Pit viper envenomation is a common emergency in many areas of the United States, with an estimated 150,000 annual cases in dogs and cats.¹ The pit viper family (Crotalidae) consists of rattlesnakes (FIGURE 1), cottonmouth moccasins (FIGURE 2), and copperheads, which are distinguished by their elliptical pupils, triangular heads, heat-sensing pits, and retractable fangs.² Mortality rates in envenomated dogs and cats range from 1% to 30%.¹

Clinical signs of envenomation vary depending on the amount of venom injected during the bite. Up to 25% of bites from venomous snakes are “dry bites” in which venom was not injected and no systemic signs develop. Clinical signs of venom injection include a distinct bite wound, often with hemorrhagic discharge, and a combination of mild to severe local tissue swelling, pain, weakness, neurologic signs, tachycardia, vomiting, and diarrhea. Envenomation can cause severe hypotension, hemorrhagic lymphedema, coagulopathy, arrhythmias, and death.³ Prompt treatment, especially with appropriate antivenom use, is critical to patient survival.¹

HISTORY AND PRESENTATION
A 1-year-old, intact male, 15-kg English springer spaniel presented to an academic satellite
emergency hospital for treatment of suspected pit viper envenomation. One hour prior, the dog was heard yelping while out hunting and found stumbling with wounds on both forelimbs and the left lateral thorax.

On presentation, the dog was laterally recumbent, tachycardic (237 beats/min), obtunded, and severely painful on palpation of the wounds. An IV catheter was placed and point-of-care diagnostic test results were consistent with pit viper envenomation. The dog’s activated clotting time (ACT) was >999 sec (reference range, 90 to 120 sec), serum was hemolyzed, numerous echinocytes were found on blood smear review, and thrombocytopenia was present. Hypotension was present (systolic blood pressure, 68 mm Hg) with intermittent ventricular tachyarrhythmias.

**TREATMENT**

Four vials of diluted F(ab’)₂ antivenom were administered as a bolus over an hour in addition to crystalloid fluid therapy. Analgesic therapy with 3 µg/kg/h fentanyl was started. The dog remained severely coagulopathic and hypotensive with progressive hemolysis; therefore, an additional 4 vials of F(ab’)₂ antivenom were administered during the second hour.

The packed cell volume (PCV) and total solids decreased from 60% and 6.1 g/dL to 28% and 3.2 g/dL, respectively, and hypotension persisted (systolic blood pressure, 50 mm Hg). Two units of packed red blood cells (pRBCs) were administered over an hour and a norepinephrine continuous-rate infusion (CRI) at 0.5 µg/kg/min was started. Crystalloid therapy was discontinued and fresh frozen plasma (FFP) was started at 100 mL/hr for oncotic support. Severe hematochezia developed. Point-of-care tests were repeated, and the dog remained severely coagulopathic (ACT >999 sec) with severely hemolyzed serum and progressive azotemia (creatinine increased from 0.7 mg/dL on presentation to 1.2 mg/dL). The PCV increased to 52% after 2 units of pRBCs.

Owing to rapidly diminishing antivenom stock at the satellite hospital, the last 3 vials of F(ab’)₂ antivenom were administered as a CRI while the dog was transported to the intensive care unit (ICU) at the main academic hospital. The dog arrived at the ICU 6 hours after original presentation and remained tachycardic (150 beats/min), tachypneic (50 breaths/min), and obtunded with severe, progressive swelling of the left forelimb and lateral chest. Coagulopathy was
improved and the ACT was 140 sec. A urinary catheter was placed and pigmenturia was noted (FIGURE 3). Repeat diagnostics showed recurrent anemia (PCV 16%), hyperlactatemia, and progressive azotemia (blood urea nitrogen 34 mg/dL, creatinine 1.8 mg/dL).

Over the next 12 hours, the dog received an additional 9 vials of F(ab’)\textsubscript{2} antivenom, 2 units of FFP, 2 units of pRBCs, and 4 units of cryo-poor plasma for oncotic support. Hypotension progressively improved and noepinephrine was discontinued. Analgesia was continued with a CRI of fentanyl, lidocaine, and ketamine. The following morning, 17 hours after original presentation, the dog’s urine output was 3 mL/kg/hr despite progressive azotemia (creatinine 2.3 mg/dL), hemolysis persisted, and swelling extended up his neck (FIGURE 4). One additional vial of F(ab’)\textsubscript{2} antivenom was diluted and administered over 6 hours.

Over the next 3 days, the dog’s PCV remained between 20% and 25%, then acutely dropped to 17%. Tachycardia developed, prompting an additional pRBC transfusion. By day 4, the dog remained weak but was ambulatory. On day 6, the dog’s azotemia was significantly improved (creatinine 1.3 mg/dL). On day 7 of hospitalization, progressive edema of the hindlimbs and ventrum developed, prompting steroid anti-inflammatory therapy based on concern for serum sickness. The dog developed phlebitis where the original catheter was placed, nausea and vomiting, and hyphema of the left eye. These were managed with antibiotics, antiemetics with parenteral nutrition, and topical steroids and atropine, respectively.

On day 8, the dog was discharged on amoxicillin/clavulanic acid, prednisone, sucralfate, topical atropine, topical prednisolone acetate, and topical silver sulfadiazine cream. He made a full recovery despite severe envenomation.

DISCUSSION
Pit vipers are known to inhabit the southeastern United States (particularly North and South Carolina, Georgia, Florida, Alabama, Mississippi, and Louisiana). In general, most snake bites occur in the spring and summer months, particularly between the months of June and October.\textsuperscript{3} Antivenom therapy is the only therapy proven to affect mortality in humans bitten by pit vipers.\textsuperscript{3} While antivenom does not reverse sequelae of venom that exist at presentation, it is recommended in the acute phase to prevent further injury in patients with progressive local pain or swelling, evidence of coagulopathy, or systemic signs including hypotension and shock. It is often used alone or in conjunction with other therapies. The dog in this case required a significant volume of pRBCs owing to gastrointestinal hemorrhage combined with severe hemolysis, as well as plasma products for oncotic support.

Antivenom Products
Three types of antivenom products are available, and understanding the differences in these products can aid clinical decision making. All antivenoms are made by inoculating horses or sheep with venom from different...
snakes to create a polyvalent antibody product that provides improved venom neutralization for a variety of snake species. Hyperimmune plasma from the horse or sheep is harvested via plasmapheresis, producing antivenom after a series of processing steps. Further classification of antivenoms depends on the processing steps. IgG antivenom uses the whole Y-shaped antibody; V-shaped F(ab′)₂ antivenom is made by cleaving the Fc (fragment crystallizable) region (made of 2 heavy chains) of the antibody off with pepsin; and Fab antivenom is made by further cleaving the F(ab′)₂ product into 2 separate Fab fragments with papain (FIGURE 5). The antigen binding site is at the end of the Fab fragment; therefore, each step creates a smaller product that retains the ability to bind venom.

Antivenom products available for treatment of dogs and cats bitten by pit vipers include whole, equine-derived antivenom crotalidae polyvalent (ACP) IgG (Antivenin; Boehringer Ingelheim, bi-vetmedica.com; Rattler Antivenin; Mg Biologics, mgbiologics.com), equine-derived crotalidae polyvalent immune F(ab′)₂ (VenomVet; MT Venom, venomvet.com), and ovine-derived crotalidae polyvalent immune Fab antivenom (CroFab; BTG International, crofab.com) (TABLE 1). Each product has differences in horse or sheep protein contamination, tissue penetration, and half-life. In general, the smaller the molecular weight of the antivenom, the better tissue penetration is expected, and the shorter the half-life due to faster clearance from the body. Whole ACP IgG products contain the Fc region of the antibody, which is thought to be more immunogenic, leading to a higher risk of acute type I and delayed type III hypersensitivity reactions. A recent publication found a 7.2% risk of allergic reaction in treated dogs, which is lower than historically reported. The most refined antivenom is Fab antivenom; however, cost of this product often precludes routine use in small animals. IgG and F(ab′)₂ products are approved for use in dogs and none of the products are approved for use in cats; however, all 3 products have been used in dogs and cats with pit viper envenomation. Choice of antivenom to stock at a practice often involves what is available at the time, shelf life, geographic region, and clinical experience.

IgG antivenom is available in both a powder form (Antivenin) and frozen liquid form (Rattler Antivenin). Antivenin must be reconstituted prior to use, which can take 10 to 15 minutes or longer. While the powder is dissolving, it is important not to shake or heat the bottle, as this can cause foaming of the product or destruction of the proteins. Once reconstituted, the product is further diluted in saline before administration and is typically administered over 30 minutes unless signs of allergic reaction develop. Antivenin has been used successfully in both dogs and cats. In veterinary medicine, the label recommendation is 1 to 5 vials.

Choice of antivenom to stock at a practice often involves what is available at the time, shelf life, geographic region, and clinical experience.

<table>
<thead>
<tr>
<th>BRAND</th>
<th>ANTIVENOM</th>
<th>TYPE</th>
<th>SNAKE VENOM USED</th>
<th>FORM</th>
<th>DILUENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antivenin</td>
<td>Crotalidae polyvalent; equine-derived</td>
<td>IgG</td>
<td>Eastern diamondback, Western diamondback, Central and South American rattlesnake, fer-de-lance</td>
<td>Powder</td>
<td>Saline</td>
</tr>
<tr>
<td>Rattler Antivenin</td>
<td>Crotalidae polyvalent; equine-derived</td>
<td>IgG</td>
<td>Western diamondback, Eastern diamondback, prairie rattlesnake, Mojave rattler type A</td>
<td>Stored</td>
<td>None; blood filter needed</td>
</tr>
<tr>
<td>VenomVet</td>
<td>Crotalidae polyvalent; equine-derived</td>
<td>F(ab′)₂</td>
<td>Fer-de-lance, lancehead, South American rattlesnake</td>
<td>Liquid</td>
<td>100–150 mL crystalloid</td>
</tr>
<tr>
<td>CroFab</td>
<td>Crotalidae polyvalent; ovine-derived</td>
<td>Fab</td>
<td>Cottonmouth, Mojave rattlesnake, Eastern diamondback, Western diamondback</td>
<td>Powder</td>
<td>250 mL 0.9% saline</td>
</tr>
</tbody>
</table>

TABLE 1 Antivenom Products
Rattler Antivenin is a frozen product with a 3-year shelf life that does not require reconstitution or dilution and can be thawed in a warm water bath in 5 minutes. A blood filter should be used for administration according to the product label.

VenomVet is a liquid product, which eliminates the time delay for reconstitution, and should be diluted in crystalloid fluid before administration.

CroFab is a lyophilized powder and requires reconstitution with further dilution in 250 mL 0.9% saline before administration. It is thought to be the least immunogenic antivenom available; however, this has yet to be determined in both human and veterinary medicine. CroFab has been shown to be effective in severe envenomation in humans, dogs, and cats. Use of Fab antivenom is not approved and is often cost prohibitive in veterinary medicine; however, some sources suggest that it is more potent than the other products and therefore less antivenom will need to be administered, negating the impact of cost.

Snakebite Scoring and Treatment
There are no evidence-based guidelines in veterinary medicine to guide dosing of antivenom, and dosing schedules have largely been derived from human literature, clinical experience, and experimental studies. Use of a snakebite severity score (SSS) should be considered as an objective tool to guide antivenom administration. A SSS with a maximum score of 20 is commonly used to assess neurologic, gastrointestinal, cardiac, coagulation, local wound, and pulmonary parameters. Clinical decisions whether to administer additional vials are often made based on trends in the SSS.

The SSS should be used with caution on initial presentation, as signs of envenomation take time. In cases of acute envenomation—when antivenom is most effective—the SSS may be low, but it can progress if the patient is left untreated.

Antivenom should be administered if there is rapid progression of edema/swelling, significant venom-induced coagulopathy, neuromuscular toxicity, or shock. Most product labels recommend initial administration of 1 to 5 vials depending on severity of signs, length of time from bite to treatment, size of snake, and size of patient, with additional vials administered every 2 hours as needed. Some sources recommend administration of antivenom as a slow CRI to minimize adverse reactions.

Adverse Reactions to Treatment
Adverse reactions to antivenom administration can be acute or delayed. The most concerning and emergent acute reaction is anaphylaxis, manifested by vomiting, ptyalism, restlessness, urticaria, facial pruritus, and/or tachypnea. Clinicians should be prepared with epinephrine in the event of anaphylaxis. Reported anaphylactoid adverse reactions include hyperemia of the sclera or pinnae, agitation, bradycardia, dyspnea, tachypnea, second-degree heart block, fever, drooling, vomiting, and tachycardia. Most of these reactions are treated by slowing the antivenom infusion rate. Pretreatment of cats with antihistamines or steroids did not influence the development of type I hypersensitivity reactions in 1 study.

Delayed type III hypersensitivity reactions, known as serum sickness, can occur after antivenom administration. Serum sickness is a systemic immune-mediated response to foreign antigen via an immune complex and complement activation that does not require prior exposure to the foreign antigen. Clinical signs manifest 3 to 21 days after exposure to the foreign antigen and include fever, lethargy, diarrhea, painful joints, lymphadenomegaly, vasculitis, urticaria, and gastrointestinal signs. Serum sickness has been reported in dogs and is treated with a tapering dose of glucocorticoids and antihistamines.

Recommended Resource

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Diana Carter
Dr. Carter earned her DVM from Michigan 
State University. She completed her small 
animal rotating internship at the University 
of Florida College of Veterinary Medicine in 
2022.

Ashley Allen-Durrance
Dr. Allen-Durrance is a clinical associate 
professor and co-service chief of the 
emergency and critical care service 
at the University of Florida College of 
Veterinary Medicine. She is boarded 
in small animal emergency and critical 
care (ECC). She earned her DVM from 
Mississippi State University and completed 
a rotating internship and ECC residency 
at the University of Florida, where she has 
remained as faculty for 8 years. Her research 
interests include envenomation, neonatal 
emergency medicine, and extracorporeal 
therapies.