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# BMJ Paediatrics Open

## Long-term sequelae secondary to snakebite envenoming: a 14-year study in a Costa Rican pediatric Hospital

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**Title:**

**Long-term Sequelae secondary to snakebite envenoming: a 14-year study in a Costa Rican pediatric Hospital**

**Short Title:**

**Sequelae secondary to snakebite envenoming: a 14-year observational study**

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**Contributors' Statement Page:**

Drs. Brenes-Chacón and Ávila-Agüero conceptualized and designed the study and data collection instruments. They collected data, carried out the initial analyses, drafted and reviewed the manuscript.

Dr. Gutiérrez contributed to the study design and the initial analyses. He critically reviewed the manuscript for intellectual content.

Drs. Camacho-Badilla, Soriano-Fallas, Ulloa-Gutierrez, and Valverde collected data, and were in charge of patients during hospitalization and follow up. They reviewed the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

## Abstract

**Objectives:** Although devastating acute effects associated with snake envenoming are well described, the long-term sequelae resulting from these envenomings have not been adequately addressed, especially in the pediatric population. The aim of our study is to describe the clinical characteristics among pediatric patients in Costa Rica who developed long-term sequelae secondary to snakebite envenoming.

**Design:** Retrospective descriptive study of pediatric patients under 13 years who were admitted with a history of a recent snakebite at the National Children's Hospital in Costa Rica from January 2001 to December 2014.

**Results:** We enrolled 74 patients admitted to our center due to recent snakebite envenoming, and separated those who did not develop sequelae (50 patients) from those who did (24 patients). Of those who presented acute complications during hospitalization, local wound infection and clinically diagnosed compartmental syndrome were significantly higher in the group that developed sequelae thereafter. Hypertrophic scars (66.7%), functional limitation (37.5%), and the need of skin graft (37.5%) were the most common sequelae. The median follow-up of patients with long-term sequelae after discharge was 25.4 mo [5.6-59.4]. No deaths were reported during this time period.

**Conclusions:** Given the high economic, personal, and healthcare burden that entails follow-up of these patients, efforts should be carried out to prevent the factors associated with sequelae among the affected population.

## Introduction

Snakebite envenoming is an important cause of morbidity and mortality on a global basis, particularly in sub-Saharan Africa, Asia and Latin America.<sup>1</sup> It affects 1.8 to 2.7 million people worldwide every year, causing between 81,000 to 138,000 deaths.<sup>1</sup> Recognized in 2017 as a Neglected Tropical Disease by the World Health Organization (WHO),<sup>2</sup> the actual burden of this disease is still unrecognized. The WHO has launched a global strategy for the prevention and control of these envenomings,<sup>2</sup> but there is still a lot to be known in the follow-up of affected patients.

Although devastating acute effects associated with snakebite envenoming are well described, the long-term sequelae resulting from these envenomings have not been adequately addressed, especially in the pediatric population.<sup>3</sup> Many studies have described the epidemiological characteristics and clinical profiles of these envenomings, both in adults and children. However, few have focused on the risk factors associated with morbidity and further complications.<sup>4</sup> The few studies carried out on sequelae following snakebites have identified several physical and psychological outcomes which exert a heavy impact in the quality of life of affected people.<sup>5</sup>

It is relevant to further analyze the sequelae that develop as a consequence of snakebite envenomings in various regions of the world. The aim of our study is to describe the clinical characteristics occurring among pediatric patients in Costa Rica who developed long-term sequelae secondary to snakebite envenoming, and provide a general overview of their outcomes.

## Patients and Methods

### Study design

Retrospective descriptive study of pediatric patients under 13 years admitted with a discharge diagnosis of a recent snakebite envenoming and who were enrolled at the National Children's Hospital in Costa Rica during a period of 14 years: from January 2001 to December 2014. Patients were identified following ICD-10 diagnosis of discharge provided by the statistic department. The National Children's Hospital is the only tertiary pediatric referral academic hospital in the country, where patients in need of specialized care are referred. Therefore, this cohort represents mostly pediatric patients transferred from regional hospitals.

All patients admitted during the time period at this health center were enrolled, and we collected demographic and clinical information, including: a) time of first medical evaluation; b) previous medical support provided; c) antivenom administration; d) clinical signs and symptoms on admission, and e) acute and long-term complications. For those who developed long-term sequelae, the follow-up time was also recorded. Severity of envenoming was classified as mild, moderate, and severe, according with the clinical manifestations on admission (Table 1).

Because of the retrospective nature of this research, patient and public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

This study was approved by the Bioethical and Research Committee of the National Children's Hospital, CLOBI – HNN, project 001-2015.

### Statistical Analysis



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3 Patients were classified in two groups: those with and those without long-term sequelae.  
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5 Continuous variables are presented as medians (25<sup>th</sup>-75<sup>th</sup> IQR) or means  $\pm$ SD according to data  
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7 distribution, and the groups were compared using Mann-Whitney or Student's *t*-test, respectively.  
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10 Categorical variables are presented as frequencies and compared using the Fisher's exact or chi-  
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12 squared tests.  
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## 19 **Results**

### 20 **Demographic Characteristics of Patients**

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23 From 2001 to 2014 we enrolled 74 patients admitted to our center due to acute snakebite  
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25 envenoming, all caused by viperid snake species, most of these by *Bothrops asper*. Patients were  
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27 separated in two groups: those who did not develop sequelae as a consequence of envenoming (50  
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29 patients), and those who developed sequelae, defined as need to follow-up because of direct  
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31 complications associated to the disease after discharge (24 patients).  
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39 Overall, the median age of both groups was similar, with a majority of male patients. Lower and  
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41 upper extremities were the most affected anatomic sites, and at the time of evaluation most of them  
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43 were classified as having moderate envenoming according to the initial signs and symptoms  
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45 presented (Table 2).  
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### 49 **Clinical findings and hospitalization evolution**

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52 No differences between the time for medical evaluation or the time for antivenom administration  
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54 were significant among groups. Regarding symptoms presented by patients at the moment of first  
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3 evaluation, most of them had locally associated edema, pain, and bleeding as the main clinical  
4 features (Table 2).  
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9 During hospitalization, some patients presented acute complications that were also analyzed.  
10 Serum sickness was observed in only 3 patients among both groups, but local wound infection and  
11 clinically diagnosed compartmental syndrome were significantly higher in the group that  
12 developed sequelae thereafter (Table 2).  
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### 19 **Sequelae among patients**

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22 Among the 24 patients with sequelae documented after discharge, scars, functional limitation of  
23 the limb affected, and the need of skin graft were the most common ones (Table 3). The median  
24 follow-up time of these patients in different specialties (plastic and reconstructive surgery,  
25 orthopedic surgery, physiatry, physiotherapy, and occupational therapy) due to the sequelae was  
26 25.4 mo [5.6-59.4].  
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### 39 **Discussion**

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42 Viperid snakebite envenomings are characterized by prominent local and systemic alterations,  
43 some of which may lead to permanent damage to various organs, thus generating long-term  
44 sequelae.<sup>6</sup> Despite the relevance of this aspect of envenomings, there have been few studies  
45 focusing on sequelae and the factors that determine their incidence. This single center study  
46 analyzed the clinical characteristics and differences among pediatric patients with snakebite  
47 envenoming, comparing those with and without long-term sequelae.  
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3 The patients of this study presented the typical local and systemic manifestations described for  
4 viperid snakebite envenomings, and particularly for those caused by *Bothrops asper*, which inflicts  
5 the vast majority of cases in Costa Rica.<sup>7</sup> Most patients developed envenomings graded as  
6 moderate in terms of severity, and all of them received the polyvalent antivenom manufactured in  
7 Costa Rica, which is used in the treatment of viperid snakebite envenomings. The incidence of  
8 adverse reactions to antivenom administration was low, in agreement with previous studies.<sup>8</sup> It is  
9 recommended that antivenom be administered within the first 3-4 hours after the event to decrease  
10 the rates of complications, mortality and long-term sequelae.<sup>1, 9-11</sup> In our cohort, nevertheless, one  
11 third of patients were treated after this recommended period of time, mostly due to delay in  
12 transportation from remote rural settings, as shown for several regions in Costa Rica.<sup>12</sup>  
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27 Little is known about the risk factors associated with the development of long-term sequelae  
28 following snakebites in children. Age and average of time lapsed to first medical evaluation and  
29 antivenom administration have been described in other studies as predictors of mortality and  
30 morbidity in adults and children.<sup>3,13</sup> In our study, when analyzing the factors associated with the  
31 development of sequelae, no differences between both groups of patients were observed regarding  
32 age, gender, anatomical site of the bite, severity of envenoming, time to reach the hospital and to  
33 receive the first dose of antivenom, and local clinical manifestations of envenoming. Thus, despite  
34 the fact that previous literature has related late medical care with a higher risk of complications,  
35 including lethality,<sup>11</sup> no association between time to reach treatment and incidence of sequelae was  
36 observed in our study.  
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51 In contrast, infections at the site of the bite and the presence of compartmental syndrome were  
52 significantly more prevalent in the long-term sequelae group. Wound infections and  
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3 compartmental syndrome have been described previously by our group to be associated with  
4 severity of envenomings.<sup>9, 10</sup> Infections are prevalent in envenomings by *B. asper*,<sup>8, 10</sup> particularly  
5 when there is local tissue damage, since tissue ischemia and necrosis favor infection by bacteria  
6 present in the venom or in the skin of the patient. Venom-induced tissue damage and local infection  
7 foster a vicious cycle of tissue necrosis, hence explaining the association between infection and  
8 sequelae in our study.  
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12 In viperid snakebite envenomings, compartment syndrome is a consequence of extravasation into  
13 the interstitial space of muscle tissue, resulting in increments in intracompartmental pressure  
14 which, when reaching values of 30-40 mmHg, interruption of arterial blood flow, ischemia and  
15 necrosis occurs. Such increase in vascular permeability is due to the direct action of venom  
16 components in the microvasculature, but also to the action of endogenous inflammatory mediators  
17 synthesized or released in the tissue as a consequence of venom-induced pathology.<sup>14</sup> Previously,  
18 our group has suggested that a cytokine response is associated with severe envenomings in bites  
19 by *B. asper*.<sup>15</sup> Of concern, a high percentage (almost 50% including both cohorts) of the pediatric  
20 patients included in this study developed compartmental syndrome which required surgical  
21 decompression, i.e. fasciotomy. Thus, the higher incidence of sequelae in children who underwent  
22 fasciotomy could be related to pressure-induced tissue damage, or to the consequences of this  
23 surgical intervention, especially regarding scar formation. It is necessary to further study the effect  
24 of compartment syndrome in these sequelae, and how to reduce its incidence.  
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49 Among the group of patients who developed sequelae, we found that the median follow-up time  
50 was considerable, exceeding a 2-year period after the event. This finding has social, psychological  
51 and institutional implications of various sorts. The children developing sequelae, as well as their  
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3 families, undergo suffering and limitations, not only physical but also psychological. In addition,  
4 the costs for the following-up of the consequences of snakebite envenoming are high, both for the  
5 affected people and for the public health system. Management of this neglected tropical disease is  
6 very costly,<sup>4</sup> and the expenses increase considerably when long-term follow-up is needed. This is  
7 another aspect of this problem that requires further studies.  
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11 Our study has limitations. Patients were enrolled in a referral center, thus the population of patients  
12 are selected to be moderate or severe envenomings, since mild cases are handled in rural hospitals.  
13 Therefore, our observations cannot be extrapolated to the rest of the country, where the risk of  
14 developing sequelae is likely to be lower. This is a retrospective study, nevertheless, given the  
15 long term of the study, the number of patients is suitable for this report.  
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## 28 **Conclusion**

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31 A 14-year study was conducted describing the clinical presentation among pediatric patients  
32 suffering snakebite envenoming with and without sequelae. Our study found that, among the acute  
33 complications, infection and compartment syndrome were significantly higher in those patients  
34 that further developed long-term sequelae. Given the high personal and healthcare burden that  
35 entails the follow-up of these patients, efforts should be carried out to prevent the factors associated  
36 with sequelae among the affected population.  
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50 **Funding Source:** No funding was secured for this study.  
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**What is Known on This Subject**

1. The WHO estimates that about 5 million snakebites occur each year, resulting in up to 138,000 deaths.
2. Almost 400,000 people left with physical and psychological sequelae and permanent disabilities.
3. There is limited knowledge on this relevant aspect of envenomings.

**What This Study Adds:**

1. This study analyzed the risk factors associated with snakebite envenoming sequelae in children.
2. It addressed the clinical factors associated and the evolution of this complication over time.
3. There is little published evidence of long-term sequelae in the pediatric group.

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**Table 1. Case definition of patients with snakebite envenoming.**

No envenoming	Patients with no local or systemic signs or symptoms
Mild envenoming	Local edema in one or two segments, pain at the bite site, absence of systemic signs or symptoms.
Moderate envenoming	Edema in three segments, local hemorrhage. Systemic symptoms (bleeding, hypotension) and blood clotting test alterations
Severe envenoming	Edema extending to the whole limb, local hemorrhage with necrosis, severe hypotension, blood clotting alterations, systemic bleeding and, in some cases, acute kidney injury.



**Table 2. Demographic and clinical findings of patients with and without snakebite sequelae**

	No sequelae n=50	With sequelae n=24	<i>p</i> value
Age, mo (range)	113 (67.3-130.5)	110 (73-130.8)	0.87
Male gender	34 (68)*	18 (75)*	0.59
Anatomical site of the bite			
Lower extremities	33 (66)	14 (58)	0.61
Upper extremities	14 (28)	10 (41.6)	0.29
Head	2 (4)	0	-
Chest	1 (2)	0	-
Severity of envenoming			
Mild	13 (26)	3 (12.5)	0.24
Moderate	36 (72)	18 (75)	>0.99
Severe	1 (2)	3 (12.5)	0.09
Time to medical evaluation (hr)			
1-4	32 (64)	17 (70.8)	0.61
5-8	0	2 (8.3)	-
9-12	3 (6)	2 (8.3)	0.66
13 +	8 (16)	1 (4.2)	0.26
No data	7 (14)	2 (8.3)	-
Time to administration of antivenom			
1-4	30 (60)	16 (66.7)	0.62
5-8	0	1 (4.2)	-
9-12	2 (4)	1 (4.2)	>0.99
13 +	11 (22)	2 (8.3)	0.20
No data	7 (14)	3 (12.5)	-
Initial signs and symptoms			
Pain	37 (74)	17 (70.8)	0.78
Local edema	47 (94)	24 (100)	0.54
Bleeding	14 (28)	10 (41.6)	0.29
Bullae formation	5 (10)	4 (16.7)	0.46
Local necrosis	0	2 (8.3)	-
Complications			
Infection	3 (6)	9 (37.5)	<b>0.0013</b>
Serum sickness	2 (4)	1 (4.2)	>0.99
Compartmental syndrome	16 (32)	20 (83.3)	<b>&lt;0.0001</b>
Need of Fasciotomy	17 (34)	21 (87.5)	<b>&lt;0.0001</b>

\*Results are presented as number of patients and percentages (in parentheses).

Categorical data are expressed as frequencies (%) and analyzed using Fisher or  $\chi^2$  test

Continuous data are expressed as median (25%-75% interquartile range) and analyzed using Mann-Whitney rank test or Student's *t* test

Values in Bold indicate significant 2-sided *p* values

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3 Abbreviations: mo, months; H, hours  
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**Table 3. Sequelae description**

Sequelae	Number of patients (frequency) n=24
Hypertrophic scar	16 (66.7)
Functional limitation	9 (37.5)
Skin graft	9 (37.5)
Deformity	2 (8.3)
Amputation	1 (4.2)

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## Long-term Sequelae secondary to snakebite envenoming: a single center retrospective study in a Costa Rican pediatric Hospital

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**Title:**

**Long-term Sequelae secondary to snakebite envenoming: a single center retrospective study in a Costa Rican pediatric Hospital**

**Short Title:**

**Sequelae secondary to snakebite envenoming: a 14-year observational study**

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2  
3 **Contributors' Statement Page:**

4 2 Drs. Brenes-Chacón and Ávila-Agüero conceptualized and designed the study and data collection  
5 3 instruments. They collected data, carried out the initial analyses, drafted and reviewed the  
6 4 manuscript.

7 5 Dr. Gutiérrez contributed to the study design and the initial analyses. He critically reviewed the  
8 6 manuscript for intellectual content.

9 7 Drs. Camacho-Badilla, Soriano-Fallas, Ulloa-Gutierrez, and Valverde collected data, and were in  
10 8 charge of patients during hospitalization and follow up. They reviewed the manuscript.

11 9 All authors approved the final manuscript as submitted and agree to be accountable for all aspects  
12 10 of the work.

## 1 Abstract

2 **Objectives:** Although devastating acute effects associated with snake envenoming are well  
3 described, the long-term sequelae resulting from these envenomings have not been adequately  
4 addressed, especially in the pediatric population. The aim of our study is to describe the clinical  
5 characteristics among pediatric patients in Costa Rica who developed long-term sequelae  
6 secondary to snakebite envenoming.

7 **Design:** Retrospective descriptive study of pediatric patients under 13 years who were admitted  
8 with a history of a recent snakebite at the National Children's Hospital in Costa Rica from January  
9 2001 to December 2014.

10 **Results:** We enrolled 74 patients admitted to our center due to envenoming, and separated those  
11 who did not develop sequelae (50 patients) from those who did (24 patients). Of those who  
12 presented acute complications during hospitalization, local wound infection and clinically  
13 diagnosed compartmental syndrome were significantly higher in the group that developed sequelae  
14 thereafter. Hypertrophic scars (66.7%), functional limitation (37.5%), and the need of skin graft  
15 (37.5%) were the most common sequelae. The median follow-up of patients with long-term  
16 sequelae after discharge was 25.4 mo [5.6-59.4]. No deaths were reported during this time period.

17 **Conclusions:** Given the high economic, personal, and healthcare burden that entails follow-up of  
18 these patients, efforts should be carried out to prevent the factors associated with sequelae among  
19 the affected population.

20



## 1 Introduction

2 Snakebite envenoming is an important cause of morbidity and mortality on a global basis,  
3 particularly in sub-Saharan Africa, Asia and Latin America.<sup>1</sup> It affects 1.8 to 2.7 million people  
4 worldwide every year, causing between 81,000 to 138,000 deaths.<sup>1</sup> Recognized in 2017 as a  
5 Neglected Tropical Disease by the World Health Organization (WHO),<sup>2</sup> the actual burden of this  
6 disease is still unrecognized. The WHO has launched a global strategy for the prevention and  
7 control of these envenomings,<sup>2</sup> but there is still a lot to be known in the follow-up of affected  
8 patients.

9 Although devastating acute effects associated with snakebite envenoming are well described, the  
10 long-term sequelae resulting from these envenomings have not been adequately addressed,  
11 especially in the pediatric population.<sup>3</sup> Many studies have described the epidemiological  
12 characteristics and clinical profiles of these envenomings, both in adults and children. However,  
13 few have focused on the risk factors associated with morbidity and further complications.<sup>4</sup> The  
14 few studies carried out on sequelae following snakebites have identified several physical and  
15 psychological outcomes which exert a heavy impact in the quality of life of affected people.<sup>5</sup>

16 It is relevant to further analyze the sequelae that develop as a consequence of snakebite  
17 envenomings in various regions of the world. The aim of our study is to describe the clinical  
18 characteristics occurring among pediatric patients in Costa Rica who developed long-term  
19 sequelae secondary to snakebite envenoming, and provide a general overview of their outcomes.

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## 1 Patients and Methods

### 2 Study design

3 Retrospective descriptive study of pediatric patients under 13 years admitted with a discharge  
4 diagnosis of a recent snakebite envenoming and who were enrolled at the National Children's  
5 Hospital in Costa Rica during a period of 14 years: from January 2001 to December 2014. Patients  
6 were identified following ICD-10 diagnosis of discharge provided by the statistic department. The  
7 National Children's Hospital is the only tertiary pediatric referral academic hospital in the country.  
8 For snake envenomings, patients in need of specialized care (such as general surgery,  
9 reconstructive surgery, orthopedic, or infectious diseases evaluations) are the ones referred to our  
10 center. Most of the patients included in this cohort were transferred in the first 24 hours after the  
11 event, mainly from regional hospitals in Costa Rica.

12 All patients admitted during the time period at this health center were enrolled, and we collected  
13 demographic and clinical information, including: a) time of first medical evaluation; b) previous  
14 medical support provided; c) antivenom administration; d) clinical signs and symptoms on  
15 admission, and e) acute and long-term complications. Acute complications were defined as  
16 complications related to the event that presented during hospitalization, such as infections,  
17 compartmental syndrome, acute bleeding, respiratory and renal abnormalities, and serum sickness,  
18 among others, were collected. Long-term complications or sequelae were defined as the presence  
19 of a condition also related to the snakebite episode, that requires long-term medical follow-up.  
20 Scar complications, functional limitation, and deformity among others, were included as long-term  
21 sequelae. They were not necessarily present at discharge and could develop along time.

1 For those who developed long-term sequelae, the follow-up time was also recorded. Severity of  
2 envenoming was classified as mild, moderate, and severe, according with the clinical  
3 manifestations on admission (Table 1).

4 Because of the retrospective nature of this research, patients and public were not involved in the  
5 design, or conduct, or reporting, or dissemination plans of this research.

6 This study was approved by the Bioethical and Research Committee of the National Children's  
7 Hospital, CLOBI – HNN, project 001-2015.

## 8 **Statistical Analysis**

9 Patients were classified in two groups: those with and those without long-term sequelae.  
10 Continuous variables are presented as medians (25<sup>th</sup>-75<sup>th</sup> IQR) or means  $\pm$ SD according to data  
11 distribution, and the groups were compared using either Mann-Whitney or Student's *t*-test,  
12 respectively. Categorical variables are presented as frequencies and compared using the Fisher's  
13 exact or chi-squared tests.

14 To determine which factors were independently associated with long-term sequelae we used a  
15 multivariable logistic regression. Variables were entered and retained into the model if they had  
16 an adjusted p-value of  $<0.25$ . All analyses were conducted using GraphPad Prism v.8 (GraphPad  
17 Software) and R for Statistical Computing, with a two-sided p-value  $<0.05$  considered statistically  
18 significant.

## 19 **Patient and Public Involvement statement**

20 As a retrospective study, patients were not involved in the recruitment and conduct of this study.

## 1 **Results**

### 2 **Demographic Characteristics of Patients**

3 From 2001 to 2014 we enrolled 74 patients admitted to our center due to acute snakebite  
4 envenoming, all caused by viperid snake species, most of these by *Bothrops asper*. Patients were  
5 separated in two groups: those who did not develop sequelae as a consequence of envenoming (50  
6 patients), and those who developed sequelae, defined as need to follow-up because of direct  
7 complications associated to the disease after discharge (24 patients).

8 Overall, the median age of both groups was similar, most of them children older than nine years  
9 of age, with a majority of male patients. Lower and upper extremities were the most affected  
10 anatomic sites, and at the time of evaluation most of them were classified as having moderate  
11 envenoming according to the initial signs and symptoms presented (Table 2).

### 12 **Clinical findings and hospitalization evolution**

13 No differences between the time for medical evaluation or the time for antivenom administration  
14 were significant among groups. Regarding signs and symptoms presented by patients at the time  
15 of first evaluation, most of them had locally associated edema, pain, and bleeding as the main  
16 clinical features (Table 2).

17 During hospitalization, some patients presented acute complications that were also analyzed.  
18 Serum sickness was observed in only 3 patients among both groups, but local wound infection and  
19 clinically diagnosed compartmental syndrome were significantly higher in the group that  
20 developed sequelae thereafter (Table 2).

## 1 **Adjusted odds of long-term sequelae**

2 We also analyzed which acute complications, were independently associated with long-term  
3 sequelae that needed extended specialized follow-up or that resulted in a long-term disability  
4 (Table 3).

5 Across both groups, wound infection or infections related to snakebite site and the need of  
6 fasciotomy were consistently associated with greater odds of long-term sequelae in our studied  
7 population.

## 8 **Sequelae among patients**

9 Among the 24 patients with sequelae documented after discharge, scars, functional limitation of  
10 the limb affected (meaning complications that diminish or eliminate the regular motor function of  
11 an extremity or part of it), and the need of skin graft were the most common ones (Table 4). Long-  
12 term sequelae included in this study go from mild (hypertrophic scars) to severe complications  
13 (amputation). Nevertheless, all of them translated in long-term follow-up and some degree of  
14 transitory or permanent disability for all patients.

15 The median follow-up time of these patients in different specialties (plastic and reconstructive  
16 surgery, orthopedic surgery, physiatry, physiotherapy, and occupational therapy) due to the  
17 sequelae was 25.4 mo [5.6-59.4]. The frequency and duration of follow-up among these patients  
18 varied widely, and it was decided by the specialist according to individual needs and progress in  
19 time.

20

## 1 Discussion

2 Viperid snakebite envenomings are characterized by prominent local and systemic alterations,  
3 some of which may lead to permanent damage to various organs, thus generating long-term  
4 sequelae.<sup>6</sup> Despite the relevance of this aspect of envenomings, there have been few studies  
5 focusing on sequelae and the factors that determine their incidence. This single center study  
6 analyzed the clinical characteristics and differences among pediatric patients with snakebite  
7 envenoming, comparing those with and without long-term sequelae.

8 The patients of this study presented the typical local and systemic manifestations described for  
9 viperid snakebite envenomings, and particularly for those caused by *Bothrops asper*, which inflicts  
10 the vast majority of cases in Costa Rica.<sup>7</sup> Most patients developed envenomings graded as  
11 moderate in terms of severity, and all of them received the polyvalent antivenom manufactured in  
12 Costa Rica, which is used in the treatment of viperid snakebite envenomings. The incidence of  
13 adverse reactions to antivenom administration was low, in agreement with previous studies.<sup>8</sup> It is  
14 recommended that antivenom be administered within the first 3-4 hours after the event to decrease  
15 the rates of complications, mortality and long-term sequelae.<sup>1, 9-11</sup> In our cohort, nevertheless, one  
16 third of patients were treated after this recommended period of time, mostly due to delay in  
17 transportation from remote rural settings, as shown for several regions in Costa Rica.<sup>12</sup>

18 Little is known about the risk factors associated with the development of long-term sequelae  
19 following snakebites in children. Age and average of time lapsed to first medical evaluation and  
20 antivenom administration have been described in other studies as predictors of mortality and  
21 morbidity in adults and children.<sup>3,13</sup> In our study, when analyzing the factors associated with the  
22 development of sequelae, no significant differences between both groups of patients were observed

1 regarding age, gender, anatomical site of the bite, severity of envenoming, time to reach the  
2 hospital and to receive the first dose of antivenom, and local clinical manifestations of  
3 envenoming. Thus, despite the fact that previous literature has related late medical care with a  
4 higher risk of complications, including lethality,<sup>11</sup> no significant association between time to reach  
5 treatment and incidence of sequelae was observed in our study.

6 In contrast, infections at the site of the bite and the presence of compartmental syndrome were  
7 significantly more prevalent in the long-term sequelae group. Logistic regression analysis made  
8 found that both infection and need of fasciotomy, were consistently associated with greater odds  
9 of long-term sequelae. Wound infections and compartmental syndrome have been described  
10 previously by our group to be associated with severity of envenomings.<sup>9, 10</sup> Infections are prevalent  
11 in envenomings by *B. asper*,<sup>8, 10</sup> particularly when there is local tissue damage, since tissue  
12 ischemia and necrosis favor infection by bacteria present in the venom or in the skin of the patient.  
13 Venom-induced tissue damage and local infection foster a vicious cycle of tissue necrosis, hence  
14 explaining the association between infection and sequelae in our study.

15 In viperid snakebite envenomings, compartment syndrome is a consequence of extravasation into  
16 the interstitial space of muscle tissue, resulting in increments in intracompartmental pressure  
17 which, when reaching values of 30-40 mmHg, interruption of arterial blood flow, ischemia and  
18 necrosis occurs. Such increase in vascular permeability is due to the direct action of venom  
19 components in the microvasculature, but also to the action of endogenous inflammatory mediators  
20 synthesized or released in the tissue as a consequence of venom-induced pathology.<sup>14</sup> Previously,  
21 our group has suggested that a cytokine response is associated with severe envenomings in bites  
22 by *B. asper*.<sup>15</sup> Of concern, a high percentage (almost 50% including both cohorts) of the pediatric

1 patients included in this study developed compartmental syndrome which required surgical  
2 decompression, i.e. fasciotomy. Thus, the higher incidence of sequelae in children who underwent  
3 fasciotomy could be related to pressure-induced tissue damage, or to the consequences of this  
4 surgical intervention, especially regarding scar formation. It is necessary to further study the effect  
5 of compartment syndrome in these sequelae, and how to reduce its incidence.

6 Among the group of patients who developed sequelae, we found that the median follow-up time  
7 was considerable, exceeding a 2-year period after the event. This finding has social, psychological  
8 and institutional implications of various sorts. The children developing sequelae, as well as their  
9 families, undergo suffering and limitations, not only physical but also psychological. In addition,  
10 the costs for the following-up of the consequences of snakebite envenoming are high, both for the  
11 affected people and for the public health system. Management of this neglected tropical disease is  
12 very costly,<sup>4</sup> and the expenses increase considerably when long-term follow-up is needed. This is  
13 another aspect of this problem that requires further studies.

14 Our study has limitations. Patients were enrolled in a referral center, thus the population of patients  
15 are selected to be moderate or severe envenomings, since mild cases are handled in rural hospitals.  
16 Therefore, our observations of patients who were not only bitten by a snake but also that required  
17 hospitalization and referral to a specialized center, can overestimate the prevalence of acute  
18 complications, and cannot be extrapolated to the rest of the country, where the risk of developing  
19 sequelae is likely to be lower. Nevertheless, demographic and several clinical features of both  
20 groups (with and without sequelae) were similar. This is a retrospective study; nevertheless, given  
21 the long term of the study, the number of patients allowed the analysis of the clinical features  
22 associated with the development sequelae.



## 1 Conclusion

2 A 14-year study was conducted describing the clinical presentation among pediatric patients  
3 suffering snakebite envenoming with and without sequelae. Our study found that, among the acute  
4 complications, infection and compartment syndrome were significantly higher in those patients  
5 that further developed long-term sequelae. Given the high personal and healthcare burden that  
6 entails the follow-up of these patients, efforts should be carried out to prevent the factors associated  
7 with sequelae among the affected population.

8  
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13 for his work, and useful thoughts about the manuscript.

## 15 What is Known on This Subject

- 16 1. The WHO estimates that about 5 million snakebites occur each year, resulting in up to  
17 138,000 deaths.
- 18 2. Almost 400,000 people suffering snakebite envenoming are left with physical and  
19 psychological sequelae and permanent disabilities. Most of this information is based on  
20 studies carried out with adult populations.
- 21 3. There is limited knowledge on relevant aspects of envenomings. The incidence of physical  
22 disabilities from envenomings is limited, and the scarce data is mainly focused on adults.

## 26 What This Study Adds:

- 27 1. Infection and compartment syndrome after envenoming were the clinical factors most  
28 associated with long-term sequelae development.

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3 1 2. Little is known about long-term sequelae in the pediatric group. This paper adds  
4 2 information of the clinical characteristics of this population.  
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**Table 1. Case definition of patients with snakebite envenoming.**

No envenoming	Patients with no local or systemic signs or symptoms
Mild envenoming	Local edema in one or two segments, pain at the bite site, absence of systemic signs or symptoms.
Moderate envenoming	Edema in three segments, local hemorrhage. Systemic symptoms (bleeding, hypotension) and blood clotting test alterations
Severe envenoming	Edema extending to the whole limb, local hemorrhage with necrosis, severe hypotension, blood clotting alterations, systemic bleeding and, in some cases, acute kidney injury.

**Table 2. Demographic and clinical findings of patients with and without snakebite sequelae**

	No sequelae n=50	With sequelae n=24	<i>p</i> value
Age, mo [range]	113 [67.3-130.5]	110 [73-130.8]	0.87
Male gender	34 (68)*	18 (75)*	0.59
Anatomical site of the bite			0.43
Lower extremities	33 (66)	14 (58)	
Upper extremities	14 (28)	10 (41.6)	
Head	2 (4)	0	
Chest	1 (2)	0	
Severity of envenoming			0.095
Mild	13 (26)	3 (12.5)	
Moderate	36 (72)	18 (75)	
Severe	1 (2)	3 (12.5)	
Time to medical evaluation, h [range]	2.0 [1.0-9.0]	2.0 [1.25-5.5]	0.76
Time to administration of antivenom, h [range]	2.0 [1.0-15.0]	2.0 [1.0-6.0]	0.84
Initial signs and symptoms			
Pain	37 (74)	17 (70.8)	0.78
Local edema	47 (94)	24 (100)	0.54
Bleeding	14 (28)	10 (41.6)	0.29
Bullae formation	5 (10)	4 (16.7)	0.46
Local necrosis	0	2 (8.3)	-
Acute complications presented during hospitalization **			
Infection	3 (6)	9 (37.5)	<b>0.0013</b>
Serum sickness	2 (4)	1 (4.2)	>0.99
Compartmental syndrome	16 (32)	20 (83.3)	<b>&lt;0.0001</b>
Need of Fasciotomy	17 (34)	21 (87.5)	<b>&lt;0.0001</b>

\*Results are presented as number of patients and percentages (in parentheses).

Categorical data are expressed as frequencies (%) and analyzed using Fisher or  $\chi^2$  test

Continuous data are expressed as median [25%-75% interquartile range] and analyzed using

Mann-Whitney rank test or Student's *t* test

Values in Bold indicate significant 2-sided *p* values

\*\* Acute complications presented during hospitalization refers to those complications presented during the initial days after snakebite, and not to long-term complications.

Abbreviations: mo, months; H, hours

**Table 3. Adjusted odds of long-term sequelae in patients with acute complications during hospitalization**

Variable	Odds Ratio	95% CI	p value
Gender	1.87	0.40 - 8.62	0.442
Acute complication: - Infection	10.85	2.28 - 51.63	<b>0.003</b>
Acute complication: - Need of Fasciotomy	13.42	0.001 - 0.30	<b>0.002</b>

CI, confidence interval

**Table 4. Sequelae description**

Sequelae	Number of patients (frequency) n=24
Hypertrophic scar	16 (66.7)
Functional limitation	9 (37.5)
Skin graft	9 (37.5)
Deformity	2 (8.3)
Amputation	1 (4.2)

\*Results are presented as number of patients and percentages (in parentheses).

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## Long-term Sequelae secondary to snakebite envenoming: a single center retrospective study in a Costa Rican pediatric Hospital

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**Title:**

**Long-term Sequelae secondary to snakebite envenoming: a single center retrospective study in a Costa Rican pediatric Hospital**

**Short Title:**

**Sequelae secondary to snakebite envenoming: a 14-year observational study**

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2  
3 **Contributors' Statement Page:**

4 Drs. Brenes-Chacón and Ávila-Agüero conceptualized and designed the study and data collection  
5 instruments. They collected data, carried out the initial analyses, drafted and reviewed the  
6 manuscript.

7  
8 Dr. Gutiérrez contributed to the study design and the initial analyses. He critically reviewed the  
9 manuscript for intellectual content.

10 Drs. Camacho-Badilla, Soriano-Fallas, Ulloa-Gutierrez, and Valverde collected data, and were in  
11 charge of patients during hospitalization and follow up. They reviewed the manuscript.

12 All authors approved the final manuscript as submitted and agree to be accountable for all aspects  
13 of the work.  
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## 1 Abstract

2 **Objectives:** Although devastating acute effects associated with snake envenoming are well  
3 described, the long-term sequelae resulting from these envenomings have not been adequately  
4 addressed, especially in the pediatric population. The aim of our study is to describe the clinical  
5 characteristics among pediatric patients in Costa Rica who developed long-term sequelae  
6 secondary to snakebite envenoming.

7 **Design:** Retrospective descriptive study of pediatric patients under 13 years who were admitted  
8 with a history of a recent snakebite at the National Children's Hospital in Costa Rica from January  
9 2001 to December 2014.

10 **Results:** We enrolled 74 patients admitted to our center due to envenoming, and separated those  
11 who did not develop sequelae (50 patients) from those who did (24 patients). Of those who  
12 presented acute complications during hospitalization, local wound infection and clinically  
13 diagnosed compartmental syndrome were significantly higher in the group that developed sequelae  
14 thereafter. Hypertrophic scars (66.7%), functional limitation of affected limb (37.5%), and the  
15 need of skin graft (37.5%) were the most common sequelae. The median follow-up of patients  
16 with long-term sequelae after discharge was 25.4 mo [5.6-59.4]. No deaths were reported during  
17 this time period.

18 **Conclusions:** Given the high economic, personal, and healthcare burden that entails follow-up of  
19 these patients, efforts should be carried out to prevent the factors associated with sequelae among  
20 the affected population.

21

## 1 Introduction

2 Snakebite envenoming is an important cause of morbidity and mortality on a global basis,  
3 particularly in sub-Saharan Africa, Asia and Latin America.<sup>1</sup> It affects 1.8 to 2.7 million people  
4 worldwide every year, causing between 81,000 to 138,000 deaths.<sup>1</sup> Recognized in 2017 as a  
5 Neglected Tropical Disease by the World Health Organization (WHO),<sup>2</sup> the actual burden of this  
6 disease is still unrecognized. The WHO has launched a global strategy for the prevention and  
7 control of these envenomings,<sup>2</sup> but there is still a lot to be known in the follow-up of affected  
8 patients.

9 Although devastating acute effects associated with snakebite envenoming are well described, the  
10 long-term sequelae resulting from these envenomings have not been adequately addressed,  
11 especially in the pediatric population.<sup>3</sup> Many studies have described the epidemiological  
12 characteristics and clinical profiles of these envenomings, both in adults and children. However,  
13 few have focused on the risk factors associated with morbidity and further complications.<sup>4</sup> The  
14 few studies carried out on sequelae following snakebites have identified several physical and  
15 psychological outcomes which exert a heavy impact in the quality of life of affected people.<sup>5</sup>

16 It is relevant to further analyze the sequelae that develop as a consequence of snakebite  
17 envenomings in various regions of the world. The aim of our study is to describe the clinical  
18 characteristics occurring among pediatric patients in Costa Rica who developed long-term  
19 sequelae secondary to snakebite envenoming, and provide a general overview of their outcomes.

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## 1 Patients and Methods

### 2 Study design

3 Retrospective descriptive study of pediatric patients under 13 years admitted with a discharge  
4 diagnosis of a recent snakebite envenoming and who were enrolled at the National Children's  
5 Hospital in Costa Rica during a period of 14 years: from January 2001 to December 2014. Patients  
6 were identified following ICD-10 diagnosis of discharge provided by the statistic department. The  
7 National Children's Hospital is the only tertiary pediatric referral academic hospital in the country.  
8 For snake envenomings, patients in need of specialized care (such as general surgery,  
9 reconstructive surgery, orthopedic, or infectious diseases evaluations) are the ones referred to our  
10 center. Most of the patients included in this cohort were transferred in the first 24 hours after the  
11 event, mainly from regional hospitals in Costa Rica.

12 All patients admitted during the time period at this health center were enrolled, and we collected  
13 demographic and clinical information, including: a) time of first medical evaluation; b) previous  
14 medical support provided; c) antivenom administration; d) clinical signs and symptoms on  
15 admission, and e) acute and long-term complications. Acute complications were defined as  
16 complications related to the event that presented during hospitalization, such as infections,  
17 compartmental syndrome, acute bleeding, respiratory and renal abnormalities, and serum sickness,  
18 among others, were collected. Long-term complications or sequelae were defined as the presence  
19 of a condition also related to the snakebite episode, that requires long-term medical follow-up.  
20 Scar complications, functional limitation, and deformity among others, were included as long-term  
21 sequelae. They were not necessarily present at discharge and could develop along time.

1 For those who developed long-term sequelae, the follow-up time was also recorded. Severity of  
2 envenoming was classified as mild, moderate, and severe, according with the clinical  
3 manifestations on admission (Table 1).

4 Because of the retrospective nature of this research, patients and public were not involved in the  
5 design, or conduct, or reporting, or dissemination plans of this research.

6 This study was approved by the Bioethical and Research Committee of the National Children's  
7 Hospital, CLOBI – HNN, project 001-2015.

## 8 **Statistical Analysis**

9 Patients were classified in two groups: those with and those without long-term sequelae.  
10 Continuous variables are presented as medians (25<sup>th</sup>-75<sup>th</sup> IQR) or means  $\pm$ SD according to data  
11 distribution, and the groups were compared using either Mann-Whitney or Student's *t*-test,  
12 respectively. Categorical variables are presented as frequencies and compared using the Fisher's  
13 exact or chi-squared tests.

14 To determine which factors were independently associated with long-term sequelae we used a  
15 multivariable logistic regression. Unadjusted model was made using all significant and relevant  
16 variables for the study independent of statistical significance. Then, variables were entered and  
17 retained into an adjusted model if they had an adjusted p-value of  $<0.25$ . All analyses were  
18 conducted using GraphPad Prism v.8 (GraphPad Software) and R for Statistical Computing, with  
19 a two-sided p-value  $<0.05$  considered statistically significant.

## 21 **Patient and Public Involvement statement**

1 As a retrospective study, patients were not involved in the recruitment and conduct of this study.

## 2 **Results**

### 3 **Demographic Characteristics of Patients**

4 From 2001 to 2014 we enrolled 74 patients admitted to our center due to acute snakebite  
5 envenoming, all caused by viperid snake species, most of these by *Bothrops asper*. Patients were  
6 separated in two groups: those who did not develop sequelae as a consequence of envenoming (50  
7 patients), and those who developed sequelae, defined as need to follow-up because of direct  
8 complications associated to the disease after discharge (24 patients).

9 Overall, the median age of both groups was similar, most of them children older than nine years  
10 of age, with a majority of male patients. Lower and upper extremities were the most affected  
11 anatomic sites, and at the time of evaluation most of them were classified as having moderate  
12 envenoming according to the initial signs and symptoms presented (Table 2).

### 13 **Clinical findings and hospitalization evolution**

14 No differences between the time for medical evaluation or the time for antivenom administration  
15 were significant among groups. Regarding signs and symptoms presented by patients at the time  
16 of first evaluation, most of them had locally associated edema, pain, and bleeding as the main  
17 clinical features (Table 2).

18 During hospitalization, some patients presented acute complications that were also analyzed.  
19 Serum sickness was observed in only 3 patients among both groups, but local wound infection and



1 clinically diagnosed compartmental syndrome were significantly higher in the group that  
2 developed sequelae thereafter (Table 2).

### 3 **Adjusted odds of long-term sequelae**

4 We also analyzed which acute complications, were independently associated with long-term  
5 sequelae that needed extended specialized follow-up or that resulted in a long-term disability  
6 (Table 3).

7 Wound infection or infections related to snakebite site and the need of fasciotomy were  
8 consistently associated with greater odds of long-term sequelae in our studied population.

### 9 **Sequelae among patients**

10 Among the 24 patients with sequelae documented after discharge, scars, functional limitation of  
11 the limb affected (meaning complications that diminish or eliminate the regular motor function of  
12 an extremity or part of it), and the need of skin graft were the most common ones (Table 4). Long-  
13 term sequelae included in this study go from mild (hypertrophic scars) to severe complications  
14 (amputation). Nevertheless, all of them translated in long-term follow-up and some degree of  
15 transitory or permanent disability for all patients.

16 The median follow-up time of these patients in different specialties (plastic and reconstructive  
17 surgery, orthopedic surgery, physiatry, physiotherapy, and occupational therapy) due to the  
18 sequelae was 25.4 mo [5.6-59.4]. The frequency and duration of follow-up among these patients  
19 varied widely, and it was decided by the specialist according to individual needs and progress in  
20 time.

1

## 2 Discussion

3 Viperid snakebite envenomings are characterized by prominent local and systemic alterations,  
4 some of which may lead to permanent damage to various organs, thus generating long-term  
5 sequelae.<sup>6</sup> Despite the relevance of this aspect of envenomings, there have been few studies  
6 focusing on sequelae and the factors that determine their incidence. This single center study  
7 analyzed the clinical characteristics and differences among pediatric patients with snakebite  
8 envenoming, comparing those with and without long-term sequelae.

9 The patients of this study presented the typical local and systemic manifestations described for  
10 viperid snakebite envenomings, and particularly for those caused by *Bothrops asper*, which inflicts  
11 the vast majority of cases in Costa Rica.<sup>7</sup> Most patients developed envenomings graded as  
12 moderate in terms of severity, and all of them received the polyvalent antivenom manufactured in  
13 Costa Rica, which is used in the treatment of viperid snakebite envenomings. The incidence of  
14 adverse reactions to antivenom administration was low, in agreement with previous studies.<sup>8</sup> It is  
15 recommended that antivenom be administered within the first 3-4 hours after the event to decrease  
16 the rates of complications, mortality and long-term sequelae.<sup>1, 9-11</sup> In our cohort, nevertheless, one  
17 third of patients were treated after this recommended period of time, mostly due to delay in  
18 transportation from remote rural settings, as shown for several regions in Costa Rica.<sup>12</sup>

19 Little is known about the risk factors associated with the development of long-term sequelae  
20 following snakebites in children. Age and average of time lapsed to first medical evaluation and  
21 antivenom administration have been described in other studies as predictors of mortality and

1 morbidity in adults and children.<sup>3,13</sup> In our study, when analyzing the factors associated with the  
2 development of sequelae, no significant differences between both groups of patients were observed  
3 regarding age, gender, anatomical site of the bite, severity of envenoming, time to reach the  
4 hospital and to receive the first dose of antivenom, and local clinical manifestations of  
5 envenoming. Thus, despite the fact that previous literature has related late medical care with a  
6 higher risk of complications, including lethality,<sup>11</sup> no significant association between time to reach  
7 treatment and incidence of sequelae was observed in our study.

8 In contrast, infections at the site of the bite and the presence of compartmental syndrome were  
9 significantly more prevalent in the long-term sequelae group. Logistic regression analysis made  
10 found that both infection and need of fasciotomy, were consistently associated with greater odds  
11 of long-term sequelae. Wound infections and compartmental syndrome have been described  
12 previously by our group to be associated with severity of envenomings.<sup>9, 10</sup> Infections are prevalent  
13 in envenomings by *B. asper*,<sup>8, 10</sup> particularly when there is local tissue damage, since tissue  
14 ischemia and necrosis favor infection by bacteria present in the venom or in the skin of the patient.  
15 Venom-induced tissue damage and local infection foster a vicious cycle of tissue necrosis, hence  
16 explaining the association between infection and sequelae in our study.

17 In viperid snakebite envenomings, compartment syndrome is a consequence of extravasation into  
18 the interstitial space of muscle tissue, resulting in increments in intracompartamental pressure  
19 which, when reaching values of 30-40 mmHg, interruption of arterial blood flow, ischemia and  
20 necrosis occurs. Such increase in vascular permeability is due to the direct action of venom  
21 components in the microvasculature, but also to the action of endogenous inflammatory mediators  
22 synthesized or released in the tissue as a consequence of venom-induced pathology.<sup>14</sup> Previously,

1 our group has suggested that a cytokine response is associated with severe envenomings in bites  
2 by *B. asper*.<sup>15</sup> Of concern, a high percentage (almost 50% including both cohorts) of the pediatric  
3 patients included in this study developed compartmental syndrome which required surgical  
4 decompression, i.e. fasciotomy. Thus, the higher incidence of sequelae in children who underwent  
5 fasciotomy could be related to pressure-induced tissue damage, or to the consequences of this  
6 surgical intervention, especially regarding scar formation. It is necessary to further study the effect  
7 of compartment syndrome in these sequelae, and how to reduce its incidence.

8 Among the group of patients who developed sequelae, we found that the median follow-up time  
9 was considerable, exceeding a 2-year period after the event. This finding has social, psychological  
10 and institutional implications of various sorts. The children developing sequelae, as well as their  
11 families, undergo suffering and limitations, not only physical but also psychological. In addition,  
12 the costs for the following-up of the consequences of snakebite envenoming are high, both for the  
13 affected people and for the public health system. Management of this neglected tropical disease is  
14 very costly,<sup>4</sup> and the expenses increase considerably when long-term follow-up is needed. This is  
15 another aspect of this problem that requires further studies.

16 Our study has limitations. Patients were enrolled in a referral center, thus the population of patients  
17 are selected to be moderate or severe envenomings, since mild cases are handled in rural hospitals.  
18 Therefore, our observations of patients who were not only bitten by a snake but also that required  
19 hospitalization and referral to a specialized center, can overestimate the prevalence of acute  
20 complications, and cannot be extrapolated to the rest of the country, where the risk of developing  
21 sequelae is likely to be lower. Nevertheless, demographic and several clinical features of both  
22 groups (with and without sequelae) were similar. This is a retrospective study; nevertheless, given

1 the long term of the study, the number of patients allowed the analysis of the clinical features  
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1 the long term of the study, the number of patients allowed the analysis of the clinical features  
2 associated with the development sequelae.

### 3 **Conclusion**

4 A 14-year study was conducted describing the clinical presentation among pediatric patients  
5 suffering snakebite envenoming with and without sequelae. Our study found that, among the acute  
6 complications, infection and compartment syndrome were significantly higher in those patients  
7 that further developed long-term sequelae. Given the high personal and healthcare burden that  
8 entails the follow-up of these patients, efforts should be carried out to prevent the factors associated  
9 with sequelae among the affected population.

11 **Funding Source:** No funding was secured for this study.

### 13 **Acknowledgments**

14 We thank Dr. Manuel Soto-Martínez for his help in some of the statistical aspects of this paper,  
15 for his work, and useful thoughts about the manuscript.

### 17 **What is Known on This Subject**

- 18 1. The WHO estimates that about 5 million snakebites occur each year, resulting in up to  
19 138,000 deaths.
- 20 2. Almost 400,000 people suffering snakebite envenoming are left with physical and  
21 psychological sequelae and permanent disabilities. Most of this information is based on  
22 studies carried out with adult populations.
- 23 3. There is limited knowledge on relevant aspects of envenomings. The incidence of physical  
24 disabilities from envenomings is limited, and the scarce data is mainly focused on adults.

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2 **What This Study Adds:**

- 3 1. Infection and compartment syndrome after envenoming were the clinical factors most  
4 associated with long-term sequelae development.
- 5 2. Hypertrophic scars, functional limitation of affected limb, and the need for skin  
6 graft were the most common sequelae"

Confidential: For Review Only

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**Table 1. Case definition of patients with snakebite envenoming.**

No envenoming	Patients with no local or systemic signs or symptoms
Mild envenoming	Local edema in one or two segments, pain at the bite site, absence of systemic signs or symptoms.
Moderate envenoming	Edema in three segments, local hemorrhage. Systemic symptoms (bleeding, hypotension) and blood clotting test alterations
Severe envenoming	Edema extending to the whole limb, local hemorrhage with necrosis, severe hypotension, blood clotting alterations, systemic bleeding and, in some cases, acute kidney injury.



**Table 2. Demographic and clinical findings of patients with and without snakebite sequelae**

	No sequelae n=50	With sequelae n=24	<i>p</i> value
Age, mo [range]	113 [67.3-130.5]	110 [73-130.8]	0.87
Male gender	34 (68)*	18 (75)*	0.59
Anatomical site of the bite			0.43
Lower extremities	33 (66)	14 (58)	
Upper extremities	14 (28)	10 (41.6)	
Head	2 (4)	0	
Chest	1 (2)	0	
Severity of envenoming			0.095
Mild	13 (26)	3 (12.5)	
Moderate	36 (72)	18 (75)	
Severe	1 (2)	3 (12.5)	
Time to medical evaluation, h [range]	2.0 [1.0-9.0]	2.0 [1.25-5.5]	0.76
Time to administration of antivenom, h [range]	2.0 [1.0-15.0]	2.0 [1.0-6.0]	0.84
Initial signs and symptoms			
Pain	37 (74)	17 (70.8)	0.78
Local edema	47 (94)	24 (100)	0.54
Bleeding	14 (28)	10 (41.6)	0.29
Bullae formation	5 (10)	4 (16.7)	0.46
Local necrosis	0	2 (8.3)	-
Acute complications presented during hospitalization **			
Infection	3 (6)	9 (37.5)	<b>0.0013</b>
Serum sickness	2 (4)	1 (4.2)	>0.99
Compartmental syndrome	16 (32)	20 (83.3)	<b>&lt;0.0001</b>
Need of Fasciotomy	17 (34)	21 (87.5)	<b>&lt;0.0001</b>

\*Results are presented as number of patients and percentages (in parentheses).

Categorical data are expressed as frequencies (%) and analyzed using Fisher or  $\chi^2$  test

Continuous data are expressed as median [25%-75% interquartile range] and analyzed using

Mann-Whitney rank test or Student's *t* test

Values in Bold indicate significant 2-sided *p* values

\*\* Acute complications presented during hospitalization refers to those complications presented during the initial days after snakebite, and not to long-term complications.

Abbreviations: mo, months; H, hours

**Table 3. Unadjusted and adjusted odds of long-term sequelae in patients with acute complications during hospitalization**

Variable	Unadjusted analysis		Adjusted analysis	
	OR [95% CI]	p value	OR [95% CI]	p value
Age, mo	1.58 [0.22-11.4]	0.65		
Gender	0.80 [0.11-5.64]	0.82	1.87 [0.40 - 8.62]	0.442
Envenoming severity	0.28 [0.03-2.38]	0.24		
Acute complications:				
Pain	0.22 [0.04-1.33]	0.1		
Bleeding	4.52 [0.75-27.2]	0.1		
Bullae formation	0.07 [0.005-1.02]	0.052		
Infection	37.9 [3.97-361.8]	<b>0.002</b>	10.85 [2.28 - 51.63]	<b>0.003</b>
Need of Fasciotomy	34.5 [4.0-296.9]	<b>0.001</b>	13.42 [0.001 - 0.30]	<b>0.002</b>

Unadjusted model was made using all significant and relevant variables for the study independent of statistical significance. Then, variables were entered and retained into an adjusted model if they had an adjusted p-value of <0.25.

Abbreviations: OR, Odds Ratio; CI, confidence interval

**Table 4. Sequelae description**

Sequelae	Number of patients (frequency) n=24
Hypertrophic scar	16 (66.7)
Functional limitation	9 (37.5)
Skin graft	9 (37.5)
Deformity	2 (8.3)
Amputation	1 (4.2)

\*Results are presented as number of patients and percentages (in parentheses).

# BMJ Paediatrics Open

## Long-term Sequelae secondary to snakebite envenoming: a single center retrospective study in a Costa Rican pediatric Hospital

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**Title:**

**Long-term Sequelae secondary to snakebite envenoming: a single center retrospective study in a Costa Rican pediatric Hospital**

**Short Title:**

**Sequelae secondary to snakebite envenoming: a 14-year observational study**

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2  
3 **Contributors' Statement Page:**

4 Drs. Brenes-Chacón and Ávila-Agüero conceptualized and designed the study and data collection  
5 instruments. They collected data, carried out the initial analyses, drafted and reviewed the  
6 manuscript.

7  
8 Dr. Gutiérrez contributed to the study design and the initial analyses. He critically reviewed the  
9 manuscript for intellectual content.

10 Drs. Camacho-Badilla, Soriano-Fallas, Ulloa-Gutierrez, and Valverde collected data, and were in  
11 charge of patients during hospitalization and follow up. They reviewed the manuscript.

12 All authors approved the final manuscript as submitted and agree to be accountable for all aspects  
13 of the work.  
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## 1 Abstract

2 **Objectives:** Although devastating acute effects associated with snake envenoming are well  
3 described, the long-term sequelae resulting from these envenomings have not been adequately  
4 addressed, especially in the pediatric population. The aim of our study is to describe the clinical  
5 characteristics among pediatric patients in Costa Rica who developed long-term sequelae  
6 secondary to snakebite envenoming.

7 **Design:** Retrospective descriptive study of pediatric patients under 13 years who were admitted  
8 with a history of a recent snakebite at the National Children's Hospital in Costa Rica from January  
9 2001 to December 2014.

10 **Results:** We enrolled 74 patients admitted to our center due to envenoming, and separated those  
11 who did not develop sequelae (50 patients) from those who did (24 patients). Of those who  
12 presented acute complications during hospitalization, local wound infection and clinically  
13 diagnosed compartmental syndrome were significantly higher in the group that developed sequelae  
14 thereafter. Hypertrophic scars (66.7%), functional limitation of affected limb (37.5%), and the  
15 need of skin graft (37.5%) were the most common sequelae. The median follow-up of patients  
16 with long-term sequelae after discharge was 25.4 mo [5.6-59.4]. No deaths were reported during  
17 this time period.

18 **Conclusions:** Given the high economic, personal, and healthcare burden that entails follow-up of  
19 these patients, efforts should be carried out to prevent the factors associated with sequelae among  
20 the affected population.

21



## 1 Introduction

Snakebite envenoming is an important cause of morbidity and mortality on a global basis, particularly in sub-Saharan Africa, Asia and Latin America.<sup>1</sup> It affects 1.8 to 2.7 million people worldwide every year, causing between 81,000 to 138,000 deaths.<sup>1</sup> Recognized in 2017 as a Neglected Tropical Disease by the World Health Organization (WHO),<sup>2</sup> the actual burden of this disease is still unrecognized. The WHO has launched a global strategy for the prevention and control of these envenomings,<sup>2</sup> but there is still a lot to be known in the follow-up of affected patients.

Although devastating acute effects associated with snakebite envenoming are well described, the long-term sequelae resulting from these envenomings have not been adequately addressed, especially in the pediatric population.<sup>3</sup> Many studies have described the epidemiological characteristics and clinical profiles of these envenomings, both in adults and children. However, few have focused on the risk factors associated with morbidity and further complications.<sup>4</sup> The few studies carried out on sequelae following snakebites have identified several physical and psychological outcomes which exert a heavy impact in the quality of life of affected people.<sup>5</sup>

It is relevant to further analyze the sequelae that develop as a consequence of snakebite envenomings in various regions of the world. The aim of our study is to describe the clinical characteristics occurring among pediatric patients in Costa Rica who developed long-term sequelae secondary to snakebite envenoming, and provide a general overview of their outcomes.

## 1 Patients and Methods

### 2 Study design

3 Retrospective descriptive study of pediatric patients under 13 years admitted with a discharge  
4 diagnosis of a recent snakebite envenoming and who were enrolled at the National Children's  
5 Hospital in Costa Rica during a period of 14 years: from January 2001 to December 2014. Patients  
6 were identified following ICD-10 diagnosis of discharge provided by the statistic department. The  
7 National Children's Hospital is the only tertiary pediatric referral academic hospital in the country.  
8 For snake envenomings, patients in need of specialized care (such as general surgery,  
9 reconstructive surgery, orthopedic, or infectious diseases evaluations) are the ones referred to our  
10 center. Most of the patients included in this cohort were transferred in the first 24 hours after the  
11 event, mainly from regional hospitals in Costa Rica.

12 All patients admitted during the time period at this health center were enrolled, and we collected  
13 demographic and clinical information, including: a) time of first medical evaluation; b) previous  
14 medical support provided; c) antivenom administration; d) clinical signs and symptoms on  
15 admission, and e) acute and long-term complications. Acute complications were defined as  
16 complications related to the event that presented during hospitalization, such as infections,  
17 compartmental syndrome, acute bleeding, respiratory and renal abnormalities, and serum sickness,  
18 among others, were collected. Long-term complications or sequelae were defined as the presence  
19 of a condition also related to the snakebite episode, that requires long-term medical follow-up.  
20 Scar complications, functional limitation, and deformity among others, were included as long-term  
21 sequelae. They were not necessarily present at discharge and could develop along time.

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3 1 For those who developed long-term sequelae, the follow-up time was also recorded. Severity of  
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5 2 envenoming was classified as mild, moderate, and severe, according with the clinical  
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7 3 manifestations on admission (Table 1).  
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11 4 Because of the retrospective nature of this research, patients and public were not involved in the  
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13 5 design, or conduct, or reporting, or dissemination plans of this research.  
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16  
17 6 This study was approved by the Bioethical and Research Committee of the National Children's  
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19 7 Hospital, CLOBI – HNN, project 001-2015.  
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## 22 23 8 **Statistical Analysis**

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26 9 Patients were classified in two groups: those with and those without long-term sequelae.  
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28 10 Continuous variables are presented as medians (25<sup>th</sup>-75<sup>th</sup> IQR) or means  $\pm$ SD according to data  
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30 11 distribution, and the groups were compared using either Mann-Whitney or Student's *t*-test,  
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32 12 respectively. Categorical variables are presented as frequencies and compared using the Fisher's  
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34 13 exact or chi-squared tests.  
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38 14 All analyses were conducted using GraphPad Prism v.8 (GraphPad Software), with a two-sided *p*-  
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40 15 value  $<0.05$  considered statistically significant.  
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## 45 17 **Patient and Public Involvement statement**

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47 18 As a retrospective study, patients were not involved in the recruitment and conduct of this study.  
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## 54 20 **Results**

## 1 **Demographic Characteristics of Patients**

2 From 2001 to 2014 we enrolled 74 patients admitted to our center due to acute snakebite  
3 envenoming, all caused by viperid snake species, most of these by *Bothrops asper*. Patients were  
4 separated in two groups: those who did not develop sequelae as a consequence of envenoming (50  
5 patients), and those who developed sequelae, defined as need to follow-up because of direct  
6 complications associated to the disease after discharge (24 patients).

7 Overall, the median age of both groups was similar, most of them children older than nine years  
8 of age, with a majority of male patients. Lower and upper extremities were the most affected  
9 anatomic sites, and at the time of evaluation most of them were classified as having moderate  
10 envenoming according to the initial signs and symptoms presented (Table 2).

## 11 **Clinical findings and hospitalization evolution**

12 No differences between the time for medical evaluation or the time for antivenom administration  
13 were significant among groups. Regarding signs and symptoms presented by patients at the time  
14 of first evaluation, most of them had locally associated edema, pain, and bleeding as the main  
15 clinical features (Table 2).

16 During hospitalization, some patients presented acute complications that were also analyzed.  
17 Serum sickness was observed in only 3 patients among both groups, but local wound infection and  
18 clinically diagnosed compartmental syndrome were significantly higher in the group that  
19 developed sequelae thereafter (Table 2).

## 20 **Sequelae among patients**

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3 1 Among the 24 patients with sequelae documented after discharge, scars, functional limitation of  
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5 2 the limb affected (meaning complications that diminish or eliminate the regular motor function of  
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7 3 an extremity or part of it), and the need of skin graft were the most common ones (Table 3). Long-  
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9 4 term sequelae included in this study go from mild (hypertrophic scars) to severe complications  
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11 5 (amputation). Nevertheless, all of them translated in long-term follow-up and some degree of  
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13 6 transitory or permanent disability for all patients.  
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18 7 The median follow-up time of these patients in different specialties (plastic and reconstructive  
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20 8 surgery, orthopedic surgery, physiatry, physiotherapy, and occupational therapy) due to the  
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22 9 sequelae was 25.4 mo [5.6-59.4]. The frequency and duration of follow-up among these patients  
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24 10 varied widely, and it was decided by the specialist according to individual needs and progress in  
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26 11 time.  
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### 34 13 **Discussion**

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37 14 Viperid snakebite envenomings are characterized by prominent local and systemic alterations,  
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39 15 some of which may lead to permanent damage to various organs, thus generating long-term  
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41 16 sequelae.<sup>6</sup> Despite the relevance of this aspect of envenomings, there have been few studies  
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43 17 focusing on sequelae and the factors that determine their incidence. This single center study  
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45 18 analyzed the clinical characteristics and differences among pediatric patients with snakebite  
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47 19 envenoming, comparing those with and without long-term sequelae.  
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53 20 The patients of this study presented the typical local and systemic manifestations described for  
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55 21 viperid snakebite envenomings, and particularly for those caused by *Bothrops asper*, which inflicts  
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1 the vast majority of cases in Costa Rica.<sup>7</sup> Most patients developed envenomings graded as  
2 moderate in terms of severity, and all of them received the polyvalent antivenom manufactured in  
3 Costa Rica, which is used in the treatment of viperid snakebite envenomings. The incidence of  
4 adverse reactions to antivenom administration was low, in agreement with previous studies.<sup>8</sup> It is  
5 recommended that antivenom be administered within the first 3-4 hours after the event to decrease  
6 the rates of complications, mortality and long-term sequelae.<sup>1, 9-11</sup> In our cohort, nevertheless, one  
7 third of patients were treated after this recommended period of time, mostly due to delay in  
8 transportation from remote rural settings, as shown for several regions in Costa Rica.<sup>12</sup>

9 Little is known about the risk factors associated with the development of long-term sequelae  
10 following snakebites in children. Age and average of time lapsed to first medical evaluation and  
11 antivenom administration have been described in other studies as predictors of mortality and  
12 morbidity in adults and children.<sup>3,13</sup> In our study, when analyzing the factors associated with the  
13 development of sequelae, no significant differences between both groups of patients were observed  
14 regarding age, gender, anatomical site of the bite, severity of envenoming, time to reach the  
15 hospital and to receive the first dose of antivenom, and local clinical manifestations of  
16 envenoming. Thus, despite the fact that previous literature has related late medical care with a  
17 higher risk of complications, including lethality,<sup>11</sup> no significant association between time to reach  
18 treatment and incidence of sequelae was observed in our study.

19 In contrast, infections at the site of the bite and the presence of compartmental syndrome were  
20 significantly more prevalent in the long-term sequelae group. Wound infections and  
21 compartmental syndrome have been described previously by our group to be associated with  
22 severity of envenomings.<sup>9, 10</sup> Infections are prevalent in envenomings by *B. asper*,<sup>8, 10</sup> particularly

1 when there is local tissue damage, since tissue ischemia and necrosis favor infection by bacteria  
2 present in the venom or in the skin of the patient. Venom-induced tissue damage and local infection  
3 foster a vicious cycle of tissue necrosis, hence explaining the association between infection and  
4 sequelae in our study.

5 In viperid snakebite envenomings, compartment syndrome is a consequence of extravasation into  
6 the interstitial space of muscle tissue, resulting in increments in intracompartmental pressure  
7 which, when reaching values of 30-40 mmHg, interruption of arterial blood flow, ischemia and  
8 necrosis occurs. Such increase in vascular permeability is due to the direct action of venom  
9 components in the microvasculature, but also to the action of endogenous inflammatory mediators  
10 synthesized or released in the tissue as a consequence of venom-induced pathology.<sup>14</sup> Previously,  
11 our group has suggested that a cytokine response is associated with severe envenomings in bites  
12 by *B. asper*.<sup>15</sup> Of concern, a high percentage (almost 50% including both cohorts) of the pediatric  
13 patients included in this study developed compartmental syndrome which required surgical  
14 decompression, i.e. fasciotomy. Thus, the higher incidence of sequelae in children who underwent  
15 fasciotomy could be related to pressure-induced tissue damage, or to the consequences of this  
16 surgical intervention, especially regarding scar formation. It is necessary to further study the effect  
17 of compartment syndrome in these sequelae, and how to reduce its incidence.

18 Among the group of patients who developed sequelae, we found that the median follow-up time  
19 was considerable, exceeding a 2-year period after the event. This finding has social, psychological  
20 and institutional implications of various sorts. The children developing sequelae, as well as their  
21 families, undergo suffering and limitations, not only physical but also psychological. In addition,  
22 the costs for the following-up of the consequences of snakebite envenoming are high, both for the

1 affected people and for the public health system. Management of this neglected tropical disease is  
2 very costly,<sup>4</sup> and the expenses increase considerably when long-term follow-up is needed. This is  
3 another aspect of this problem that requires further studies.

4 Our study has limitations. Patients were enrolled in a referral center, thus the population of patients  
5 are selected to be moderate or severe envenomings, since mild cases are handled in rural hospitals.  
6 Therefore, our observations of patients who were not only bitten by a snake but also that required  
7 hospitalization and referral to a specialized center, can overestimate the prevalence of acute  
8 complications, and cannot be extrapolated to the rest of the country, where the risk of developing  
9 sequelae is likely to be lower. Nevertheless, demographic and several clinical features of both  
10 groups (with and without sequelae) were similar. This is a retrospective study; nevertheless, given  
11 the long term of the study, the number of patients allowed the analysis of the clinical features  
12 associated with the development sequelae.

### 13 **Conclusion**

14 A 14-year study was conducted describing the clinical presentation among pediatric patients  
15 suffering snakebite envenoming with and without sequelae. Our study found that, among the acute  
16 complications, infection and compartment syndrome were significantly higher in those patients  
17 that further developed long-term sequelae. Given the high personal and healthcare burden that  
18 entails the follow-up of these patients, efforts should be carried out to prevent the factors associated  
19 with sequelae among the affected population.

20  
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### What is Known on This Subject

1. The WHO estimates that about 5 million snakebites occur each year, resulting in up to 138,000 deaths.
2. Almost 400,000 people suffering snakebite envenoming are left with physical and psychological sequelae and permanent disabilities. Most of this information is based on studies carried out with adult populations.
3. There is limited knowledge on relevant aspects of envenomings. The incidence of physical disabilities from envenomings is limited, and the scarce data is mainly focused on adults.

### What This Study Adds:

1. Infection and compartment syndrome after envenoming were the clinical factors most associated with long-term sequelae development.
2. Hypertrophic scars, functional limitation of affected limb, and the need for skin graft were the most common sequelae"

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**Table 1. Case definition of patients with snakebite envenoming.**

No envenoming	Patients with no local or systemic signs or symptoms
Mild envenoming	Local edema in one or two segments, pain at the bite site, absence of systemic signs or symptoms.
Moderate envenoming	Edema in three segments, local hemorrhage. Systemic symptoms (bleeding, hypotension) and blood clotting test alterations
Severe envenoming	Edema extending to the whole limb, local hemorrhage with necrosis, severe hypotension, blood clotting alterations, systemic bleeding and, in some cases, acute kidney injury.

**Table 2. Demographic and clinical findings of patients with and without snakebite sequelae**

	No sequelae n=50	With sequelae n=24	<i>p</i> value
Age, mo [range]	113 [67.3-130.5]	110 [73-130.8]	0.87
Male gender	34 (68)*	18 (75)*	0.59
Anatomical site of the bite			0.43
Lower extremities	33 (66)	14 (58)	
Upper extremities	14 (28)	10 (41.6)	
Head	2 (4)	0	
Chest	1 (2)	0	
Severity of envenoming			0.095
Mild	13 (26)	3 (12.5)	
Moderate	36 (72)	18 (75)	
Severe	1 (2)	3 (12.5)	
Time to medical evaluation, h [range]	2.0 [1.0-9.0]	2.0 [1.25-5.5]	0.76
Time to administration of antivenom, h [range]	2.0 [1.0-15.0]	2.0 [1.0-6.0]	0.84
Initial signs and symptoms			
Pain	37 (74)	17 (70.8)	0.78
Local edema	47 (94)	24 (100)	0.54
Bleeding	14 (28)	10 (41.6)	0.29
Bullae formation	5 (10)	4 (16.7)	0.46
Local necrosis	0	2 (8.3)	-
Acute complications presented during hospitalization **			
Infection	3 (6)	9 (37.5)	<b>0.0013</b>
Serum sickness	2 (4)	1 (4.2)	>0.99
Compartmental syndrome	16 (32)	20 (83.3)	<b>&lt;0.0001</b>
Need of Fasciotomy	17 (34)	21 (87.5)	<b>&lt;0.0001</b>

\*Results are presented as number of patients and percentages (in parentheses).

Categorical data are expressed as frequencies (%) and analyzed using Fisher or  $\chi^2$  test

Continuous data are expressed as median [25%-75% interquartile range] and analyzed using

Mann-Whitney rank test or Student's *t* test

Values in Bold indicate significant 2-sided *p* values

\*\* Acute complications presented during hospitalization refers to those complications presented during the initial days after snakebite, and not to long-term complications.

Abbreviations: mo, months; H, hours

**Table 3. Sequelae description**

Sequelae	Number of patients (frequency) n=24
Hypertrophic scar	16 (66.7)
Functional limitation	9 (37.5)
Skin graft	9 (37.5)
Deformity	2 (8.3)
Amputation	1 (4.2)

\*Results are presented as number of patients and percentages (in parentheses).