HEALTHCARE CHARGES INCURRED FROM SCORPION ENVENOMATION TREATED WITH *CENTRUROIDES* F(ab')$_2$ ANTIVENOM

A thesis submitted to the University of Arizona College of Medicine – Phoenix
in partial fulfillment of the requirements for the degree of Doctor of Medicine

Alexa Roberts
Class of 2019

Mentor: Ayrn O'Connor, MD

Abstract

Introduction: *Centruroides* F(ab')$_2$ antivenom (AV) is a safe and effective treatment for bark scorpion envenomation; however, concern exists regarding the substantial charges associated with this therapy and resulting unexpected costs of treatment. This retrospective review seeks to quantitate patient charges associated with antivenom use to better understand its impact on patient and healthcare economics.

Methods: This is a retrospective review of 527 patients presenting to a hospital system with severe scorpion envenomation between April 2013 and May 2015. Included patients had *Centruroides* scorpion envenomation and received AV. They were excluded if they were not a grade III or IV envenomation, did not receive antivenom or their clinical records were not available. Patient charges and hospital costs were acquired from institutional financial records and were included if total costs were accurate as defined by costs > $2500. Clinical manifestations, length of stay (LOS), method and amount of AV administration were abstracted. Continuous data were reported as medians with interquartile range and linear regression was utilized to determine predictors of outcomes.

Results: All patients had a grade 3 or 4 envenomation and received AV. The total number of vials received were 1 (18.2)% to a maximum of 7 (0.4%) with most patients receiving three vials (46.7%). Most patients received three vials of antivenom initially (52.6%) as compared to one vial (43.6%) and only few receiving two vials (3.8%). Median total charges were $28,060 ($18,805 - $33,742). Linear regression showed that total charges were predicted by total number of vials administered and LOS (adjusted R^2 of 0.75). Charges of care were found to increase by $7901.59 per vial of AV and by $415.48 for each hour of LOS. The only predictors of total charges were age, number of vials and total length of stay. Correlation between total charges and costs was poor.

Conclusions: Despite established safety and efficacy, anticipated patient charges appear to influence the manner in which bark scorpion antivenom is administered by healthcare providers.

Table of Contents

List of Tables and Figures

INTRODUCTION

There are on average, sixteen thousand scorpion envenomations reported to US poison control center annually with approximately 1400 (8%) referred to healthcare facility for treatment. (Mowry 2013 - 15) Of those that had an envenomation recorded with the poison control center, death occurred in 0.002% of cases from 2013 to 2015. Historically, severe scorpion envenomation in Arizona was treated with a whole IgG antivenom (AV) made from goat serum this was available only in Arizona and its use was on a compassionate basis. The manufacturing of this antivenom was discontinued and stocks were exhausted in 2004. When this AV became unavailable care of severe scorpion envenomation was largely supportive which in pediatric patients often necessitated admission to ICU for titration of benzodiazepines and opioids and at times intubation and mechanical ventilation. It was during this period one study noted a 500% increase in admissions for scorpion envenomation. (Lovecchio, Pizon) In 2011 an FDA approved AV became available in the United States. This product has been used in Mexico for many years and its effectiveness is well established. The current FDA-approved dosing stipulates an initial dose of 3 vials followed by additional 1 vial doses every 30-60 minutes as clinical signs necessitate. The rare but main adverse reaction of concern being hypersensitivity reactions.

In international markets this product is available at a cost of approximately fifty dollars per vial. (Volentine 2017)(In the US there have been several reports in the lay press highlighting the unexpectedly high patient charge associated with treatment with *Centruroides* $F(ab')_2$ antivenom (AV). Healthcare providers in regions with a high prevalence of *Centruroides* envenomations are well aware of its cost, and some utilize alternative dosing regimens in an effort to are mitigate costs and preserve resources. (Bush 2015)

The primary objective of this retrospective review was to quantitate the financial impact of treatment with this AV by presenting charges billed to the patient in comparison to costs of treatment with AV. Secondary outcomes included total dose of AV, its method of administration, specifically initial dose. In addition, clinical manifestations, grade of envenomation, complications and adjunctive treatments utilized were evaluated.

METHODS

This study was an IRB approved retrospective review of patients presenting to a hospital system (data obtained from 11 healthcare facilities) with severe scorpion envenomation from April 2013 to May 2015. These cases were identified via search of pharmacy and financial records for patients that received *Centruroides* F(ab')2 antivenom. The electronic health record for all subjects receiving AV for which total charges and costs were available were reviewed and data abstracted. Inclusion criteria were those with clinical signs of severe scorpion envenomation that received antivenom. Exclusion criteria included patients not receiving antivenom or if clinical records were unavailable.

Study Subjects

Pharmacy and financial records were queried to identify patients receiving AV and their total charges vs direct costs between April 2013 and May 2015. Any patients without a clinical findings consistent with severe scorpion envenomation or who did not receive antivenom were excluded from further review.

Outcome Measures

The primary objective of this study is to describe patient charges and hospital costs related to care of severe scorpion envenomation using *Centruroides* $F(ab')_2$ antivenom (AV), including variables that predicted total charges. Secondary outcomes included, amount of AV utilized, method of administration of AV (initial dose), clinical manifestations, complications, length of stay in patients who present for care following severe bark scorpion envenomation.

Data Collection & Definitions

Financial records were obtained from query of institutional software, TSI, and included billed charges, hospital cost, and fraction reimbursed associated with the visit. Clinical data was abstracted from the electronic medical record (Cerner) onto a pre-designed data abstraction sheet by four of the authors after undergoing an instructional session to ensure consistency. Data abstracted was subsequently entered into a spreadsheet (Excel 2000, version 9.0.2770;

Microsoft Redmond WA) by two members of the study staff. In addition to total charges and direct costs, antivenom administration with total number of vials received by each patient and the method of delivery and adverse reactions to AV were abstracted in addition to clinical details. The clinical information collected included: age, gender, time and date of scorpion sting, onset of symptoms, patient complaints, any treatments prior to arrival, all medications given, IV fluids, oxygen administration, procedures. Additionally, clinical signs of envenomation and physical exam findings were collected, including vital signs, maximal temperature, oxygen saturation, pain, cranial nerve and neuromuscular involvement, peak creatine phosphokinase (CPK) and creatinine, EKG, whether a chest x-ray was performed and if evidence of aspiration was present were all recorded. Finally, length of stay in hours and patient outcomes including complications or relevant clinical data were recorded.

The following definitions were used: rhabdomyolysis defined as CPK ≥ 1000 IU/L; hypoxia O_2 saturation <90%, fever temperature > 38^o C; hypertension (HTN) adult SBP> 140 or DBP> 90 mmHg, tachycardia adults heart rate > 100 beats per minute, tachypnea adults respiratory rate > 20 breaths per minute. Hypertension, tachycardia and tachypnea for pediatric patients were based on vital sign measurements exceeding age-based norms as published in Pedi STAT.

Grade of envenomation was based on the previously published criteria as outlined in the table below. Grade assigned by clinician providing care was abstracted and compared to grade assigned by member of the study staff performing the chart review. Severe envenomation is defined as Grade III or higher.

Statistics

Categorical variables were reported as valid percent to account for missing data. Continuous data were reported as median with interquartile range, and linear regression was utilized to determine predictors of outcomes. Logistic regression was used to determine predictors of in-patient admission.

Figure 1. Clinical Grading & Definitions of Scorpion Envenomation

Grade	Clinical Manifestation
I	Local pain and/or paraesthesias
II	Grade I, plus pain and/or paraesthesias remote from the site of the sting
III	Either Cranial nerve dysfunction (blurred vision, wandering eye movements, hypersalivation, trouble swallowing, tongue fasciculation, problems with upper airway, slurred speech) or skeletal neuromuscular dysfunction (jerking of extremities, restlessness, severe involuntary motor activity)
IV	Both cranial nerve and skeletal neuromuscular dysfunction

RESULTS

527 patients with severe scorpion envenomation that received antivenom therapy were included. Median (IQR) age was 4 (1.83-9) years with a range of 0.25 to 83 years. All subjects had clinical findings consistent with severe envenomation. No adverse reactions (hypersensitivity reactions) to AV occurred.

Median (IQR) total charges was $28,060 ($18,805 - $33,742). Linear regression analysis revealed that total number of vials administered, and length of stay were the strongest predictor of total charges (adjusted R^2 of 0.75). Charges of care increased by $7901.59 per vial of AV and by $415.48 for each hour of LOS, both with $p < 0.001$.

Cost data was available for 54.8% (N=289) of the study population. Median (IQR) cost was $8065 ($5607-$10,086). Linear regression identified age ($p<0.001$), total number of vials ($p<0.001$), and LOS ($p< 0.45$) as statistically significant predictors of cost (adjusted R^2 of 0.73). Median (IQR) fraction of reimbursement was 35.7% (10.9-48.0%)

Each additional vial of antivenom administered increased total cost by $2540 ($p <0.01$), and each additional hour of length of stay increased total cost by $33 per hour ($p=0.045$).

Method of initial antivenom administration did not affect cost, however the total number of vials did. And a relatively significant correlation between cost and charges was found ($R^2=0.78$)

Median (IQR) LOS is 4.0 (3.0-5.0) hours. Linear regression analysis found that total number of vials of AV and age were predictors of length of stay but method of AV administration was not.

The majority of patients were discharged from the emergency department, only 5.1% (27/527) were admitted. Logistic regression was performed to evaluate variables predictive of admission. Age > 16 years, hypoxia, fever, and treatment with benzodiazepines were all statistically significant predictors of admission, see figure 2.

Figure 2. Predictors of Admission in treatment of Severe Envenomation

Variable	Odds Ratio	P value
Age > 16 years*	7.91	<0.001
Hypoxia	7.36	<0.001
Fever	7.20	0.002
Treatment with Benzodiazepines	2.85	0.039

*After inspecting an ROC curve, a cut-off of 16 years of age provided the best balance of sensitivity and specificity and was used as the age cut-off in performing logistic regression.

The total number of vials are summarized in Table 1, with a minimum of 1 (18.2%) to a maximum of 7 (0.4%) with most receiving 3 vials (46.7%). Method of administration is summarized in Table 2. Most patients received 3 vials of antivenom initially (52.6%) as compared to 1 vial (43.6%) and with only few receiving 2 vials (3.8%) as the initial dose.

Table 1. Total Number of Vials Received for Severe Envenomation

Number of Vials	Percent (%)
1	18.2
2	16.5
3	46.7
4	14.2
5	3.8
6	0.2
7	0.4

Table 2. Method of Administration: Initial number of vials administered

Initial Administration (# of Vials)	Percent (%)
1	43.6
2	3.8
3	52.6

Chi square test found the most common signs in patients receiving three vials initially were those consistent with respiratory or bulbar involvement including hypoxia (65.4%, p=0.003), dyspnea (61.1%, p=0.046), and dysphagia/dysarthria (59.4%, p=0.043) See Table 3.

Table 3: Factors Strongly Associated with Initial dose of Three Vials

Clinical Component	Percent	Population Fraction	Significance ($p<0.05$)
Intubation	100.0	5/5	0.039
Hypoxia	65.4	34/52	0.003
Dyspnea	61.1	69/113	0.046
Dysarthria/Dysphagia	59.4	101/170	0.043

Table 4 summarizes the clinical manifestations of severe scorpion envenomation in this population. There were no deaths and despite hypoxia and respiratory distress occurring in 10% and 17.5% of patients respectively, only five were intubated. Adjunctive treatments utilized in this population of patients with severe scorpion envenomation are summarized in Table 5.

Table 4: Clinical Signs and Symptoms of Severe Scorpion Envenomation

Clinical Manifestation	Percent
Abnormal Eye Movement	94.7
Pain	94.5
Peripheral Motor Activity	85.4
Tachycardia	73.7
Hypertension	71.4
Hypersalivation	68.9
Tachypnea	63.4
Visual Changes	56.0
Difficulty swallowing/speaking	32.3
Emesis	30.2
Pareasthesias*	28.1
Dyspnea	21.4
Ataxia	20.7
Respiratory Distress	17.5
Hypoxia	10.0
Diaphoresis	8.2
Fever	5.5

Table 5: Adjuncts Utilized in Addition to Treatment with AV

Adjunctive Therapy	Percent
Opiates	54.3
Benzodiazepines	41.2
Intravenous Fluids	38.2
Diphenhydramine	17.7
Atropine	4.6
Intubation	0.9

DISCUSSION

Centruroides F(ab')$_2$ antivenom (AV) is an effective treatment for severe scorpion but as the lay press reported and this study confirmed patient incur high charges when receiving this therapy. The negative economic impact may be a contributing factor in some clinicians deviating from the recommended dosing of an initial dose of 3 vials. A significant portion of this study's population (43.6%) received an initial dose of 1 vial based on their clinical presentation. The cumulative dose to reach resolution of symptoms was greater than 3 vials in 56.5% of this study's cases. As illustrated by the results above, the main correlation of increasing total charges was antivenom use. There were no other significant predictors of increased total charges when analyzed via regression analysis.

Although the original intent of this study was to compare patient charges to hospital costs; however accurate data regarding costs could not be obtained. 45.1% of the reported costs were <$2500 which was inaccurate given patients received a minimum of one vial of AV which would have resulted in higher costs. The source of the inaccurate cost data could not be identified nor rectified we attempted to account for this by statistically analyzing only data with total costs greater than $2500 so as to improve the precision and reduce the inaccuracy of flawed cost data for 237 cases. Although we recognize this is a limitation of the study the authors felt it was important to include as it underscores the difficulty both physicians and patients face by the lack of transparency in healthcare economics with little ability to be properly informed about the patient charge and the cost of care.

This retrospective review aimed to quantitate billed charges associated with antivenom use to better understand its impact on patient outcomes and healthcare economics. Based on our data adjusted to exclude inaccurate cost (less than $2500) the median total charges associated with antivenin treatment of a severe bark scorpion envenomation were $28,060 which is significantly lower than the reports in the media of upwards of $80,000. This is likely secondary to variances not in in antivenin method of administration, but a manifestation of out- of- network healthcare coverage in as the woman in the media reports was treated at an out of network facility, increasing her total charges significantly. Additionally, in comparing media reports to the cost

and charge data, there is limited access to what, if any, adjunctive therapies were administered and their effect on the final charges. However, as the average American has approximately $17,000 in savings a healthcare bill of tens of thousands of dollars can completely derail an individual or family, and the results of this study can serve to facilitate conversation between patients and their providers on guiding treatment while being mindful of cost and healthcare resources.

Although dosing guidelines suggest a 3 vial protocol, it should be noted that in 43.5% of cases, the cumulative dose needed to resolve symptoms was limited to 1-2 vials. This amounts to cost savings of $2540 per vial not needed and the cost of monitoring for per additional hour of $33 is worthy of consideration in management of severe scorpion envenomations without signs of airway compromise or severe neurologic symptoms. As the current climate of the United States healthcare system is one of many layers and basic estimated costs are frequently shrouded in medicolegal jargon the data of this study provides a basis for which to explore observation vs additional pharmacologic intervention in appropriate cases.

By increasing these conversations, it is possible that the use of adjunctive therapies would increase overall and could be explored in further studies. Currently, it is not uncommon to require pharmacologic therapy for pain, agitation & anxiety control as the scorpion venom is a powerful neurotoxin and time to resolution of symptoms even with antivenom administration can take up to several hours to reach its peak efficacy in binding the venom and reducing its clinical effects. Additionally, the preparation of the antivenom can often present as a time-consuming process as it is kept in a lyophilized powder form that requires rehydration and dilution with sterile saline prior to its infusion over a 10 minute period of time. Adjunctive therapies such as opiates and benzodiazepines have variable efficacy in managing symptoms associated with severe envenomations, likely based on individual tolerance and pain thresholds. It is notable that when analyzing our data if a patient was hypoxic and received treatment with benzodiazepines they were 21 times more likely to be admitted.

In the southwestern United States, envenomation by the bark scorpion, *Centruroides sculpturatus*, can result in a spectrum of illness ranging from mild to fatal. Its venom blocks

inactivation of neuronal sodium channels resulting in increased influx of sodium. This produces increased duration and amplitude of the neuronal action potential and enhanced release of neurotransmitters such as acetylcholine and norepinephrine. Clinically this manifests as cholinergic and adrenergic stimulation, producing a myriad of signs and symptoms such as skeletal motor and parasympathetic stimulation. Although the pathophysiology of bark scorpion envenomation is well understood, the accumulation of charges related to these envenomations is more opaque. Although costly, antivenom treatment has been shown to reduce patient's length of stay after hospital presentation from 12 hours to only four hours. (Boyer 2009).In a report published by the VA Pharmacy Benefits Management Services, the average cost of treatment associated with 3 vials post envenomation was approximately $8000 however there was no data released surrounding charges and total costs as it related to therapeutic treatment.(National 2012)

The results of this study indicate that median charges for treatment of scorpion envenomation with AV are approximately thirty thousand dollars, with the only predictor of increased total charges being age, total number of vials and overall length of stay. Interestingly, the presence of more severe signs of envenomation such as hypoxia, intubation or respiratory distress were not predictors of increased total charges. Of the 527 cases reviewed, there were no documented adverse effects or anaphylactic reactions in the administration of antivenom. The dichotomous style of antivenom administration predominating in three-vials initially and one vial initially was an unexpected finding. However, these results may be influenced by a discontinued institutional policy that in the past required antivenom to be dosed one vial at a time with re-evaluation of the patient, in an attempt to preserve resources and control costs. Another possible reason for this method of antivenom administration is that healthcare facilities near the Biotechnology Institute in Mexico, where the antivenom is created, tend to use an administration protocol that favors giving one vial initially as well.

LIMITATIONS

There were several limitations to this study. The first limitation was the retrospective nature of the study, which made it difficult to ascertain various details such as timing of symptoms, as well as the accuracy of the provider's evaluation of the severity of envenomation. Additionally, although access was obtained to the financial data providing patient charges and costs it was found after detailed review that despite accurate charge data, a subset of patients included in the study had incredibly low total costs, under $2500. This could not be explained or corrected when explored by the investigators, and additional information sought by the financial department of the hospital system. Despite this significant limitation, we the authors felt that the 289 cases for which there was accurate cost and charge data available the results merited exploration. Therefore, data collected was analyzed conditionally and costs amounting to less than $2500 were excluded from the dataset as to prevent skewing data with inaccurate outliers.

FUTURE DIRECTIONS

The current climate of the US healthcare system is one that continues to bear difficulties for consumers and providers alike in the often-elusive details and unclear costs of care. The importance of recognition, triage and treatment of severe scorpion envenomation in combination with its recent media coverage provided an opportunity to bring to light the realities of cost of care in the US healthcare system, and future studies investigating overarching costs of care and assessment of financial literacy are warranted to increase transparency between insurance coverage, patients and their healthcare providers.

CONCLUSION

Despite its high cost to patients and hospital systems, *Centruroides* F(ab')$_2$ antivenom remains a safe and effective therapy for severe scorpion envenomation in both the adult and pediatric population. This study demonstrates that healthcare providers are aware of the cost of therapy and often make attempts to minimize cost to their patients and healthcare system. Despite these efforts, in the majority of cases the recommended dosing regimen of three vials is required to achieve symptom resolution, in addition to improving total length of stay.

Total number of AV vials administered was the strongest predictor of total billed charges. Despite apparent attempts by healthcare providers to minimize vials of AV given the majority of patients required 3 or more vials of AV.

REFERENCES

1. Boyer, L. V., Theodorou, A. A., Berg, R. A., Mallie, J., Chávez-Méndez, A., García-Ubbelohde, W., Hardiman, S. & Alagón, A. (2009). Antivenom for critically ill children with neurotoxicity from scorpion stings. *New England Journal of Medicine*, *360*(20), 2090-2098.

2. Bond GR. Antivenin administration for *Centruroides* scorpion sting: risks and benefits. Ann Emerg Med. 1992;21(7):788–791. doi: 10.1016/S0196-0644(05)81022-4. [PubMed] [Cross Ref]

3. Armstrong, E. P., Bakall, M., Skrepnek, G. H., & Boyer, L. V. (2013). Is scorpion antivenom cost-effective as marketed in the United States?. *Toxicon*, *76*, 394-398.

4. National PBN Monograph Template Rev20091005. (2012, January).

5. Gateau T, Bloom M, Clark R. Response to specific *Centruroiodes sculpturatus* antivenom in 151 cases of scorpion stings. Clin Toxicol. 1994;32(2):165–171. doi: 10.3109/15563659409000446

6. Gold, J. (2011, November 28). Treating A Scorpion Sting: $100 In Mexico Or $12,000 In U.S. https://khn.org/news/treating-a-scorpion-sting-100-in-mexico-or-12000-in-u-s/

7. Roberts, C., & Roberts, C. (2019, January 10). Arizona woman feeling the pain from a $83,046 bill for anti-venom drug after seeking medical treatment for scorpion sting. https://www.nydailynews.com/news/national/arizona-woman-feeling-pain-83-046-bill-anti-venom-drug-seeking-medical-treatment-scorpion-sting-article-1.1152754

8. James B Mowry, Daniel A. Spyker, Louis R. Cantilena Jr, Naya McMilian, Marsha Ford (2014) 2013 Annual Report of the American Association of Poison Control Centers' National Data System (NPDS): 31st Annual Report 52:10 1038-1280

9. James B Mowry PharmD, Daniel A. Spyker PhD, MD, Daniel E. Brooks MD, Naya McMilan DrPH, MS & Jay L. Schauben PharmD (2015) 2014 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 32nd Annual Report, Clinical Toxicology, 53:10, 962-1147, DOI:10.3109/15563650.2015.1102927

10. James B. Mowry, Daniel a Spyker, Daniel E. Brooks, Ashlea Zimmerman & Jay L. Scauben (2016) 2015 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 33rd Annual Report, Clinical Toxicology, 54:10, 924-1109, DOI: 10.1080/15563650.2016.1245421

11. Pedi STAT. James Kempema (n.d.). https://qxmd.com/pedi-stat

12. Volentine, J. (2017, August 08). Scorpion antivenin cheaper in Mexico than USA. Retrieved from https://www.abc15.com/news/state/why-is-scorpion-antivenin-so-affordable-in-mexico-but-not-in-america

13. Bush, S. P., Ruha, A., Seifert, S. A., Morgan, D. L., Lewis, B. J., Arnold, T. C., . . . Boyer, L. V. (2015, January). Comparison of F(ab')2 versus Fab antivenom for pit viper envenomation: A prospective, blinded, multicenter, randomized clinical trial. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4364250/

APPENDIX

1 – DATA ABSTRACTION SHEET

ADULT SCORPION STINGS: DATA ABSTRACTION SHEET

(record findings at peak symptoms, whether upon presentation or if after obs prd)

SUBJECT #		**Age**				
				Time of sting		
Date		**Sex**		**Time sx onset**		
				Time to HCF		
Signs:	**eyes**	yes	no	**Vitals:**	**HR**	
	motor act.	yes	no		**BP**	
	hypersal	yes	no		**RR**	
	diaphoresis	yes	no		**Max Temp**	
	resp distress	yes	no		**O2sat**	
	vomiting	yes	no		**(RA/O2)**	
	if yes:	pre-hosp	ED			
	ataxia	yes	no			

Antivenom Given	yes	no	available / not available

Patient complaints:	pain	diff ambulating	
	paresthesias	other	(i.e swelling, rash, wheezing)
	diff swallowing		
	visual sxs		
	dyspnea		

Treatment prior to hospital arrival:

DPH
atropine
APAP
NSAID
intubation
benzo/dose: _____
opiate/dose: _____
IVF
other:

Treatment in hospital:(circle)

IVF
O2 via: _____
atropine
intubation
benzo: _____
opiate: _____
other:

CPK? no yes: peak _____ **Rhabdo?** yes
max Cr: _____ time since sting:

EKG? no yes results _____

CXR? no yes aspiration? no yes

Length of stay: _____ hours

Comments/Complications: _____

Other relevant information: _____