*Rev. Inst. Med. Trop. Sao Paulo*
*55(5):295-301, September-October, 2013*
*doi: 10.1590/S0036-46652013000500001*

## REVIEW

# ACUTE KIDNEY INJURY CAUSED BY *Crotalus* AND *Bothrops* SNAKE VENOM: A REVIEW OF EPIDEMIOLOGY, CLINICAL MANIFESTATIONS AND TREATMENT

**Polianna L.M.M. ALBUQUERQUE(1,2), Camilla N. JACINTO(2), Geraldo B. SILVA JUNIOR(2,3), Juliana B. LIMA(2), Maria do Socorro B. VERAS(1) & Elizabeth F. DAHER(2)**

## SUMMARY

Ophidic accidents are an important public health problem due to their incidence, morbidity and mortality. An increasing number of cases have been registered in Brazil in the last few years. Several studies point to the importance of knowing the clinical complications and adequate approach in these accidents. However, knowledge about the risk factors is not enough and there are an increasing number of deaths due to these accidents in Brazil. In this context, acute kidney injury (AKI) appears as one of the main causes of death and consequences for these victims, which are mainly young males working in rural areas. Snakes of the *Bothrops* and *Crotalus* genera are the main responsible for renal involvement in ophidic accidents in South America. The present study is a literature review of AKI caused by *Bothrops* and *Crotalus* snake venom regarding diverse characteristics, emphasizing the most appropriate therapeutic approach for these cases. Recent studies have been carried out searching for complementary therapies for the treatment of ophidic accidents, including the use of lipoic acid, simvastatin and allopurinol. Some plants, such as *Apocynaceae*, *Lamiaceae* and *Rubiaceae* seem to have a beneficial role in the treatment of this type of envenomation. Future studies will certainly find new therapeutic measures for ophidic accidents.

**KEYWORDS:** Snakebites; Ophidic accidents; Acute kidney injury; Complications.

## INTRODUCTION

Snakes have evoked human curiosity since the ancient Egyptian civilizations and the book of Genesis shows the snake as the personification of Evil. In ancient Brazil, the lethal danger of ophidic accidents scared the Portuguese explorers. With the development of hyperimmune sera, a new phase in the study of ophidic accidents began, which is still of scientific interest to this day.

Ophidic accidents are still an important problem in public health due to their high frequency and severity[3]. There are approximately three thousand known snakes' species and 20% are venomous[34].

There are four clinically relevant venomous snakes' genera in Latin America: *Bothrops, Crotalus, Lachesis* and *Micrurus*[34]. Snakes of the *Bothrops* genus are responsible for the majority of accidents, and this is partly due to their vast geographical distribution and aggressive behavior when feeling threatened[38].

Due to its high vascularity, the kidney is highly susceptible to toxins[44]. The snakes of the genus *Bothrops* and *Crotalus* can cause severe systemic reactions, and acute kidney injury (AKI) is one of the most severe complications of snakebites[2].

The knowledge of these complications by the health care professional is essential for an adequate approach of patients victims of accidents with venomous snakes. The aim of this study is to review the aspects of AKI caused by the venom of the *Bothrops* and *Crotalus* genera regarding their diverse characteristics, emphasizing the most appropriate therapeutic approach for these cases.

## EPIDEMIOLOGICAL ASPECTS OF OPHIDIC ACCIDENTS

According to the World Health Organization (WHO), the presence of venomous snakes occurs in all the regions of the globe and is a public health problem, especially in tropical areas. Envenomation due to snakebites is considered one of the main neglected tropical diseases, affecting the poor rural populations of Africa, Asia, Latin America and Oceania[22].

The WHO estimates the occurrence of 2,500,000 snakebites per year, resulting in 125,000 deaths worldwide and approximately 100,000 survivors with severe consequences[16,34]. Latin America is the third most affected geographical area, after Africa and Asia[5,16].

In Brazil, these accidents have shown a 32.7% increase in the period between 2004 and 2009, according to data from the Ministry of Health

(1) Toxicological Assistance Center, Instituto Dr. José Frota. Fortaleza, Ceará, Brazil.
(2) Post-Graduation Program in Medical Sciences, School of Medicine, Federal University of Ceará. Fortaleza, Ceará, Brazil.
(3) School of Medicine, Health Sciences Center, University of Fortaleza. Fortaleza, Ceará, Brazil.
**Correspondence to:** Elizabeth De Francesco Daher. R. Vicente Linhares 1198. 60135-270 Fortaleza, Ceará, Brasil. Phone/Fax: +55 85 32249725, +55 85 32613777. E-mail: ef.daher@uol.com.br, geraldobezerrajr@yahoo.com.br, pollylemos@yahoo.com.br

(http://portal.saude.gov.br/portal/arquivos/pdf/clipping_30_07_2010.pdf).

The epidemiological pattern of these accidents has remained unchanged for the last 100 years. The most affected individuals are young males (15-49 years), working in rural areas. The accidents occur mainly during the day, preferentially affecting the lower limbs, and most cases are caused by the *Bothrops* genus[6]. This pattern has been observed in many regions of Brazil[9,25,31].

Regarding seasonality, the occurrence of ophidic accidents is, in general, related to weather factors and to increased human activity in rural areas. There is a higher incidence between the months of September and March in the South, Southeast and Midwest regions of Brazil, and between January and May in the Northeast region[3].

The sub-notification of these accidents in some regions of Brazil has been observed in some studies[27,38]. However, the Northeast region has registered an increase in the incidence of ophidic accidents in the last years, with an incidence similar to the that observed in other regions in 2010 (15.5 accidents/100,000 inhabitants) (http://portal.saude.gov.br/portal/arquivos/pdf/tabela_inc_casos_serpente_01_04_2011.pdf).

## PATHOPHYSIOLOGY MECHANISMS OF ACUTE KIDNEY INJURY DUE TO SNAKEBITES

The renal manifestations of ophidic accidents have a broad clinical spectrum. Proteinuria, hematuria and renal failure are among the most common manifestations of snakebites[42].

The pathophysiology of AKI due to snakebites has not been completely elucidated. Renal lesions can be caused by the isolated or combined action of different ischemic or nephrotoxic mechanisms, triggered by the venom action in the body[3]. Experimental studies suggest a multifactorial pathogenesis for this type of AKI, which includes the following mechanisms: renal ischemia resulting from hypovolemia and hypoperfusion, thrombotic microangiopathy due to the deposit of fibrin in the glomerular capillaries and direct cytotoxic action of the venom on the renal tubules[23].

Proteinuria varies according to the snake species, and proteinuria levels > 1g/24h are not common[24]. Hematuria is frequently observed in accidents involving many snakes' species, and can be microscopic or macroscopic. The outcome of hematuria is usually favorable. However it can be associated with acute tubular necrosis, which has a higher severity outcome[42].

The occurrence of pigment nephropathy results from the action of the phospholipase $A_2$ enzyme, which induces rhabdomyolysis[42]. BRAGA *et al.*[11] demonstrated renal abnormalities after infusion of phospholipase $A_2$ isolated from *Bothrops insularis* in Wistar rats. Some abnormalities observed in this study were related to increased perfusion pressure, renal vascular resistance, urinary flow and glomerular filtration rate, as well as decreased sodium and chloride transport. The proximal tubular cells showed hydropic alterations, evidenced by brush border discontinuity and desquamation to the tubular lumen, which can reflect the activity of phospholipase $A_2$ and production of derivatives from arachidonic acid.

AKI is one of the main complications of ophidic accidents, which is described in all the types of snakes, being more common in accidents caused by the genus *Bothrops* and *Crotalus* in South America, and by the *Vipera russelli* in Asia, showing relevant morbimortality. AKI is the main cause of death among the victims of snakebites who survive the early effects of envenomation by *Bothrops* and *Crotalus*[38]. Although bothropic accidents are ten times more frequent than crotalic ones, the incidence of AKI is similar, which suggests a higher nephrotoxicity of the latter[13,17,35,40].

## PATHOPHYSIOLOGY OF RENAL LESION IN BOTHROPIC ACCIDENTS

The most commonly described anatomopathological lesion in bothropic accidents is acute tubular necrosis (ATN), but interstitial nephritis, cortical necrosis and glomerular changes have also been described[34,38].

BURDMANN *et al.*[13] demonstrated, in an experimental study, the morphological and functional changes induced by these accidents. There was a significant decrease in glomerular filtration rate and renal blood flow, as well as intravascular hemolysis, characterized by a decrease in hematocrit and increase in the levels of LDH and hemoglobin. Optic and electronic microscopy showed massive fibrin deposition in the glomerular capillaries, associated with proximal and distal tubular necrosis. These would be the main mechanisms involved in the genesis of AKI, although a direct effect of the venom on the kidney could not be ruled out.

Experimental studies with *Bothrops moojeni* venom have demonstrated glomerular injury, tubular degeneration and desquamation, hematuria and decrease in glomerular filtration rate, with increased urinary sodium excretion, no alteration in arterial blood pressure and no fibrin deposit in the glomerular capillaries[7]. Other studies have demonstrated a direct effect of the bothropic venom on the kidneys, leading to tubular and glomerular injury[8,14,30].

A series of variables seem to be involved in the development of AKI after ophidic accidents: patients' age and body surface area, snake's age, amount of inoculated venom, area of the bite and time between the accident and administration of specific anti-venom sera. Associated comorbidities, such as hypertension, diabetes, coronary artery disease and previous nephropathies, can also make the patients more susceptible to the venom effects[18].

The prevalence of AKI induced by bothropic accidents varies between 1.4 and 38%, depending on the species involved[12,33,38]. Mortality varies from 13 to 19%[34]. Peak AKI incidence varies from a few hours after the accident to 96 h after the snakebite and is commonly diagnosed in the first 24-48 h. Need of dialysis varies from 33 to 75% of cases[3,36,45].

## PATHOPHYSIOLOGY OF KIDNEY INJURY IN CROTALIC ACCIDENTS

Diverse mechanisms have been proposed to explain the kidney injury caused by crotalic venom, including rhabdomyolysis, hemolysis, shock, intravascular coagulation and a possible direct nephrotoxic effect[18].

As the venom is excreted by the kidneys, the mechanisms of concentration and tubular transport favor the occurrence of direct cellular toxicity[36]. Crotalic venom is a complex mix of enzymes, toxins and peptides, with crotoxin being one of the main responsible for the nephrotoxicity.

MONTEIRO *et al.*[29] demonstrated that crotoxin causes systemic lesions and skeletal muscle injury. Crotoxin was the main responsible for acute nephrotoxicity in isolated kidneys of rats, being associated with glomerular and tubular changes.

## CLINICAL MANIFESTATIONS

Snake venom consists of more than 20 different substances, of which effects have not yet been completely studied. The protein fraction (enzymes, non-enzymatic toxins and non-toxic proteins) comprises 90-95% of its weight[38].

The bothropic venom, despite the variability of its composition between species from different regions and within the same species, depending on the snake's age, in general, shows a mechanism characterized by proteolytic, coagulant and hemorrhagic action, leading to local and systemic characteristic manifestations[38]. The action of proteases, hyaluronidases, phospholipases and inflammatory mediators leads to local tissue injury, with early onset of pain, edema, bleeding and bullous lesions, which can complicate with abscesses and tissue necrosis. Among the systemic manifestations, hemorrhagic events (epistaxis, gingivorrhagia, hematuria, hemoptysis, central nervous system bleeding) are associated to coagulation disturbances secondary to the activation of factor X and to an action similar to that of thrombin, leading to coagulation factor consumption, as it occurs during the process of intravascular coagulation[3,22].

Neurotoxicity and myotoxicity are other typically reported consequences, especially in the crotalic accidents. The first is caused by the action of crotoxin, a neurotoxin that comprises 50% of the protein fraction of crotalic venom and acts in the pre-synaptic membrane of the neuromuscular junction, leading to a descending progressive paralysis, which can be fatal when involving the bulbar and respiratory musculature[18]. In turn, the myotoxic action leads to rhabdomyolysis, which can result in myoglobinemia, hyperkalemia and AKI. Hypotension and shock are other possible complications that have been described[23,34].

According to the clinical manifestations, the ophidic accident can be classified as mild, moderate or severe, which is important to guide the therapeutic measures to be adopted. The severity of these accidents is based on local manifestations (presence of pain, edema and ecchymosis), systemic manifestations (hemorrhage, shock, anuria), coagulation time and time to administrate the antiophidic sera. Severe cases are considered when there are intense local manifestations, severe hemorrhage/shock/anuria, abnormal coagulation time and need for a higher dose of anti-ophidic sera[3].

The specific treatment consists in the administration of anti-ophidic sera, produced from the sensitization of diverse animals, especially equines. In Brazil, the Butantan Institute (São Paulo), Ezequiel Dias Foundation (Minas Gerais) and Vital Brazil Institute (Rio de Janeiro) are responsible for the production of these immune derivatives for the public health system.

Recently, Brazilian researchers evaluated the neutralizing action of the extract from a native plant against the toxic activity of the bothropic venom in rats. *Schizolobium parahyba,* popularly known as "guapuruvu" and commonly used in the central region of the country to treat snakebites, was effective to protect against the effects induced by the enzymatic and biological action of the venom of some species from the *Bothrops* genus*,* constituting a promising sustainable therapeutic option for these accidents[38].

## SNAKEBITE-INDUCED ACUTE KIDNEY INJURY APPROACH

Throughout history, the treatment of ophidic accidents varied from surgical excisions to topical therapy[46]. The recommendations have changed with time and the anti-ophidic sera has been used with increasing frequency. The use of tourniquets was indicated in the past, in order to isolate the injured member in an attempt to decrease venom dissemination in the body, but it is no longer indicated due to its inefficiency.

In kidney injuries caused by animal toxins, AKI secondary to renal ischemia is the most common type[43]. Multiple factors contribute to this fact, such as hemodynamic changes, inflammatory reactions and direct nephrotoxic effect of the venom (Fig. 1)[44]. The knowledge of these factors is of huge importance as it provides subsidies to an effective therapy.

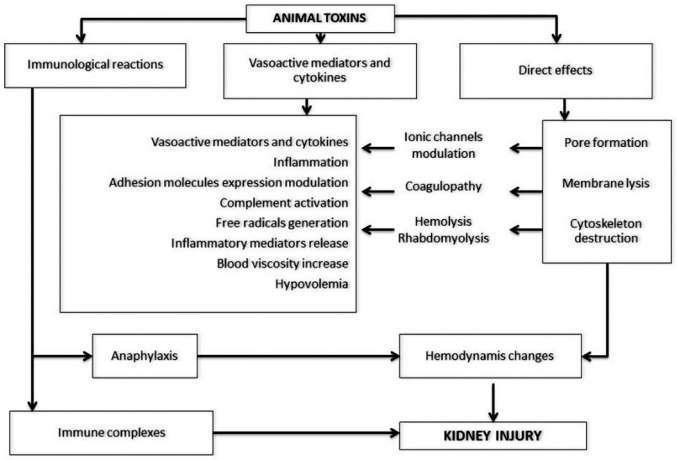


**Fig. 1 -** Pathophysiology of kidney injury induced by animal toxins. Adapted from SITPRIJA *et al.*

The first action to be undertaken when treating a snakebite victim is to soothe the patient, as the hyperdynamic state accelerates venom dissemination[1]. The patient should be placed in a comfortable position, with the affected limb elevated at the heart's level[1].

To better detail the AKI approach, we divided it in support measures (initial approach), classical measures for AKI and specific measures.

The supportive measures includes: hypovolemia correction; broad spectrum antibiotics administration in severe bite cases (for instance, clindamycin and ceftriaxone; ciprofloxacin and clindamycin; ampicillin/sulbactam); tetanus prophylaxis; monitoring of the local edema evolution; careful assessment of the response to specific antivenom therapy; early

detection of local and systemic complications; surgical procedures and rehabilitation (in severe cases of local complications)[32].

Early treatment of hypovolemia is a fundamental measure for AKI prevention. The use of isotonic solutions (Ringer's lactate or saline) is required to restore circulating volume[32]. Urinary volume should be measured every hour, mainly in severe cases. Normally, adolescents and adults have a urinary volume higher than 0.5 mL/kg/h (30-40 mL/h) and children higher than 1.0 to 2.0 mL/kg/h.

Antibiotic use is controversial, as there have been few clinical trials and there are different snakes' species with different potentials to cause infection[32]. However, biological samples should be collected for culture performance in order to provide the identification of any agent causing infection and the correspondent antimicrobial sensitivity pattern[32]. According to AMARAL *et al.*[3], the use of antibiotics should be indicated when there is evidence of infection. The bacteria isolated from lesions secondary to snakebites are mainly *Morganella morganii*, *Escherichia coli*, *Providencia sp* and *Streptococcus* group D.

Monitoring of local edema evolution and bleeding should be performed every hour in the first day and every 6 hours thereafter[32].

The therapeutic approach to AKI induced by ophidic accidents is summarized in Table 1.

**Table 1**
Therapeutic approach to acute kidney injury caused by ophidic accidents

| | |
|---|---|
| Supportive measures (Initial approach) | Hypovolemia correction, administration of large-spectrum antibiotics in moderate to severe cases, tetanus prophylaxis, surveillance of the response to specific antivenom therapy, early detection of local and systemic complications, surgical procedures and rehabilitation (in severe cases of local complications) |
| Classic measures for AKI | Correct approach of fluid and electrolyte disturbances, use of diuretics and vasoactive drugs (when indicated) |
| Specific measures | Antiophidic sera (immunoglobulin, antivenom) is the only specific treatment for envenomation by snakebites. |

Attention should also be paid to the systemic signs of severity, including persistent bleeding, neurological symptoms (ptosis, paresthesia, visual abnormalities, vertigo, etc.), cardiovascular abnormalities (hypotension, arrhythmia, shock) and kidney injury (AKI, hemoglobinuria, myoglobinuria, etc.)[21]. Among the local complications, compartment syndrome is clinically suspected in the presence of tense edema, dysesthesia, proprioception alteration and movement limitation, with or without decreased capillary refill time. Prompt intervention is required in these cases, through the administration of intravenous mannitol or surgery (fasciotomy)[32].

The use of intramuscular injections (such as antitetanic vaccine) should be avoided in the first 48 hours after the accident or when there is coagulopathy persistence[32].

The classical measures for AKI include fluid correction and electrolyte management, judicious use of diuretics and vasoactive drugs[26].

The adequate volemic status is the main measure for AKI prevention and is also indicated to treat AKI. There are no specific guidelines for hemodynamic optimization and renal function preservation; however, one can extrapolate the recommendations from other causes of AKI to that caused by snakebites[26]. It is important to be careful when administrating fluids to patients with comorbidities, such as heart and liver disease, in order to avoid fluid overload and its complications.

The use of diuretics in AKI treatment is controversial. MACEDO *et al.*[26] suggest that it is possible to try to increase urinary volume with loop diuretics, but if there is no adequate response, increasing doses should be avoided. Regarding the use of natriuretics, large studies are required to confirm its benefit in AKI treatment[26]. Vasoactive agents are considered in the cases with organ perfusion impairment and the use of dopamine in order to prevent or treat AKI is not recommended[26].

The complications associated to AKI (acute pulmonary edema, electrolyte and acid-base disturbances) that are refractory to clinical treatment should be promptly treated with renal replacement therapy. The need for dialysis in victims of ophidic accidents has been described by SITPRIJA *et al.*[41], and this treatment also improves myalgia symptoms.

Regarding specific measures, the anti-ophidic sera (immunoglobulin, antivenom) is the only specific treatment for snakebites. The sera are produced by fractioning plasma obtained from domestic animals hyper-immunized against the venoms. When administered to humans, it neutralizes the venom responsible for the accident, and, in some cases, it also neutralizes venoms from related species[47]. It is very important to have in mind that the early administration of anti-ophidic sera is one of the most effective measures to prevent AKI induced by *Bothrops* and *Crotalus* accidents.

The identification of the snake and the classification of accident severity are the first steps for the correct prescription of anti-ophidic sera. Another important step is the anaphylaxis surveillance during its administration, as this is an heterologous immunoglobulin.

In cases of envenomation by *Bothrops* sp., the administration of antibothropic serum (ABS) should be instituted as early as possible, and when it is not available, the anticrotalic (ACS) or antibothropic- lachesis (ABLS) serum should be administered[3].

If the coagulation time remains unchanged 24 hours after serum therapy, an additional dose is indicated, with two ampoules of antivenom sera[3].

Some laboratory tests are important in bothropic accidents, including time of coagulation, complete blood count (it can reveal leukocytosis with neutrophilia and thrombocytopenia), urinalysis (to screen for proteinuria, hematuria and leukocyturia) and other tests according to the patient's

**Table 2**
Classification of crotalic accidents regarding severity and recommended specific therapy

| Manifestations and treatment | Classification - Initial evaluation | | |
|---|---|---|---|
| | Mild | Moderate | Severe |
| Myasthenic fascies and blurred vision | Absent or late | Mild or evident | Evident |
| Myalgia | Absent or mild | Mild | Intense |
| Coagulation time (CT) | Normal or altered | Normal or altered | Normal or altered |
| Red or brown urine | Absent | Poor evident or absent | Present |
| Oliguria or anuria | Absent | Absent | Present or absent |
| Serum therapy (# ampoules) ABS/ABCS* | 5 | 10 | 20 |
| Administration via | | Intravenous | |

* ABS = anti-bothropic serum/ABCS = anti-bothropic - crotalic serum.

evolution, with special attention to electrolytes, urea and creatinine to detect AKI[3].

In crotalic accidents, the dose of anticrotalic sera varies according to the severity of the case. It is important to note that the same dose is administered to adults and children, and the ACS sera can also be used[3], according to what is shown in Table 2.

As the crotalic toxin has myotoxic, neurotoxic and coagulant actions, rhabdomyolysis is an important factor in AKI genesis in these accidents. According to BOSCH *et al.*[10], preventive and therapeutic measures for rhabdomyolysis-induced AKI includes: (1) monitoring of volemic status, central venous pressure and urinary volume, (2) evaluation of serum levels of creatine kinase (CK), myoglobin, aldolase, lactate-dehydrogenase, alanine aminotransferase, aspartate aminotransferase, (3) monitoring of levels of urea, creatinine, sodium, potassium, total and ionized calcium, phosphorus, magnesium, uric acid, albumin, platelet count, white and red blood cell count, (4) evaluation of urine sediment and dipstick, (5) volemic restoration with isotonic saline solution, at a rate of approximately 400 mL/h, monitoring of central venous pressure, (6) obtaining a urinary output of 3 mL/kg/h, (7) frequent monitoring of potassium levels, (8) correction of hypocalcemia only if it is symptomatic or if there is severe hypercalcemia, (9) if the urine pH is below 6.5, alternate each liter of saline solution with dextrose or 0.45% solution with 100 mmoL bicarbonate, (10) consider treatment with mannitol, discontinuing it if there is improvement in diuresis (> 20 mL/h); if it does not occur, (11) maintain volemic infusion until myoglobinuria decreases and (12) consider renal replacement therapy if there is no response to therapy or if there is persistent hyperkalemia (> 6.5 mEq/L), oliguria (< 0.5 mL/kg/h, in 12 hours), anuria, hypervolemia and refractory metabolic acidosis.

The knowledge of early and late reactions to the administration of anti-ophidic sera and its correct treatment is important to prevent fatal complications. The adverse effects of anti-ophidic sera are: type I acute reactions, due to reactions of circulating immunoglobulin E to horse proteins; anaphylactoid reactions due to direct degranulation of mastocytes and serum sickness (a late allergic reaction caused by immune complexes)[1].

The early reactions occur in 4.6 to 87.2% of cases in the first two hours after serum administration. They have low severity and the patient should be under observation for 24 hours due to the risk of onset of more severe late reactions[3]. Signs and symptoms include urticarial rash, tremors, coughing, nausea, abdominal pain, pruritus and facial rash. More severe manifestations, such as anaphylactic reactions, are rare. In these cases, the patients can also have arrhythmias, hypotension, shock and respiratory failure[3].

The late reactions occur five to 24 days after serum administration and can cause fever, arthralgia, lymphadenomegaly, urticarial rash and proteinuria. The incidence of serum sickness is underestimated, as many patients do not return to the health care center. The use of corticosteroids (prednisone) 1 mg/kg/day (maximum 60 mg) for five to seven days[3] is indicated for the treatment of this complication.

The use of intravenous corticosteroids, promethazine and adrenaline can be therapeutic for anaphylactic reactions to heterologous sera. As premedication such as $H_2$-antagonists, such as cimetidine (maximum 300 mg) or ranitidine[3] can also be used. SILVA *et al.*[39] demonstrated, in a randomized study with 752 patients with acute reactions to heterologous sera in the first 48 hours, that the use of subcutaneous adrenalin decreased the risk of severe adverse reactions in the first hour; however, neither hydrocortisone nor promethazine showed clear benefits.

The therapeutic measures are of huge importance in the management of victims of ophidic accidents and the early administration is fundamental to prevent AKI occurrence. CASTRO *et al.*[14], in an experimental study with bothropic venom, showed that the ideal renal protection was obtained when the administration of the venom and the sera were performed at the same time. In a prospective study with 100 victims of crotalic accidents, it was demonstrated that the delay in the administration of antiophidic sera (> 2h) was an independent risk factor for AKI development[33].

## FUTURE PERSPECTIVES

Some studies have searched for complementary therapies for the treatment of ophidic accidents. BARONE *et al.*[4], through an experimental study using *Bothrops jararaca* venom in AKI induction in rats, demonstrated the beneficial effects of lipoic acid and simvastatin

on hyperuricemia, renal oxidative stress and serum levels of urea and creatinine, creating new perspectives for the investigation of these drugs as adjuvant agents in bothropic envenomation therapy.

An experimental study with rats with AKI induced by *Crotalus durissus terrificus* envenomation evidenced the association between hyperuricemia and kidney injury in these animals, as well as the beneficial effect of allopurinol on renal function recovery, preventing death in these animals [20].

MOLANDER *et al.*[28] created a database of plants used in ophidic accidents in the world, selecting countries from different continents (Brazil, Nicaragua, China and Nepal). The most common plants were those from the families *Apocynaceae*, *Lamiaceae* and *Rubiaceae*. It was observed that the use of the same plant in different regions and further studies are required to better investigate the role of these plants in the treatment of snakebite envenomation.

SAUL *et al.*[37], upon considering that the snakes' toxins first reach the lymph nodes before entering circulation, studied the use of a nitric oxide ointment in 15 patients and obtained satisfactory results regarding the inhibition of lymphatic transport of the toxin.

All these studies can be used as a base for the development of new research in ophidic accidents and its complications.

## RESUMO

**Lesão renal aguda causada pelo veneno das cobras *Crotalus* e *Bothrops:* revisão da epidemiologia, das manifestações clínicas e do tratamento**

Os acidentes ofídicos são importante problema de saúde pública devido à incidência, morbidade e mortalidade. Aumento do número de casos tem sido registrado no Brasil nos últimos anos. Vários estudos apontam para a importância do conhecimento das complicações clínicas e do tratamento adequado desses acidentes. Entretanto o conhecimento dos fatores de risco não é suficiente, e existe número crescente de óbitos devido a esses acidentes no Brasil. Neste contexto, a injúria renal aguda (IRA) aparece como uma das principais causas de óbito e sequela nestas vítimas, que são principalmente homens trabalhadores de zonas rurais. Os gêneros *Bothrops* e *Crotalus* são os principais responsáveis pelo envolvimento renal nos acidentes ofídicos na América do Sul. O presente estudo faz uma revisão da literatura sobre a IRA causada pela picada das serpentes dos gêneros *Bothrops* e *Crotalus* em suas diversas características, enfatizando a abordagem terapêutica mais adequada para estes casos. Estudos recentes tem sido realizados para a busca de terapias complementares para o tratamento dos acidentes ofídicos, incluindo o uso de ácido lipóico, sinvastatina e alopurinol. Algumas plantas, como a *Apocynaceae*, *Lamiaceae* e *Rubiaceae* parecem ter papel benéfico no tratamento destes envenenamentos. Estudos futuros irão certamente encontrar novas estratégias terapêuticas para os acidentes ofídicos.

## REFERENCES

1. Adukauskiene D, Varanauskiene E, Adukauskaite A. Venomous snakebite. Medicina (Kaunas). 2011;47:461-7.

2. Amaral CFS, Rezende NA, Silva OA, Ribeiro MMF, Magalhães RA, Reis RJ, *et al.* Insuficiência renal aguda secundária a acidentes ofídicos botrópico e crotálico: análise de 63 casos. Rev Inst Med Trop Sao Paulo. 1986;28:220-7.

3. Amaral CFS, Bucaretchi F, Araújo FAA, Cardoso JLC, Campos JA, Azevedo-Marques MM, *et al.* Manual de diagnóstico e tratamento de acidentes por animais peçonhentos. 2ª ed. Brasília: Ministério da Saúde, Fundação Nacional de Saúde; 2001.

4. Barone JM, Alponti RF, Frezzatti R, Zambotti-Villela L, Silveira PF. Differential efficiency of simvastatin and lipoic acid treatments on *Bothrops jararaca* envenomation-induced acute kidney injury in mice. Toxicon. 2011;57:148-56.

5. Barraviera B. Estudo clínico dos acidentes ofídicos. J Bras Med. 1993;65:209-50.

6. Bochner R, Struchiner CJ. Epidemiologia dos acidentes ofídicos nos últimos 100 anos no Brasil: uma revisão. Cad Saúde Pública. 2003;19:7-16.

7. Boer-Lima PA, Gontijo JA, Cruz-Hofling MA. Histologic and functional renal alterations caused by *Bothrops moojeni* snake venom in rats. Am J Trop Med Hyg. 1999;61:698-706.

8. Boer-Lima PA, Gontijo JA, Cruz-Hofling MA. *Bothrops moojeni* snake venom-induced renal glomeruli changes in rat. Am J Trop Med Hyg. 2002;67:217-22.

9. Borges CC, Sadahiro M, Santos MC. Aspectos epidemiológicos e clínicos dos acidentes ofídicos ocorridos nos municípios do Estado do Amazonas. Rev Soc Bras Med Trop. 1999;32:637-46.

10. Bosch X, Poch E, Grau JM. Rhabdomyolysis and acute kidney injury. N Engl J Med. 2009;361:62-72.

11. Braga MD, Martins AM, Amora DN, de Menezes DB, Toyama MH, Toyama DO, *et al.* Purification and biological effects of C-type lectin isolated from *Bothrops insularis* venom. Toxicon. 2006;15:859-67.

12. Bucaretchi F, Herrera SR, Hyslop S, Bacarat EC, Vieira RJ. Snakebites by *Crotalus durissus* ssp in children in Campinas, São Paulo, Brazil. Rev Inst Med Trop Sao Paulo. 2002;44:133-8.

13. Burdmann EA, Woronik V, Abdulkader RC, Saldanha LB, Barreto OC, *et al.* Snakebite induced acute renal failure: an experimental model. Am J Trop Med Hyg. 1993;48:82-8.

14. Castro I, Burdmann EA, Seguro AC, Yu L. *Bothrops* venom induces direct renal tubular injury: role for lipidic peroxidation and prevention by antivenom. Toxicon. 2004;43:833-9.

15. Chippaux JP. Control of ophidism in Brazil: a model for Africa. J Venom Anim Toxins Incl Trop Dis. 2010;16:188-90.

16. Chippaux JP. Snake bites: appraisal of the global situation. Bull World Health Organ. 1998;76:515-24.

17. Cupo P, Azevedo-Marques MM, Hering SE, Menezes JB. Acidentes ofídicos: análise de 102 casos. In: XXI Congresso da Sociedade Brasileira de Medicina Tropical, São Paulo, 1985. Livro de resumos.

18. Daher EF, Fernandes TA, Aguiar CN. Crotalic poisoning: epidemiology, acute renal failure and other clinical features. Rev Eletrônica Pesquisa Médica. 2008;2:1-10.

19. Feitosa R, Melo I, Monteiro HS. Epidemiologia dos acidentes por serpentes peçonhentas no estado do Ceará - Brasil. Rev Soc Bras Med Trop. 1997;30:295-301.

20. Frezzatti R, Silveira PF. Allopurinol reduces the lethality associated with acute renal failure induced by *Crotalus durissus terrificus* snake. PLoS Neglected Trop Dis. 2011;5:1-8.

21. Ghosh MK. Management of snakebites cases by national treatment protocol at Jalpaiguri District Hospital in West Bengal in the year 2010 – a retrospective study. J Indian Med Assoc. 2011;109:29-36.

22. Gutiérrez JM, Theakston DG, Warrell DA. Confronting the neglected problem of snake bite envenoming: the need for a global partnership. PLoS Med. 2006;3:e150.

23. Gutiérrez JM, Escalante T, Rucavado A. Experimental pathophysiology of systemic alterations induced by *Bothrops asper* snake venom. Toxicon. 2009;54:976-87.

24. Kanjanabuch T, Sitprija V. Snakebite nephrotoxicity in Asia. Semin Nephrol. 2008;28:363-72.

25. Lima JS, Martelli Júnior H, Martelli DR, Silva MS, Carvalho SF, Canela JR, *et al.* Perfil dos acidentes ofídicos no norte do Estado de Minas Gerais, Brasil. Rev Soc Bras Med Trop. 2009;42:561-4.

26. Macedo E, Bouchard J, Metha R. Prevention and Nondialytic Management of Acute Kidney Injury. In: Floege J, Johnson R, Feehally J, editors. Comprehensive clinical Nephrology. 4th ed. New York: Elsevier Saunders; 2010. p. 830- 42.

27. Mise YF, Lira-da-Silva RM, Carvalho FM. Envenenamento por serpentes do gênero *Bothrops* no estado da Bahia: aspectos epidemiológicos e clínicos. Rev Soc Bras Med Trop. 2007;40:563-73.

28. Molander M, Saslis-Lagoudakis CH, Jager AK, Ronsted N. Cross-cultural comparison of medicinal floras used against snakebites. J Ethnopharmacol. 2012;139:863-72.

29. Monteiro HS, da Silva IM, Martins AM, Fonteles MC. Actions of *Crotalus durissus terrificus* venom and crotoxin on the isolated rat kidney. Braz J Med Biol Res. 2001;34:1347-52.

30. Nascimento JM, Franchi GC Jr., Nowill AE, Collares-Buzato CB, Hyslop S. Cytoskeletal rearrangement and cell death induced by *Bothrops alternatus* snake venom in cultured Madin-Darby canine kidney cells. Biochem Cell Biol. 2007;85:591-605.

31. Oliveira FN, Brito MT, Morais IC, Fook SM, Albuquerque HN. Accidents caused by *Bothrops* and *Bothropoides* in the state of Paraíba: epidemiological and clinical aspects. Rev Soc Bras Med Trop. 2010;43:662-7.

32. Otero-Patiño R. Epidemiological, clinical and therapeutic aspects of *Bothrops asper* bites. Toxicon. 2009;54:998-1011.

33. Pinho FM, Zanetta DM, Burdmann EA. Acute renal failure after *Crotalus durissus* snakebite: a prospective survey on 100 patients. Kidney Int. 2005;67:659-67.

34. Pinho FM, Yu L, Burdmann EA. Snakebite-induced kidney injury in Latin America. Semin Nephrol. 2008;28:354-62.

35. Pinto RNL, Souza LCS, Silva AM, Pereira LIA, Andrade JG. Estudo clínico-epidemiológico de 774 casos de acidentes ofídicos. In: XXIII Congresso da Sociedade Brasileira de Medicina Tropical, Curitiba, 1987. Livro de resumos.

36. Santos MFL, Farani MC, Rocha PN. Insuficiência renal aguda em acidentes ofídicos por *Bothrops* sp. and *Crotalus* sp: revisão e análise crítica da literatura. J Bras Nefrol. 2009;31:132-8.

37. Saul ME, Thomas PA, Dosen PJ, Isbister GK, O´Leary MA, Whyte IM, *et al*. A pharmacological approach to first aid treatment for snakebite. Nat Med. 2011;17:809-11.

38. Sgrinolli L, Mendes G, Carlos G, Burdmann E. Acute kidney injury caused by *Bothrops* snake venom. Nephron Clin Pract. 2011;119:131-7.

39. Silva HA, Pathmeswaran A, Ranasinha CD, Jayamanne S, Samarakoon SB, Hittharage A, *et al.* Low- dose adrenaline, promethazine, and hydrocortisone in prevention of acute adverse reactions to antivenom following snakebite: a randomised, double- blind, placebo controlled trial. PLoS Med. 2011;8:1-10.

40. Silveira PV, Nishioka SA. South American rattlesnake bite in a Brazilian teaching hospital. Clinical and epidemiological study of 87 cases, with analysis of factors predictive of renal failure. Trans R Soc Trop Med Hyg. 1992;86:562-4.

41. Sitprija V, Sribhibhadh R, Benyajati C. Haemodialysis in poisoning by sea-snake venom. Br Med J. 1971;3:218-9.

42. Sitprija V. Snakebite nephropathy. Nephrology (Carlton). 2006;11:442-8.

43. Sitprija V. Animal toxins and the kidney. Nat Clin Pract Nephrol. 2008;4:616-27.

44. Sitprija V, Sitprija S. Renal effects and injury induced by animal toxins. Toxicon. 2012;60:943-53.

45. Vêncio D. Estudo do ofidismo em Goiás: comprometimento da função renal. Rev Goiana Med. 1988;34:95-116.

46. Walker JP, Morrison RL. Current management of copperhead snakebite. J Am Coll Surg. 2011;212:470-3.

47. World Health Organization. Guidelines for production, control and regulation of snake antivenom immunoglobulins. Geneve: WHO Press; 2010. p. 7.

Received: 21 January 2013
Accepted: 27 March 2013