



Acute adverse events associated with the administration of Crotalidae polyvalent immune Fab antivenom within the North American Snakebite Registry

Kurt Kleinschmidt, Anne-Michelle Ruha, Sharan Campleman, Jeffrey Brent & Paul Wax

To cite this article: Kurt Kleinschmidt, Anne-Michelle Ruha, Sharan Campleman, Jeffrey Brent & Paul Wax (2018): Acute adverse events associated with the administration of Crotalidae polyvalent immune Fab antivenom within the North American Snakebite Registry, Clinical Toxicology, DOI: [10.1080/15563650.2018.1464175](https://doi.org/10.1080/15563650.2018.1464175)

To link to this article: <https://doi.org/10.1080/15563650.2018.1464175>



Published online: 24 Apr 2018.



Submit your article to this journal [↗](#)



Article views: 34



View related articles [↗](#)



View Crossmark data [↗](#)

CLINICAL RESEARCH



Acute adverse events associated with the administration of Crotalidae polyvalent immune Fab antivenom within the North American Snakebite Registry

Kurt Kleinschmidt^a, Anne-Michelle Ruha^b, Sharan Campleman^c, Jeffrey Brent^d and Paul Wax^a

^aDepartment of Emergency Medicine, Division of Medical Toxicology, University of Texas Southwestern Medical Center, Dallas, TX, USA;

^bDivision of Medical Toxicology and Precision Medicine, University of Arizona College of Medicine, Phoenix, AZ, USA; ^cAmerican College of Medical Toxicology, Phoenix, AZ, USA; ^dDistinguished Clinical Professor of Medicine, University of Colorado School of Medicine, Denver, CO, USA

ABSTRACT

Background: Crotalidae Polyvalent Immune Fab (Fab Antivenom) is the primary Viperid antivenom used in the United States since 2000. Adverse event data associated with its use are limited. The purpose of this study is to describe the prevalence of acute adverse events associated with the use of Fab antivenom.

Methods: The American College of Medical Toxicology's Toxicology Investigators Consortium maintains a prospective case registry of poisoned and envenomated patients managed by medical toxicologists at the bedside. This registry includes the North American Snakebite sub-registry. We performed a review of 438 cases entered into the Snakebite sub-registry.

Results: A total of 373 (85.2%) received at least one vial of Fab Antivenom. Forty percent were children. Adverse events occurred in 10 patients (2.7%) of whom six were adults. Rash was the most common adverse event. More severe adverse events (hypotension, bronchospasm, and/or angioedema) occurred in four (1.1%) patients. Prophylaxis was administered prior to Fab antivenom in 4.0%. Eight patients received various treatments for their adverse events. Neither the initial number of Fab antivenom vials, atopic history, nor prior envenomation correlated with the prevalence of adverse events.

Discussion: This prevalence of adverse events was lower than in previous studies and in a meta-analysis of 11 studies. The types of adverse events and treatments used are consistent with those in previous reports. There were no prior reports of prophylaxis use with which to compare.

Conclusion: The prevalence of Fab antivenom adverse events in the North American Snakebite Registry was 2.7%.

ARTICLE HISTORY

Received 15 September 2017

Revised 31 January 2018

Accepted 8 April 2018

Published online 20 April 2018

KEYWORDS

Adverse event; antivenom; envenomation; Fab antivenom; toxinology

Introduction

Most snakebites in North America involve the Viperids, which include three genera and over 30 species of rattlesnakes, copperheads, and cottonmouths [1]. Snakebites are uncommon but not rare; 3664 pit viper envenomations were reported to the National Poison Data System in 2015 [2]. Given that not all cases are reported to poison centers it is likely that the number of snakebites that occurred in the US in 2015 was greater.

The primary antivenom in the United States prior to the year 2000 was the Wyeth (Madison, NJ, USA) (Crotalidae) Polyvalent antivenom, a whole equine IgG antivenom. While effective, it was associated with a high rate of acute adverse events (AEs), 18–33%, including anaphylactoid and anaphylactic reactions [3–5].

In 2000, the United States' Food and Drug Administration approved Crotalidae Polyvalent Immune Fab (CroFab[®], BTG International Inc., West Conshohocken, PA) (Fab Antivenom). Fab Antivenom is derived from ovine Fab (monovalent

immunoglobulin fragments obtained from healthy sheep flocks immunized with *Crotalus atrox* (Western Diamondback rattlesnake), *Crotalus adamanteus* (Eastern Diamondback rattlesnake), *Crotalus scutulatus* (Mojave rattlesnake), and *Agkistrodon piscivorus* (Cottonmouth or Water moccasin). It is likely that most immunologic reactions to antivenom are related to the antigenic Fc antibody fragment. Thus, it was anticipated that this newer antivenom, containing only the Fab portion of the antibody, would reduce the prevalence of AEs because it contained only the Fab fragment of the IgG antibody [6–8].

Previous reports of AEs associated with Fab Antivenom were based upon small prospective or retrospective series [7–19], though a meta-analysis of 11 studies has been published [20]. Retrospective data may result in underreporting of AEs in safety studies [21].

The North American Snakebite Registry (NASBR), a subset of the American College of Medical Toxicology's (ACMT) Toxicology Investigators Consortium (ToxIC), is a multicenter case registry of data collected in real time of poisoned and

envenomated patients managed by medical toxicologists at the bedside. This study describes the prevalence of acute AEs associated with the use of Fab Antivenom in patients reported to the NASBR.

Methods

The ToxIC Registry is a voluntary, nationwide, toxico-surveillance system established in 2010 by the ACMT. The registry gathers data in real time on cases managed at the bedside by medical toxicologists. The registry requires participating medical toxicologists to enter all patient consultations via a password-protected, encrypted, on-line data collection system maintained by the ACMT. Data include demographics and detailed medical information including patient history, physical examination performed at the bedside by medical toxicologists, and additional diagnostic tests when performed.

The ToxIC Registry is compliant with the Health Insurance Portability and Accountability Act and was approved by the Western Institutional Review Board as all patient data are de-identified and there are no patient interventions resulting from being in the registry. Depending on individual site policies and procedures, further approval by their respective Institutional Review Boards was obtained. A detailed description of the registry was published previously [22]. For the complete ToxIC registry, investigators from 50 active sites, involving 101 separate facilities, submitted cases in 2015. Eighty-one percent of the accredited medical toxicology fellowship programs in the United States participate in the ACMT ToxIC Registry. Most sites are university-affiliated institutions [23]. The ToxIC registry consists of data obtained at the actual time of patient evaluation and management. Obtaining the data for the registry at the actual time of patient care enables the investigators to have complete and accurate data. The timing of the upload of the data by the investigators to the registry site will vary; some do so during the patient's hospitalization and some will collect data on case report forms and upload soon after patient discharge.

The NASBR was created in 2012 by a group of medical toxicologists with expertise in snake envenomation. The data instrument was reviewed and revised by medical toxicologists who had previously entered snakebite cases into the ToxIC registry. Fourteen ToxIC Registry sites in 10 states participated in the NASBR during the time period included in this study.

Data collected within the NASBR include information about the snake (type, species, native/non-native, wild/captive); additional patient characteristics and medical history; and exposure and event characteristics, including clinical, diagnostics, treatments, complications, and outcomes. Outcomes included the duration of hospital stay, the need for critical care, and procedural interventions such as the administration of pressor agents or intubation. Specific details of Fab Antivenom use were collected including the total number of vials of Fab Antivenom administered, prophylaxis given prior to Fab Antivenom (antihistamines, steroids, epinephrine), specific AEs (rash, angioedema, bronchospasm, hypotension, and other with explanation), and the treatment rendered for the AEs

(antivenom stopped or infusion rate changed, steroids, antihistamines, epinephrine, albuterol, and no treatment).

For the current study, we performed a review of cases entered into the NASBR from 1 January 2013 to 31 December 2015. Descriptive statistics are used to report results.

Results

There were 450 patients entered into the NASBR during the 3-year enrollment period. Five non-native species and three coral snake envenomations were excluded due to non-eligibility for Fab Antivenom, leaving 442 cases potentially eligible to receive Fab Antivenom. Four NASBR registry cases receiving antivenom were enrolled by a ToxIC participating site into a blinded, randomized clinical trial (RCT); therefore, the patients' true exposure to Fab Antivenom remains unknown. These cases were also excluded from this analysis. None of the RCT-excluded cases either received pre-antivenom prophylaxis or reported an adverse event associated with the antivenom. From the remaining 438 cases, 373 (85.2%) received at least one vial of Fab Antivenom, forming the observation group in this study. Among the patients who received the antivenom, 149 (39.9%) were children <18 years of age and most were from Arizona ($N = 151$; 40.5%) and Texas ($N = 120$; 32.2%).

Adverse events associated with the Fab Antivenom occurred in 10 of 373 (2.7%) patients (Table 1). Six adults had a total of 15 AEs and four children had a total of 8 AEs.

The most common AE for adults occurred in .9% for each of six different events – rash, hypotension, bronchospasm, bradycardia, diaphoresis, and vomiting. Rash was the most common event in children, occurring in 2.7% (Table 1). Of the two patients who had bradycardia, one had a pain-inducing extremity evaluation at the time and the primary investigator at that site felt that the bradycardia was a vagal effect. Hypotension, bronchospasm, and angioedema are more severe AEs than rash or urticaria. These occurred in four (1.1%) of the 373 patients who received at least one vial of Fab Antivenom.

Prophylaxis for allergic reactions was administered to 15 (4.0%) of the patients who received Fab Antivenom. Children (4.0%) and adults (4.0%) received prophylaxis equally. Antihistamines were the primary agents used in children. Among adults, there was a broader mix of antihistamines, steroids, or a combination of these agents (Table 2). None of the 15 cases who received prophylaxis prior to administration of Fab Antivenom had an AE related to the antivenom.

Eight of the 10 patients who sustained an AE received treatment (Table 3). One child with a rash and one adult with diaphoresis and bradycardia received no treatment. Antihistamines were the most common treatment; used in six patients. Epinephrine was used in two patients: one had rash, urticaria, and angioedema (antivenom was stopped in this patient). Epinephrine was also used in a patient who had rash, hypotension, angioedema, and vomiting. Besides the patient noted above, antivenom was stopped in a second patient who had experienced anterior chest rash; throat, abdominal, and full body pains; and agitation.

The number of vials of Fab Antivenom administered did not correlate with the occurrence of an AE. The mean initial bolus

Table 1. Adverse events (AE) after Fab antivenom (Fab AV) in adults and children (age <18)^a.

	Adults		Children		All ages combined	
	N	% Fab AV cases	N	% Fab AV cases	N	% Fab AV cases
At least one adverse event	6	2.7%	4	2.7%	10	2.7%
Number of AE per patient						
1 Adverse Event	1	0.5%	2	1.3%	3	0.8%
2 Adverse Event	3	1.3%	1	0.7%	4	1.1%
≥3 Adverse Event	2	0.9%	1	0.7%	3	0.8%
Prevalence of individual AE						
Rash	2	0.9%	4	2.7%	6	1.6%
Hypotension	2	0.9%	0	0.0%	2	0.5%
Angioedema	1	0.5%	1	0.7%	2	0.5%
Bronchospasm	2	0.9%	0	0.0%	2	0.5%
Other						
Agitation	0	0.0%	1	0.7%	1	0.3%
Bradycardia	2	0.9%	0	0.0%	2	0.5%
Diaphoresis	2	0.9%	0	0.0%	2	0.5%
Diarrhea	1	0.5%	0	0.0%	1	0.3%
Numbness (Oral)	1	0.5%	0	0.0%	1	0.3%
Pain	0	0.0%	1	0.7%	1	0.3%
Urticaria	0	0.0%	1	0.7%	1	0.3%
Vomiting	2	0.9%	0	0.0%	2	0.5%
Totals	15		8		23	

^aTotal patients treated with Fab AV: Adults N = 224; Children N = 149.**Table 2.** Prophylaxis administration prior to Fab antivenom (Fab AV) in adults and children (age <18)^a.

	Adults		Children		All ages combined	
	N	% Fab AV Cases	N	% Fab AV Cases	N	% Fab AV Cases
Antihistamine	5	2.2%	5	3.3%	10	2.7%
Antihistamine and Steroids	3	1.3%	1	0.7%	4	1.0%
Steroids	1	0.5%	0	0.0%	1	0.3%
Totals	9	4.0%	6	4.0%	15	4.0%

^aTotal patients treated with Fab AV: Adults N = 224; Children N = 149.**Table 3.** Treatment of adverse events (AE) in adults and children (age <18)^a.

Treatment	Adults		Children		All ages combined	
	N	% Patients treated with modality ^a	N	% Patients treated with modality ^a	N	% Patients treated with modality ^a
Steroids or Corticosteroids	2	33.3%	0	0.0%	2	22.0%
Antihistamine	3	50.0%	3	75.0%	6	60.0%
Epinephrine	1	16.7%	1	25.0%	2	20.0%
AV Infusion – Slowed	2	33.3%	0	0.0%	2	20.0%
AV Infusion – Stopped	0	0.0%	2	50.0%	2	20.0%
No Tx	1	16.7%	1	25.0%	2	20.0%
Totals	8		7		15 ^b	

^aNumber of Patients with an AE: Adults N = 6; Children N = 4; Total N = 10.^bMost patients received more than one treatment modality.

of antivenom was 4.5 vials for the 10 patients who had an AE versus 4.8 vials in those who did not have an AE. The mean number of total vials administered in the complete course of treatment was 7.1 with a range of 4–14 vials in those who had an AE versus 10.6 with a range of 1–56 vials in those who did not. Previous atopic histories did not correlate with AEs. Three of the patients with AEs reported medication allergy histories; one to penicillin and morphine, one to ibuprofen, and one to trazodone. No patients with an AE had been previously bitten by a snake and none had previously received Fab Antivenom. Among the population that did not have an AE, 23 had received a prior snakebite and 12 had received antivenom.

Discussion

The prevalence of acute AEs is an important consideration in the determination if an antivenom for a Vipereid envenomation

will be used. The Wyeth equine (Crotalidae) Polyvalent antivenom used prior to the year 2000 was associated with a high rate of anaphylactoid and anaphylactic reactions. Acute AEs associated with the Wyeth antivenom occurred in 18–36% of 272 total patients in three separate studies [3–5]. The Fab Antivenom was developed because it was thought that by removing the immunogenic Fc portion of the antivenom there would be a lower rate of AEs.

The reported prevalence of AEs associated with Fab Antivenom has varied from 4.6% to 14% [7–19], and a meta-analysis of 11 studies showed a frequency of AEs of 8% [20]. The adverse event frequency in our series, 2.7%, is lower than in these previously reported series. In the two premarketing open-label, multi-center trials, 42 patients 11 years of age or older received Fab Antivenom and six (14%) had allergic reactions [7,9]. Four were treated and two received no treatment. Of the four who were treated, all had urticaria.

One also had wheezing and dyspnea and one also had cough. Two of these had their infusions stopped; one with cough and urticaria improved and the infusion was restarted but similar signs reoccurred and the infusion was stopped fully. In the other patient; the urticaria, dyspnea, and wheezing cleared and the infusion was restarted with a concomitant epinephrine infusion and the patient did well [7,9]. In a prospective, open-label, single-center series of 15 patients who received Fab Antivenom after envenomation by Southern Pacific Rattlesnakes, two patients had AEs [10]. One developed a rash that cleared after diphenhydramine and cimetidine and the stopping of antivenom. One patient with a history of myocardial infarction (MI) developed chest pain, nausea, and diaphoresis but had no typical signs or symptoms of hypersensitivity. The patient was treated with nitroglycerin and droperidol and the antivenom was stopped. The paper did not comment if the chest pain was confirmed to be an MI [10]. Thus, eight (14%) of 57 patients had AEs in these three prospective studies.

Retrospective series have addressed the prevalence of acute AEs associated with Fab Antivenom. All of these series specifically included patients who had received Fab Antivenom only. In series that contained primarily adult populations, 22 (4.6%) of 480 patients had AEs [10–16]. In series containing only children, 7 (5.9%) of 118 patients had AEs [17–19]. Combining the adults and children, there were 598 total patients of whom 29 (4.8%) had AEs. In a retrospective review of the national poison data system from 2000 to 2007, after 2004, when most of the old Wyeth antivenom had been used or expired, overall AEs reported was just over 3%. It is possible that some antivenoms were miscoded in this poison center study [24].

A meta-analysis of 11 studies published between 1997 and 2010 addressed hypersensitivity reactions among patients treated with Fab Antivenom therapy after North American crotaline envenomation [20]. This analysis specifically included patients who received Fab Antivenom only; the earliest studies included were prospective ones using Fab Antivenom. The study included 504 patients of which 88% were from retrospective studies. Acute adverse event data were available in 386 of the patients. Rash was the most common reaction. Also, other reactions reported were urticaria, wheezing, dyspnea, hypertension, tongue and lip swelling, tachycardia, dizziness, chest pain, and nausea. The prevalence of acute AEs was 8% (95% confidence interval = 5–11%). Three of the studies reported a total of five of 287 patients who had their Fab Antivenom stopped before completion following acute AEs [20].

The reasons for our population having fewer AEs than in previous prospective and retrospective studies are not clear. Medical toxicologists participating in the NASBR are aware of the AEs associated with Fab Antivenom and are experienced in the treatment of snakebites. Since the data in the NASBR are prospectively collected in a way that specifically collects information on AEs, it is likely that most were ascertained. However, it is possible that more subtle AEs were missed. This would not explain the adverse event rate in our registry being less than in retrospective studies where AEs are less often reported than in prospective studies [21].

The types of AEs in our series are similar to prior publications. Rash, including urticaria, was the most common adverse event in our series. Most of the AEs in our patients were like those noted in a recent review of anaphylaxis [25]; rash, hypotension, angioedema, bronchospasm, diaphoresis, diarrhea, urticaria, and vomiting. Five of our AEs would be uncommon reactions including agitation, pain, bradycardia, and oral numbness; however, site investigators did report them, suggesting that the AEs were related to the Fab Antivenom. The NASBR dataset did not enable us to assess the relationship between AEs and the Fab Antivenom using the Naranjo scale [26]. In Dart's two premarketing trials, all six patients with an AE had urticaria/hives [7,9]. In a retrospective review of envenomations treated with Fab Antivenom, rash and itching were the most common symptoms [13]. In a single children's hospital in Arkansas, urticaria and pruritus were the most common AEs in the 82 patients [17]. In a multicenter retrospective chart review of envenomations treated with Fab Antivenom from 2002 to 2004, 15 (6.1%) of 247 patients experienced acute AEs, most of which were rash or itching [11].

Anaphylaxis to Fab Antivenom has occurred as reflected by case reports and series. One patient, 40 min into an infusion, developed urticaria, angioedema of the oropharynx, wheezing, flushing, hypoxia, and hypotension. He was treated with antihistamines and an epinephrine infusion and his reaction fully cleared and the antivenom was continued with no further reactions [6]. In another case, a patient with known allergies to arthropods developed urticaria and hypotension while receiving six vials in 250 mL after the infusion had been increased to 250 mL per hour. These signs cleared after stopping the infusion and treating with antihistamines and steroids. The infusion was started again and angioedema of the tongue occurred as the infusion was completed. The patient did well [8]. In a multicenter retrospective chart review of envenomations treated with Fab Antivenom from 2002 to 2004, four (1.6%) of 247 patients had serious AEs including combinations of hypotension or oral-facial swelling [11]. Our series is consistent with this review in that 1.1% of our patients had more severe AEs; hypotension, bronchospasm, or angioedema.

In our series, there was no correlation with the initial amount of antivenom and the occurrence of AEs. The initial bolus of Fab Antivenom was similar in the AEs group and the non-AEs group, 4.5 and 4.8 vials, respectively. This is consistent with a multicenter review of 247 patients that also found no association between the number of vials of Fab Antivenom used and acute AEs [11]. Of note, in our study, the patients who did not have an AE received more total Fab Antivenom (10.6 vials) than those who did have an AE (7.4 vials). It is possible that the patients with AEs received less Fab Antivenom after the initial bolus because the providers were concerned over the AEs.

Our data did not enable us to directly assess the impact of the rate of infusion of the Fab Antivenom upon the occurrence of AEs. We had two cases where infusions were slowed after AEs, but the patients were eventually able to complete therapy. There are other reports where therapy continued after an initial slowing of the infusion. Holstege et al. [27]

reported a 16-year-old who received 6 vials in 250 mL with no AEs at slower rates, but once the rate was increased to 640 mL per hour, the patient developed urticaria, facial edema, a voice change, and tachycardia. The patient improved after antihistamines and steroids and the infusion was restarted at a slower rate with no reoccurrence. In the multicenter retrospective chart review of 247 envenomations treated with Fab Antivenom, the antivenom was slowed in two. The AEs for these patients cleared with antihistamines and/or steroids [11]. In the two cases of anaphylaxis noted above, infusions were temporarily stopped and restarted [6,8].

There are limitations to our study. Any data in a registry, including a sub-registry such as the NASBR, are limited by the voluntary nature of the reporting. However, the NASBR has a formal quality assurance program such that all records are reviewed and omissions are identified and corrected when possible. This registry reflects only patients cared for at the bedside by medical toxicologists; thus, the cases reported may have been more severely ill exposures. Industry sponsored, prospective trials often enable very detailed patient evaluations; doing assessments that are more intensive than done by practicing toxicologists. However, medical toxicologists will likely still have a greater focus on antivenom-related AEs than most clinicians. Many of the reporting centers are large academic medical centers; thus, events occurring at smaller community facilities may not be well represented. The generalizability of the findings are limited in most of our patients who were from Arizona and Texas, the number of patients in our sub-registry is low compared to the NPDS data, and the number of AEs was a small sample size.

Conclusions

In the NASBR, within ACMT's ToxIC Registry, the prevalence of acute AEs associated with the use of Fab Antivenom was 2.7%. While this study has its limitations, this sub-registry study is the largest non-poison center data set except for the aforementioned meta-analysis. However, the meta-analysis contained mostly retrospective study patients. Our data were collected in real time by medical toxicologists experienced in the treatment of snakebites and the use of Fab Antivenom. Also, the data obtained were very specific for assessing all aspects of AEs, including prophylaxis and treatment, a feature that cannot be matched by retrospective studies. In conclusion, the NASBR provides the strongest support yet, and is consistent with prior publications, that Fab Antivenom is safe with a low rate of AEs.

Acknowledgements

The 2013–2015 Toxicology Investigator's Consortium Snakebite Study (TICSS) group: Anna Arroyo-Plascencia, Vikhyat S. Bebart, 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.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This study was supported by BTG International Inc, Unrestricted Educational Grant.

References

- [1] Seifert SA, Boyer LV, Benson BE, et al. AAPCC database characterization of native U.S. venomous snake exposures, 2001–2005. *Clin Toxicol.* 2009;47:327–335.
- [2] Mowry JB, Spyker DA, Brooks DE, et al. 2014 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 32nd annual report. *Clin Toxicol.* 2015;53:962–1147.
- [3] Offerman SR, Smith TS, Derlet RW. Does the aggressive use of polyvalent antivenin for rattlesnake bites result in serious acute side effects? *West J Med.* 2001;175:88–91.
- [4] Jurkovich GJ, Luterman A, McCullar K, et al. Complications of Crotalidae antivenin therapy. *J Trauma.* 1988;28:1032–1037.
- [5] Tanen D, Ruha A, Graeme K, et al. Epidemiology and hospital course of rattlesnake envenomations cared for at a tertiary referral center in Central Arizona. *Acad Emergency Med.* 2001;8:177–182.
- [6] Clark RF, McKinney PE, Chase PB, et al. Immediate and delayed allergic reactions to Crotalidae polyvalent immune Fab (ovine) antivenom. *Ann Emerg Med.* 2002;39:671–676.
- [7] Dart RC, Seifert SA, Carroll L, et al. Affinity-purified, mixed mono-specific crotalid antivenom ovine Fab for the treatment of crotalid venom poisoning. *Ann Emerg Med.* 1997;30:33–39.
- [8] Lepak MR, Bochenek SH, Bush SP. Severe adverse drug reaction following Crotalidae Polyvalent Immune Fab (Ovine) administration for copperhead snakebite. *Ann Pharmacother.* 2015;49:145–149.
- [9] Dart RC, Seifert SA, Boyer LV, et al. A randomized multicenter trial of crotalinae polyvalent immune Fab (ovine) antivenom for the treatment for crotaline snakebite in the United States. *Arch Intern Med.* 2001;161:2030–2036.
- [10] Bush SP, Green SM, Moynihan JA, et al. Crotalidae polyvalent immune Fab (ovine) antivenom is efficacious for envenomations by Southern Pacific rattlesnakes (*Crotalus helleri*). *Ann Emerg Med.* 2002;40:619–624.
- [11] Lavonas EJ, Kokko J, Schaeffer TH, et al. Short-term outcomes after Fab antivenom therapy for severe crotaline snakebite. *Ann Emerg Med.* 2011;57:128–137.
- [12] Ruha AM, Curry SC, Beuhler M, et al. Initial postmarketing experience with crotalidae polyvalent immune Fab for treatment of rattlesnake envenomation. *Ann Emerg Med.* 2002;39:609–615.
- [13] Cannon R, Ruha AM, Kashani J. Acute hypersensitivity reactions associated with administration of crotalidae polyvalent immune Fab antivenom. *Ann Emerg Med.* 2008;51:407–411.
- [14] 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.
- [15] Lavonas EJ, Gerardo CJ, O'Malley G, et al. Initial experience with Crotalidae polyvalent immune Fab (ovine) antivenom in the treatment of copperhead snakebite. *Ann Emerg Med.* 2004;43:200–206.
- [16] Nazim MH, Gupta S, Hashmi S, et al. Retrospective review of snake bite victims. *W V Med J.* 2008;104:30–34.
- [17] Farrar HC, Grayham T, Bolden B, et al. The use and tolerability of Crotalidae Polyvalent Immune FAB (Ovine) in pediatric envenomations. *Clin Pediatr.* 2012;51:945–949.

- [18] Offerman SR, Bush SP, Moynihan JA, et al. Crotaline Fab antivenom for the treatment of children with rattlesnake envenomation. *Pediatrics*. 2002;110:968–971.
- [19] Pizon AF, Riley BD, LoVecchio F, et al. Safety and efficacy of Crotalidae Polyvalent Immune Fab in pediatric crotaline envenomations. *Acad Emerg Med*. 2007;14:373–376.
- [20] Schaeffer TH, Khatri V, Reifler LM, et al. Incidence of immediate hypersensitivity reaction and serum sickness following administration of Crotalidae polyvalent immune Fab antivenom: a meta-analysis. *Acad Emerg Med*. 2012;19:121–131.
- [21] Weinger MB, Slagle J, Jain S, et al. Retrospective data collection and analytical techniques for patient safety studies. *J Biomed Inform*. 2003;36:106–119.
- [22] Wax PM, Kleinschmidt KC, Brent J. The Toxicology Investigators Consortium (ToxIC) registry. *J Med Toxicol*. 2011;7:259–265.
- [23] Farrugia LA, Rhyee SH, Campleman SL, et al. The toxicology investigators consortium case registry – the 2015 experience. *J Med Toxicol*. 2016;12:224–247.
- [24] Spiller HA, Bosse GM, Ryan ML. Use of antivenom for snakebites reported to United States poison centers. *Am J Emerg Med*. 2010;28:780–785.
- [25] Commins SP. Outpatient emergencies: anaphylaxis. *Med Clin North Am*. 2017;101:521–536.
- [26] Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30:239–245.
- [27] Holstege CP, Wu J, Baer AB. Immediate hypersensitivity reaction associated with the rapid infusion of Crotalidae polyvalent immune Fab (ovine). *Ann Emerg Med*. 2002;39:677–679.