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Acute kidney injury after snakebite accident treated in a Brazilian tertiary care centre

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SUMMARY AT A GLANCE

The manuscript describes the epidemiology and clinical features of AKI among victims of snake bite in Brazil. Importantly, a significant proportion did not show full renal functional recovery.

ABSTRACT:

Aim: **Acute kidney injury (AKI) is one of the main causes of morbidity and mortality in cases of envenomation by venomous snakes. The present study was carried out to investigate the clinical and laboratory manifestations in accidents with venomous snakes and the risk factors associated with AKI in these accidents.**

Methods: **A retrospective study was carried out with patients victims of snakebite admitted to a reference centre. AKI was defined according to the RIFLE and AKIN criteria.**

Results: **A total of 276 patients were included, of which 230 (83.7%) were males. AKI was observed in 42 cases (15.2%). The mean genus involved in the accidents was *Bothrops* (82.2%). Mean age of patients with AKI was higher than in patients without AKI (43 ± 20 vs. 34 ± 21 years, $P = 0.015$). The time elapsed between the accident and medical care was higher in the AKI group (25 ± 28 vs. 14 ± 16h, $P = 0.034$), as well as the time elapsed between the accident and the administration of antivenom (30.7 ± 27 vs. 15 ± 16 h, $P = 0.01$). Haemodialysis was required in 30% of cases and complete renal function recovery was observed in 54.8% of cases at hospital discharge. There were four deaths, none of which had AKI. Factors associated with AKI were haemorrhagic abnormalities ($P = 0.036$, OR = 6.718, 95% CI: 1.067–25.661) and longer length of hospital stay ($P = 0.004$, OR = 1.69, 95% CI 1.165–2.088).**

Conclusion: **Acute kidney injury is an important complication of snakebite accidents, showing low mortality, but high morbidity, which can lead to partial renal function recovery.**

Envenomation by venomous snakes belongs to the group of main neglected tropical diseases[1] and constitutes an important public health problem. It has a worldwide distribution, affecting mainly rural populations in Asia, Africa, Latin America and Oceania.[1] In Latin America, there are four groups of clinically relevant poisonous snakes: *Bothrops*, *Crotalus*, *Lachesis* and *Micrurus*.[2]

In Brazil, there has been an increase in the number of envenomation accidents caused by poisonous animals reported from 1986 to mid-2012, according to data from the Ministry of Health (http://portal.saude.gov.br/portal/arquivos/pdf/clipping30072010.pdf). The main venomous snakes involved in this type of accident in Brazil are similar to those observed in Latin America. Acute kidney injury (AKI) is a result of the accidents with the genus *Bothrops* and *Crotalus*.[2]

Snakebite-associated AKI in tropical countries and its impact on morbidity and mortality has been the subject of some studies.[2,3] The clinical picture resulting from snakebites varies according to the involved species and the amount of inoculated venom. Systemic manifestations consist mainly of renal,[3] haemorrhagic (haematuria, haematemesis, brain and cavity haemorrhages) and neurological alterations, common in Crotalus accidents (paresthesia, paralysis with craniocaudal

progression, starting with ptosis and ophthalmoplegia, which may develop into paralysis of the respiratory muscles resulting in acute respiratory failure).[4]

The present study was carried out to investigate the characteristics of AKI associated with venomous snakebites and the involved risk factors.

METHODS

Patients

This is a retrospective study carried out in a tertiary hospital in the city of Fortaleza, state of Ceará, Brazil.

We included all the patients treated at Instituto Dr. José Frota from January 2003 to December 2012, with a history of poisonous snakebite. All the patients included in the study were hospitalized due to the accident.

The victims of non-poisonous ($n = 243$) or non-identified snakebites ($n = 628$) were excluded. One patient that was diagnosed with heart failure (clinical syndrome that result in any structural or functional impairment of ventricular filling or ejection of blood – ejection fraction ≤40%, according to the Guidelines of the American Heart Association),[5] was excluded. This patient, victim of a venomous snakebite, had heart failure, but not AKI.

The snakes were identified by the patients themselves. In some cases, the patients brought the snake to the hospital. The physician assessed the site of the bite and classified the snake through anamnesis and laboratory exams were requested.

A semistructured form was used for data collection from each patient, containing epidemiological, clinical and laboratory information.

The study protocol was reviewed and approved by the Committee of Ethics from Instituto Jose Frota, in Fortaleza, Brazil (protocol 119/12).

Definitions

Acute kidney injury was defined according to the RIFLE and AKIN classifications, according to creatinine levels within the first 48 h after hospital admission.[6,7] Baseline creatinine was the one measured 48 h before its elevation. Three or more serum creatinine measurements were obtained from each patient studied during this period. A time constraint of 48 h for the diagnosis of AKI was proposed. Creatinine measurements were performed using the modified kinetic Jaffé method, at 500 nm, without deproteinization. Patients were classified according to the worst criteria (creatinine or urine output). Oliguria was considered as urinary volume <400 mL/day after 24 h of adequate volume replacement.

Renal function recovery was based on the creatinine levels at the time of hospital discharge. Partial recovery of renal function at the time of discharge was considered as creatinine above the basal level (i.e., patients still classified as one of the RIFLE or AKIN stages at the time of hospital discharge).

Study groups

Patients were classified into two groups: patients with normal renal function (Non-AKI) and patients with AKI. When comparing the two groups, differences in clinical manifestations, laboratory findings and risk factors for AKI were assessed.

Clinical and laboratorial parameters

At physical examination, signs and symptoms were evaluated and the following aspects were recorded: age, gender, snake species, severity of accident, the median time between the accident and the administration of the antivenom, dose of antivenom, length of hospital stay and haemorrhagic manifestations. The use of herbal remedies was investigated, and their use constituted an exclusion criterion, as some herbs are nephrotoxic and could be responsible for AKI development.

The following laboratory parameters were evaluated: serum creatinine, urea, sodium, potassium, haematocrit, haemoglobin, leukocytes, platelets, prothrombin time (PT) and partially activated thromboplastin time (aPTT).

Treatment protocol

Patients were classified according to the severity of the snakebite accident using the Brazilian Ministry of Health criteria, based on local and systemic clinical manifestations established in specific tables for each accident (see appendix). The administration of specific antivenom was performed according to those criteria.

Statistical analysis

The results are expressed in tables and means (mean ± SD) for quantitative variables. Univariate and multivariate analyses of clinical and laboratory data were performed using the SPSS program, release 21.0, 2012 for MacBook (SPSS Inc. Chicago, IL, USA), to investigate the possible risk factors associated with acute kidney injury.

The Kolmogorov-Smirnov test was used to verify the normal distribution of continuous variables. The Levene test was used to compare the variability of the means. In the of normal data distribution, the comparison between two means was made by Student's *t*-test. In case of non-normal data, the Mann–Whitney test was applied and the variables were expressed as medians. Analysis of variance (ANOVA) was used to compare means between three or more independent groups, with a post-hoc analysis through Bonferroni's method. Pearson's χ^2 test, likelihood ratio and Fisher's exact test were used for association and homogeneity tests in the distribution of categorical data.

Odds ratio was estimated when the association was significant. Confidence intervals of 95% were calculated. The factors included in the multivariate model (logistic regression) through the Backward method, were those factors that showed statistical significance level <20% in the univariate analysis (Mann–Whitney and χ^2 test). Statistical significance was set at 5% ($P < 0.05$).

RESULTS

Demographic and clinical characteristics at admission

A total of 276 patients were included in the study; 230 (83.7%) were males; 146 (85.5%) lived in rural areas.

The AKI group ($n = 42$) had a mean age of 43 ± 20 years (median 48), of which 32 (76.2%) were males and 38 (90.5%) were from the rural area. Of the snake species involved in the accident, 30 (71.4%) were *Bothrops*, 10 (23.8%) *Crotalus* and two (4.8%) *Micrurus*. As for the severity of the accident, nine (21.4%) were mild, 19 (45.2%) moderate and 14 (33.3%) severe. The median time between the accident and antivenom administration was 24 h (3–96 h). The median time of hospital stay was 8 days, (2–38 days). The median dose of administered antivenom was 8 vials (0–33 vials) (Table 1).

The non – AKI group ($n = 198$) had a mean age of 34 ± 21 years (median 33), of which 198 (84.6%) were males and 198 (85.3%) were from the rural area. Of the snake species involved in the accident, 197 (84.2%) were *Bothrops*, 18 (7.7%) *Crotalus* and 17 (7.3%) *Micrurus*. As for the severity of the accident, 30 (12.8%) were mild, 154 (65.8%) moderate and 50 (21.4%) severe. The median time between the accident and antivenom administration was 9 h (1–72 h). The median time of hospital stay was 3 days, (1–8 days). The median dose of administered antivenom was 8 vials (0–25 vials) (Table 1).

Table 1 Demographic characteristics of patients who developed or not acute kidney injury (AKI), victims of accidents with venomous snakes

	AKI ($n = 42$)	Non-AKI ($n = 234$)	*P*
Gender			
Male	32 (76.2%)	198 (84.6%)	0.182
Female	10 (23.8%)	36 (15.4%)	
Age (years)†	43 ± 20	34 ± 21	0.015
Area			
Rural	38 (90.5%)	198 (85.3%)	0.47
Urban	4 (9.5%)	34 (14.7%)	
Snake species			
Bothrops	30 (71.4%)	197 (84.2%)	0.015
Crotalus	10 (23.8%)	18 (7.7%)	
Micrurus	2 (4.8%)	17 (7.3%)	
Lachesis	–	2 (0.9%)	
Severity of accident			
Mild	9 (21.4%)	30 (12.8%)	
Moderate	19 (45.2%)	154 (65.8%)	0.741
Severe	14 (33.3%)	50 (21.4%)	
Time between the accident and antivenom administration (hours)‡	24.0 (3–96)	9.0 (1–72)	0.01
Length of hospital stay (days)‡	8.0 (2–38)	3.0 (1–8)	<0.001
Dose of antivenom (vials)‡	8 (0–33)	8 (0–25)	0.196

†Values expressed as mean ± standard deviation. ‡Values expressed as median (minimum – maximum). Significant Mann–Whitney test: $P < 0.05$.

Distribution of patients according to the RIFLE and AKIN classifications

Acute kidney injury was observed in 42 (15.2%) patients according to the AKIN and 41 (18.9%) patients according to the RIFLE criteria. Patients were classified as AKIN 1 (15; 35.7%), AKIN 2 (3; 7.1%), AKIN 3 (24; 57.1%), R (12; 29.2%), I (5; 12.2%) and F (24; 58.5%). Due to the small number of patients in each group, only two groups were used in the analysis: AKI and non-AKI, determined by serum creatinine, according to the AKIN criteria.

Comparison of laboratory tests and clinical findings

A comparison of clinical characteristics between patients classified as AKI and non-AKI is summarized in Table 2. The groups differed regarding the presence of haemorrhagic alterations (OR 3.016, $P = 0.001$) and lesion site (OR 0.47, $P = 0.022$). As for PT (OR 0.383, $P = 0.005$) and aPTT (OR 0.478, $P = 0.042$) alterations in the groups, there was statistical difference between them. The presence of myalgia showed a tendency to significance, but did not differ between the groups ($P = 0.053$).

Among the patients with haemorrhagic alterations ($n = 274$), 19 developed concomitant AKI.

The mean values of creatinine and urea at admission and at discharge were higher in the AKI group (Table 3). Haemoglobin (9.4 ± 2.5 vs. 12.7 ± 2.5, $P < 0.0001$) and haematocrit (28.9 ± 9.0 vs. 39.1 ± 11.0; $P = 0.002$) levels and platelet count (95 690 ± 79 200.8 vs. 212 227 ± 90 913; $P < 0.0001$) were lower in the AKI group. Leukocyte count (13 568.3 ± 5178.4 vs. 11 135 ± 3011.5; $P = 0.044$) was lower in the non-AKI group (Table 3).

Table 2 Clinical aspects of acute kidney injury (AKI) and non-AKI groups in victims of accidents with venomous snakes

	AKI ($n = 42$)	Non-AKI ($n = 234$)	*P*	OR	95%CI	
					LL	UL
Nervous system alteration	12 (28.6%)	38 (16.4%)	0.06	2.042	0.960	4.34
Haemorrhagic manifestation	22 (52.4%)	62 (26.7%)	0.001	3.016	1.541	5.905
Local lesion	24 (57.1%)	172 (74.5%)	0.022	0.457	0.232	0.902
Palpebral ptosis or diplopia	7 (16.7%)	18 (7.8%)	0.065	2.378	0.926	6.107
Myalgia	8 (19%)	21 (9.1%)	0.053	2.364	0.970	5.764
Altered PT	9 (21.4%)	88 (37.9%)	0.005	0.383	0.187	0.784
Altered aPTT	8 (19%)	71 (30.3%)	0.042	0.478	0.220	1.037

Platelets, prothrombin time (PT) and partially activated thromboplastin time (aPTT). χ^2 test. Significant $P < 0.05$.

Table 3 Comparison of laboratory findings between the groups of patients that developed acute kidney injury (AKI) and those who did not develop it (Non-AKI)

	AKI (*n* = 42)	Non-AKI (*n* = 274)	*P*
Sodium (mEq/L)†	137.4 (± 5.2)	140 (± 5.7)	0.06
Potassium (mEq/L)†	4.5 (± 0.9)	4.0 (± 0.4)	0.17
Creatinine at AKI diagnosis (mg/dL)†	3.07 (± 2.7)	0.94 (± 0.38)	<0.0001
Creatinine at discharge (mg/dL)†	3.0 (± 2.9)	0.9 (± 0.35)	<0.0001
Urea at AKI diagnosis (mg/dL)†	107.1 (± 74.1)	37.6 (± 27.5)	<0.0001
Urea at discharge (mg/dL)†	72.9 (± 50.72)	32.4 (± 16.3)	<0.0001
Haemoglobin (g/dL)‡	9.42 (± 2.46)	12.7 (± 2.52)	<0.0001
Haematocrit (%)‡	28.86 (± 9.0)	39.1 (± 11.0)	0.002
Leukocyte count (/mm^3)‡	13568.3 (± 5178.4)	11135 (± 3011.45)	0.044
Platelet count (/mm^3)‡	95690.0 (± 79200.8)	212227 (± 90913)	<0.0001

†Mann–Whitney. ‡Student's *t*-test. Significant: $P < 0.05$.

Clinical outcome

Among the patients who developed AKI, 25 (64.1%) achieved renal function recovery, 12 (30.8%) had partial recovery, no patient died and two (5.1%) were transferred to another reference hospital. Of the patients who did not have AKI (non-AKI) four (1.7%) died, and two (0.9%) were transferred to another hospital.

The causes of death were gastrointestinal bleeding (1), CNS haemorrhage (1), anaphylaxis to the antivenom (1) and haemorrhagic diastasis (1). Of the patients who developed AKI, 13 (30.6%) underwent haemodialysis.

Risk factors for AKI

Independent factors associated with AKI were the presence of haemorrhagic alterations on admission (OR = 6.718, 95% CI = 1.067 to 25.661, $P = 0.036$) and a longer hospital length of stay (OR = 1.698, 95% CI = 1.165–2.088, $P = 0.004$), as shown in Table 4.

Table 4 Factors associated with acute kidney injury (AKI) in 276 patients, victims of accidents with venomous snakes

Acute Kidney Injury	*P*	OR	95%CI	
			LL	UL
Length of hospital stay	0.004	1.698	1.165	2.088
Haemorrhagic manifestation	0.036	6.718	1.067	25.661

Variables analyzed: myalgia, days of hospitalization, haemorrhagic alterations, age, lesion site, *Bothrops sp*, time until antivenom administration, altered prothrombin time (PT) and altered partially activated thromboplastin time (aPTT).

DISCUSSION

The present study showed important clinical and laboratory aspects of snakebite-associated AKI. As the kidney is a highly vascularized organ, it is very susceptible to toxins.[8] AKI is an important complication of envenomation accidents, being one of the main causes of mortality.[9]

The predominance of the male gender was observed in the group that developed AKI (76.2%), as well as in the group who did not develop it (84.6%), with no difference between these groups regarding gender. Many studies in the literature have demonstrated the predominance of males in snakebite accidents.[10–14] However, studies have shown that the distribution of the male gender was not different in the groups that did or did not develop AKI.[15–17] Feitosa *et al*.[18] has described the predominance of males in the state of Ceará, Brazil (over 70%). Borges *et al*.,[19] in a study carried out in the Amazon region, also showed a predominance of males (81.3%).

Patients who developed AKI in the study were older, with a significant statistical difference between the groups. Some studies have shown a prevalence of AKI in older patients.[16,17] Pinho *et al*.[15] showed a predominance of AKI in younger patients, as they concentrate larger amounts of venom in a lower body surface area. On the other hand, older patients would have less viable glomerular mass, which could make them more susceptible to toxins.

The predominant area of origin in both AKI (90.5%) and non-AKI (85.3%) groups was the rural area, with no statistical difference between the groups, corroborated by the fact that the accident is associated with people's activities in the countryside. Akani *et al*.,[20] in their study, highlighted a strong correlation between human activity type (rural or urban) and the occurrence of snakebite accidents.

In our study, the snake species distribution in the AKI and non-AKI groups showed a predominance of the *Bothrops* genus in both groups, consistent with the fact that this is the most prevalent snake species in Brazil, with more than 30 species being found throughout the national territory.[8] Other studies have obtained the same finding.[13,14,21] The second most prevalent species involved in snakebite accidents in this study is the *Crotalus*. It is important to note the strong association between the *Crotalus* species and the development of AKI. AKI is more commonly seen in Crotalus than in *Bothrops* accidents, as the crotalic venom is more nephrotoxic.[22]

As for the severity of the accidents, most were classified as being of moderate severity followed by severe, as observed in both groups (AKI and non-AKI), with no statistical difference. According to Amaral *et al*.[4] most snakebite accidents reported are mild ones, which corroborates the findings of Lima *et al*.,[12] Oliveira *et al*.,[14] and Lemos *et al*.[21] Mise *et al*.[11] described the prevalence of moderate cases followed by severe cases, data that are consistent with the findings in our study.

Many studies have shown a tendency to the development of AKI in patients that waited longer between the snakebite

and antivenom administration.[15–17] In our study, the multivariate analysis showed no significant difference between AKI and non-AKI groups regarding the time elapsed between the bite and antivenom administration, which is in conflict with data from some studies that defined longer time between the bite and antivenom administration as an independent risk factor for the development of AKI.[15,16] As this is a retrospective study, there may have been variables that were not informed, which could have influenced the analysis of this parameter (time elapsed between the snakebite and antivenom administration). The small sample size may have interfered with the results.

Regarding the length of hospital stay, AKI and non-AKI groups differed significantly, which was consistent with the literature.[15–17] There was an association between length of stay and the development of AKI, which may represent major clinical complications for the patient, leading to longer hospital stays.

The presence of haemorrhagic disorders, even without coagulation alterations, was an important finding in this study. Bleeding is one of the most important effects induced by snakebites. Damage to the microvasculature is a consequence of metalloproteinase action, which leads to distension, oedema and rupture of capillary walls.[23] Santoro *et al*.[24] showed the presence of a platelet-inhibitory factor found in the plasma of rabbits injected with *Bothrops* venom and described the presence of fibrin thrombi in the histological analysis of lungs and kidneys of these rabbits, suggesting that renal abnormalities can occur even without coagulation alterations (PT and aPTT).

The association between haemorrhagic manifestations and AKI development may represent a typical feature of the venom of poisonous snakes found in north-eastern Brazil, mainly represented in the study by the *Bothrops* species. However, the association between haemorrhagic manifestations and AKI development should be interpreted with caution, considering the confidence interval was too long.

Fonseka *et al*.[25] demonstrated that haemorrhagic manifestations secondary to snakebites can be severe. Silva *et al*.[26] reported the presence of petechiae and severe congestion in the lungs, kidneys and gastrointestinal tract in victims of snakebite accidents. Maduwage *et al*.[27] reported cases of fatal snakebite accidents that developed consumptive coagulopathy and AKI. Moriarity *et al*.,[28] based on a retrospective study, concluded that coagulation tests should be requested for all patients, as it would be impossible to identify which groups would be more susceptible to bleeding. The importance of haemorrhagic manifestations as a risk factor for the development of AKI can indicate a particular physiopathological aspect of the snakes found in north-eastern Brazil.

In the present study, laboratory parameters showed higher levels of urea and creatinine in patients with AKI, when compared to the non-AKI group. These results were expected, according to the use of AKIN and RIFLE classifications. The haemoglobin and haematocrit levels in the group that developed AKI were lower, with a statistically significant difference ($P < 0.0001$, $P = 0.002$). This fact may represent haemorrhagic alterations secondary to *Bothrops* poisoning, resulting from the action of zinc-containing metalloproteinases, which produce lesions in the basal capillary membrane, associated with thrombocytopenia and coagulation disorders.[4] The haemoglobin and haematocrit levels were not included in the multivariate analysis, as several cases' records lacked this information.

Athappan *et al*.[16] described the presence of intravascular haemolysis as an independent risk factor for the development of AKI (OR = 3.2, $P = 0.01$), which justifies the decrease in platelet and haemoglobin levels in our sample. Platelets can also be reduced due to the coagulation system activation and intravascular fibrin formation after factor X activation by the bothropic venom.[29]

The study mortality was 1.4% in snakebite accidents with poisonous snakes, which was considered low, consistent with data in the national literature,[4,12,14,21] showing the low lethality of snakebites. Most patients were cured; however, 13 patients persisted with renal function deficit until hospital discharge.

In summary, AKI was an important complication of snakebite accidents in our study. Morbidity can be high, leading to persistent kidney dysfunction. A longer duration of hospital stay and the presence of haemorrhagic alterations were independent risk factors for the development of AKI.

As the present is a retrospective study, one of its limitations was the lack of information in the medical records, which prevented some statistical inferences. Prospective studies may further elucidate the factors that lead to snakebite-associated AKI. At admission, some patients showed higher levels of creatinine with no variation during hospitalization. This fact should be seen as a limitation/bias in the diagnosis of AKI (these cases were excluded from the analysis, as they did not meet the RIFLE or AKIN criteria). This is a single-centre study and it is necessary to perform similar investigations in other centres to better analyze the results and to assess the impact of these accidents in our country.

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APPENDIX

Table A1 Bothropic accident: classification regarding severity and recommended antivenom

Manifestations and treatment	Classification		
	Mild	Moderate	Severe
LOCAL – pain/oedema/ecchymosis	Absent or discrete	Evident	Intense†
SYSTEMIC – severe haemorrhage/shock/anuria	Absent	Absent	Present
Time of coagulation (TC‡)	Normal or Altered	Normal or Altered	Normal or Altered
Antivenom (no. vials) ABS/ABCS/ABLS	2–4	4–8	12
Route of administration	Intravenous		

†Intense local manifestations may be the only criterion for severity classification. ‡Normal TC: up to 10 min; prolonged TC: from 10 to 30 min; incoagulable TC: >30 min. ABCS, anti-bothropic-crotalic serum; ABLS, anti-bothropic-lachetic serum; ABS, anti-bothropic serum. Source: Adapted from the Ministry of Health, 2001.

Table A2 Crotalic accident: classification regarding severity and recommended antivenom

Manifestations and treatment	Classification – initial evaluation		
	Mild	Moderate	Severe
Myasthenic facies and blurred vision	Absent or delayed	Discrete or evident	Evident
Myalgia	Absent or discrete	Discrete	Intense
Time of coagulation (TC)	Normal or altered	Normal or altered	Normal or altered
Red or brown urine	Absent	Little evident or absent	Present
Oliguria or anuria	Absent	Absent	Present or absent
Antivenom (no. vials) ACS/ABCS	5	10	20
Route of administration	Intravenous		

ABCS, anti-bothropic-crotalic serum; ACS, anti-crotalic serum. Source: Adapted from the Ministry of Health, 2001.

Table A3 Elapidae accident: classification regarding severity and recommended antivenom

Clinical manifestations	Antivenom (no. vials) AES	Route of administration
Due to the risk of acute respiratory failure, they must be considered severe	10	Intravenous

AES, anti-Elapidae serum. Source: Adapted from PINHO; PEREIRA, 2001.