndrome has previously been described in the human literature secondary to myonecrosis from envenomation.\textsuperscript{1} Although surgical intervention was previously performed, it has been determined that most affected patients respond to further antivenin treatment alone, and fasciotomy is rarely necessary.\textsuperscript{1-3,7}

**PREVENTION**

A *C. atrox* toxoid rattlesnake vaccine (Red Rock Biologics) intended for prophylaxis against the effects of rattlesnake envenomation by the western diamondback rattlesnake is available.\textsuperscript{43} The vaccine produces antibodies that are thought to cross-protect against the venom of many other rattlesnake species.\textsuperscript{43} The theory behind the vaccination is that it elicits production of IgG, which would then neutralize the venom following envenomation, leading to slowed systemic venom absorption and subsequent lessening of clinical signs. In the company’s murine trials, a higher dose of venom was required to kill vaccinated mice than those that were unvaccinated.\textsuperscript{44} No peer-reviewed canine studies on the efficacy of this vaccine have been published, and its benefits have not been documented in veterinary medicine at this time. Further studies are needed before the vaccine can be deemed beneficial.

**CONCLUSION**

Rattlesnakes are responsible for most North American snake envenomations. Venom contents vary widely among snake species and across geographic distribution among snakes of the same species. Mortality rates secondary to rattlesnake envenomation are low as long as timely treatment is received. The mainstays of treatment are fluid therapy and antivenin administration. A new, more effective antivenin is available that has fewer side effects in humans. Because of its short half-life, this antivenin requires redosing up to at least 18 hours, which may limit its use in animals because of cost. However, this antivenin should be considered in treating known Mojave rattlesnake envenomation because it can reverse the neurologic effects.

**REFERENCES**


30. Antivenin (Crotalidae) Polyvalent package insert, Fort Dodge.


43. *Crotalus atrox* toxoid (rattlesnake vaccine) product information, Red Rock Biologics.


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**ARTICLE #3 CE TEST**

This article qualifies for 2 contact hours of continuing education credit from the Auburn University College of Veterinary Medicine. Subscribers may purchase individual CE tests or sign up for our annual CE program. Those who wish to apply this credit to fulfill state relicensure requirements should consult their respective state authorities regarding the applicability of this program. CE subscribers can take CE tests online and get real-time scores at CompendiumVet.com.

1. **What percentage of snakebites is considered dry bites with no envenomation?**
   a. 10%
   b. 20% to 35%
   c. 50%
   d. 65%

2. **Coagulopathy from snake envenomation and DIC are alike in that they both**
   a. frequently cause massive hemorrhage.
   b. activate factor XIII.
   c. cause elevated FDPs.
   d. cause antithrombin depletion.

3. **Coagulopathy from rattlesnake envenomation should be treated with**
   a. fresh-frozen plasma, as needed.
   b. antivenin.
   c. heparin.
   d. all of the above

4. **Which was found to induce echinocyte formation on canine blood in vitro?**
   a. collagenase
   b. myotoxin a
   c. phospholipase A₂
   d. zinc-based metalloproteinases

5. **Which statement regarding ACP is incorrect?**
   a. It can be used to treat envenomation by many different rattlesnake species.
   b. It has renal clearance and a short half-life.
   c. It is associated with a higher rate of anaphylaxis and serum sickness than is the Fab antivenin.
   d. It is ideally administered within 4 hours of envenomation.

6. **Which statement regarding serum sickness is correct?**
   a. It has recently been reported in a dog.
   b. It is a type III hypersensitivity reaction.
   c. It usually occurs 1 week after antivenin administration but can occur 3 days to 3 weeks after.
   d. all of the above

7. **Prophylactic antibiotics for rattlesnake envenomation are not usually administered to humans because**
   a. rattlesnakes have minimal natural flora in their oral cavity.
   b. the rate of wound infection is low.
   c. these drugs have not been proven to prevent infection.
   d. b and c
8. Which statement regarding the *C. atrox* toxoid rattlesnake vaccine is correct?
   a. It is intended to provide protection against many species of rattlesnakes.
   b. Administration of it induces IgG production.
   c. A higher dose of venom was needed to induce death in mice that were vaccinated compared with those that were not.
   d. All of the above

9. Which statement about anaphylactic and anaphylactoid reactions is incorrect?
   a. They both cause reactions directly mediated by IgE.
   b. They can be treated with diphenhydramine, corticosteroids, and epinephrine, if needed.
   c. They can be life threatening.
   d. It can be almost impossible to tell them apart.

10. Which statement regarding skin testing before antivenin administration is correct?
    a. Skin testing accurately predicts which patients will react to antivenin administration.
    b. Skin testing does not delay antivenin administration.
    c. Both false-positive and false-negative results are reported.
    d. The antivenin manufacturer does not recommend skin testing before antivenin administration.