Rattlesnake envenomation in horses: 58 cases (1992–2009)

C. Langdon Fielding, DVM, DACVECC; Nicola Pusterla, DVM, PhD, DACVIM; K. Gary Magdesian, DVM, DACVIM, DACVECC, DACVCP; Jill C. Higgins, DVM; Chloe A. Meier

Objective—To characterize signalment, clinical and laboratory findings, treatment, and outcome in horses with rattlesnake envenomation in northern California.

Design—Retrospective case series.

Animals—58 client-owned horses evaluated for rattlesnake envenomation at 2 referral hospitals from 1992 to 2009.

Procedures—Records of horses with rattlesnake envenomation were reviewed, and data concerning signalment, clinical and laboratory findings, treatment, and outcome were collected. In addition, a rattlesnake-bite severity score (RBSS) was assigned to each horse. Variables were compared between horses that survived and those that did not.

Results—The overall mortality rate was 9%. Nine horses received antivenin; no complications were reported and none of the 9 died. The most common laboratory findings associated with severity of envenomation were thrombocytopenia, hypoproteinemia, hyperlactatemia, and a high RBSS.

Conclusions and Clinical Relevance—Most horses in this study had a good prognosis after being bitten by rattlesnakes. Laboratory and clinical examination findings may be useful for identifying horses with a poorer prognosis. Treatment with antivenin may be beneficial and warrants further evaluation. (*J Am Vet Med Assoc* 2011;238:631–635)

EQUINE

Rattlesnakes belong to a group of venomous snakes, the pit vipers, which are responsible for most snake bites in humans and small animals.[1] Results of studies[2,3] of rattlesnake bites in dogs suggest mortality rates as low as 1%. Likewise, in humans, the mortality rate is extremely small when medical care is implemented.[4–6] In horses, only 1 large retrospective study[7] has been conducted, involving 32 horses in Colorado between 1973 and 1993 and revealing a mortality rate of 25%. An older survey in horses[8] found that 20% of rattlesnake bites resulted in death. The reasons for the higher mortality rates in horses versus other species remain unclear.

The aforementioned equine studies took place > 15 years ago, and medical management of rattlesnake bites has since changed.[7] Advances in supportive care and the use of antivenin[a] may have led to an improvement in outcome. Corticosteroids and antimicrobials have been used as treatments, but recently, both have been questioned in the treatment of humans and other animals with rattlesnake envenomation.[9–11]

Use of equine-derived antivenin for treating horses after rattlesnake bites has been described.[9,12] This treatment has not been evaluated in horses to our knowledge, although it has been used in many affected humans[5,10] and in 23% of affected dogs in 1 report.[2] Serum sickness has been described as a complication of treatment with equine-derived antivenin in humans,[13] and research is needed to determine whether adverse effects arise when the antivenin is used in horses. Such research would be particularly important given the higher mortality rate for rattlesnake bites in horses versus other animals.

Abbreviation

RBSS	Rattlesnake-bite severity score

The dose of equine-derived antivenin (1 to 5 vials) for treatment of horses with rattlesnake envenomation has been described,[9,12] but no published data exist to support this recommendation. On the product insert, a dose of 10 to 50 mL of rehydrated antivenin is recommended.[14] Given the doses required in people (> 15 to 20 vials in some situations), the use of antivenin may not be a practical treatment for horses.[10] A newer recombinant product[a] is available, and its use has been evaluated in human trials.[15] However, the cost of this product may also make it prohibitive in horses.

A scoring system for severity of rattlesnake bites[9] (RBSS) was recently adapted for horses to aid in the recognition of more serious cases and to facilitate rapid treatment. The RBSS system has yet to be applied to a large group of horses. As in humans and dogs, the RBSS system could be used clinically and also in the evaluation of new treatments for rattlesnake envenomation.[16] The purpose of this study was to characterize signalment, clinical and laboratory findings (including RBSS), treatment, and outcome in horses with rattlesnake envenomation in northern California.

From the Loomis Basin Equine Medical Center, PO Box 2059, Loomis, CA 95650 (Fielding, Higgins, Meier); and the Department of Medicine and Epidemiology, School of Veterinary Medicine, University of California-Davis, Davis, CA 95616 (Pusterla, Magdesian).

Address correspondence to Dr. Fielding (langdonfielding@yahoo.com).

Materials and Methods

Case selection—A retrospective, computer-generated search was performed of all medical records of snakebites in horses treated at the Loomis Basin Equine Medical Center (hospital 1) during a 5-year period (2004 to 2009) and at the Veterinary Medical Teaching Hospital, School of Veterinary Medicine, University of California-Davis, (hospital 2) during a 17-year period (1992 to 2009).

Medical records review—Data obtained from the medical records included signalment, physical examination findings, laboratory results (hematologic and serum biochemical analyses), treatment, and outcome. Data concerning medications administered by referring veterinarians were not collected because it was incomplete for many horses.

Snakebite scoring—An RBSS was calculated for each horse at admission when data were available by use of a method described elsewhere (**Appendix**).[9] As an example, for a horse without any signs of respiratory distress (respiratory score = 0) and with tachycardia with a heart rate of 64 beats/min (cardiovascular score = 2), swelling of the head from a bite to the muzzle that extended onto the neck (wound score = 3), and a platelet count of 60,000 cells/µL (hemostasis score = 2), the RBSS would be 7.

Data analysis—Data were analyzed with the aid of a statistical software package[b] and are summarized as mean ± SD for normally distributed data and median (range) for non-normally distributed data. Data from surviving and nonsurviving horses were compared by use of the Mann-Whitney *U* test for data that were not normally distributed and an unpaired *t* test for data that were normally distributed. A significance level of $P < 0.05$ was used.

Results

Animals—Fifty-eight equids were identified as having rattlesnake bites on the basis of historical data and physical examination findings. Twenty-nine horses originated from each of the 2 referral hospitals. Breed information was available for 55 (95%) horses. There were 26 (45%) Quarter Horses, 12 (21%) Arabians, 4 (7%) Miniatures, 2 (3%) Thoroughbreds, and 2 (3%) American Paint Horses. Eight (14%) other represented horse breeds included 1 each of Morgan, Missouri Fox Trotting Horse, Appaloosa, Haflinger, warmblood, Peruvian Paso, Paso Fino, and Pony of the Americas. One miniature donkey was also included. There were 26 (45%) geldings, 5 (9%) stallions, and 27 (47%) mares. The median age of all horses was 7.0 (range, 0.08 to 28) years.

Clinical and laboratory findings—Initial findings were summarized (**Table 1**). Most horses evaluated were bitten in the summer months (**Figure 1**). Two of the 58 (3%) horses had a bite to the lower limb, and the remaining 56 (97%) horses were bitten in the face. Respiratory distress was evident in 33 (57%) horses upon initial evaluation. Head swelling was present in 56 (97%) horses (**Figure 2**), lower limb swelling was present in 1 horse, and the amount and location of swelling was not recorded for 1 horse. Of the horses with head swelling, 18 (32%) had additional swelling that had progressed into the neck region.

Gastrointestinal sounds were recorded for 56 horses, of which 26 (46%) had a decrease in borborygmi. Of

Table 1—Characteristics of horses evaluated at 2 veterinary referral hospitals that did (n = 53) and did not (5) survive rattlesnake bites between 1992 and 2009.

Parameter	All horses	Surviving horses	Nonsurviving horses	*P* value
Age (y)	7.0 (0.08–28)	7.5 (0.08–28)	7.8 ± 6.8	0.60
Duration of hospitalization (d)	4 (1–11)	4 (1–11)	1 (1–7)	0.03
Rectal temperature (°C)	37.9 ± 0.5	37.9 ± 0.5	37.3 (36.6–38.2)	0.19
Heart rate (beats/min)	44 (32–200)	44 (32–200)	68 (40–76)	0.22
Respiratory rate (breaths/min)	20 (8–84)	20 (8–84)	20 (20–20)	NA
RBSS	4 (2–10)	4 (2–9)	10 (8–10)	< 0.001
Platelet count (× 10^3 cells/µL)	123 ± 71	129 ± 69	16 (5–77)	0.02
PCV (%)	33 ± 6	33 ± 6	32 (13–42)	0.86
WBC (× 10^3 cells/µL)	10.4 ± 3.2	10.5 ± 3.2	8.6 (6.2–10.5)	0.29
Neutrophils (× 10^3 cells/µL)	8.1 ± 3.1	8.3 ± 3.0	3.0 (2.7–8.4)	0.09
Lymphocytes (× 10^3 cells/µL)	1.4 (0.3–5.6)	1.4 (0.3–5.6)	3.0 (1.8–3.5)	0.06
PT (s)	18 ± 5	17 ± 3	26 (24–30)	< 0.001
PTT (s)	126 (34–200)	125 (34–175)	170 (70–200)	0.13
Total plasma proteins (g/dL)	6.1 ± 0.8	6.2 ± 0.7	4.4 (4.0–4.8)	0.01
Lactate (mmol/L)	2.0 (1.0–8.6)	1.9 (1.0–5.3)	6.3 (3.9–8.6)	0.02
Creatine kinase (U/L)	900 (146–15,000)	919 (146–15,000)	263 (258–15,000)	0.68
Aspartate aminotransferase (U/L)	328 (171–1,164)	330 (178–1,164)	216 (171–1,006)	0.47
Albumin (g/dL)	2.8 ± 0.4	2.8 ± 0.4	2.3 (2.1–2.5)	0.03
Calcium (mg/dL)	11.2 (5.9–13.7)	11.2 (5.9–13.7)	10.0 (9.9–10.8)	0.18
Total bilirubin (mg/dL)	2. 6 ± 1.1	2.6 ± 1.1	1.9 (1.8–3.1)	0.65
γ-Glutamyltransferase (U/L)	12 (6–34)	12 (6–34)	7 (6–10)	0.04
Globulins (g/dL)	3.7 ± 0.8	3.8 ± 0.8	3.3 (2.4–3.4)	0.14
BUN (mg/dL)	18 ± 5	18 ± 5	15 (15–20)	0.50
Creatinine (mg/dL)	1.3 (0.8–2.2)	1.3 (0.8–2.2)	1.6 (1.1–1.8)	0.48
Glucose (mg/dL)	149 ± 35	145 ± 31	197 (126–245)	0.15

Values are given as mean ± SD or as median (range).
Values of $P < 0.05$ were considered significant.
NA = Not applicable. PT = Prothrombin time. PTT = Partial thromboplastin time.

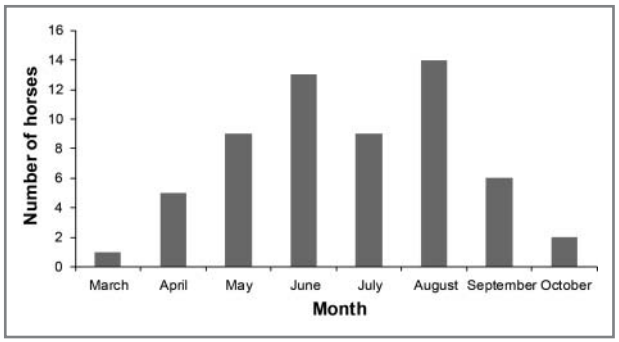

Figure 1—Monthly distribution of rattlesnake bites in 58 horses evaluated at 2 veterinary referral hospitals between 1992 and 2009. No horses with rattlesnake bites were identified during the months of November, December, January, or February.

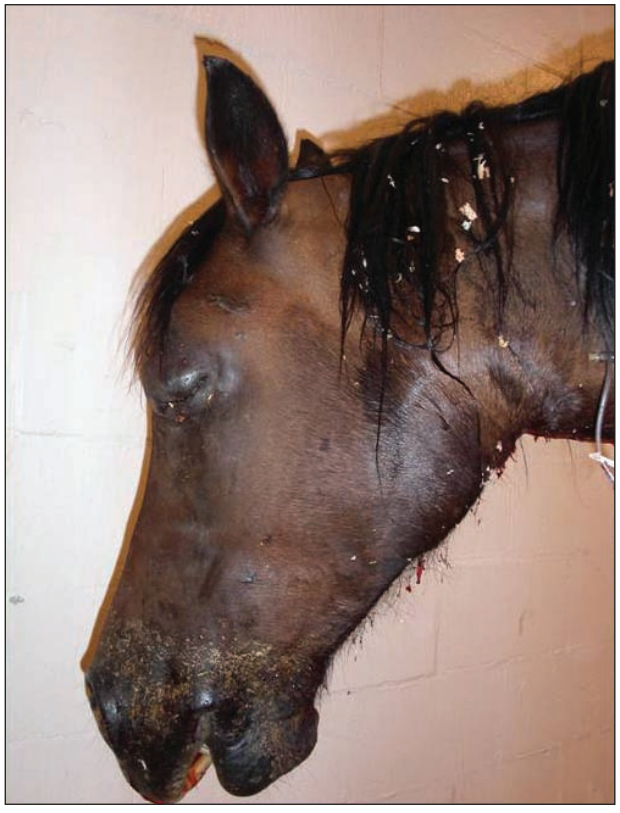
Figure 2—Photograph of typical head swelling following a rattlesnake bite in a horse.

the 52 horses for which demeanor was recorded, 4 (8%) were described as depressed. Eight (15%) horses in the study had spontaneous bleeding from the eyes, ears, nose, or tracheotomy site. None of this bleeding was specifically reported in association with the bite site.

The median (range) RBSS for all horses in the study was 4 (2 to 10; total possible score, 13). The score could not be calculated in 9 horses because of missing data. All horses with an RBSS < 8 survived.[9] Six horses had an RBSS ≥ 8, and 3 of these horses did not survive.

Additional abnormalities included an episode of colic during hospitalization of 1 horse that resolved with minimal medical treatment and an episode of diarrhea that was classified as mild and resolved in another horse. Other findings included 1 horse with atrial fibrillation that resolved with snakebite treatment (without antiarrhythmic treatment) and 1 horse that developed bilateral facial nerve paralysis. The paralysis gradually resolved over a 2- to 3-week period.

Treatment—Nine (16%) of the horses received equine-derived rattlesnake antivenin. Six were from hospital 1, and 3 were from hospital 2. Three horses received 2 vials IV, and the remaining 6 horses received 1 vial IV. No adverse reactions were recorded during treatment. None of the horses receiving antivenin were euthanized (0%); therefore, the mortality rate of horses not receiving antivenin was 10%.

Exact timing of the treatment with antivenin was not recorded for all horses, but at least 3 horses did not begin treatment with this product until > 24 hours after admission to the hospital. In all of these horses, clinical signs of swelling and thrombocytopenia began to resolve within 24 hours after antivenin administration. Two of the study horses received an initial vial of antivenin and were then monitored for 24 hours. When clinical and laboratory values did not improve, an additional vial was administered.

All horses but 1 received antimicrobials. Fourteen (24%) of the horses received only 1 antimicrobial as follows: gentamicin (n = 10 horses), ceftiofur (3), and penicillin G procaine (1). Thirty-nine (67%) horses received a combination of 2 antimicrobials, which included penicillin G procaine–gentamicin (23/40), penicillin G potassium–gentamicin (5/40), ampicillin-gentamicin (6/40), and ceftiofur-gentamicin (5/40). Four horses received a combination of 3 antimicrobials, which included penicillin G procaine, gentamicin, and metronidazole (n = 2); penicillin G potassium, gentamicin, and metronidazole (1); or ceftiofur, ampicillin, and gentamicin (1).

All horses but 1 received NSAIDs. Flunixin meglumine alone was administered to 51 (88%) horses, phenylbutazone alone was administered to 3 (5%) horses, a combination of phenylbutazone and flunixin meglumine was administered to 2 (3%) horses, and a combination of phenylbutazone and ketoprofen was administered to 1 (2%) horse. The medications were administered PO or IV.

Antihistamines (hydrosine, PO; diphenhydramine, IV; or both) were administered to 4 (7%) horses. Corticosteroids were administered to 23 (40%) horses, with 21 receiving dexamethasone (IV, IM, or PO) and 2 receiving prednisolone (PO). Four horses received additional analgesic medication in the form of butorphanol. Twenty-three (40%) horses received an IM injection of tetanus toxoid. Information was not available to determine whether the remaining horses had received tetanus toxoid within the previous 6 months.

Isotonic crystalloids were administered IV to 33 (57%) horses. No problems related to catheter insertion sites were listed in the medical records. Two (3%) horses received furosemide IV, 2 (3%) received dimethyl sulfoxide IV, 1 (2%) received aminocaproic acid IV, and 1 (2%) received a dobutamine infusion. Eight (14%) horses received a plasma transfusion (1 to 2 L/horse, when recorded), and 2 (3%) horses received a whole blood transfusion (approx 16 mL/kg each).

Thirty-three (57%) horses required the placement of a tracheotomy insert for maintenance of an airway.

No complications were reported with this procedure. Two (3%) additional horses had tubing placed within the nares to maintain a patent airway.

Outcome—Four of the 58 (7%) horses were euthanized, and 1 (2%) of the horses died during hospitalization. This resulted in an overall mortality rate of 9%. The mortality rates were similar between hospital 1 (10%) and hospital 2 (7%). All 4 euthanized horses deteriorated in condition despite treatment and had a guarded prognosis. More specifically, all were treated in the intensive care unit with plasma transfusions, whole blood transfusions, or both, and 1 horse received inotropic support in the form of dobutamine. It was not possible to ascertain from the medical record whether finances played a role in the decision for euthanasia. The median duration of hospitalization for all 58 horses was 4 (1 to 11) days.

Discussion

The present study was designed to examine patient and treatment characteristics and outcomes in horses with rattlesnake envenomation in northern California. The mortality rate of the study horses (9%) was lower than that in another study[7] involving horses (25%). However, the rate remains higher than the mortality rates reported for rattlesnake bites in dogs and people (≤ 1%).[2,4–6] Although changes in medical treatment may have accounted for some of the improvement in horse mortality rates, it is also possible that study location played some role. Prairie rattlesnakes were described as the most likely source of bites in the previous study,[7] but the Northern Pacific rattlesnake would be more common in the area of California in which the present study took place.[4,7] Differences in venom between these snakes may account for some of the disparity in clinical signs and mortality rates. However, a retrospective study[4] in humans involving a similar geographic location (northern California) had a case fatality rate of 0%, but use of antivenin was relied upon heavily in the treatment approach.

Our study was not designed to test the effect of a specific treatment in horses with rattlesnake bites; theoretically, that would be best achieved through a randomized controlled clinical trial. However, it was interesting to notice that none of the horses receiving the equine-derived rattlesnake antivenin died or were euthanized. The mean RBSS for the horses receiving antivenin was 5 ± 2, compared with 4 ± 2 for the rest of the horses in the study, but the difference was not significant ($P = 0.09$). This finding is, at the very least, hypothesis generating. The use of antivenin in humans has reduced mortality rates from as high as 25% to 0.5% according to 1 medical review.[10] Antivenin was used in 3 animals in a study[17] of rattlesnake bites in New World camelids, and only 1 camelid survived, but the timing of the treatment may have been delayed. A recent study[3] of antivenin dose in dogs with rattlesnake bites did not find a benefit with larger doses. However, the results may not apply to horses. Given our findings, it is not possible to conclude whether antivenin is beneficial in the treatment of horses with rattlesnake bites.

Although follow-up was not possible for all horses receiving antivenin in our study, the condition of 5 of these horses at the time of writing was known and clinical signs of liver disease had not developed. Clinically relevant adverse reactions were not observed during the treatment; however, additional studies are needed to evaluate the safety of antivenin use in horses. Cost may be the biggest limiting factor for its use in horses, as the price can range from $400 to $800/vial.

The timing of administration of antivenin is likely important to efficacy. Recommendations for humans support early administration because antivenin may be most effective when given in the first 4 hours following a bite.[10] One of the reports[3] regarding rattlesnake bites in dogs describes patients that were evaluated and treated within a few hours after the bite (median time, 1 hour), but the authors were not able to analyze whether the interval to treatment with antivenin played a role in survival. Many horses in the present study were brought in for veterinary care > 12 to 24 hours after being bitten. In many situations, it was impossible to know exactly when the bite occurred because of housing on pasture and infrequent monitoring of the horses at home. This delay in treatment may have contributed to the higher mortality rate in the study horses, compared with that in other species. Although antivenin was administered > 24 hours after the initial bite in at least 2 of the horses in the present study, the treating veterinarians still perceived a response to treatment in the form of improved swelling and increasing platelet counts. Additional research would be needed to support this finding, but there is some evidence in humans to suggest there may be a benefit to antivenin administration even when delayed.[10]

Other treatments in the study reported here included antimicrobials, corticosteroids, and antihistamines. These treatments are no longer recommended for the treatment of rattlesnake bites in people, and their use is now being questioned in horses and dogs.[9–11,18] A study[3] in dogs did suggest that antihistamine administration was associated with an increased probability of survival; however, the study was retrospective in design. It was not possible to identify any beneficial or adverse effects of specific treatments on mortality rate in this study. The use of antimicrobials for snakebites in horses is advocated by some authors,[19] but additional research is needed to support antimicrobial use for this purpose.

The RBSS system developed by one of the authors (CLF) appeared to be a useful tool for identifying horses that may have a higher risk of death from rattlesnake bites. A similar type of system has been used in other species and can be particularly helpful for identifying a deteriorating condition.[15,20] The RBSS system may also be a useful tool for grading the benefits of specific treatments, and additional research in this regard is warranted.

Complications following rattlesnake bites in horses in other studies[7,21] have included cardiac abnormalities, including congestive heart failure. One of the horses in our study had an arrhythmia (atrial fibrillation), but no other horses had arrhythmias or even tachycardia that persisted beyond discharge from the hospital. The lack of cardiac problems in the study horses may have represented a regional difference between the studies and the species of snake involved.

The present study of rattlesnake bites in horses demonstrated a better prognosis for survival than has been reported elsewhere. However, more research is needed to determine the efficacy of specific treatments. Horses with an RBSS of 8 or higher should be watched particularly carefully; more aggressive treatment may be warranted in such situations. Equine-derived rattlesnake antivenin was not associated with any complications and may provide clinical benefits; however, additional research is needed to support or refute our findings.

a. Crotalidae polyvalent immune Fab, Protherics Inc, Brentwood, Tenn.
b. GraphPad InStat, GraphPad Software Inc, San Diego, Calif.

References

1. Juckett G, Hancox JG. Venomous snakebites in the United States: management review and update. *Am Fam Phys* 2002;65:1376–1374.
2. Hackett TB, Wingfield WE, Mazzaferro EM, et al. Clinical findings associated with prairie rattlesnake bites in dogs: 100 cases (1989–1998). *J Am Vet Med Assoc* 2002;220:1675–1680.
3. McCown JL, Cooke KL, Hanel RM, et al. Effect of antivenin dose on outcome from crotalid envenomation: 218 dogs (1988–2006). *J Vet Emerg Crit Care* 2009;19:603–610.
4. Butner AN. Rattlesnake bites in Northern California. *West J Med* 1983;139:179–183.
5. Corneille MG, Larson S, Stewart RM, et al. A large single-center experience with treatment of patients with crotalid envenomations: outcomes with and evolution of antivenin therapy. *Am J Surg* 2006;192:848–852.
6. Walter FG, Stolz U, Shirazi F, et al. Epidemiology of severe and fatal rattlesnake bites published in the American Association of Poison Control Centers' Annual Reports. *Clin Toxicol (Phila)* 2009;47:663–669.
7. Dickinson CE, Traub-Dargatz JL, Dargatz DA, et al. Rattlesnake venom poisoning in horses: 32 cases (1973–1993). *J Am Vet Med Assoc* 1996;208:1866–1871.
8. Parrish HM, Scatterday JE. A survey of poisonous snakebites among domestic animals in Florida. *Vet Med (Praha)* 1957;52:135–139.
9. Fielding CL. Rattlesnake envenomation. In: Robinson NE, Sprayberry KA, eds. *Current therapy in equine medicine*. 6th ed. St Louis: Saunders Elsevier, 2009;930–932.
10. Gold BS, Barish RA, Dart RC. North American snake envenomation: diagnosis, treatment, and management. *Emerg Med Clin North Am* 2004;22:423–443.
11. LoVecchio F, Klemens J, Welch S, et al. Antibiotics after rattlesnake envenomation. *J Emerg Med* 2002;23:327–328.
12. Landolt GA. Management of equine poisoning and envenomation. *Vet Clin North Am Equine Pract* 2007;23:31–47.
13. LoVecchio F, Klemens J, Roundy EB, et al. Serum sickness following administration of antivenin (Crotalidae) polyvalent in 181 cases of presumed rattlesnake envenomation. *Wilderness Environ Med* 2003;14:220–221.
14. Antivenin [package insert]. Fort Dodge, Iowa: Fort Dodge Laboratories, 2001.
15. Lavonas EJ, Schaeffer TH, Kokko J, et al. Crotaline Fab antivenom appears to be effective in cases of severe North American pit viper envenomation: an integrative review. *BMC Emerg Med* 2009;9:13.
16. Dart RC, Hurlbut KM, Garcia R, et al. Validation of a severity score for the assessment of crotalid snakebite. *Ann Emerg Med* 1996;27:321–326.
17. Dykgraaf S, Pusterla N, Van Hoogmoed LM. Rattlesnake envenomation in 12 New World camelids. *J Vet Intern Med* 2006;20:998–1002.
18. Najman L, Seshadri R. Rattlesnake envenomation. *Compend Contin Educ Pract Vet* 2007;29:166–176.
19. Tennent-Brown BS, van Eps AW. Emergency diseases seen in Australia and New Zealand. In: Orsini JA, Divers TJ, eds. *Equine emergencies*. 3rd ed. St Louis: Saunders Elsevier, 2008;681–689.
20. Peterson ME. Snake bite: pit vipers. *Clin Tech Small Anim Pract* 2006;21:174–182.
21. Lawler JB, Frye MA, Bera MM, et al. Third-degree atrioventricular block in a horse secondary to rattlesnake envenomation. *J Vet Intern Med* 2008;22:486–490.

Appendix

Rattlesnake-bite severity scoring system for horses.

Variable	Score	Signs
Respiratory system	0	Unremarkable (8–20 breaths/min)
	1	Mild signs of respiratory distress
	2	Tachypnea present and increased work of breathing
	3	Severe respiratory distress with or without cyanosis
Cardiovascular system	0	Unremarkable (32–50 beats/min)
	1	Mild tachycardia ($>$ 50 but $\leq$ 60 beats/min)
	2	Moderate tachycardia ($>$ 60 but $\leq$ 80 beats/min) or blood lactate concentration $>$ 2.5 but $\leq$ 4.0 mmol/L
	3	Severe tachycardia ($>$ 80 beats/min) or blood lactate concentration $>$ 4.0 mmol/L
Wound appearance	0	No swelling
	1	Mild swelling involving only the nose or distal portion of the limb
	2	Moderate swelling involving the entire head or distal portion of the limb
	3	Severe swelling spreading to the neck or trunk
Hemostasis	0	No abnormalities
	1	PT and PTT higher than reference limits but $<$ a 25% increase or $<$ 120,000 but $\geq$ 100,000 platelets/µL of blood
	2	PT and PTT $>$ 25% but $\leq$ 50% higher than reference limits or $<$ 100,000 but $\geq$ 50,000 platelets/µL of blood
	3	PT and PTT $>$ 50% but $\leq$ 100% higher than reference limits or $<$ 50,000 but $\geq$ 20,000 platelets/µL of blood
	4	PT and PTT $>$ 100% higher than reference limits or $<$ 20,000 platelets/µL with signs of spontaneous bleeding

PT = Prothrombin time. PTT = Partial thromboplastin time.