Acute kidney injury in *Bothrops* sp. and *Crotalus* sp. envenomation: critical review of the literature

**ABSTRACT**

Introduction: Snakebites represent a serious problem all over the world. We reviewed the literature on the main complication of snakebites: acute renal failure (ARF). We emphasize *Bothrops* sp. and *Crotalus* sp. envenomation, since those are the most common poisonous snakes in Brazil. We focused on the different aspects of ARF in this context, such as epidemiology, pathogenesis, clinical characteristics, and risk factors, as well as prevention and treatment.

Keywords: Acute renal failure, Crotalus, Bothrops, snakebite.

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**INTRODUCTION**

Snakebite envenomation is a serious public health problem in tropical areas of the world due to the high incidence and associated morbimortality. According to the World Health Organization (WHO), approximately 2.5 million snakebite envenomations are reported all over the world every year, resulting in 125,000 deaths. However, it is very difficult to determine accurately the real incidence of this problem. Recent studies estimate that the annual incidence of snakebite envenomation reaches 5.5 million, with 20,000 to 94,000 deaths. The majority of snakebites occur in Africa and Asia, with Latin America in the third place.

In Brazil, more than 20,000 snakebites, with a mortality rate of about 0.45%, are notified every year to the Ministry of Health. Approximately 85% of those cases are due to *Bothrops* sp., and 7.7% to *Crotalus* sp.; the remaining cases are associated with *Lachesis* sp. and *Micrurus* sp. Acute renal failure (ARF) is the main complication of snake envenomation and it is associated with an increase in mortality. Although bothropic envenomation is 10 times more frequent than crotalic envenomation, the absolute number of cases of ARF in both cases is similar, since crotalic venom is more nephrotoxic. The incidence of snakebites is usually related with climatic factors and human activities in rural areas. Male rural workers, aged 15 to 49 years, are affected more often. The lower limbs are the sites of choice for snakebites, followed by the upper limbs.

Whenever possible, identification of the snake helps evaluate the severity, prognosis, and adequate treatment of the snakebite. The main differential element between poisonous and non-poisonous snakes is the loreal fossa, the thermoreceptor orifice located between the eye and the nostril (Figure 1a). As a rule, poisonous snakes have well-developed and mobile loreal fossa and well-developed inoculators fangs in the anterior aspect of the maxillary region. The shape of the tail helps identify the genus: *Bothrops* sp. are characterized by a smooth tail, *Crotalus* sp. are characterized by a tail with a rattle, and *Lachesis* sp. are characterized by a prickly tail horn (Figure 1b). *Micrurus* sp. snakes do not have a loreal fossa and have a poorly developed and fixed inoculator apparatus in the anterior maxillary region, but they are also venomous and, therefore, represent the exception to the rule (Figure 2). Those snakes, popularly known as coral snakes, have specific characteristics, such as red, black, and white rings. One should not forget the false coral snake, a non-venomous snake whose color pattern is similar to that of *Micrurus* sp.

Even when the snake is not caught, the differentiation between crotalic and bothropic bites can, often, be made based on the clinical manifestations of the victim. In general, crotalic bites are characterized by mild
local and important systemic manifestations, while the opposite is seen in bothropic bites (Table I).

Bothrops sp.: In bothropic envenomation, the venom is concentrated at the site of the snakebite, causing severe proteolytic injury, which is its main characteristic. Local pain and edema are present in almost all cases, but hematomas, blisters, necrosis, and abscesses are also seen. Bothropic venom also causes hemorrhages and nephrotoxicity, leading to systemic manifestations that, although less frequent than in crotalic envenomation, can be severe. The main local complications are secondary to infections and gangrene. Systemic symptoms, such as severe hemorrhage, circulatory collapse, and ARF, can also be seen. A significant proportion of patients develop changes in clotting time, with incoagulability reaching 40% in one study.

Crotalus sp.: In crotalic envenomation, the clinical picture is determined by the myotoxic, neurotoxic, clotting, and nephrotoxic activities of the venom, ranging from asymptomatic cases to ARF, circulatory collapse, and death. Usually, mild paresthesia, erythema, pain, and edema develop at the site of the snakebite, while systemic manifestations dominate. The patient may complain of diplopia and blurred vision, while the physical exam shows midryasis, ptosis (uni- or bilateral), and flaccidity of the muscles of the face, characterizing neurotoxic facies. Complaints of myalgia and dark urine are also frequent, reflecting the presence of rhabdomyolysis and myoglobinuria. Less frequent manifestations include gingival bleeding and epistaxis, besides non-specific complaints, such as vomiting, somnolence, and feeling the presence of a strange body in the throat. The main complications include ARF, respiratory failure, and circulatory shock. Laboratorial changes include elevated markers of muscle damage (CPK, AST, ALT, LDH) and changes in clotting time.
### Table 1  MAIN CLINICAL MANIFESTATIONS IN CROTALIC AND BOTHROPIC ENVENOMATION

<table>
<thead>
<tr>
<th>Venom effects</th>
<th>Local manifestations</th>
<th>Systemic manifestations</th>
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<tbody>
<tr>
<td><strong>Crotalus</strong></td>
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<tr>
<td>Neurotoxic</td>
<td>Mild edema</td>
<td>Myasthenic facies</td>
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<td>Myotoxic</td>
<td>Paresthesia</td>
<td>Rhabdomyolysis</td>
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<td>Coagulant</td>
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<td>ARF</td>
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<td>Nephrotoxic</td>
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<td>Coagulopathy</td>
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<td><strong>Bothrops</strong></td>
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<tr>
<td>Local proteolytic</td>
<td>Severe edema</td>
<td>Coagulopathy</td>
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<tr>
<td>Hemorrhagic</td>
<td>Ecchymosis and blisters</td>
<td>ARF</td>
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<td>Nephrotoxic</td>
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<td>Bleeding</td>
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<td>Secondary infection</td>
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<td>Gangrene</td>
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<td>Compartment syndrome</td>
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### Acute Renal Failure

**Bothrops sp.:**

**Incidence of ARF:** Acute renal failure is rare in bothropic snakebite, with an incidence ranging from 1.6 to 5%.\(^{10,13,15,16}\) However, a study on Bothrops jararacussu showed a 13% incidence of ARF, suggesting a difference in nephrotoxicity among the different snakes of the *Bothrops* sp.\(^{17}\) Additionally, discrepancies in the definition of ARF could also explain the difference in the incidence of ARF among the studies.

**Pathogenesis:** Although most of the bothropic venom remains in the skin after the snakebite and, therefore, causes mainly local changes, a minority of patients can develop systemic manifestations, such as ARF. The pathogenesis of the kidney damage in bothropic envenomation is not fully known. Experimental studies using isolated kidney showed that bothropic venom is capable of producing renal tubular toxicity.\(^{18}\) Other authors suggest a direct proteolytic effect of the venom on the glomeruli,\(^{19}\) which is associated with morphologic changes.\(^{20}\) However, in the intact animal, other factors can contribute, indirectly, for the development of ARF, such as rhabdomyolysis and hemolysis, especially when associated with hypovolemia, in addition to changes in the coagulation system that can cause fibrin deposition in glomerular capillaries.\(^{21}\) Finally, some fractions of the venom, such as Bothrops toxin-1, which is one of the main fractions of the Bothrops jararacussu venom, have a phospholipase A\(_2\)-like activity.\(^{22}\) Phospholipase A\(_2\) is an enzyme capable of promoting the release of arachidonic acid from the cellular membrane.

**Arachidonic acid** is a precursor of inflammatory mediators, such as prostanoids (prostaglandins and thromboxanes), which have vasoactive effects and, therefore, are capable of changing glomerular hemodynamics and glomerular filtration rate.

**Characteristics of ARF:** Acute renal failure occurs almost always in the first 24 hours after the snakebite, whereas the reduction in urine output may not be seen until the second or third day.\(^{23,24,25}\) A delay in the administration of the specific serum is considered an important risk factor for ARF,\(^{10,11,13,26,27}\) although there are reports of ARF occurring despite prompt administration of the specific serum.\(^{24,25}\) Most cases (approximately 90%) of ARF due to bothropic envenomation are oliguric.\(^{24,25,28}\) The oliguric phase lasts from 1 to 3 weeks, with a mean of 2 weeks (13.5 ± 5.8 days in the series of Amaral et al,\(^{24}\), and 11.25 ± 3.73 days in the study of Da Silva et al.\(^{25}\)). Protein and red blood cells can be present in the urine.\(^{10,27}\) Acute tubular necrosis is the most common renal injury in bothropic envenomation; however, some cases evolve with bilateral cortical necrosis.\(^{11,28,29}\) In the study of Amaral et al.,\(^{24}\) approximately 22% of the cases of ARF presented cortical necrosis, which was suspected when patients remained oligoanuric or with elevated levels of BUN (blood area nitrogen) and creatinine for more than 3 weeks. In those cases, a renal biopsy should be done to confirm the diagnosis. Later, radiographic imaging tests can show calcification of the renal parenchyma.\(^{23,25,29}\) Those patients develop chronic renal failure and present higher mortality rates.
Studies with patients with bothropic envenomation in intensive care units at the end of the 1970s and beginning of 1980s demonstrated a mortality rate of about 20%, most of them due to acute pulmonary edema in the oliguric phase. In those studies, approximately 74% of the patients required dialysis.\textsuperscript{24,25}

**Risk Factors for ARF:** The time between the snakebite and the administration of the specific serum is the main determinant for the development of ARF, demonstrating a direct correlation with its incidence.\textsuperscript{7,10,11,13,26,27} Additionally, age also seems to be an important factor. Some studies indicate that the elderly have a greater tendency towards ARF \textsuperscript{15,30} as well as a higher mortality rate.\textsuperscript{11} One can speculate that the greater susceptibility of elderly patients to ARF after snakebites is due to the smaller volume of functional renal mass in those patients (physiological, associated with aging, or secondary to hypertensive, diabetic, or ischemic nephropathy, which is more common in this population). One study reported a greater incidence of ARF in children.\textsuperscript{26} It has not been determined whether the severity of the local injury (severe edema, blisters, ecchymosis) or systemic manifestations (such as bleeding) are associated with ARF.\textsuperscript{1,15} Other factors, such as the use of tourniquets and decreased blood coagulability, have not been consistently associated with a higher risk of ARF.\textsuperscript{15,31}

**Prevention and treatment:** Early administration of the specific serum is the main preventive measure of kidney damage. Other general measures should be observed to prevent the summation of nephrotoxic insults: 1) avoid iodinated contrasts for imaging studies; 2) avoid non-steroidal anti-inflammatory drugs; and 3) avoid nephrotoxic antibiotics. Proper renal perfusion should also be maintained by the intravenous administration of fluids and other hemodynamic support measures. Unfortunately, studies evaluating the different strategies for prevention of ARF in bothropic envenomation are lacking. Therefore, an evidence-based recommendation for prevention of ARF in bothropic envenomation is one of the factors that could explain its greater nephrotoxicity when compared to bothropic envenomation. A detailed analysis of the mechanisms of kidney injury in rhabdomyolysis is not the objective of this paper, but it can be found in the work of Vanholder et al.\textsuperscript{42}

**Characteristics of ARF:** In crotalic envenomation, the oliguric phase tends to have a shorter duration than in bothropic envenomation, ranging from 6 to 14 days\textsuperscript{24,25} (mean 9.6 ± 4 days, in the series of Amaral et al.,\textsuperscript{24} and 8.93 ± 3.73 days, in the study of Da Silva et al.).\textsuperscript{25} Similarly, studies on specific recommendations on when to start dialysis and the type and frequency of dialysis are also lacking. In clinical practice, the same strategies used for the management of acute tubular necrosis in other settings, such as sepsis, are recommended.\textsuperscript{32,33}

**Crotalus sp.:**

**Incidence of ARF:** It is known that ARF in crotalic envenomation is much more frequent than in bothropic snakebite. However, the incidence depends on the criteria used to define ARF; more sensitive criteria result in a higher incidence, and vice-versa. As mentioned previously, for many years, several studies used different definitions of ARF, resulting in different incidence rates of this occurrence, ranging from 12% to 18.4%.\textsuperscript{11,34,35} However, a recent study that used more sensitive criteria for ARF (glomerular filtration rate < 60 mL/min/1.73m²) reported an incidence of 29%.\textsuperscript{6} Therefore, as suggested in 2004 by an expert panel, it is essential that further studies adopt a single criterion for ARF.\textsuperscript{36}

**Pathogenesis:** In crotalic envenomation, the renal concentration of venom can be up to 50% higher than its plasma concentration.\textsuperscript{37} Since the excretion of this venom is predominantly renal, the mechanisms of tubular concentration and transport favor the development of direct renal toxicity. In experimental studies using isolated kidney, investigators demonstrated that crototoxin, followed by gyrotoxin, is the main component responsible for the direct nephrotoxicity of the crotalic venom.\textsuperscript{38,39} Besides this toxic tubular effect, other factors are likely involved in the pathogenesis of ARF. Phospholipase A$_2$ is also present in crotalic venom, and Martin et al. demonstrated that endothelial\textsuperscript{40} and immune system cells, such as macrophages,\textsuperscript{41} are capable of producing arachidonic acid-derived inflammatory mediators in response to crotalic venom. As mentioned before, those mediators can contribute to the development of ARF predominantly due to their hemodynamic actions. But rhabdomyolysis is probably the main mechanism of renal injury in crotalic envenomation. The greater frequency of rhabdomyolysis in crotalic envenomation is one of the factors that could explain its greater nephrotoxicity when compared to bothropic envenomation. Studies with patients in ICUs who, in theory, show more severe compromise, reveal that most patients develop oliguria\textsuperscript{24,25,28,43} or normal urine output,\textsuperscript{16,24,25,44} depending, most likely, on the degree of renal damage. Studies with patients in ICUs who, in theory, show more severe compromise, reveal that most patients develop oliguria\textsuperscript{24,25,28,43} while most patients diagnosed with ARF through more sensitive parameters, i.e., including patients with less severe compromise, had normal urine output.\textsuperscript{4} In crotalic envenomation, most cases of ARF are secondary to acute tubular necrosis,
and cases secondary to cortical necrosis have not been reported, indicating different pathophysiological mechanisms of renal damage than in bothropic envenomation. As a consequence, very seldom a patient with ARF secondary to cortical necrosis will develop end-stage renal disease requiring long-term dialysis. Acute interstitial nephritis secondary to the administration of specific serum has been reported. A recent study demonstrated that only 24% of patients with bothropic envenomation require dialysis, contrasting with older studies in which approximately 69% of patients required dialysis; peritoneal dialysis was the method used most often in the past.

**Risk factors for ARF:** Delay in treatment, myasthenic facies, myalgia, and severe elevation of muscle enzymes are correlated with ARF. Similar to bothropic envenomation, it is known that a delay in the administration of the specific serum is related with the development of ARF. Delay in medical treatment is associated with more severe cases, more complications, and a greater incidence of ARF, indicating the need for decentralized patient care.

Retrospective studies on ARF in bothropic envenomation demonstrated that myalgia and neurotoxic facies are predictors of ARF in patients older than 40 years. A recent prospective study demonstrated that all patients that developed ARF had myalgia and neurotoxic facies. Markers of muscle damage tend to be elevated both in patients with ARF and in those who do not develop ARF. However, CPK, AST, ALT, and LDH levels are significantly higher in patients who develop ARF. Creatinine phosphokinase levels greater than 2,000 U/L represent a risk factor for ARF. Reddish urine secondary to myoglobinuria is seen in more than 80% of the cases of bothropic envenomation and, and, therefore, is not a good clinical parameter to identify patients at a greater risk for the development of ARF. Whether the age of the patient has a role in the development of ARF in bothropic envenomation is controversial. Retrospective studies demonstrated a positive correlation between ARF and advanced age. In other studies, younger patients showed a greater tendency to develop ARF, although, in children, the incidence of this complication is similar to that of other age groups. Thus, since studies are not conclusive, greater attention to patients in extremes of age is recommended. Adequate urine output on admission (> 90 mL/h) seems to be a protective factor against ARF. Increasing the urine output, to reduce the exposure of tubular cells to venom and myoglobin, is another strategy to prevent the development of ARF in bothropic envenomation. Prolonged clotting time on admission is not a predictor of ARF, although it is more frequent in patients who develop this complication. After rattlesnake bites, the urinalysis may show glucose, protein, leukocytes, epithelial cells, and casts.

Those findings are much more frequent in patients with a diagnosis of ARF. As expected in acute tubular necrosis, the fractional excretion of sodium is elevated in those patients. Complications secondary to ARF, such as volume, electrolyte, hematologic, respiratory, neurologic, and hemodynamic changes, are common in both bothropic and cortical envenomation. Hypercalcemia and uremia are the most common metabolic abnormalities followed by a tendency towards hyperphosphatemia and hypocalcemia. Studies in ICU patients showed a mortality of approximately 13% among patients who evolved with ARF. Additionally, the development of ARF increases the time and costs of hospitalization.

**Prevention and treatment:** General measures described for the prevention of ARF in bothropic envenomation are also valid in cortical envenomation: 1) early administration of specific serum; 2) avoidance of nephrotoxins; and 3) avoidance of hypovolemia. However, due to the high prevalence of rhabdomyolysis in cortical envenomation, some specific measures are applicable in those cases. They are aimed at preventing/correcting factors that predispose to the development of ARF in rhabdomyolysis, like volume depletion, tubular obstruction, aciduria, and an increase in free radicals. Note that studies evaluating different strategies in the management of rhabdomyolysis in cortical envenomation are lacking; the recommendations listed below are extrapolated from studies on rhabdomyolysis from other causes.

Increasing urine output, to decrease the intratubular concentration of myoglobin, decrease the exposition time of tubular cells to the pigment and minimize the risks of precipitation and consequent tubular obstruction, is the main measure to prevent or reduce renal damage. This can be achieved by the vigorous administration of fluids followed by diuretics. It should be mentioned that diuretics should only be used after adequate volume expansion.

As for volume expansion, specific rules on the type and amount of fluid do not exist. The use of normal saline (NS) seems adequate, but some authors suggest the use of sodium bicarbonate solution. The potential advantages of the administration of bicarbonate include attenuation of acidemia, reduction in the tendency towards hyperkalemia, and by alkalinizing the urine, reduction in the tendency towards the intratubular precipitation of myoglobin. A recent review on the subject suggested the administration of at least 3–6 liters of fluid per day, which can be as high as 10 liters/day, as long
as adequate monitoring is instituted. The same authors suggest the administration of one liter of sodium bicarbonate solution (100 mmol in 1,000 mL of 5% glucose) with 10 mL of 15% mannitol for each liter of NS administered. In theory, furosemide acidifies the urine, which is not desirable in rhabdomyolysis, representing an advantage of mannitol over this drug.

It should be emphasized that vigorous volume administration should be avoided in oliguric or anuric patients with important elevation of nitrogen waste products. In those cases, where renal damage has already occurred, volume replacement does not reverse the process and may lead to life threatening hyperkalemia and pulmonary edema. The same applies to mannitol and sodium bicarbonate; the latter can cause important metabolic alkalosis in patients with severe oligoanuric ARF. One should not forget that Ringer’s lactate, widely used in volume expansion in ICUs and emergency rooms, has potassium chloride and should, therefore, be avoided in patients with hyperkalemia and/or oligoanuric ARF.

Similar to bothropic envenomation, the literature does not have enough data allowing for specific recommendations regarding dialysis in crotalic envenomation.

**Conclusions**

Acute renal failure is the main complication of snakebites, developing both in bothropic and crotalic envenomation. Although crotalic envenomation is more nephrotoxic, the absolute number of cases of ARF in both cases is similar due to the higher number of cases of bothropic envenomation. Acute tubular necrosis is the most frequent renal injury in both cases and it is usually reversible. However, some patients with ARF secondary to bothropic envenomation develop bilateral cortical necrosis leading to end-stage renal disease, which requires maintenance renal replacement therapy. Late and inadequate specific serum administration is an important risk factor for ARF. High level data evaluating strategies to prevent and treat ARF in snake envenomation are lacking in the literature. Therefore, the management of those patients ends up being similar to that of patients with ARF from other causes.

**References**


