Epidemiology and Hospital Course of Rattlesnake Envenomations Cared for at a Tertiary Referral Center in Central Arizona

DAVID A. TANEN, MD, ANNE-MICHELLE RUHA, MD, KIMBERLIE A. GRAEME, MD, STEVEN C. CURRY, MD

Abstract. **Objective:** To describe the demographics and primary inpatient treatment of victims of rattlesnake bites (RSBs) referred to a teritiary referral poison treatment center in central Arizona, and to compare the frequency of local tissue complications and hematologic toxicity during hospitalization in children with those for adults. **Methods:** This was a chart review of patients diagnosed as having RSB by a toxicology service between July 1994 and April 2000. Data collected included: age, sex, date, bite location, time to and length of hospitalization, time to and amount of antivenin, serial hematologic studies, and inpatient complications. **Results:** Of 241 patients admitted, 236 charts met inclusion criteria. The majority of RSB victims were male (81%). Children (≤13 years) represented 22%. Most RSBs (78%) occurred between April and September. Mean time (±SEM) to presentation was 1.7 ± 0.2 hours. Antivenin was administered to 77% of patients, with an average (±SEM) of 28.5 ± 0.9 vials administered. Hematologic abnormalities included: coagulopathy (60%), hypofibrinogenemia (49%), and thrombocytopenia (33%). No statistically significant difference in the above parameters was detected between upper- and lower-extremity envenomations, or between children and adults. Immediate antivenin reactions occurred in 36% of patients. Hemorrhagic bullae formation occurred in 22%, occurring most frequently in upper extremities. Operative procedures were required in 3.4% of patients. Hospitalization averaged 2.5 ± 0.1 days. There was no fatality. **Conclusions:** In Arizona, RSB victims were typically adult males with upper-extremity bites. Hematologic abnormalities were common. Local tissue complications were more common with upper-extremity envenomations. No statistically significant difference was detected in frequency of hematologic disorders or local tissue complications when children were compared with adults. **Key words:** rattlesnake; snake; envenomations; bites; children; toxicity. ACADEMIC EMERGENCY MEDICINE 2001; 8:177–182

BITES from poisonous snakes occur frequently in the United States, with estimates ranging from 1,700 to 8,000 per year.[1–3] In Arizona, rattlesnake envenomations are relatively common and account for most venomous snake bites. Rattlesnakes belong to the family Crotalidae and are known as pit vipers. Their venom comprises a mixture of enzymes, metals, and other compounds designed to immobilize, kill, and begin digestion of prey. Envenomations to humans may occur through unintentional interaction or, more commonly, following intentional encounters with snakes. Envenomation may result in marked tissue edema, necrosis, hypotension, and severe hematotoxicity. Rarely, envenomation results in disseminated intravascular coagulation (DIC) or death.[4,5]

Our toxicology service primarily admits patients to two hospitals in the Phoenix area and cares for 40–60 patients bitten by rattlesnakes per year. We serve as a referral center for poisoned patients and regularly admit rattlesnake bite victims from throughout Arizona. The snake most commonly associated with human envenomation in central and southern Arizona is *Crotalus atrox* (western diamondback).[6] Other species responsible for envenomations referred to our center include *C. scutulatus scutulatus* (mojave), *C. cerastes cerastes* (sidewinder), *C. molossus molossus* (black tail), *C. tigris* (tiger), *C. mitchelli* (spotted), and *C. viridis decolor* (faded midget).

We believe our management has been consistent over the past six years, and it has been described previously.[5] Patients are evaluated for envenomation by assessing swelling, tenderness, adenopathy, and hematologic abnormalities. The decision to administer antivenin is based on the presence of progressive swelling and/or hemato-

From the Department of Medical Toxicology, Good Samaritan Regional Medical Center, Phoenix, AZ (DAT, AMR, KAG, SCC); and the Departments of Surgery (KAG) and Clinical Medicine (SCC), University of Arizona College of Medicine, Tucson, AZ.
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Address for correspondence and reprints: Steven Curry, MD, Department of Medical Toxicology, 925 East McDowell Road, 2nd Floor, Phoenix, AZ 85006. Fax: 602-239-4138; e-mail: steven.curry@bannerhealth.com

TABLE 1. Demographics of the Population and Characteristics of the Rattlesnake Bites (RSBs)

Population (236 patients)	
Males	81%
Females	19%
Children	22%
Location of RSB (236 patients)	
Upper extremity	60.2%
Lower extremity	39.4%
Other	0.4%
Dry bites*	3.0%
Times from RSB (mean ± SEM)	
Time to health care facility	1.7 ± 0.2 hr
Time to antivenin infusion	5.3 ± 0.3 hr

*No clinical evidence of envenomation.

logic abnormalities, provided there are no contraindications. When indicated, we generally infuse 20 vials of Crotalidae Polyvalent Antivenin (Wyeth-Ayerst Pharmaceuticals, St. Davids, PA) intravenously over one to two hours as an initial dose. The initial dose of antivenin (20 vials) was based on many years of experience during which time we observed that patients receiving lower doses (e.g., 10 vials) almost always required additional dosing to reach at least 20 vials before adequate control was achieved. In very severe envenomations (e.g., shock, bleeding), we have infused initial doses of 30 vials of antivenin. Subsequent antivenin infusions, after the initial dose, are based on further progression of swelling and/or hematologic abnormalities.

The natural course of rattlesnake envenomation includes progressive swelling and hematologic toxicity, manifesting as coagulopathy, hypofibrinogenemia, and thrombocytopenia. Hemorrhagic skin bullae (blebs) at the site of envenomation are not uncommon. Compartment syndrome and the need for fasciotomy are rare, despite marked swelling.[2,3,5]

Beginning in July 1994, patients admitted to our inpatient medical toxicology service or seen in consultation for rattlesnake bite were entered into a computerized database. The purpose of this retrospective chart review was to assess the demographics, treatment, and inpatient complications associated with rattlesnake envenomations in patients referred to our facility, and to contrast the incidence of local tissue complications and hematologic abnormalities in adults with those in children, and in upper extremities with those in lower extremities. To the best of our knowledge, this descriptive study is the largest reported series of rattlesnake bites in Arizona.

METHODS

Study Design. This was a descriptive study of all patients admitted to our medial toxicology service since July 1994 with a diagnosis of rattlesnake bite. A computer-generated search of the medical records of all patients admitted to a medical toxicology referral service with a diagnosis of rattlesnake bite from July 1994 to April 2000 was conducted. Institutional review board approval was obtained.

Study Setting and Population. Our toxicology service admits patients to two hospitals in Phoenix, Arizona, and the patients included in this study are drawn from the records of these hospitals.

Study Protocol. Records were screened, and pertinent data were abstracted and entered into a computer database. The following data were collected: age, sex, date of bite, area of body bitten, time until hospital care, time until antivenin, amount of antivenin infused, hematologic parameters [prothrombin time (PT), plasma fibrinogen concentration, and platelet count], length of hos-

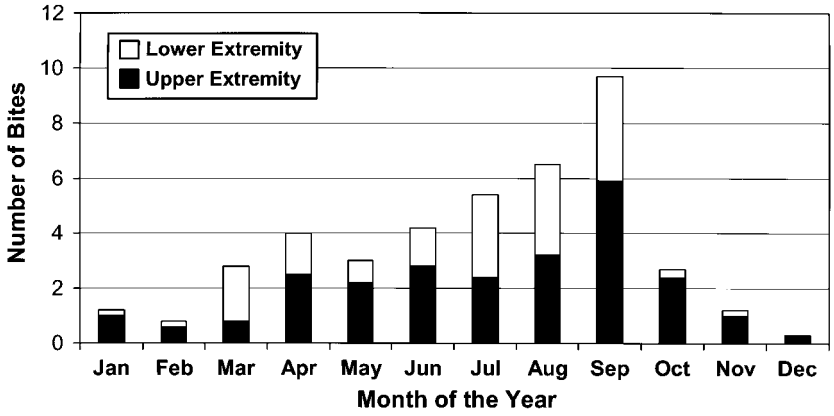

Figure 1. Monthly distribution of rattlesnake bites contrasting upper- and lower-extremity envenomations.

pitalization, immediate antivenin hypersensitivity reactions, need for blood products or operative procedures, and development of localized hemorrhagic skin bullae.

Children were defined by age ≤13 years. Coagulopathy was defined as PT > 14 sec; hypofibrinogenemia as plasma fibrinogen < 170 mg/dL; and thrombocytopenia as blood platelet count <120,000/mm^3. "Dry bites" were defined as those bites that did not result in swelling, hematologic abnormalities, or regional lymph node pain.

Immediate reactions to antivenin were defined as urticaria, pruritus (accompanied or unaccompanied by hypotension), or suspected manifestations of bronchospasm (cough, wheeze, or dyspnea). Operative procedures were defined as digit dermotomy[7] or fasciotomy and did not include the unroofing of hemorrhagic bullae. The determination of need for operative procedures during initial hospitalization was based on clinical evaluation (cold, pale finger without capillary refill) and/or elevated compartment pressures in consultation with an orthopedist or hand surgeon experienced in the treatment of rattlesnake envenomations.

Data Analysis. Statistical analyses were carried out with Epistat (Epistat Services, Richardson, TX, 1986). A two-tailed Student's t-test was used to compare means between groups of continuous variables. For categorical data, a two-tailed Fisher's exact test was used. We set a significant p-value of 0.0085 after using the Bonferroni method to correct for multiple comparisons.

RESULTS

We identified 241 patients admitted with the diagnosis of rattlesnake bite during the period from July 1994 to April 2000. Two hundred thirty-nine charts were available for review. Three charts were excluded because the patients were enrolled in an experimental protocol for the evaluation of a new antivenin, leaving 236 charts to review.

Males composed 81% of the patients. More than 99% of envenomations (235/236) were to the extremities, with the upper extremities representing the majority of the envenomations (142/236, or 60%). There was one bite to the tongue. Envenomations occurred in all months, but most envenomations (78%) occurred between April and September (Fig. 1). Three percent (7/236) of the rattlesnake bites were classified as dry bites (Table 1).

Children aged ≤13 represented 22% (51/236) of patients and, like adults, were predominantly male (69%). Children differed from the overall group, however, in that they were bitten predominantly on the lower extremities (69%) (Fig. 2).

TABLE 2. Number of Vials of Antivenin (Mean ± SEM) Administered to Children vs Adults and Upper-extremity Envenomations (UEEs) vs Lower-extremity Envenomations (LEEs)

	Total No. of Patients	No. of Vials of Antivenin	p-value
Children	44	28.2 ± 1.9	0.86
Adults	138	28.6 ± 1.1	
UEEs	114	27.6 ± 1.1	0.24
LEEs	67	30.0 ± 1.7	

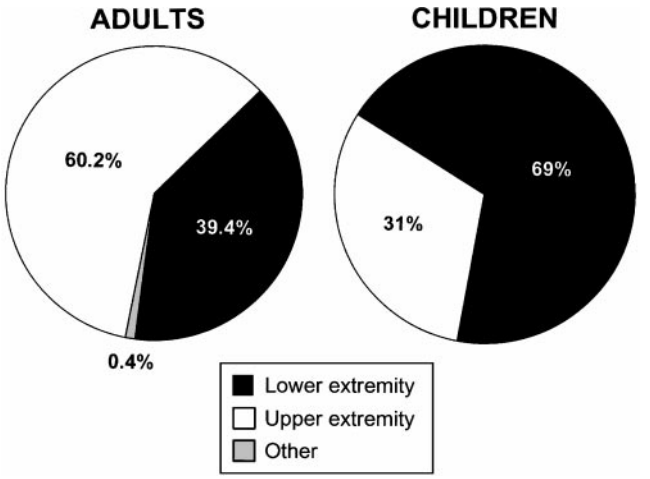

Figure 2. Comparison of rattlesnake bite locations between children and adults.

Mean time (±SEM) to presentation to a health care facility was 1.7 ± 0.2 hours after the bite. Antivenin was administered to 77% (181/236) of patients. Average amount of antivenin administered per patient was 28.5 ± 0.9 vials (range 5 to 60 vials) with a mean time to initiation of 5.3 ± 0.3 hours from the time of envenomation. Although some health care facilities initiated antivenin treatment prior to transfer, most did not, and much of the time difference between presentation and initiation of treatment reflected the transfer time to our facilities. There was no statistically significant difference detected in the amount of antivenin infused between children and adults or between upper- and lower-extremity envenomations (Table 2).

Hematologic abnormalities were common: 60% (142/235) of the patients developed a coagulopathy, 49% (112/234) developed hypofibrinogenemia, and 33% (77/235) developed thrombocytopenia. There was no statistically significant difference detected in the frequency of hematologic abnormalities between children and adults or between upper- and lower-extremity envenomations (Table 3). None of our patients experienced DIC.

Digital dermotomy or fasciotomy was per-

formed in 3.4% (8/236) of the patients. Five patients underwent digital dermotomy for swollen, white, cold, pulseless fingers. Three additional patients received fasciotomies. A 17-year-old boy with a bite to the thenar eminence developed a cold, pulseless, rock-hard hand and fingers within 90 minutes of presentation and was taken directly to the operating room for fasciotomy without measurement of intracompartmental pressures since surgical revascularization would have been indicated if compartmental pressures would have been low—he did well with decompression alone. An 8-year-old girl was bitten over the medial aspect of her elbow and, within three hours, developed tense swelling of the entire forearm with paralysis of the hand and complete absence of radial and ulnar pulses, even by Doppler. Again, immediate surgical intervention was performed without pressure measurements for similar reasons. Finally, a 1-year-old boy suffered a bite just below his tibial tuberosity. His leg was moderately swollen and he was hypotensive despite large fluid challenges and dopamine infusion. Compartmental pressures in his anterior, lateral, and posterior leg compartments were 65, 57, and 80 mm Hg, respectively. He underwent fasciotomies at the bedside in the intensive care unit and did well.

Hemorrhagic skin bullae were noted in 22% (51/236) of the patients. There was a clinically and statistically significant increase in the formation of hemorrhagic skin bullae in upper-extremity envenomations when compared with lower-extremity ones ($p < 0.001$). No significant difference in bullae formation or the need for an operative procedure could be detected when children were compared with adults (Table 4). Thirty-six percent (66/182) of the patients receiving antivenin developed immediate reactions to antivenin infusion, primarily manifesting as rash, with a minority (12) having symptoms of mild bronchospasm.

Blood products were administered to two children, one of whom was a child who received antivenin but had significant bleeding into a lower extremity after a fasciotomy was performed. The other child also received antivenin, but suffered a marked non-hemolytic anemia for unclear reasons during his hospital stay.

Hospital stay averaged 2.5 ± 0.1 days (range 1 to 14 days). There was no fatality.

DISCUSSION

Most of our snake bite victims were adult males. Relatively few bites occurred in the winter; most were in the summer and fall. This pattern is consistent with the desert habitat in central Arizona where increased snake activity occurs during the warmer months.[3,6,8] Children made up less than a fourth of envenomations, but the male:female ratio remained similar to that of the overall group. These distributions are similar to those reported previously.[8–10]

Dry bites have previously been reported to center around 25%.[3,5,11] The low percentage of patients suffering dry bites in our study reflects referral bias to a tertiary care center. Patients who had dry bites were likely evaluated by emergency physicians and deemed safe for discharge. The few patients with dry bites who were admitted (7) represented patients with comorbid disease or patients with lower-extremity bites whom we decided to monitor in the hospital but who never showed signs of envenomation. When analyzing the prevalence of dry bites for all patients who contacted the poison center, we previously reported a dry bite rate of 25%.[5]

Similar to other series, the majority of envenomations in our patients were to the upper extremities.[8,9] However, children differed from the overall group in that most of their envenomations were to the lower extremities. This discrepancy in the bite location may be a representation of what has been previously described as the legitimacy of a rattlesnake bite, with children suffering from unintentional encounters while adult envenomations may result from intentional interaction with the snakes.[9]

Hematologic abnormalities were common in our patients, with coagulopathy present in 60%, hypofibrinogenemia in 49%, and thrombocytopenia in 33%. Hypofibrinogenemia results from fibrinolysins and thrombin-like enzymes in snake venom. These venom components lead to depletion of fibrinogen and elevation of fibrin/fibrinogen degradation products, both of which can contribute to

TABLE 3. Frequency of Hematologic Abnormalities between Children and Adults and between Upper-extremity Envenomations (UEE) and Lower-extremity Envenomations (LEE)

	Total No. of Patients	% with Coagulopathy	Total No. of Patients	% with Hypofibrinogenemia	Total No. of Patients	% with Thrombocytopenia
Children	51	67	51	61	51	33
Adults	184	59	183	44	184	33
UEE	142	62	141	50	142	33
LEE	92	59	92	48	92	33

elevation of PT. Furthermore, snake venom contains nonspecific proteases that can degrade clotting factors or activate the coagulation cascade, also serving to prolong clotting times.[5,12,13]

The mechanism of venom-induced thrombocytopenia is unclear, but is thought mainly to be secondary to the action of phospholipases contained in the venom that damage platelet membranes and trigger platelet destruction.[5,14]

The frequency of hematologic abnormalities are higher than what has been reported previously in smaller studies and may represent referral bias since our patients were screened for envenomation prior to transfer to our institution.[8,11,15]

Traditionally, treatment of rattlesnake envenomation consists of intravenous fluid hydration, supportive care, and selective administration of antivenin.[5] Crotalidae Polyvalent Antivenin can be used to treat all crotalid envenomations in North America. It is derived from the serum of horses that have been previously inoculated with crotalid venoms. Since the antivenin consists of antibodies and horse serum, it can induce anaphylactic and anaphylactoid reactions. Therefore, risks and benefits of this treatment must be weighed before administration. A history of previous treatment with a horse-serum-derived product (e.g., crotalid, coral snake, or Latrodectus antivenin) or a history of significant atopy or asthma may exclude a patient from antivenin treatment. Another consideration is beta-blocker use, which has been shown to increase the frequency of anaphylaxis and hinder the treatment of anaphylactoid reactions.[16] Blood products such as fresh frozen plasma or platelets are generally ineffective in reversing the coagulopathy, hypofibrinogenemia, or thrombocytopenia associated with rattlesnake envenomations because they are rapidly consumed by circulating venom.[17]

The number of vials of antivenin routinely administered in the care of the envenomated patient has increased compared with when the product was first introduced. Patients who were treated with antivenin in our series received an average of about 28 vials, with a range of 5 to 60 vials. Although we routinely start with 20 vials of antivenin, 17 of the 236 patients received 5 to 19 vials prior to arrival at our facility, and we did not believe further antivenin was indicated. Some of these patients had minor envenomations, while the others were observed and clinically did not require further antivenin therapy.

Our results are in accord with previous studies. Kunkel et al. noted that 5 to 25 vials may be necessary during the first six hours.[2] Wingert and Chan have given up to 43 vials, but reported a median dose of 10 vials.[8] Holstege and colleagues estimated that, on average, an envenomated patient in the southwest receives 30 to 35 vials.[5]

TABLE 4. Soft-tissue Complications between Children and Adults and between Upper-extremity (UEE) and Lower-extremity Envenomations (LEE)

	Total No. of Patients	Patients with Hemorrhagic Bullae	Patients Needing Operative Procedures*
Children	51	7 (14%)	2 (4%)
Adults	184	44 (24%)	6 (3%)
UEE	142	46 (32%)	7 (5%)
LEE	93	5 (5%)	1 (1%)

*Operative procedures were defined as dermotomies or fasciotomies.

In our study, approximately a third of patients developed anaphylactic or anaphylactoid reactions that manifested primarily as urticarial rashes. These were easily controlled with hydroxyzine alone or in combination with a low-dose epinephrine drip. A small fraction of these patients developed mild bronchospasm, but this quickly abated with treatment. This frequency of immediate reactions appears to be higher than that previously reported and probably reflects lack of routine pretreatment with antihistamines along with administration of larger doses of antivenin over the first two hours.[8,10,11,18] Because of the relative frequency of anaphylactoid and anaphylactic reactions, we routinely premix an epinephrine drip (1 mg of epinephrine in 250 mL NS) and hang it at the bedside. When we deem it necessary, we start the epinephrine infusion at 60 mL/hr (4 μg/min) in adults (0.05 μg/kg/min in children), and titrate it as needed to control the reaction, as described previously.[5] In our experience, we have not seen any morbidity associated with the use of epinephrine in this manner.

It was not the purpose of our study to examine the incidence of serum sickness secondary to antivenin infusion, since this usually occurs three to 30 days after antivenin infusion and only rarely represents an inpatient complication. It has been our anecdotal experience that virtually all of our patients treated with antivenin develop serum sickness, which is easily controlled with oral corticosteroids.[5] None of our patients required readmission to the hospital for serum sickness.

Digital dermotomy or fasciotomy was performed infrequently in our patients (8 of 236 patients). The low incidence of dermotomy or fasciotomy in our population is similar to those of other previously reported studies.[3,7,8] Decisions to perform these procedures were based primarily on our clinical judgment in conjunction with an orthopedist or hand surgeon who was experienced in the treatment of rattlesnake envenomation. In the absence of a cold, pulseless extremity, compartmental pressure measurement proved important in mak-

ing the diagnosis of a compartment syndrome in one patient.

Hemorrhagic skin bullae formation was not uncommon and in our study occurred at a significantly higher frequency in upper-extremity envenomations. Bullae were usually unroofed at the bedside with subsequent pain relief after decompression of fluid. Bullae decompression was performed without regard to any underlying hematologic abnormalities.

It has been previously suggested that children may suffer greater morbidity than adults from rattlesnake envenomations because of their smaller mass, and that they would require higher doses of antivenin.[8,18–20] In dosing antivenin based on clinical response, children and adults received similar amounts of antivenin in our series, and we could detect no difference in the frequency of hematologic abnormalities or the frequency of local wound complications when children were compared with adults.

Limitations and Future Questions

Potential limitations of this report include our retrospective collection of data by chart reviews. For example, hematology studies were not always drawn at the same time following envenomation in all patients. Furthermore, our experience may not apply to the bites of some rattlesnake species found in other parts of the United States. For example, thrombocytopenia by the timber rattlesnake (not found in Arizona) frequently is refractory to treatment with Crotalidae Polyvalent Antivenin. Finally, referral bias certainly explains why almost all of our patients were envenomated, and might have resulted in the transfer of more seriously ill patients to our facility. Future similar studies may clarify these issues.

Conclusions

The rattlesnake envenomations in Arizona typically involved adult males who were bitten on extremities. Most envenomations occurred between April and September. There was no fatality, but hematologic abnormalities and the administration of antivenin were common. Antivenin administration was associated with anaphylactoid or immediate hypersensitivity reactions in a third of our patients, but these reactions were mild and easily controlled.

Hemorrhagic skin bullae occurred more frequently after envenomations of the upper extremities as compared with the lower extremities. The need for operative procedures such as digital dermotomy and fasciotomy was infrequent. The average length of hospital stay was less than 3 days.

When children were compared with adults there was no clinical or statistically significant difference detected in the amount of antivenin infused, hematologic parameters, need for operative procedures, or skin bullae formation.

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