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REVIEW ARTICLE

Crotalic Accidents In Brazil: Actualities And Perpectives

Acidentes Crotálicos No Brasil: Atualidades E Perspectivas

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ABSTRACT

Introduction: Ophidian accidents are neglected events in tropical and in developing countries, including Brazil. Serpents of the *Crotalus* genus (rattlesnakes) are those that produce the highest case-fatality in the country. **Purpose**: to address the main aspects of the accident caused by *Crotalus*, with emphasis on the snakes biology, the clinical approach to snake bites and the therapeutic properties of the venom of these animals. **Methods**: literature review with a defined search strategy, using the PubMed, LILACS and SciELO databases. **Results**: Inoculation of crotalic venom produces discrete local signs, but systemic repercussions can occur, especially neurological alterations and acute renal failure. Laboratory evaluation is important to help distinguish from other ophidian accidents and to estimate the severity of the condition. Anticrotalic serum must be administered as soon as possible, based on the estimated amount of inoculated venom. Most of the morbid events occur in the rainy season (higher temperature), mainly affecting young men who work in rural areas. The adoption of protective measures and health education, aimed at the population most commonly involved, are relevant strategies for preventing and reducing the number of cases. In addition, crotalic venoms have antimicrobial actions, antiplatelets functions and ophthalmological applicability (strabismus). **Conclusion**: Knowledge of the different aspects of crotalic injuries is essential for an adequate diagnostic and therapeutic approach to such morbid conditions. The pharmacological properties of crotalic venom components should be better investigated in the next few years, given the possibilities of their use for the treatment of different human diseases.

Keywords: *Crotalus*; Rattlesnake; Crotoxin.

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Introduction

Snake accidents – also known as ophidism – are events triggered by snakes through the introduction of toxins, by the animal›s inoculating apparatus, into the victim›s body, leading to local and/or systemic changes.[1] In tropical countries, these events are a significant problem of public health, in view of the high frequency of its occurrence and severity.[2] Snake accidents are part of the list of neglected tropical diseases of the World Health Organization (WHO),[3,4] with an estimated occurrence of 2.7 million of cases annually on the planet.[3] In Brazil, data from the Ministry of Health indicate that the occurrence of these morbid events has increased significantly in the country, highlighting the increase in the incidence rate per 100,000 inhabitants from 6.8 to 13.3 from 2000 to 2015.[5,6,7]

Injuries produced by snakes occur more frequently in rural workers, as this is the habitat where these animals are commonly found,[4] affecting mostly males,[5] with a predominance between the second and fifth decades of life.[4] In Brazil, the venomous snakes that generally cause more evident clinical repercussions in affected individuals are represented by the genera Bothrops, *Crotalus*, Lachesis and Micrurus.[6,7] Snakes belonging to the genus *Crotalus* – popularly known as rattlesnakes – are among the main causative agents of accidents. Especially in South America, the species *Crotalus durissus* is considered clinically the most relevant. According to data released by the National Disease Notification System (Sistema Nacional de Notificação de Doenças – SINAN),[7] in 2017, rattlesnakes caused 2,506 cases with a lethality of 0.71%.[1] The envenoming caused by such a genus may be severe and possibly fatal, in the absence of adequate treatment.[8] It It is of great importance that when receiving the victim of ophidism, health professionals are capable of detecting the clinical aspects of encumbrances by genders existing in Brazil,[1] thus guiding the indication of specific therapeutic conduct, whose delay may result in serious consequences.[9,10]

Despite the harmful potential of crotalic venom, its components have been investigated – with promising results – for the treatment of different nosological entities in human medicine, with special emphasis on antimicrobial action, such as antiplatelet agents and ocular diseases (strabismus).

Based on these brief notes, this article will present (1) current concepts about the crotalic accident – covering the etiology, pathophysiology, clinic, diagnosis, treatment and prevention – and (2) perspectives for the use of crotalic venom for the treatment of *Homo sapiens* diseases.

Methods

Search strategy

The search for articles was undertaken in the following electronic databases: US National Library of Medicine (PubMed – https://pubmed.ncbi.nlm.nih.gov/), Latin American and Caribbean Health Sciences Literature (LILACS) – https://lilacs.bvsalud.org/) and Scientific Electronic Library Online (SciELO – https://www.scielo.br/).

At first, the research was directed to the search for original articles, with no date restrictions, with thematic that related: (I) Accidents caused by snakes and (II) Handling snake accidents. The keywords for the investigation were chosen according to the Health Sciences Descriptors (DeCS/MeSH – https://decs.bvsalud.org/) of the Virtual Health Library, used with the Boolean operator "AND": "Brazil", " Crotalid Venoms", "*Crotalus*", "Drug Design", "Drug Development" and "Snake Venoms" (Table 1).

Study characteristics, articles selection and exclusion/inclusion criteria

The inclusion of the studies was based on the following criteria: (a) original articles, (b) information on the diagnosis of accidents by snakes of the genus *Crotalus* in Brazil and (c) information on the therapeutic conduct of accidents by snakes of the genus *Crotalus* present in the country.

Thus, all manuscripts that could be considered as belonging to at least one of the following items were excluded: (i) articles focusing on other animals than snakes, (iii) texts that address thematic related to accidents by other genera of snakes than *Crotalus* and (iv) manuscripts that did not describe the diagnosis and/or treatment of accidents caused by rattlesnakes. Articles were analyzed until December 31, 2020 and, it is noteworthy, no restrictions were established regarding language, location or type of study. After the analysis, 41 articles were selected – which were complemented with other texts, such as book chapters and official documents from national and foreign institutions – to compose this review. The information was collected in topics – (1) The genus *Crotalus*, (2) Pathophysiology: actions of crotalic venom, (3) clinical findings, (4) laboratory evaluation, (5) treatment, (6) epidemiology, (7) prophylaxis and control and (8) therapeutic properties of crotalic venom – presented below.

Results and discussion

The Genus *Crotalus* Linnaeus, 1758[11]

Snakes of the genus *Crotalus* – known as rattlesnakes, boicininga or boiquira – are venomous and endowed with large venom-inoculating teeth in the anterior region of the maxilla, being, therefore, solenoglyphs.[10,12] The rattlesnake reaches a meter in length, has a little agile behavior and attacks only when very excited. Its most prominent and exuberant feature is a rattle at the tip of the tail (Fig. 1), which produces a characteristic sound that helps in recognizing the animal.[12,13]

Natural History and Ecology

The genus *Crotalus* is integrated of terrestrial snakes. Their feeding is basically composed of vertebrates (that is, they are carnivores); the smaller species commonly feed on lizards and the larger ones feed on lizards when young and small mammals and birds when adult.[14] Males of *Crotalus durissus* exhibit bodies, tails and paravertebral stripes, often longer than females, which it is closely linked to reproductive success. Female rattlesnakes are described to have, generally, wider bodies.[15] They are live-bearing animals, with biennial reproduction. Copulation takes place at the beginning of the dry season, citing the occurrence of ritual combats in the period of search for females for copulation.[15,16,17] Females store male sperm in the posterior uterus until fertilization, at the end of the dry season16. As a result, between six to twenty-two offspring are born (average of 14), from the middle of the rainy season to the beginning of the dry season.[13,16] The male›s copulatory organs, also known as hemipenis, are located inside the tail, in its portion initial. Sperm are stored in the vas deferens throughout the year.[16,17,18]

Taxonomy

The Viperidae family is mostly the group of snakes with a healthy capacity for envenoming in attacks on humans, being represented, in Brazil, mainly by the genera Bothrops, Lachesis and *Crotalus*.[19,20,21] The genus *Crotalus* includes approximately 70 species and subspecies.[17] In Brazil, the only one described is *Crotalus durissus*, which occurs throughout the country (Table 2).

Table 1. Search strategy used in the literature review and the results found in the databases.

Search strategy	LILACS	PubMed	SciELO
"*Brazil*" AND "*Crotalus*"	80	544	103
"*Brazil*" AND "*Crotalid Venoms*"	43	1145	1
"*Brazil*" AND "*Crotalus*" AND "*Snake Venoms*"	2	107	1
"*Drug Design*" AND "*Crotalus*"	0	9	0
"*Drug Design*" AND "*Crotalid Venoms*"	0	12	0
"*Drug Development*" AND "*Crotalus*"	0	4	0
"*Drug Development*" AND "*Crotalid Venoms*"	0	10	0

Deadline for research: 12/31/2020.
Source: elaborated by the authors.

Figure 1. Rattlesnake: *Crotalus durissus*. Image that belongs to the archive of the João Moojen Zoology Museum, Federal University of Viçosa.

Geographic distribution

Rattlesnakes occur in nature in open formations throughout South America (except Chile and Ecuador)[17] and can be seen in forest edges, open fields, dry, sandy and rocky areas of the Cerrado, Caatinga and Campos Sulinos, being rarely found in the coast or in dense areas of the Amazon and Atlantic Forest (Table 3).[8,13]

It is noteworthy that human activities, climate change and plant successions can determine changes in the distribution and abundance of species.[18] The constant degradation of forests – replaced by pastures and agricultural fields – has favored the expansion of the original distribution of rattlesnakes, as they adapt very well to deforested areas and have been relatively quick to colonize them.[19,20]

Pathophysiology: actions of crotalic venom

Crotalic venom is a complex mixture of proteins and polypeptides that interfere in various physiological processes.[5,24,25,26] Characteristically, it presents neurotoxic, myotoxic and coagulant actions, determining variable effects in different animal species.[27,28,29,30] The main aspects of the pathogenesis of accidents caused by *Crotalus* are described in the following topics.

Coagulant action

The coagulant action of the venom activates the coagulation factor X and prothrombin, acting similarly to that described for thrombin, thus leading to the transformation of fibrinogen into fibrin and the consumption of coagulation factors and platelets. The glycoprotein components gyrotoxin – molecular mass of 35 kDa and action similar to thrombin[31] – and convulxin – molecular mass of about 68 kDa, related to platelet aggregation[31] – participate in these processes. In fact, hemorrhage is triggered by the inactivation of coagulation factors and/or excessive consumption of platelets.[31,32] Such events favor disseminated intravascular coagulation, leading to the formation of microthrombi in multiple organs, which can be deposited in renal capillaries and potentially corroborate the development of acute renal failure.[6,10,30]

The most commonly affected areas in bleeding episodes are the digestive system, the central nervous system (CNS), the airways and the skin. However, despite the alterations in the coagulation tests, the hemorrhagic manifestations are mild and of little intensity in the accident caused by *Crotalus*.[6,33]

Neurotoxic action

Components of *Crotalus* venom – mainly the crotoxin fraction (a protein formed by two subunits, crotapotin and phospholipase A2, the latter may be involved in several pathophysiological effects, with specific action in the hydrolysis of phospholipids in the plasma membrane) – they can act in the presynaptic region, preventing the release of acetylcholine, which causes neuromuscular blockage.[34,35,36,37] The clinical expression of this pathophysiological substrate is the occurrence of paralysis of muscle groups, eventually with impairment of ventilatory mechanics. The convulxin component is related to the occurrence of balance alterations and visual disturbances[31]. Events related to neurotoxicity usually occur in the first hours after the accident.[35,36]

Myotoxic action

Myotoxic activity is not restricted to the wound site. In fact, systemic involvement may ensue, with evolution to rhabdomyonecrosis, myoglobinemia and myoglobinuria and possible development of acute renal failure. The component that causes this action is the crotoxin fraction,[37] but there is also the participation of crotamine, a polypeptide with a molecular mass of approximately 4.8 kDa.[31] When crotoxin produces systemic repercussions, myoglobin may be released into the blood and lymphatic system, with subsequent rhabdomyolysis and increased levels

Table 2. Taxonomy of the *Crotalus* genus in Brazil.

CATEGORIES	SPECIES
Kingdom	Animalia
Phylum	Chordata
Class	Reptilia
Order	Squamata
Family	Viperidae
Genus	*Crotalus*
Species	*Crotalus durissus*
Geographic forms	*Crotalus durissus cascavella, Crotalus durissus collilineatus, Crotalus durissus durissus, Crotalus durissus marajoensis, Crotalus durissus ruruima, Crotalus durissus terrificus*

Sources: Reproduced from NCBI Taxonomy (2020), Arctos (2020).[10]

Table 3. Distribution of geographical forms of *Crotalus durissus* in Brazil.[13,22,23]

Geographic forms in Brazil	Distribution
Crotalus durissus terrificus	Wide distribution: Fields and forest edges in the southern region, extending through the west of Brazil, passing through São Paulo, Minas Gerais, Mato Grosso until reaching open areas of the Amazon.
Crotalus durissus cascavella	Wide distribution: Caatingas from northeastern Brazil to its limits with the Amazon.
Crotalus durissus collilineatus	Wide Distribution: Cerrados of São Paulo, Mato Grosso, Minas Gerais, Federal District and Goiás.
Crotalus durissus durissus	Restricted distribution: Amapá.
Crotalus durissus ruruima	Restricted distribution: Typical of the savannas and open areas of Roraima.
Crotalus durissus marajoensis	Restricted distribution: Exclusive to open areas of Ilha de Marajó, Pará.

Source: adapted from Melgarejo (2003)13; Costa & Bérnils (2018).[22]

of creatine phosphokinase (CPK), lactic dehydrogenase (LDH) and aspartate aminotransferase (AST).[38] It was observed in experimental animals – rats, mice and rabbits – the occurrence of paralysis and extension of the hind legs, in addition to spontaneous and irregular contractions in the diaphragm, due to the action of crotamine in ion channels.[39,40]

Nephrotoxic action

In crotalic accidents, toxin concentrations up to 50% higher than those described in plasma can be detected at the renal level,[41] which corroborates the occurrence of acute renal failure in these accidents.[42] Studies have suggested that crotalic venom has activity toxic over the renal parenchyma, leading to changes such as acute glomerulonephritis, acute tubular necrosis and cortical necrosis.[41,43] Lesions are associated with direct cell toxicity, with the participation of crotoxin and, to a lesser extent, of gyrotoxin.[41] The time interval between the sting and the onset of oliguria or anuria can vary from eight hours to three days.[41]

In addition to the mechanisms described, the secondary lesion due to the myotoxic action of the venom is noteworthy, with the development of rhabdomyolysis and consequent vasoconstriction and renal hypoperfusion, which aggravates the typical organ dysfunction observed in victims of crotalic entangling.[44, 45]

Clinical findings

Snake accidents are conditions that must be treated promptly, under the risk of serious clinical complications and, eventually, rapid evolution to death. In view of this information, it is of fundamental importance that health professionals know how to identify these events. The main feature of the clinical diagnosis of a rattlesnake accident – which can help differentiate it from other envenomings (*Bothrops*, for example) – is the paucity of local signs. However, this does not represent a constant pattern, as there may be a small edema and numbness in the bite area, emphasizing that this change in sensitivity may persist for several months.[46]

During the clinical course, some important symptoms and signs may appear, especially: decreased vision acuity, nystagmus, ophthalmoplegia, diplopia (movements related to combined vision), bilaterally dilated pupils and eyelid ptosis (composing the neurotoxic Rosenfeld facies, also known as myasthenic facies); anorexia, changes in taste and smell, in addition to drooling; disturbances in the state of consciousness (in this case, it is important to use

the Glasgow Coma Scale); mild or severe systemic myalgia (may be accompanied by edema of muscle groups) and, in more severe cases, paralysis of respiratory muscles and paralysis of the velopalatine muscles (which can lead to respiratory failure).[6,10] Neuroparalytic changes usually have, craniocaudal progression. When performing funduscopy, bilateral venous engorgement is observed, accompanied by papila blurring. In crotalic envenomations it is not common for hemorrhages to appear – when they do occur, they are usually slight –, even in cases where the clotting time is increased. Up to 48 hours after the accident, the occurrence of renal changes is typical, often noticed by changes in the color of the urine (becomes reddish or brownish, in a context of myoglobinuria), this condition has the potential to progress to recognized acute renal failure as the main complication – and cause of death – of stinging by *Crotalus*.[47,48,49]

In the same way as described in other accidents caused by snakes,[5,10] the time elapsed between the inoculation of the venom and the application of specific serum therapy has an impact on the evolution of the clinical picture.[1,10,48,49]

Differential diagnosis

If the animal is not visualized, the anamnesis and clinical examination are essential to distinguish the type of encumbrance.[1,6,10] The most relevant differential diagnosis is the elipid accident (caused by ophids of the genus *Micrurus*), since this can present with myasthenic face and other neurological disorders; however, this condition does not cause muscle and kidney injuries, in addition to blood clotting alterations, findings that are usually present in crotalic accidents.[35,37]

Laboratory evaluation

The most commonly used complementary exam for the evaluation of the victims – suspected or confirmed – of snake accidents is the measurement of the clotting time (TCoag). This is a widely used test because it is easy to perform and confirms the non-coagulation of blood, present in different types of envenoming, including the accident caused by *Crotalus*. TCoag interpretation should be based on the following parameters: (i) normal: TCoag ≤ 10 minutes; (ii) extended: 10 < TCoag < 30 minutes; (iii) incoagulable: TCoag ≥ 30 minutes.[1,10] After treatment, the TCoag is expected to return to normal within 12 hours; if this does not occur, another dose of serum should be added to normalize the condition.[24,28,35]

The blood count can also be used as a parameter for the evaluation of patients bitten by snakes, given its potential to identify left shift and relative lymphopenia, accompanied or not by thrombocytopenia, findings that may be present in snakebites. Another laboratory test that may be altered is the erythrocyte sedimentation rate (ESR), in this case, usually with a moderate increase.[24,28,35]

Biochemical assessment is equally important. It should be noted that in crotal accidents, muscle enzymes – such as CPK, LDH and AST – are usually elevated, due to the myotoxicity of the venom.[25,28] Renal function must be analyzed, which must include the measurement of nitrogenous slag – urea and creatinine – and electrolytes (chlorine, potassium and sodium), tests that are very useful for the characterization of kidney damage.[1,25,28] To corroborate the analysis of this sphere, the renal function, the abnormal elements and sedimentoscopy (AES) – also called "urine summary" or "type I urine" – will be indicated, which may show myoglobinuria (due to severe muscle damage), glycosuria, proteinuria, and hematuria.[25]

Treatment

The therapeutic approach to crotalic accidents should start, if possible, before the patient arrives at the hospital.[10] In fact, at the scene of the accident, some measures can already be taken – preceding the individual›s transport to the treatment unit – which reinforces the importance of scientific dissemination of knowledge about snakebite, a factor that can contribute to different people's knowledge what to do in a case of snake injury. First, it is necessary to ensure the patient›s safety, removing him from the enclosure, which helps to reduce the chance of new bites involving the venomous animal.[6,10,28] In addition, it is recommended to calm the victim and, continuously, seek keep it in a comfortable position and the affected area in a functional position, with as little movement as possible (ie, remaining at rest), in order to promote a maximum slowdown absorption of the venom, as muscle contraction can increase this process.[25,35]

The use of a tourniquet usually worsens local lesions, by concentrating the venom in the bite region, especially in accidents in which there are proteolytic components in the venom (highlight for *Bothrops* and *Lachesis* genus). Some "popular measures", such as biting and sucking the bite site and the application of certain "products" to the affected area – such as garlic, coffee, manure, tobacco and kerosene – need to be formally discouraged, because in addition to not changing the patient›s prognosis, they can lead to the appearance of secondary infections.[1]

At the health unit, the following care actions should be carried out:[1,28,31,35,50] (1) detailed clinical assessment of the patient, with a view to verifying the need for ventilatory support; (2) investigation of the bite region (local care must be immediate and precise, cleaning with water, soap and potassium permanganate, if available); (3) blood collection for TCoag analysis and other laboratory tests (see previous section); (4) administration of antivenom serum, if this is the best approach for the case; (5) reinforce the victim›s reassurance and guidance to remain at rest. Such care is essential and must be taken as soon as the patient is admitted to the health service.[25,35] Furthermore, it is noteworthy that in the first hours, especially, it is essential to maintain a thorough clinical follow-up of the victim, along with annotation of the your vital signs and your urinary output.[25]

In these patients, the administration of heparin is not indicated, since it is not efficient in neutralizing the components contained in the venom.[28,35] It is also useful to comment that the use of drugs with sedative activity for the CNS should be avoided, under penalty of interfering in the assessment of the patient›s state of consciousness.[35]

Specific treatment: serum therapy

The proper use of serum therapy – in this case, anticrotalic serum (CAS) – is a fundamental measure for the management of the case, especially if used as early as possible, since it reduces the risk of complications and progression to death.1,50 The serum is provided by the Ministry of Health, and must be kept refrigerated, between 2°C and 8°C. The venom neutralizing capacity is informed

Table 4. Number of ampoules of specific antivenom indicated for each type and severity of the accident.[1]

Antivenom	Severity	Number of ampoules
SAC or SABC	Mild: mild neuroparalytic changes; no myalgia, darkening of urine or oliguria	5
	Moderate: evident neuroparalytic changes; Mild myalgia and myoglobinuria (dark urine)	10
	Severe: evident neuroparalytic changes; intense myalgia and myoglobinuria, oliguria	20

Source: Reproduced from Brazil (2021).[1]

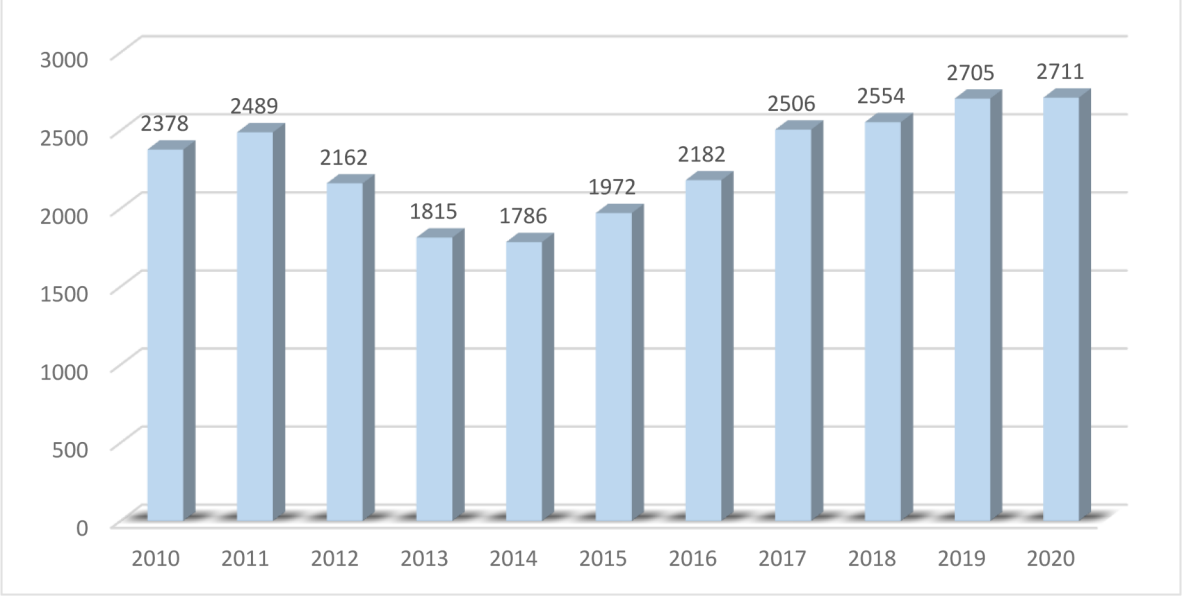

Figure 2. Number of cases due to snakebite envenomings by *Crotalus* in Brazil (2010-2020).
Source: DATASUS - http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sinannet/cnv/animaisbr.def

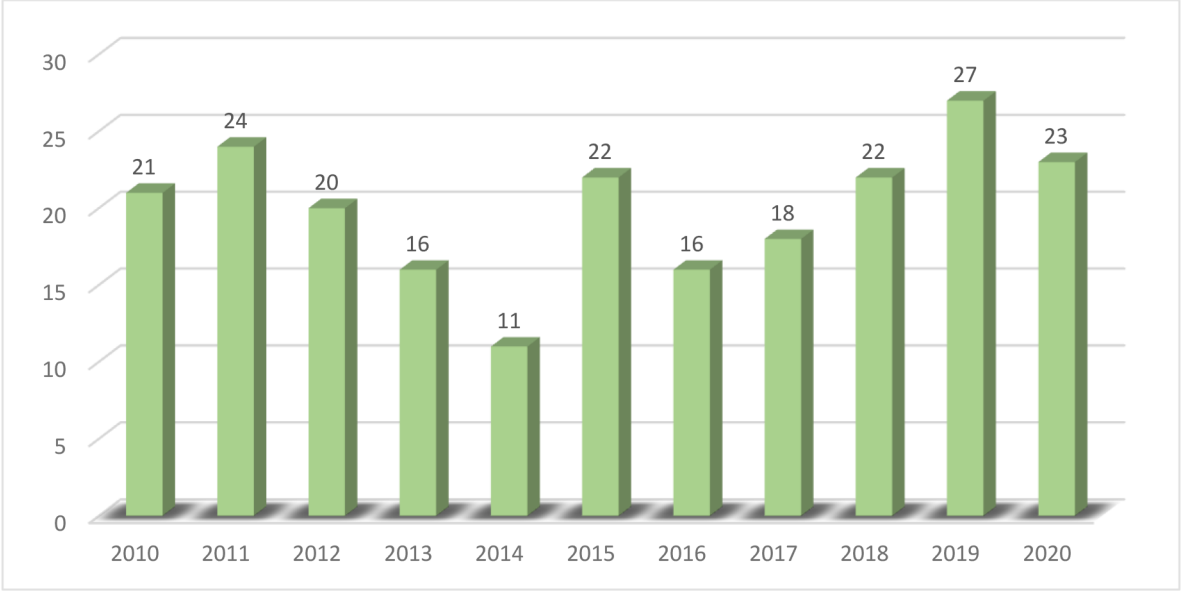

Figure 3. Number of deaths due to snakebite envenomings by *Crotalus* in Brazil (2010-2020).
Source: DATASUS - http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sinannet/cnv/animaisbr.def

on the packaging of each product. The maximum time for the use of the antivenom serum, after the inoculation of the venom by the animal, is still not well understood; however, research shows that, even after days, the antivenom still has some use in minimizing the impact of systemic manifestations. Contrary to popular belief, the amount of serum to be applied does not depend on the victim›s weight, but on the approximate calculation of the amount of venom injected by the snake, which is based on the analysis of the set of clinical manifestations presented by the patient (Table 4).[1,50] Regarding the determination of the dose of the antivenom to be administered, the most adequate would be the measurement of the serum concentration of the venom in the patient; however, such conduct is not practicable. Thus, currently, the dose is determined from animal studies.[28,35,50]

The administration of serum should be done in a single dose, intravenously (drip). The immunobiological may or may not be diluted in isotonic solution. During the entire period of treatment and a few hours after the end of this application, the healthcare professional must observe the patient. Adverse reactions may arise during serum therapy, such as anaphylactic shock; therefore, drugs that reverse such effects should always be available (corticosteroids, antihistamines and epinephrine), as well as material for ventilatory assistance.[51] The management of the patient with anaphylaxis should be immediate, due to the imminent risk of arrest respiratory and/or cardiac. Initially, care should initially focus on the airways, considering the possibility of periglottic or glottic edema, so that the material necessary for possible orotracheal intubation should be available. In addition, epinephrine should be promptly administered intramuscularly or intravenously if the patient presents with very severe signs; it is also necessary to offer supplemental oxygen and monitor the cardiopulmonary status.[35] Due to the imprecision of the results, the intradermal test is no longer recommended. Some authors still advocate the use of parenteral antihistamines in advance, but this effect is not widely accepted.[28,35] The general lines of approach to anaphylaxis should be complemented with specific references on the topic.[51,52]

The risk/benefit ratio for administering the serum, in each situation, must always be evaluated in detail, especially in those contexts in which the patient has already been exposed to antiophidic serum therapy. The situation will deserve even more attention in those cases in which there is a history of serious reactions to the use of the aforementioned immunobiological and the victim›s condition is mild or moderate. In such scenarios, the advantage regarding the application of the serum should be rethought.[1,5]

Particular measures

Some special measures must be taken in cases of crotalic accidents. To reduce the chances of developing acute renal failure, abundant hydration is indicated, considering also the use of mannitol (for 3 to 5 days) or furosemide to ensure adequate diuresis. Also related to possible kidney damage, some authors recommend the use of sodium bicarbonate to alkalinize the urine, but this measure is not consensual.[10,25] The observation of the patient for signs of shock should be rigorous; if such condition is identified, procedures for managing circulatory failure should be implemented immediately.[35,48] If acute renal failure occurs, dialysis treatment should be performed. If the patient has signs and symptoms of respiratory failure, ventilatory support should be instituted.[1,48,49]

Response to treatment

Crotalic accidents will lead to an adequate response to the adopted therapy, especially in those patients whose medical care is instituted earlier. Renal failure usually evolves well with adequate treatment.[35,41] Respiratory failure is usually reversed within a few days of starting serum administration.[27,42]

Epidemiology

The World Health Organization (WHO) estimates that approximately 5.4 million people are affected by ophidian accidents per year, with 2.7 million cases of envenoming.[53] It is estimated that up to 140,000 deaths can occur, with one The number of amputations and other permanent disabilities is three times greater each passing year.[3,46,53] In Brazil, venomous snakes are found that generate important clinical repercussions throughout the country. The risk of progression to death is relevant, especially in those contexts where there is no infrastructure for adequate early care. In 2019, there were 24,463 cases of envenoming by snakes by the genera *Bothrops*, *Crotalus*, *Micrurus* and *Lachesis*, with 129 reported deaths; Of this total number of cases, 2,705 were caused by rattlesnakes (Fig. 2), with a total of 27 deaths caused by these snakes (Fig. 3).[54] The highest incidence observed in the country was in the Northeast region, with 1,132 cases and 16 deaths reported.[54]

There is a strong impact of seasonality on accidents; in fact, most morbid events occur in hot weather months and characterized by heavy rainfall. Snake-related accidents are more frequent from January to April, a period of increased rainfall and hot weather, which is in line with other studies of equatorial and subequatorial scope.[55] It should be commented, also in epidemiological terms, that the rural population – especially rural workers – is particularly affected by accidents caused by venomous snakes, with emphasis on young individuals (between 15 and 49 years old) of the male sex.[1,10,56] This context refers to the fact these individuals are more exposed to these animals, on many occasions without the minimum safety requirements for work activities.10 Indeed, many episodes of snakebite fall into the category of occupational accidents (Fig. 4),[56] citing the feet and legs as the body areas most affected by snake bites, followed by the upper limbs (hand and forearm).[1] The location of the bite is related to earth habits, snakes, the size of the animal and the limitation of the range of the boat, which reaches approximately one third of its length.

The occurrence of related snakebites has a relevant influence in social and economic terms, as it is often a condition that particularly affects economically active individuals, who need to withdraw from work during their recovery time.[56,57] Furthermore, part of the victims survives with sequelae, which has an impact on the affected population, often dependent on work that requires motor and bodily skills.[5,6]

Prevention

Prophylactic measures for ophidian accidents include the adoption of simple behaviors, such as:[1,5,10,57] (1) use closed shoes, leggings or high boots, in addition to leather gloves (if there is a need to handle the earth or materials accumulated

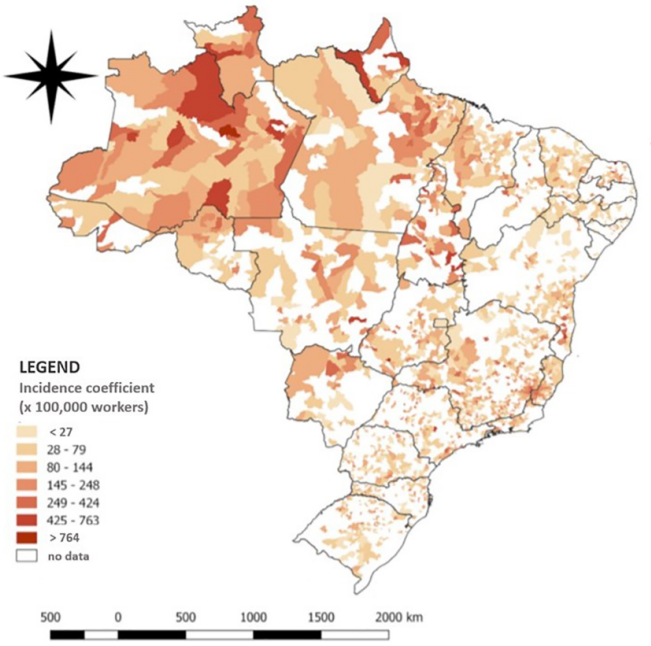

Figure 4. Incidence coefficient (x100,000) by snake bite in field, forest and water workers, by municipality, Brazil, 2017. SOURCE: Acidentes de trabalho por animais peçonhentos entre trabalhadores do campo, floresta e águas, Brasil 2007 a 2017. Available at: https://portalarquivos2.saude.gov.br/images/pdf/2019/marco/29/2018-059.pdf.

on the ground); (2) pay attention to the places where you step and/or put your hands for support; (3) do not approach holes in the ground or hollows in trees without proper protection; (4) keep the surroundings of the houses clean, with emphasis on gardens, backyards, cellars and barns; (5) avoid approaching undergrowth areas, especially at dawn and dusk.

The dissemination of good information about ophidian accidents to populations – emphasizing prevention and pre-hospital behaviors that should be adopted in cases of accidents – is very important in prophylactic terms, with a view to minimizing the serious consequences of this relevant public health problem in Brazil.

Therapeutic potential of crotallic pevenous

The applicability of crotoxin, the main component of the South American rattlesnake venom, in different fields of biopharmacology (identification of new antimicrobials, for example), has shown interesting perspectives in terms of the treatment of human diseases.[58-65]

The use of products obtained from *Crotalus* toxins has been investigated for the treatment of fungal diseases, with emphasis on candidiasis – a disease produced by different *Candida* species[59] –, a growing problem related to the indiscriminate use of antimicrobials.[60,61] In this context, a study performed by Canelli et al.[61] showed that crotoxin, incorporated into a mouthwash, applied against two *Candida* species related to periodontitis (*Candida tropicalis* and *Candida dubliniensis*), showed significantly greater in vitro antibiofilm effects than nystatin (this drug served as a positive control treatment). The antifungal action of the venom seems to be linked to phospholipase A2, probably through a process of thinning and destabilization of the membrane lipid bilayer, resulting in permeabilization and expulsion of cell contents, inhibition of macromolecule biosynthesis and promotion of the expression of autolytic enzymes.[61] Also in terms of antimicrobials, the identification, from the crotalic venom, of bordonein-L – a type of L-amino acid oxidase (LAAO) – which has shown, in in vitro studies, action against *Leishmania amazonensis* promastigotes and cytotoxicity is noteworthy directed to fibroblasts.[62]

Another applicability of crotoxin in clinical practice concerns its ability to induce paralysis of the extrinsic ocular muscles, especially observed in the superior rectus muscle, through blocking neurotransmission at the neuromuscular junction, and this action can be used for the treatment of strabismus.[63] The effect is similar to that of botulinum toxin[64] and no signs of systemic actions of the component from the crotalic venom were observed. The occurrence of eyelid ptosis was noted, which was transient in almost all animals involved in the study, remaining for a maximum of 14 days.[63]

In addition to the aforementioned properties, the venom of snakes from the Viperidae family commonly have non-enzymatic proteins, called disintegrins, the most abundant of which, tzabcanin, is found mainly in South American rattlesnakes. Such components have the potential to inhibit platelet aggregation and adhesion cellular.[65] Disintegrins have domains called colombistatins, which contribute to the anti-platelet aggregation effect and, equally, to the inhibition of adhesion of human skin melanoma cancer cell lines to collagen type 1.[66]

In a search for substances capable of acting on platelet function with potential milder adverse effects, the towaglerix peptide was found – in the snake venom of the species *Tropidolaemus wagleri*,[67] from previous studies carried out with toxins produced by *C. durissus terrificus* – which has the ability to inhibit collagen-induced platelet aggregation by blocking the GPVI receptor (type C lectin protein of snake venom) in platelets, reducing cases of severe hemorrhage and thrombocytopenia caused by commonly used antiplatelet agents. 68 This is one of the first studies to design small

mass peptides derived from toxins produced by snakes with antithrombotic activity and targeting the GPVI of platelets, which opens up important frontiers of investigation, especially when considering that drugs already in use, as tirofiban and eptifibatide, were identified from snake venoms, respectively and the species *Echis carinatus*[69] and *Sistrurus miliarus barbouri*.[70]

Final considerations

The approach to crotalic accidents represents the core of this article. The elements related to the biology of snakes, the pathophysiological actions of venoms – coagulant, neurotoxic, myotoxic and nephrotoxic – with the respective clinical presentations, diagnosis and treatment – serotherapy and additional measures – and the epidemiological and prophylactic aspects of the ophidism by *Crotalus*. The huge importance of the qualification of health professionals for the early recognition of the conditions produced by *Crotalus* was highlighted, allowing the indication of the appropriate therapy, which contributes to the reduction of the deleterious effects that currently result in risk of sequelae and death for the victims.

As an update on the topic – especially in terms of advances in research in the field of biopharmacology – the potential therapeutic applicability of compounds from crotalic venoms was reviewed, with emphasis on the antimicrobial use (perspectives for *Candida* and *Leishmania*), ophthalmological (strabismus) and antithrombotic (action on platelet aggregation). The recognition of this research front opens possibilities to identify the role of snakes – and other venomous animals – not only as accident promoters (ophidism), but also as living beings that can contribute to health and quality of life of people.

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