Snakebite-Induced Acute Kidney Injury in Latin America

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Summary: There are 4 genera of venomous snakes in Latin America: *Bothrops*, *Crotalus*, *Lachesis*, and *Micrurus*. Acute kidney injury (AKI) has been reported consistently after *Bothrops* and *Crotalus* envenomations. In fact, these 2 genera of snakes are responsible, along with the Russell's viper, for the majority of cases of snakebite-induced AKI reported worldwide. Although the *Bothrops* snakes are the leading cause of venomous snakebites in Latin America, the absolute number of AKI cases seen after *Bothrops* and *Crotalus* snakebites is similar. In this article the main characteristics of *Bothrops* and *Crotalus* snakes and their venoms, the clinical picture, and the pattern of accidents, risk factors, and mechanisms of renal injury are reviewed.
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There are around 3,000 species of snakes, of which approximately 19% are venomous. The World Health Organization estimates the occurrence of 2,682,500 accidents by poisonous snakes per year worldwide, with 125,345 deaths and about 100,000 severe sequelae. Most of these accidents occur in tropical regions, where they represent a serious public health burden because of its incidence, morbidity, and mortality. Latin America is the third most affected area after Africa and Asia.[1,2]

Snakebites are more common in the rainy seasons and are related to the increase of human activity in rural areas. The most affected group is 25- to 49-year-old men. Lower limbs are the most frequently injured site.

Venomous snakebite mortality rates vary in different regions of the world. In Asia, especially in India, Myanmar, and Malaysia, there are more than 2 million cases of snake envenomation per year, mostly by the *Vipera russelli* snake, with approximately 100,000 deaths.[1] In Nigeria, there are 600 cases per 100,000 inhabitants, with a mortality rate of 12%, and the *Echis* sp snakes are responsible for most of the accidents.[3] In Australia, the incidence is 3 to 18 cases per 100,000 inhabitants,[4] and *Pseudonaja* and *Notechis* account for most of the deaths. In Europe, the United States, and Canada, snakebite envenomation is relatively rare, with 15 to 30 fatal cases among 8,000 accidents per year.[1,5]

Epidemiologic data on snakebite envenomation in Latin America are scarce. In Brazil, there are 20,000 accidents by venomous snakes per year, an incidence of 13.5 accidents/100,000 inhabitants, and a mortality rate of about 0.45%.[6] *Bothrops* snakes (jararaca and jararacuçu) are responsible for 90.5%, *Crotalus* (South American rattlesnake) are responsible for 7.7%, *Lachesis* (surucucu and surucutinga) are responsible for 1.4%, and *Micrurus* (coral) are responsible for 0.4% of the cases when the type of serpent was identified. *Crotalus* (1.9%)

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and *Bothrops* (0.3%) have the highest lethality rates.[6]

Acute kidney injury (AKI) is one of the main complications after snakebite envenomation and it is an important cause of mortality for these patients. Snakebite-induced renal injury has been reported with almost all venomous snakes, however, AKI is more frequent with the *Vipera russelli* in Asia and the *Bothrops* and *Crotalus* in South America.[7,8]

AKI AFTER *CROTALUS* ENVENOMATION

Crotalus Snake

The South American rattlesnake belongs to the *Viperidae* family, *Crotalinae* subfamily, *Crotalus* genus, and is represented in Brazil by a single species, *Crotalus durissus*, distributed into 5 subspecies,[9] of which *Crotalus durissus terrificus* and *Crotalus durissus collilineatus* are the most important ones.[6]

Crotalus durissus snakes are robust and may reach 1 meter in length.[10,11] They are not very agile and are less aggressive than *Bothrops* snakes. Its most notable characteristic is the presence of a rattle at the end of its tail, which facilitates its identification.[6,12] These snakes usually are found in open fields, dry areas, sand, rocks, and, rarely, along the ocean shore. They have vespertine and crepuscular habits, eat small rodents, and their most common predators are birds.[6,12,13]

Crotalus venom is a complex combination of enzymes, toxins, and peptides.[14] The main toxic components are crotoxin, crotamine, gyroxin, convulxin, and a thrombin-like enzyme.[15,16] Crotoxin represents more than 50% of the proteins in the venom and is responsible for its high toxicity.[16] It has neurotoxic,[17] myotoxic,[18-21] and nephrotoxic activity.[22-24] Consequently, *Crotalus* venom effects are multifactorial and the most important clinical manifestations are neurotoxicity, myotoxicity, nephrotoxicity, and coagulating activity.[15,25-27]

Clinical Manifestations

The clinical picture of the *Crotalus* envenomation includes mild local and systemic manifestations that usually are severe. Eyelid ptosis, blurred and/or double vision, ophthalmoplegia, and facial muscle paralysis are manifestations of the venom neurotoxicity. In addition, myotoxicity provokes generalized rhabdomyolysis, which is manifested clinically by generalized myalgia and myoglobinuria. The coagulating action, caused by the thrombin-like enzyme, produces blood incoagulability and afibrinogenemia in 40% to 50% of patients, but bleeding is a rare manifestation.[6,28]

AKI Prevalence

AKI is the major complication in patients surviving the initial venom effects and it is considered the main cause of death in these accidents.[26,28-30] Although the *Crotalus* snakebite occurs 10 times less frequently than the *Bothrops* snakebite, the absolute number of AKI cases reported with both snake genera is similar,[31] suggesting increased nephrotoxicity for *Crotalus* venom. The prevalence of AKI associated with *Crotalus* envenomation ranges from 10% to 29% (Table 1).[28,32-35] To date, only the study by Pinho et al[35] was prospective, evaluating 100 consecutive patients and assessing sequentially their creatinine clearances. This study found the highest prevalence of AKI.[35]

Table 1. AKI Prevalence After *Crotalus* Envenomation

Study	Type	n	AKI Diagnosis	% AKI
Pinto et al, 1987[32]	Retrospective	114	Creatinine increase	18
Silveira and Nishioka, 1992[33]	Retrospective	87	Urea and creatinine increase	18
Jorge and Ribeiro, 1992[28]	Retrospective	249	Presence of oligoanuria	13
Bucaretchi et al, 2002[34]	Prospective	31	Creatinine increase (children $<$15 y)	10
Pinho et al, 2005[35]	Prospective	100	Creatinine clearance ($<$60 mL/min/1.73m^2)	29

Pathophysiology of AKI

Experimental and clinical studies suggest that the pathogenesis of *Crotalus* venom–induced AKI likely is related to rhabdomyolysis, renal vasoconstriction, and direct tubular cell toxicity.

In 1985, Azevedo-Marques et al[18] showed clinically that the *Crotalus* venom causes rhabdomyolysis and myoglobinuria associated with AKI. Later, it was shown that the venom, more specifically crotoxin, induces systemic and selective muscle injury in skeletal muscle groups composed of type I and IIa oxidative fibers, which are rather vascularized and rich in myoglobin.[19,21] An experimental study confirmed that sublethal doses of *Crotalus* venom cause early rhabdomyolysis associated with significant renal blood flow and glomerular filtration rate decrease, without systemic blood pressure reduction.[36]

Kidneys are particularly vulnerable to toxins because of the high blood flow and the ability to concentrate substances in the urine.[31] *Crotalus* venom is excreted predominantly through the kidneys and the toxic components have direct and indirect action on renal cells.[27,36] Crotoxin is probably the most important component responsible for renal injury.[22,23]

Other factors potentially associated with *Crotalus* venom–induced AKI such as shock, hypotension, hemolysis, sepsis, or use of nephrotoxic drugs have not been confirmed in clinical and experimental studies.[35-37]

Risk Factors for the Development of AKI After *Crotalus* Snakebite

Time Period for Antivenom Administration

One milliliter of *Crotalus* antivenom (CAV), which consists largely of immunoglobulin F(ab')$_2$ fragments, neutralizes 1.5 mg of *C durissus* venom.[6] Circulating venom already is not observed at 1 hour after CAV administration, whereas CAV titer remains high for up to 24 hours after therapy.[38,39] The amount of CAV to be administered currently is determined by the severity of the accident. The period between the snakebite and administration of the specific antivenom is an important factor for the development of complications because the venom will remain active until it becomes neutralized.

We recently showed that a time interval greater than 2 hours between a *Crotalus* snakebite and administration of the specific antivenom increases the risk of AKI development 10-fold.[35] In a consistent way, experimental data disclosed that CAV administration was only effective in preventing renal proximal tubular injury when it was performed simultaneously with the addition of the venom.[40] Previous studies also have suggested a correlation between renal injury and the time interval between the snakebite and CAV administration, and it was observed that the longer it took for CAV administration the higher the risk for AKI.[20,33,34]

These results disclose how important it is to decentralize the venomous snakebite treatment to allow early administration of CAV effective doses. Antivenom always should be available at health centers and emergency services of small communities rather than concentrated in reference centers or hospitals.

Rhabdomyolysis

Crotalus venom causes rhabdomyolysis with a significant increase of creatine phosphokinase (CK) serum levels. After a *Crotalus* snakebite, patient enzyme levels at admission greater than 2,000 UI/L were associated with a 12-fold increase of the risk of developing AKI.[35] The most effective prophylactic measure for the prevention of rhabdomyolysis-induced AKI is extracellular volume expansion with saline solution, associated with sodium bicarbonate and mannitol.[41,42] This solution should be started as early as possible and maintained until myoglobinuria disappears. However, a recent prospective study failed to show the efficacy of this treatment in the prevention of AKI development after the *Crotalus* snakebite[35] despite a urinary pH of greater than 6.5, which is considered ideal for the prevention of myoglobin-induced renal injury.[6,41,43,44] It is possible that this lack of protection was related to the delay to start this preventive maneuver or to the intensity of the muscle injury (median CK serum levels, 50,000 IU/L). Finally, it is possible that without the protective maneuver the prevalence of AKI would be higher than observed.

Patient Age

In a retrospective study, Silveira and Nishioka[33] showed that older age was associated with a greater risk of developing AKI. They concluded that for patients older than 40 years of age, the presence of myalgia and neurotoxic facies were predictive factors of renal injury.

In contrast, our prospective study showed that children (<12 y) had a prevalence of *Crotalus* snakebite–induced AKI almost 3 times greater than adults.[35] The Health Ministry's recommendation for antivenom administration does not take into account the victims' age and therefore children and adults will receive similar amounts of antivenom, related only to the severity of the accident rather than their age.[6] However, children have lower blood volume and less body surface, leading to a greater concentration of the venom and to more severe systemic actions.[45] These results strongly suggest that the recommendation for antivenom administration in children must be deeply reviewed.

Urinary Volume

The maintenance of a urinary flow of 30 to 40 mL/h is recommended for adults and 1 to 3 mL/kg/h for children to prevent AKI after *Crotalus* envenomation.[6,43] In the study by Pinho et al,[35] diuresis greater than 90 mL/h at admission of *Crotalus* snakebite victims was protective against AKI development. A higher urinary flow may allow decreased exposure of renal tubular cells to myoglobin and to the venom, with consequent injury attenuation and prevention of tubular lumen obstruction by myoglobin cylinders and cellular debris.

Characteristics of AKI

AKI develops early after *Crotalus* envenomation, occurring within the first 24 to 48 hours after the accident. This suggests that direct venom nephrotoxicity may occur in the clinical setting as experimentally shown.[6,26,35,46]

Dialysis was necessary in 24% of the cases in the study by Pinho et al.[35] Previous studies reported a greater need of dialysis, ranging from 68% to 77% of patients. This discrepancy probably is related to the low sensitivity of AKI diagnostic criteria used in these studies, which had identified only cases of severe renal injury.[26,33,47]

The high fractional sodium excretion values found in patients developing AKI after *Crotalus* envenomation suggest renal proximal tubule cell injury. In fact, histologic injury usually found in *Crotalus* snakebite victims is acute tubular necrosis, although cases of interstitial nephritis also have been reported.[18,35,47–49]

Mortality rates reported for AKI after *Crotalus* envenomation range from 8% to 17%. In addition, the majority of the snakebite victims are young and previously healthy individuals.[26,33,35,47]

AKI AFTER *BOTHROPS* ENVENOMATION

Bothrops Snake

Snakes of the *Bothrops* genus belong to the *Viperidae* family and *Crotalinae* subfamily. There are more than 30 species distributed from southern Mexico to Argentina and Brazil. The most important species are *Bothrops asper* in Central America and *Bothrops atrox*, *Bothrops erythromelas, Bothrops neuwiedi, Bothrops moojeni, Bothrops jararaca, Bothrops jararacussu*, and *Bothrops alternatus*, found in Brazil, especially in grassland regions (called *cerrados*) and tropical forests.[6,50] They have a smooth tail and different colors, depending on the species and their geographic region. *Bothrops* snakes live in rural areas and in the outskirts of large cities and they prefer humid environments such as forests, plantation areas, and places where there is a proliferation of rodents (eg, bars, silos, and wood deposits). They have nocturnal or crepuscular habits and an aggressive defensive behavior.[6,12]

Bothrops Venom

Bothrops venom has proteolytic, coagulant, and hemorrhagic activity. A direct nephrotoxic action of the venom also has been shown.

Different venom activities usually are related to the presence of specific components. However, different toxins may have a synergistic activity to induce a particular effect and certain toxins may have several activities. This variability of toxins and activities also may be observed in different species of *Bothrops*.[51]

Local manifestations at the bite site such as edema, blisters, and necrosis are caused by venom proteolytic action. Lesions result from the activity of proteases, esterases, hyaluronidases, and phospholipases (phospholipase A2) released by inflammatory mediators, action of hemorrhagins on the vascular endothelium, and the procoagulant action of the venom.[6,51,52]

Bothrops venoms activate, either alone or simultaneously, factor X and prothrombin. They also have thrombin-like activity, converting fibrinogen into fibrin. These actions produce coagulation disorders and may lead to blood incoagulability. *Bothrops* venom may induce platelet function abnormalities as well as low platelet count. Hemorrhagic manifestations result from the action of hemorrhagins, metalloproteinases containing zinc, which produce injuries of the capillary basal membranes, associated with low platelet count and coagulation abnormalities. Moreover, hemorrhagins are potent inhibitors of platelet aggregation.[6,51]

It should be emphasized that for the same species, the composition of venom may vary according to the animal's age (young *B jararaca* and *B moojeni* venoms have greater procoagulant activity and lower local inflammatory activity compared with venom from adult snakes), geographic distribution, and individual characteristics.[26,29,53-56]

Clinical Manifestations

The clinical picture usually is characterized by early and progressive pain and edema at the bite site. Bruises, blisters, and bleeding also frequently are observed at the venom inoculation area. In most severe cases, there is necrosis of soft tissues with abscess formation and the development of compartmental syndrome, which may result in functional or anatomic loss of the bitten limb.[6,29] Systemic manifestations include bleeding (pre-existing skin injuries, gingival bleeding, epistaxis, hematemesis, and hematuria), nausea, vomiting, sudoresis, and hypotension. The most severe systemic complications are shock, AKI, septicemia, and disseminated intravascular coagulation-like syndrome.[6,30,57]

Prevalence of AKI

The reported prevalence of AKI after *Bothrops* envenomation ranges from 1.6% to 38.5% (Table 2). All studies were retrospective and none used creatinine clearance (calculated or measured) or a more sensitive method for the study of renal function.[32,58-65]

Pathophysiology of AKI

Etiopathogeny of AKI associated with *Bothrops* envenomation has been related to hemodynamic changes, myoglobinuria, hemoglobinuria, coagulation abnormalities, and venom direct nephrotoxicity.[8,31,66]

Table 2. AKI Prevalence After *Bothrops* Envenomation

Study	Type	n	AKI Diagnosis	% AKI
Cupo et al, 1985[58]	Retrospective	67	Creatinine increase	10.5
Pinto et al, 1987[32]	Retrospective	616	Creatinine increase	1.6
Queiroz and Moritz, 1989[59]	Retrospective	114	Method unknown	6
Kouyoumdjian et al, 1990[60]	Retrospective	57	Creatinine increase	6
Nishioka and Silveira, 1992[61]	Retrospective	292	Creatinine increase	5
Ribeiro and Jorge, 1997[62]	Retrospective	3,139	Creatinine increase	1.6
Rodríguez Acosta et al, 2000[63]	Retrospective	60	Method unknown	1.6
Bucaretchi et al, 2001[64]	Retrospective	73	Creatinine increase (children <15 y)	1.4
Otero et al, 2002[65]	Retrospective	39	Method unknown	38.5

The development of hypotension or shock is a rare event after a *Bothrops* snakebite. Venom may cause hemodynamic abnormalities as a result of sequestration of fluids at the bite site, bleeding, and release of vasoactive substances. It should be noted that the administration of antivenom may cause hypotension or shock as a result of a hypersensitivity reaction.[31,51,67]

Venom may cause localized muscular injury, but it does not have a systemic myotoxic effect similar to the *Crotalus* venom and it does not induce significant CK increase. Thus, myoglobinuria is unlikely to be an important factor in the pathogenesis of renal injury.[29,51,68,69]

Bothrops venom is considered hemolytic in vitro and there are clinical reports of anemia and hemolysis after *Bothrops* envenomation, as well as reports of hemoglobinuria after administration of *Bothrops* venom to rats. Hemoglobinuria might contribute to renal injury, worsening renal vasoconstriction, glomerular coagulation, and tubular nephrotoxicity.[68-70]

Intravenous injection of *B jararaca* venom into rats caused a marked and early decrease of glomerular filtration, renal plasma flow, and diuresis, accompanied by increases in renal vascular resistance and fractional excretion of sodium. There was no hypotension or CK increase. Venom also caused marked fibrinogen consumption and intravascular hemolysis. Renal histologic analysis showed an extensive intraglomerular deposition of fibrin thrombi and acute tubular necrosis.[31]

In fact, Boer-Lima et al[67,71] studied renal abnormalities induced by *B moojeni* venom in rats and observed a significant decrease of glomerular filtration, occurring in absence of hypotension, and the development of acute tubular necrosis. Later, the same group showed that *B moojeni* venom caused glomerular injury including mesangiolysis, microaneurysms, and glomerular basal membrane abnormalities associated with proteinuria.

In an isolated perfused rat kidney model, it was shown that *B jararaca* venom caused direct acute tubular nephrotoxicity and platelet activating factor might be involved.[72] Indeed, Castro et al[66] showed that the *B jararaca* venom caused in vitro injury in isolated renal proximal tubules and *Bothrops* antivenom was effective only in preventing injury when administered simultaneously with venom.

Risk Factors for the Development of AKI After *Bothrops* Snakebite

Several risk factors have been related to *Bothrops* venom–induced AKI, such as patient age, snake size, species, amount of injected venom, time interval between the bite and administration of the antivenom, and the amount and route of the antivenom administered.[69] A positive correlation between the patient's age and AKI prevalence has been reported.[61] A retrospective clinical-epidemiologic study performed in Colombia with 39 victims of poisoning by *B asper* showed that the time interval between the accident and administration of the antivenom of more than 2 hours was associated with the development of AKI, as well as with the risk of death and permanent injuries.[65]

Characteristics of AKI

Renal dysfunction after *Bothrops* poisoning occurs early, usually is severe and oliguric, with the need for dialysis varying from 33% to 75% of cases.[26,47,69] The most frequent renal structural injury found is acute tubular necrosis, although cases of bilateral cortical necrosis, interstitial nephritis, and acute glomerulonephritis with mesangial proliferation also have been reported. Mortality rate of *Bothrops* venom–induced AKI range from 13% to 19%.[26,31,46,47,65,67,70,71]

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