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ORIGINAL ARTICLE

The Epidemiology, Clinical Course, and Management of Snakebites in the North American Snakebite Registry

Anne-Michelle Ruha[1] · Kurt C. Kleinschmidt[2] · Spencer Greene[3] · Meghan B. Spyres[4] · Jeffrey Brent[5] · Paul Wax[2,6] · Angela Padilla-Jones[1] · Sharan Campleman[6] · On Behalf of the ToxIC Snakebite Study Group

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Abstract The American College of Medical Toxicology established the North American Snakebite Registry (NASBR), a national database of detailed, prospectively collected information regarding snake envenomation in the United States, in 2013. This report describes the epidemiology, clinical course, and management of snakebites in the NASBR. All cases entered into the NASBR between January 1, 2013 and December 31, 2015 were identified. Descriptive statistics are used to report results. Fourteen sites in 10 states entered 450 snakebites. Native species comprised 99% of cases, almost all of which were pit viper bites. 56.3% were identified as rattlesnakes and 29.4% as copperheads. 69.3% were male and 28.2% were children age 12 and under. Fifty-four percent of bites were on the lower extremity. Twenty-seven percent of patients with lower extremity bites were not wearing shoes. Common tissue findings associated with envenomation were swelling, ecchymosis, and erythema. Systemic effects and hematologic toxicity were more common in rattlesnake than copperhead or cottonmouth envenomations. Crotalidae Polyvalent Immune Fab antivenom was given to 84% of patients. Twelve patients (4.3%) were re-admitted to the hospital after completion of treatment. Eight were re-treated with antivenom. The NASBR gathers detailed data on venomous snakebites across the US. In its initial years, useful information has already been gained. Data regarding footwear will inform public health interventions and education, and information regarding the clinical presentation may help physicians better anticipate effects and manage snakebite. As the number of cases in the NASBR grows, associations between patient-related factors and outcomes may be studied.

Keywords Snake · Snakebite · Envenomation · Antivenom

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✉ Anne-Michelle Ruha
Michelle.ruha@bannerhealth.com

[1] Division of Medical Toxicology and Precision Medicine, Department of Medicine, University of Arizona College of Medicine, Phoenix, AZ, USA

[2] Department of Emergency Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA

[3] Departments of Emergency Medicine and Pediatrics, Baylor College of Medicine, Houston, TX, USA

[4] Department of Emergency Medicine, Division of Medical Toxicology, University of Southern California, Los Angeles, CA, USA

[5] University of Colorado, School of Medicine, Aurora, CO, USA

[6] American College of Medical Toxicology, Phoenix, AZ, USA

Background

On average, 5000 venomous snakebites are reported to poison centers in the United States (US) each year [1]. Snake envenomation is responsible for significant morbidity and even mortality in some victims. Despite the large impact snakebites have on affected individuals, it is a relatively uncommon event, and many physicians have never encountered a patient with this diagnosis. Medical toxicologists are unique among physician specialists in that they receive specific training in the management of snakebites. In hospitals around the country that offer medical toxicology services, medical toxicologists are typically involved in the bedside care of patients with snake envenomation.

Current understanding of the pathophysiology of snake venom, factors that may influence morbidity and mortality after snakebite, and ideal management of patients suffering from snake envenomation is incomplete. Much of what is known derives from retrospective case series describing geographically limited cohorts of patients with snake envenomation and case reports of unusual presentations following a snakebite. Even well-designed, prospective trials of treatment of snake envenomation with antivenom tend to be small, with the largest recent trial including only 121 cases distributed across 18 centers in eight states throughout the US [2]. The largest published US series of snakebites derives from national poison center data, which provide very limited and non-verified information regarding clinical presentations, response to treatment, and outcomes [1].

In an attempt to enhance scientific knowledge of the complex processes inherent to snake envenomation in humans, the American College of Medical Toxicology (ACMT) established the North American Snakebite Registry (NASBR) in 2013. Prior to establishment of the NASBR, there was no national database of detailed, prospective information regarding snake envenomation in the United States. The NASBR is a sub-registry of the larger Toxicology Investigators Consortium (ToxIC) Registry, a toxicology surveillance and research tool that prospectively gathers de-identified patient information from medical toxicologists that care for patients at almost 100 healthcare facilities around the country [3]. In order to participate in the Toxicology Investigators Consortium and enter cases into the ToxIC Registry and the NASBR sub-registry, medical toxicologists must perform direct, in-person evaluations of patients in the inpatient or ambulatory setting. Telephone consultations are not sufficient for participation and the ToxIC Registry database is not affiliated with poison centers. Participation in the Registry is voluntary and ACMT invites all medical toxicology physicians who engage in the clinical practice of medical toxicology to participate.

The purpose of the NASBR is to gather de-identified, detailed, prospective information regarding snakebites, including patient characteristics, clinical effects of envenomation, response to treatment and outcomes. Case information in the NASBR is provided by medical toxicologists across the United States who are directly involved in the bedside care of the patient, assuring a high degree of accuracy of the toxicological data entered.

The purpose of this report is to present data on the epidemiology, clinical course, and management of snakebites in the US obtained over the first 3 years following creation of the NASBR.

Methods

In 2012, the ACMT established a focus group of individuals with expertise in snake envenomation to create a detailed data collection tool for the NASBR. All ToxIC Registry participants with a history of entering snakebite cases into the Registry were invited to review and comment on the proposed data collection tool, which lead to revision and creation of the final data collection instrument. In early 2013, all ToxIC Registry sites were invited to participate in the new NASBR. Invitations were distributed through email, social media, announcements at national society meetings, and personal communication with practicing medical toxicologists in snake-endemic regions. Prior to joining, prospective participants were asked to sign a memorandum of understanding in which they agreed to enter all of their snakebite cases into the NASBR.

The initial data collection tool included: (1) snake information including snake type and whether the involved snake was wild or captive; (2) patient information including demographics, medical and substance use history; and (3) bite information, including bite site, clinical signs and symptoms, diagnostic findings, treatments, complications, and outcomes. Information was collected throughout the initial hospitalization and treatment phase, and during out-patient follow up when available. “Initial presentation” was used to describe the entire time period from when the bite occurred through when treatment was considered to be complete, usually at the time of discharge from the hospital. “Follow-up” was used to indicate patient assessments occurring after the initial presentation. Follow-up was used to identify late morbidity, including the need for re-treatment and/or re-admission to the hospital. Events or effects occurring during the follow-up period are described as “late” as opposed to “early” effects that occurred during the initial presentation. For example, bleeding could occur during the initial presentation and thus be described as “early,” or it could occur after completion of treatment and thus be described as “late.” Neurotoxicity was defined as paresthesias, fasciculations or myokymia, or objective weakness. Method of species identification was not reported in the Registry and the determination of snake type was taken

as that reported by the treating medical toxicologist. Means of determination of intoxication by ethanol or other drugs of abuse was not included in the data collection form.

Some additions to the data collection tool were made after year one as a result of feedback from participants. These additions included fields to indicate whether patients with lower extremity bites were wearing footwear, and if so, what kind, and whether the bite occurred in an occupational setting. Another change that was instituted at the beginning of year two was improved data quality oversight, with a dedicated research nurse with experience in snake envenomation reviewing all data entered and communicating with sites to resolve missing or incongruous data.

Cases were entered into a password-protected, encrypted, on-line data collection interface maintained by ACMT. The NASBR, like the ToxIC Registry, is compliant with the Health Insurance Portability and Accountability Act (HIPAA) and does not collect any protected health information. Per HIPAA requirements age for individuals 90 or over were recorded as greater than 89. The determination of the mean age used age 89 for all patients with age over 89. While the ToxIC Registry and associated sub-registries have been reviewed by the Western Institutional Review Board, each participating site is requested to obtain consent from their own IRB if Western IRB determinations are not recognized as equivalent to local IRB determinations.

All cases entered into the NASBR between January 1, 2013 and December 31, 2015 were identified. Descriptive statistics are used to report results.

Results

Results are presented in Figs. 1, 2, 3, 4, and 5 and Tables 1, 2, 3, 4, 5, 6, 7, 8, and 9. Fourteen sites participated in the NASBR, distributed across 10 states (Fig. 1). In year one, 8 sites entered cases, in year two 14 sites, and in 2015, 10 sites. A total of 450 cases were entered over the 3-year period. Figure 2 provides the number and types of native pit viper bites reported by state. Most cases were from Arizona (36.4%) and Texas (35.1%).

Snakes

The vast majority (99%) of snakebites entered into the registry were from native species (Fig. 2). Over 99% of these were pit vipers, with only three coral snakebites reported (all *Micrurus tener)*. Rattlesnakes were responsible for 56.3% of bites and Copperheads for 29.4%. Five non-native snakebites were reported, with species identified as *Crotalus durissus*, *Trimeresurus albolabris*, *Trimeresurus insularis*, an African Bush Viper (*Atheris spp.*), and one unknown species. Encounters with wild snakes resulted in 97% of bites, while 3% followed interactions with captive snakes. Nineteen percent of bites were reported to follow intentional interaction with the snake. (Fig. 3, Table 1) Of those intentional human-snake interactions, 91% involved male patients and all were associated with upper extremity envenomations. Of the upper extremity bites, 42.6% were reported to follow intentional interactions with the snake.

Fig. 1 Location of 14 sites participating in the North American Snakebite Registry between 2013 and 2015

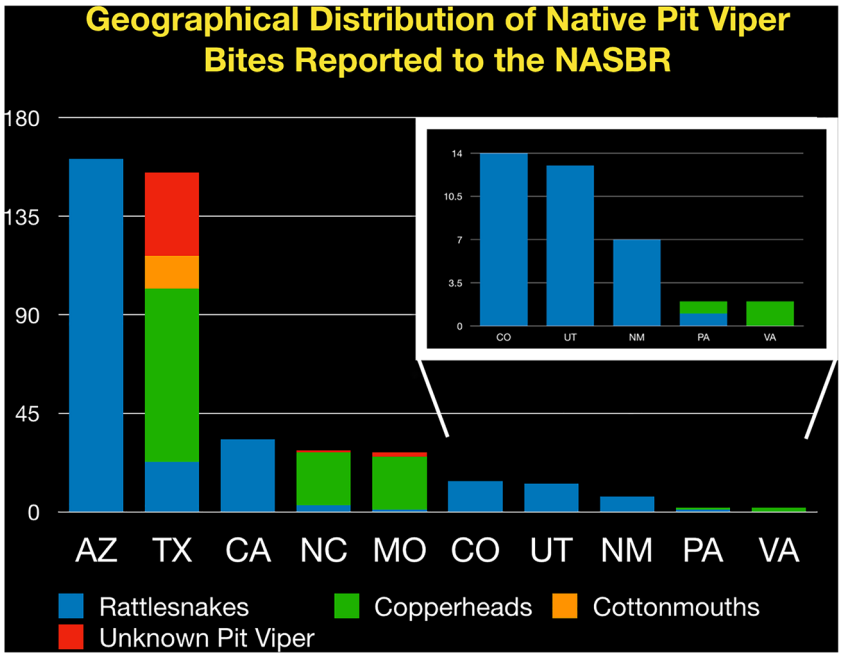

Fig. 2 Total NASBR $n = 450$. Native pit viper $n = 442$ (three coral snake and five non-native snake bites not included in this figure). Rattlesnakes $n = 256$; copperheads $n = 130$; cottonmouths $n = 15$; unknown pit vipers $n = 41$

The specific species was reported in 49 of the 256 (19.1%) native rattlesnake bites. (Table 2) Of these, the most common species identified were *Crotalus atrox* (Western Diamondback rattlesnake) in 18 cases and *Crotalus oreganus lutosus* (Great Basin rattlesnake) in 12 cases.

Demographics

Demographics and bite location for all patients are provided in Table 3. Patients ranged in age from 1 year to greater than 89 years, with a mean age of 34.9 years. 69.3% were men and 28.2% were children age 12 and under (mean age 6.6 years). No pregnant patients were reported. Data on race and Hispanic ethnicity were collected as of July 2014. Among the 304 cases reporting these fields (2014–2015), 84.5% occurred in Caucasians, with 5.3% of cases in Native Americans and 6.6% reporting their race as other. The majority of bites, 245 of 450 (54.2%), were on the lower extremity; however, more than half of bites in men (54.8%) were to the upper extremity. By comparison, only 22.5% of bites in women were to the upper extremity. Bites on the upper extremity occurred most often on a digit (146 of 202; 72.3%), while lower extremity bite locations were more evenly distributed between the foot, ankle or leg. Bites to toes were rare (6.7%).

In children 18 years of age and under, lower extremity bites were much more common than upper extremity bites (69.5 vs. 29.5%). The proportion of bites to the lower extremity in children (69.5%) was higher compared to adults (43.2%).

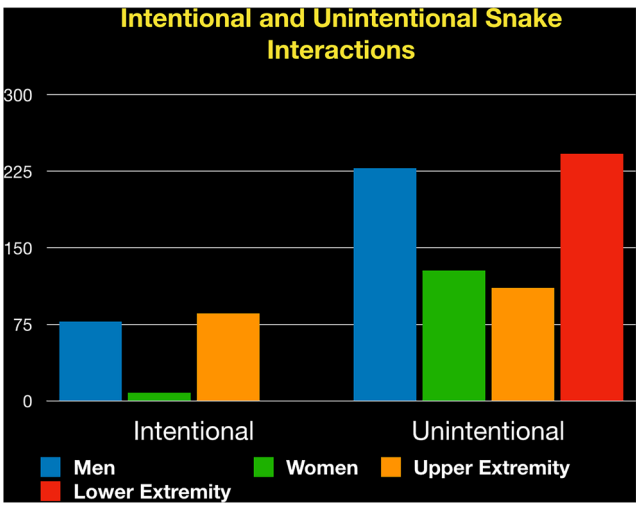

Fig. 3 Native and non-native snake bites. Eight of 450 cases not included due to missing interaction detail

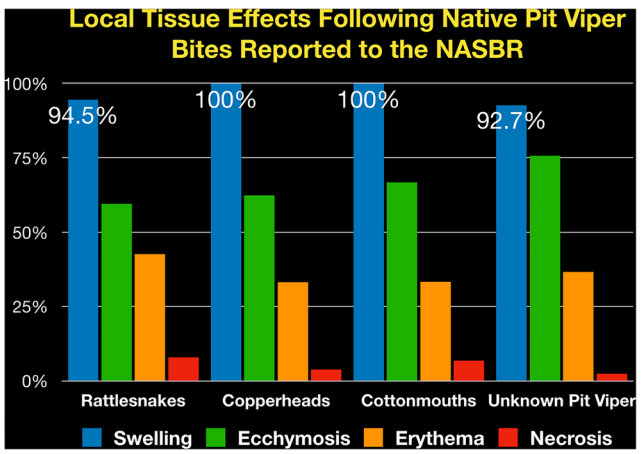

Fig. 4 Rattlesnakes $n = 256$; copperheads $n = 130$; cottonmouths $n = 15$; unknown pit vipers $n = 41$

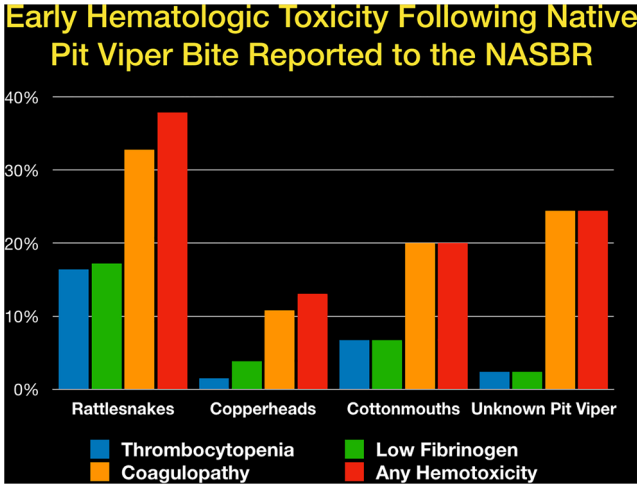

Fig. 5 Rattlesnakes $n = 256$; copperheads $n = 130$; cottonmouths $n = 15$; unknown pit vipers $n = 41$. Thrombocytopenia = platelets ≤ 120 K/mm^3; low fibrinogen = fibrinogen ≤ 170 mg/dL; coagulopathy = prothrombin time (PT) ≥ 15 s; any hemotoxicity = laboratory finding for at least one threshold value (platelets, fibrinogen and/or PT)

Of the 194 cases of lower extremity envenomation reported in 2014–2015, 27% were not wearing shoes at the time of the bite. For the 84 cases in which the type of shoes worn was reported, 64.3% wore sandals or flip-flops. During this time period there were 27 (11%) bites that were reported as occupational, and these have been described separately [4].

Chronic medical conditions were diverse. Hypertension was reported in 57 (12.7%), asthma in 14 (3.1%), and diabetes mellitus in 13 (2.9%) patients. Use of antiplatelet or anticoagulant medications was reported in 24 (5.3%) and 6 (1.3%) patients, respectively. Three patients used both type of medications. Tobacco use was reported in 66 (14.7%) patients and ethanol use within 4 h of the snakebite in 38 (8.4%). Twenty-seven patients (6%) reported stimulant, marijuana or prescription opioid use.

Twenty-three patients (5.1%) reported a previous snakebite. Up to five previous snakebites were reported in individual patients. Of these 23 cases, 12 had previously received antivenom, although the specific type of antivenom was not reported.

Clinical Presentation

Local tissue findings were reported in 100% of patients with native pit viper bites. A breakdown of findings by type of snake is presented in Fig. 4 and Table 4. Swelling was present in 96.2% of patients. Ecchymosis, present in 62%, was the next most common finding, followed by erythema in 38.9% of cases. Necrosis was most common in rattlesnake bites, occurring in 7.8%.

Systemic effects are reported in Table 5. Vomiting was the most common systemic effect, occurring in 13.6% of cases. However, vomiting occurred prior to administration of opioid analgesics in only 7.2%. The next most common systemic effect was bleeding, occurring in 6.3% of cases. Although most often associated with rattlesnake envenomation, bleeding was also reported with copperhead bites. Neurotoxicity was reported in 5.2% of cases, again with rattlesnake bites responsible for the most reports.

Of the 28 patients reported to have bleeding, this was described as nuisance bleeding in all cases, manifesting as epistaxis, gingival bleeding, or oozing blood from wounds. One of these 28 patients reported use of an antiplatelet medication. There were no cases of severe bleeding reported during the initial presentation.

Assessment

Laboratory findings during the initial presentation are described in Fig. 5 and Table 6. Thrombocytopenia, defined as platelet count ≤ 120 K/mm^3, and hypofibrinogenemia, defined as fibrinogen ≤ 170 mg/dL, occurred at similar rates and were more common findings in rattlesnake versus copperhead or cottonmouth envenomations.

Progression of envenomation was assessed using various methods, with most clinicians reporting use of several parameters (up to five) to assess progression. These included asking patient how pain and swelling are doing (83%), monitoring leading edge of swelling (63%), sequential measurement of extremity circumference (62%), clinical judgment without

Table 1 Snake interactions (native and non-native species)

Interaction	Total *n* (%)	Men *n* (%)	Women *n* (%)	UE only *n* (%)	LE only *n* (%)	Other/multiple location *n* (%)
Intentional	86 (19.1)	78 (25.0)	8 (5.8)	86 (42.6)	0 (0.0)	0
Unintentional	356 (79.1)	228 (73.1)	128 (92.8)	111 (55.0)	242 (98.8)	3 (100.0)
Missing*	8 (1.8)	6 (1.9)	2 (1.4)	5 (2.5)	3 (1.2)	0
Totals	450	312	138	202	245	3

$N = 450$ includes eight cases with no interaction detail (*); % based on column totals; *UE* = upper extremity ($N = 202$ UE only); *LE* = Lower extremity ($N = 245$ LE only); multiple location/other = UE and LE or UE and face/neck or groin/torso ($N = 3$ cases)

Table 2 Rattlesnake Species

Rattlesnakes	Number (%)
Unknown species	207 (80.9)
Western diamondback (*Crotalus atrox*)	18 (7.0)
Great Basin (*Crotalus oreganus lutosis*)	12 (4.7)
Prairie (*Crotalus viridis*)	5 (2.0)
Sidewinder (*Crotalus cerastes*)	3 (0.8)
Southern Pacific (*Crotalus oreganus helleri*)	3 (0.8)
Grand Canyon (*Crotalus oreganus abyssus*)	2 (0.4)
Arizona Black (*Crotalus cerberus*)	1 (0.2)
Massasauga (*Sistrurus catenatus*)	1 (0.2)
Mojave (*Crotalus scutulatus*)	1 (0.2)
Pygmy (*Sistrurus millarius*)	1 (0.2)
Speckled (*Crotalus mitchelli*)	1 (0.2)
Timber (*Crotalus horridus*)	1 (0.2)

N = 256 (100%) rattlesnake bites

objective measurement (33%), monitoring laboratory studies (20%), and calculation of snakebite severity score (0.9%).

Concern for compartment syndrome was documented in eight patients, with only two undergoing measurement of compartment pressure. The compartment pressures in these two cases were reported at 69 and 65 mmHg.

Treatment

Thirty-eight patients (8.4%) were reported to have received some type of field therapy after pit viper bite. The extremity was immobilized in 15 patients. Field therapy not supported by standard consensus recommendations occurred in 33 cases [5]. Tourniquets were placed in 14 cases, ice was applied in 10, a suction or Sawyer device was used in seven, and two patients incised the wound. The mean time from the bite to a healthcare facility was 2.75 h, with a range of 15 min to 6 days. Initial therapy in the emergency department included elevation of the extremity in 92.9% of patients. Opioids were administered to 83% of patients, anti-emetics to 33%, and antibiotics to 6%. Intravenous fluid resuscitation was used in 22% of patients. Five patients received vasopressors, four to treat hypotension and one to treat an allergic reaction. Two patients were intubated.

Eighty-four percent of patients with pit viper envenomation were treated with the antivenom Crotalidae Polyvalent Immune Fab (FabAV; CroFab®). Four additional patients with copperhead envenomation were enrolled in a placebo-controlled trial and received a blinded study drug. Time to treatment with antivenom and details regarding dosing are provided in Table 7. Forty-seven percent of patients treated with FabAV received maintenance doses of antivenom after

Table 3 Bite locations (native and non-native species)

Location	Total *n* (%)	Men *n* (%)	Women *n* (%)	≤ 18 years^ *n* (%)	≥ 19 years^ *n* (%)
UE bite	202 (44.9)	171 (54.8)	31 (22.5)	56 (29.5)	146 (56.4)
Finger	146 (32.4)	125 (40.1)	21 (15.2)	44 (23.2)	102 (39.4)
Hand	40 (8.9)	32 (10.3)	8 (5.8)	9 (4.7)	31 (12.0)
Forearm	8 (1.8)	8 (2.6)	0	1 (0.5)	7 (2.7)
Upper arm	2 (0.4)	2 (0.6)	0	1 (0.5)	1 (0.4)
Multiple UE sites	5 (1.1)	3 (1.0)	2 (1.4)	1 (0.5)	4 (1.5)
UE NOS*	1 (0.2)	1 (0.3)	0	0	1 (0.4)
LE bite	245 (54.2)	138 (44.2)	107 (77.5)	132 (69.5)	112 (43.2)
Toe	30 (6.7)	18 (5.8)	12 (8.7)	21 (11.1)	8 (3.1)
Foot	93 (20.7)	43 (13.8)	50 (36.2)	49 (25.8)	44 (17.0)
Ankle	74 (16.4)	37 (11.9)	37 (26.8)	37 (19.5)	37 (14.3)
Lower leg	45 (10.0)	37 (11.9)	8 (5.8)	23 (12.1)	22 (8.5)
Thigh	1 (0.2)	1 (0.3)	0	1 (0.5)	0
Multiple LE sites	1 (0.2)	1 (0.3)	0	0	1 (0.4)
LE NOS*	1 (0.2)	1 (0.3)	0	1 (0.5)	0
Groin/Torso	1 (0.2)	1 (0.3)	0	1 (0.5)	0
UE and LE sites	1 (0.2)	1 (0.3)	0	0	1 (0.4)
UE (hand) and Face/neck	1 (0.2)	1 (0.3)	0	1 (0.5)	0
Totals	450	312	138	190	259

UE upper extremity, *LE* lower extremity

*Location on UE or LE not specified

^Age missing for one male patient with LE bite (toe)

Table 4 Local tissue effects following native pit viper bites

Clinical Finding	Rattlesnakes (*n* = 256)	Copperheads (*n* = 130)	Cottonmouths (*n* = 15)	Unknown pit viper (*n* = 41)
Swelling *n* (%)	242 (94.5)	130 (100.0)	15 (100.0)	38 (92.7)
Ecchymosis *n* (%)	152 (59.4)	81 (62.3)	10 (66.7)	31 (75.6)
Erythema *n* (%)	109 (42.6)	43 (33.1)	5 (33.3)	15 (36.6)
Necrosis *n* (%)	20 (7.8)	5 (3.8)	1 (6.7)	1 (2.4)

% based on species total *n*

the doses given to obtain control of the envenomation. Maintenance doses were identified as such, as opposed to additional doses given after control, on an "as needed" basis. The number of maintenance doses ranged from 2 to 12 vials. Maintenance doses were used in 43.5% of copperhead bites and 25.4% of rattlesnake bites treated with antivenom. Acute adverse reactions to antivenom were reported in 2.7% of patients. Additional details regarding adverse events have been published separately [6].

A total of 34 patients (7.6%) received at least one dose of antibiotics during their stay. Use was described as "prophylactic" or "empiric" in 94% of cases. Only two patients were reported to have a confirmed infection during the initial hospitalization, with one of these due to a pre-existing staphylococcus infection and unrelated to the snakebite. The second patient underwent multiple procedures (multiple incision and drainage, multiple debridements, skin graft) during initial treatment. After hospital discharge, the patient was re-admitted to the hospital due to an abscess and underwent additional treatment including surgery.

Twenty-five procedures were performed during the initial hospitalization. Debridement of bullae was the most common, accounting for 18 (72%) procedures, and was performed only in patients with upper extremity bites. Six patients, two with lower and four with upper extremity bites, had a fasciotomy. Of these, two (both lower extremity bites) had documentation of elevated compartment pressure prior to the procedure. One patient underwent a dermotomy.

Two patients received packed red blood cells during their initial treatment. Both had documented pre-existing anemia as the indication for the transfusion and neither were reported to have envenomation-related bleeding.

Outcomes

Among all pit viper envenomation cases, 205 patients (46.6%) were admitted to an intensive care unit (ICU), with one-half for less than 24 h. Total hospital length of stay was documented in 24-h increments and is reported in Table 8. Total length of stay was less than 48 h in 78.4% of cases. Forty percent of cottonmouth envenomations were hospitalized between 49 and 72 h, and length of stay lasting more than 72 h was most common in rattlesnake bites, reported in 9.4% of cases.

Two hundred and eighty patients, 63.3% of native pit viper bites, received some form of follow-up assessment including

Table 5 Systemic effects following native pit viper bite

Clinical Effect *n* (%)	Rattlesnakes (*n* = 256)	Copperheads (*n* = 130)	Cottonmouths (*n* = 15)	Unspecified pit viper (*n* = 41)
Vomiting	32 (12.5)	17 (13.1)	3 (20.0)	8 (19.5)
prior to opioids	20 (7.8)	7 (5.4)	2 (13.3)	3 (7.3)
after opioids	12 (4.7)	6 (4.6)	1 (6.7)	3 (7.3)
Diarrhea	5 (2.0)	2 (1.5)	1 (6.7)	0
Hypotension	13 (5.1)	2 (1.5)	0	0
Tachycardia	16 (6.3)	3 (2.3)	0	2 (4.9)
Angioedema	5 (2.0)	0	0	0
Neurotoxicity	21 (8.2)	1 (0.8)	1 (6.7)	0
*Rhabdomyolysis	10 (3.9)	0	1 (6.7)	2 (4.9)
^Bleeding	21 (8.2)	4 (3.1)	0	3 (7.3)
#Respiratory Failure	2 (0.8)	0	0	0

*Rhabdomyolysis defined as CPK ≥ 1000 IU/L; % based on species total *n*

^Bleeding that occurred early, during initial treatment phase

Respiratory failure = requiring mechanical ventilation

Table 6 Early Hematologic Toxicity following Native Pit Viper Bite

Finding *n* (%)	Rattlesnakes (*n* = 256)	Copperheads (*n* = 130)	Cottonmouths (*n* = 15)	Unspecified pit viper (*n* = 41)
Thrombocytopenia (platelets ≤ 120 K/mm^3)	42 (16.4)	2 (1.5)	1 (6.7)	1 (2.4)
Hypofibrinogenemia (fibrinogen ≤ 170 mg/dL)	44 (17.2)	5 (3.8)	1 (6.7)	1 (2.4)
Coagulopathy (PT >15 sec)	84 (32.8)	14 (10.8)	3 (20.0)	10 (24.4)
Any hemotoxicity	97 (37.9)	17 (13.1)	3 (20.0)	10 (24.4)

Total number of native pit viper cases *N* = 442; % based on species total *n*

Table includes only initial presentation

Any hemotoxicity = laboratory finding for at least one threshold value (platelets, fibrinogen and/or PT)

the majority of the rattlesnake (73.4%) and copperhead (55.4%) bites. However, laboratory studies were repeated as part of the follow-up assessment in only 1 of the 130 patients with copperhead bite. In contrast, 62.9% of rattlesnake bite patients had at least one follow-up laboratory assessment. See Table 9. Timing for first follow-up laboratory assessment ranged from 1 to 20 days following antivenom treatment. Late bleeding was reported to be present in five patients. Bleeding complications included one major (vaginal) and four nuisance (sites: gingiva, rectal fissure, cat scratch wound, nose) reports. The patient with the late major bleeding episode was re-admitted and treated with antivenom and platelet transfusion. None of the patients with late bleeding reported use of anticoagulant or antiplatelet medications.

Twelve patients (4.3% of those with follow-up) were re-admitted after initial presentation and hospital discharge, 11 with rattlesnake and 1 with a copperhead bite. Among the 11 re-admissions post-rattlesnake envenomation, five patients received additional antivenom due to late hematologic toxicity (with one report of bleeding) while three received additional antivenom for treatment of swelling. Two of these patients were re-admitted twice. One patient received additional antivenom on both re-admissions. The first was for late hypofibrinogenemia occurring 5 days after last FabAV treatment, and the second was after an additional 8 days for recurrent thrombocytopenia. The second patient with two re-admissions was re-treated with FabAV due to recurrent thrombocytopenia 6 days after last FabAV treatment, and was re-admitted again 9 days later for treatment of an abscess. Two additional patients were re-admitted due to late thrombocytopenia but did not receive additional antivenom, and another was re-admitted for treatment of an abscess. One patient with a copperhead envenomation was re-admitted for pain and swelling but refused treatment with antivenom.

There were no deaths reported. The median length of follow-up after the envenomation was 9 days (IQR = 6–12). Thirty of the 280 patients (10.7%) with follow-up information were reported to have residual functional deficit at the final follow-up. Loss of mobility in the hand or foot was reported most often (19 cases, 63.3% of those reporting deficit), followed by residual deficit in the knee or elbow (13.3%) or digit (26.7%).

Table 7 Crotalidae Polyvalent Immune Fab antivenom treatment for native pit viper bite

	n	Time to AV hours [@] [median (IQR)]	Initial AV dose (# vials) [median (IQR)]	Total AV dose[^] (# vials) [median (IQR)]
All patients*	371	3.0 [2–5]	4 [4–6]	10 [6–14]
Age 19+	216	2.5 [2–4]	5 [4–6]	10 [6–14]
Age ≤ 18	154	3.5 [2–6]	4 [4–6]	10 [6–12]
Rattlesnakes	229	2.5 [2–4]	6 [4–6]	10 [6–15]
Copperheads	93	4 [2.5–8]	4 [4–5]	6 [4–10]
Cottonmouths	13	3 [2–5.5]	4 [4–4]	10 [10–18]
Unspecified pit vipers	26	5 [3–10]	4 [4–6]	10 [6–12]

Total *N* = 371 based on any Native Pit Viper receiving antivenom (excludes n = 4 cases involved RCT)

*Excludes 1 case with missing age

@Excludes 10 cases missing time to antivenom

^Excludes 3 cases missing vial detail (initial and total vial)

Table 8 Initial hospital length of stay

Snake Type	<24 h n (%)	25–48 h n (%)	49–72 h n (%)	>72 h n (%)
Rattlesnakes (n = 256)	73 (28.5)	109 (42.6)	45 (17.6)	24 (9.4)
Copperheads (n = 130)	57 (43.8)	60 (46.2)	7 (5.4)	3 (2.3)
Cottonmouths (n = 15)	3 (20.0)	5 (33.3)	6 (40.0)	0
Unknown pit viper (n = 41)	24 (58.5)	15 (36.6)	2 (4.9)	0
Coral (n-3)	2 (66.7)	1 (33.3)	0	0

Excludes non-native cases; data missing for five rattlesnake, two copperhead and one cottonmouth case; % based on species total

Discussion

In most parts of North America, snakebite is an uncommon or rare event. Even in states such as Texas or Florida, where the greatest number of snakebites are reported, the number of patients presenting to any given hospital annually with the diagnosis is quite low, and most physicians have never encountered a patient with a snake envenomation [1]. Despite approximately 5000 cases of venomous snakebite reported to poison centers each year, even the largest published case series and studies are generally limited to a few hundred cases. In such reports, cases often derive from a single center or geographic region [1, 7–10]. While clinical trials of antivenom may better represent the geographic diversity of species responsible for snakebite in the US, these studies also tend to be limited by small numbers [2, 11]. National poison center data – based studies include the largest numbers of patients with snakebites and can provide interesting epidemiological information, but rarely contribute useful clinical information to the medical literature [1, 12, 13].

The NASBR is the first and only national, multicenter registry for collection of detailed information relating to snake envenomation. In the first 3 years of existence of the NASBR, 450 snakebite cases were entered into the registry. Distribution of cases among men, women, and children age 18 years and younger was very similar to that which has been reported in other national databases [1, 14]. The predominance of rattlesnake and copperhead bites reported to the registry, as compared to cottonmouth, coral snake and non-native venomous snakebites, is also comparable to that noted in poison center based studies of North American snakebites [1, 15].

In the NASBR, more bites were located on the lower extremity than the upper extremity. Although exceptions exist, lower extremity bites typically occur following an unexpected encounter with a snake, while upper extremity bites are more likely to result from a person attempting to handle a snake. One study of snakebite in the US found the majority of bites to result from such intentional interactions. The concept has been described as bite "legitimacy" [16]. The predominance of upper extremity bites reported in numerous studies is consistent with intentional interactions with the snake [16–19]. Contrary to these historical reports, our results reflect a change in this pattern, and are more consistent with a recent study of snakebite reports in the media, which found 68% of bites to be legitimate encounters [20].

The association between snakebite and presence or type of shoes worn at the time of the bite has not been previously examined. We found that more than a quarter of patients were

Table 9 Late hematologic toxicity in rattlesnake envenomation

State	Total cases	Total cases with any follow-up *n* (% total)	Late bleeding *n* (%)[1]	Re-admission* *n* (%)[1]	Re-treatment with AV *n* (%)[1]	≥ 1 follow-up with laboratory assessment *n* (%)[1]	Platelet count ≤ 120 K/mm^3 *n* (%)[2]	Fibrinogen ≤170 mg/dL *n* (%)[2]	PT ≥ 15 s *n* (%)[2]	Any late hemotoxicity[@] *n* (%)[2]
All	256	188 (73.4)	5 (2.7)	7 (3.7)	5 (2.7)	161 (85.6)	39 (24.2)	39 (24.2)	29 (18.0)	69 (42.9)
AZ	161	139 (86.3)	4 (2.9)	4 (2.9)	3 (2.2)	131 (94.2)	32 (24.4)	37 (28.2)	27 (20.6)	60 (45.8)
CA	33	12 (36.4)	1 (8.3)	3 (25.0)	2 (16.7)	9 (75.0)	4 (44.4)	1 (11.1)	0	4 (44.4)
NM	7	7 (100.0)	0	0	0	7 (10.0)	2 (28.6)	0	0	2 (28.6)
UT	13	7 (53.8)	0	0	0	6 (85.7)	0	0	1 (16.7)	1 (16.7)
CO	14	7 (50.0)	0	0	0	4 (57.1)	1 (25.0)	0	0	1 (25.0)
TX	23	12 (52.2)	0	0	0	4 (33.3)	0	1 (25.0)	1 (25.0)	1 (25.0)
NC	3	2 (66.7)	0	0	0	0	0	0	0	0
PA	1	1 (100.0)	0	0	0	0	0	0	0	0
MO	1	1 (100.0)	0	0	0	0	0	0	0	0

AV antivenom; follow-up based on contact post discharge from initial hospitalization

[1] *N* = 188 rattlesnake bites (73.4%) with at least one follow-up; % based on total (and by state) with any follow up

[2] *N* = 161 rattlesnake bites (62.9%) with at least one follow-up with labs; % based on total (and by state) with labs at follow-up

[@] Any late hemotoxicity at F/U, Fib ≤ 170 mg/dL, PT ≥ 15 s, and/or platelets ≤ 120 K/mm3

*Re-admissions include only those re-admitted for hematologic toxicity; 1/7 patients re-admitted and re-treated twice

not wearing any shoes at the time of the bite. The majority of those who were wearing shoes wore sandals or flip-flops. This finding provides evidence to support public education to wear protective footwear in regions where venomous snakes are endemic.

The NASBR illustrates the spectrum of clinical findings that may occur following snake envenomation in the US. While local tissue swelling and necrosis are well-known effects of pit viper envenomation, other local effects receive less attention in the medical literature, despite being much more common than necrosis. In the initial hours to days after a bite, erythema results from inflammatory effects of venom. Erythema was reported in 39% of patients in this series. Despite uniform recommendations against routine use of antibiotics in the management of North American snakebites, 7.6% of patients received at least one dose [21, 22]. A greater awareness of the expectation of the finding of erythema may lead to less unnecessary antibiotic use.

Early nuisance-type bleeding was reported in 6.3% of cases. A previous large retrospective review of patients with rattlesnake envenomation in Arizona found only 2.0% of patients to have early bleeding [10]. Considering that the NASBR population includes copperhead and cottonmouth envenomations, which are less likely to experience bleeding due to the lower incidence of venom-induced coagulopathy and thrombocytopenia, our rate of bleeding is surprisingly high. This is most likely due to the prospective nature of the data collection in the NASBR and represents a more accurate rate of bleeding than has been found when charts are reviewed retrospectively.

Patients who take anticoagulant or antiplatelet medications have been reported to have greater bleeding risk following rattlesnake envenomation than patients not on these medications [10]. In the NASBR, there were 27 (6.0%) patients taking anticoagulants or antiplatelet medications and only one was reported to have nuisance bleeding at initial presentation. Thus, in this geographically diverse population that includes both rattlesnake and copperhead envenomations, these medications did not appear to increase risk of bleeding.

Other patient-related factors such as co-morbid conditions, medication use, and substance use have the potential to affect the severity of an envenomation. However, there has been very little investigation into how these factors may influence the severity and specific findings associated with envenomation and/or response to treatment. It is logical that conditions such as cardiovascular disease, asthma, or diabetes may complicate a patient's presentation and recovery. The small number of cases included in previous studies have not allowed evaluation of these associations. As cases accumulate in the NASBR, a closer examination of the relationship between patient-related factors and morbidity after snakebite can be undertaken.

Another important finding in this study is in regard to compartment syndrome. Compartment syndrome is uncommon following snake envenomation, and recommendations exist against the once common practice of performing fasciotomy without first documenting elevated compartment pressure (ICP) [23, 24]. Only eight (1.8%) patients in this study were reported to have findings on exam that were concerning for diagnosis of compartment syndrome. Six received fasciotomies yet only two had ICP measured to confirm elevated compartment pressures. In one of the cases where fasciotomy was performed without documentation of ICP, the medical toxicologist indicated the procedure was done before their involvement. These data reaffirm the rarity of compartment syndromes following North American snake bites and serve to emphasize the need for documentation of elevated compartment pressures before fasciotomies are done.

The only antivenom available to treat native crotaline envenomations during the time of this study was Crotalidae Polyvalent Immune Fab (FabAV; CroFab®). The manufacturer-recommended initial dose for FabAV is 4–6 vials. Initial doses as low as one vial were reported in the NASBR, which may reflect limited availability of antivenom at the transferring facility or the initial treating clinician's lack of familiarity with treatment of snake envenomation. As per the US Food and Drug Administration dosing guidelines for FabAV, maintenance doses should be given after control of the envenomation has been established [25]. However in 2011, a treatment algorithm for management of pit viper envenomation with FabAV was published which suggested that in some situations, such as with minor envenomations or in facilities where close observation by a physician expert is available, maintenance doses may not be necessary [5]. Our results demonstrate a higher rate of maintenance use in treatment of copperhead envenomations than in rattlesnake envenomations. This is surprising since copperhead envenomations are generally less severe than rattlesnake envenomations. The pattern most likely reflects different practices among participating sites. Some medical toxicologists choose to withhold routine maintenance doses due to the high cost of FabAV and instead watch patients for early recurrent venom effects and provide as-needed doses of antivenom [26]. The doses of maintenance therapy that were reported in the NASBR ranged from 2 to 12 vials. Standard maintenance therapy involves administration of two vials every 6 h for three doses, totaling six vials. Deviations from this standard may occur when clinicians decide to terminate maintenance therapy early or extend maintenance therapy, however, reasons for using non-standard doses were not documented in the NASBR.

Due to the risk for late hemotoxicity following treatment of rattlesnake envenomation with FabAV, it has been recommended that all patients have platelets and fibrinogen checked 2–3 days after last FabAV dose and again 5–7 days after last dose, at a minimum [5]. Only 62.9% of rattlesnake

envenomation patients in the NASBR had laboratory follow-up documented, however, patients may have followed with their primary care providers and laboratory results may not have been available to the medical toxicologists participating in the NASBR. Only a single patient out of 450 was reported to develop a major late bleeding complication. This low incidence is consistent with two previous studies which found very low rates of late major bleeding complications [10, 27].

Limitations

The NASBR includes sites distributed across the United States, but does not include some states where a large number of bites occur, such as Florida. As a result, the NASBR misses Eastern coral snake envenomations, which produce more severe clinical manifestations than the Texas coral snake. The strength of the NASBR is also dependent on accurate and complete reporting of data from participating sites. Although sites are routinely contacted to provide clarification or missing data, sometimes omissions occur resulting in incomplete data. Lastly, the initial data collection tool of the NASBR, which included the date range of this report, did not determine level of certainty with species identification.

Conclusions

The North American Snakebite Registry is a powerful tool for gathering data on venomous snakebites across the United States. In its initial years, useful information has already been gained. Data regarding footwear will inform public health interventions and education, and information regarding the frequency and severity of clinical findings may help physicians better anticipate effects and manage snakebite. As the number of cases in the NASBR grows, associations between patient-related factors and outcomes may be studied.

The 2013-2015 ToxIC Snakebite Study Group: Anna Arroyo-Plascencia, Vikhyat S. Bebarta, Michael C. Beuhler, William Boroughf, Jeffrey Brent, Daniel Brooks, Sharan Campleman, E. Martin Caravati, James D. Cao, Nathan Charlton, Steven Curry, Michael Darracq, William Dribben, Kimberlie Graeme, Spencer Greene, Benjamin Hatten, Kennon Heard, C William Heise, Janetta Iwanicki, Angela Padilla-Jones, Aaron Min Kang, William P Kerns II, Thomas Kibby, Joshua King, Ronald Kirschner, Kurt Kleinschmidt, Ken Kulig, Michael Levine, Rachel Levitan, Elizabeth Moore, Philip Moore, Michael Mullins, Eleanor Oakley, Ayrn O'Connor, Nancy Onisko, Angie Padilla-Jones, Tammy Phan, Frank LoVecchio, Anne-Michelle Ruha, Steven A. Seifert, Daniel J Sessions, Aaron Skolnik, Eric Smith, Meghan Spyres, An Tran, S. Eliza Halcomb, Evan S. Schwarz, Shawn M. Varney, Rais Vohra, Brandon J. Warrick, Sam G. Wang, Paul Wax, Brian J. Wolk.

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Compliance with Ethical Standards

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