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Bothrops Snakebite Envenomings in the Amazon Region

Dabor Resiere [1] · Wuelton Monteiro [2,3] · Stephanie Houcke [4] · Jean Marc Pujo [5] · Cyrille Mathien [4] · Claire Mayence [4] · Rémi Neviere [1] · Didier Hommel [4] · Jacqueline de Almeida Gonçalves Sachett [2,6] · Hossein Mehdaoui [1] · José María Gutiérrez [7] · Hatem Kallel [4]

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Abstract

Purpose of Review Snakebite envenoming is a neglected tropical disease with a high burden in the Amazon basin. Our review aimed to give information about the epidemiology and the management of SB in the Amazon region.

Recent Findings The Amazon basin, which comprises the largest portion of tropical rainforest on earth, includes territories of nine South American countries. The Amazon harbors a rich herpetofauna, among which the species of the *Bothrops* genus (family Viperidae) cause the highest number of bites and envenomings. The management of snakebite envenomings poses a difficult challenge for the public health systems of these countries for several reasons: bites occur in remote rural locations far from urban centers and health facilities; there are transportation difficulties for; health posts and personnel are in insufficient numbers; and antivenoms are insufficiently available in some regions. In addition, the species causing the highest number of accidents, i.e. *Bothrops atrox*, often causes severe envenomings.

Summary The present review summarizes the main aspects of envenomings by *Bothrops* sp. snakes in the Amazonia, including the epidemiology, pathophysiology, clinical manifestations, and therapy of envenomings. In a context of global efforts to reduce the impact of snakebite envenomings, there is a need for international cooperative efforts by public health authorities and civil society in these countries.

Keywords Amazonia · Snakebite · *Bothrops* sp. · *Bothrops atrox* · Epidemiology · Pathophysiology · Antivenom

Introduction

Snakebite envenoming is a neglected tropical disease having its highest burden in sub-Saharan Africa, Asia, and Latin America. It is estimated that 1.8 to 2.7 million cases of snakebite envenoming occur every year worldwide, resulting in 81,000 to 138,000 fatalities and an estimated 400,000 people left with some type of permanent physical and psychological sequelae [1••]. Snakebites predominantly affect young agricultural workers in socially and economically vulnerable settings, thus being a typical "disease of poverty" [2].

This article is part of the Topical Collection on *Amazonian Diseases in Isolate Populations*

✉ Hatem Kallel
Kallelhat@yahoo.fr

1 Intensive Care Unit, Martinique University Hospital, Fort-de-France, Martinique

2 Escola Superior de Ciências da Saúde, Universidade do Estado do Amazonas, Manaus, Amazonas, Brazil

3 Diretoria de Ensino e Pesquisa, Fundação de Medicina Tropical Dr. Heitor Vieira Dourado, Manaus, Amazonas, Brazil

4 Intensive Care Unit, Cayenne General Hospital, Cayenne, French Guiana

5 Emergency Department, Cayenne General Hospital, Cayenne, French Guiana

6 Diretoria de Ensino e Pesquisa, Fundação Alfredo da Matta, Manaus, Amazonas, Brazil

7 Instituto Clodomiro Picado, Facultad de Microbiología, Universidad de Costa Rica, San José, Costa Rica

In Latin America, a high incidence of snakebite envenomings occur in the Amazon basin, a large portion of South America drained by the Amazon river and its tributaries, which covers an area of more than 6 million km^2, being the largest tropical rainforest in the world. The Amazon basin includes territories of several countries, i.e., Bolivia, Brazil, Colombia, Ecuador, French Guiana, Guyana, Peru, Suriname, and Venezuela (Fig. 1).

Given its biodiversity, the Amazon harbors a rich fauna of venomous snakes. Hence, snakebite envenoming is a common occurrence and a relevant public health issue in this region of the world.

Snakebites are considered preventable injuries, and most of the envenomings result from a lack of preventive reflexes, notably including wearing individual protection devices, especially for workers engaging in rural activities. As the lower and upper limbs are the most frequently bitten body areas, the use of jackboots, leggings, and gloves are the major primary prevention measures. Some simple additional measures, such as keeping clean household surroundings and closing garbage, help in keeping away small rodents, which are part of the snakes' diet. In the Amazonian context, it is common for people to walk or perform agricultural duties barefoot, particularly in some indigenous communities, hence increasing the likelihood of snake bites. Community-based education campaigns for the most affected groups about safe habits is essential. There is no systematic program of interventions for prevention of snakebites as an occupational hazard in many regions of the Amazon.

The outcomes of snakebite envenomings are often influenced by cultural beliefs. Riverine, indigenous, and rural people often use devices such as tourniquets and even chemicals such as alcohol (ingested and applied to the bite) as an attempt to reduce the venom effects. Herbal extracts are also largely used in snakebites, especially where antivenoms are scarce or not available [3–5]. Puncture and suction at the site of the bite, in an attempt of remove the venom, are also common practices among patients. Most of these interventions are ineffective and, in some cases, harmful. Antivenom availability is poor in some regions of high snakebite incidence in the Amazon. In addition to the lack of skilled health professionals for the administration of antivenom, the lack of health care facilities in remote rural areas impairs the access to liquid antivenom because it requires a cold chain system for conservation. Such difficulties, often lead people to seek alternative therapies.

The present review summarizes the main aspects related to snakebite envenoming in the Amazon, including the description of the most common venomous snakes and the epidemiology, pathophysiology, clinical aspects, and treatment of envenomings. Recommendations for improving the management of snakebites in the region are also discussed.

Venomous Snakes in the Amazon

Due to its size and biodiversity, the Amazon region harbors many species of venomous snakes of the *Viperidae* and

Fig. 1 Map of the Amazon region

Elapidae families [6]. The vast majority of snakebites are inflicted by viperid species, and only less than 1% of cases correspond to bites by elapids, i.e., coral snakes of the genus *Micrurus* [7]. Viperid species in Amazon are classified in the genera *Bothrops*, *Bothrocophias*, *Crotalus*, and *Lachesis*. The most abundant species and the one that causes most accidents is *Bothrops atrox*. In addition, other species such as *B. brazili*, *B. bilineatus*, *B. taeniatus*, and *Botrocophias hyoprora* have a regional distribution. Moreover, subspecies of the rattlesnake *Crotalus durissus* and the subspecies of the bushmaster *Lachesis muta* also occur in various regions of the Amazon [6]. A study in Amazonian Ecuador identified *B. atrox* and *B. bilineatus* as the species causing the majority of bites, followed by *B. taeniatus*, *B. brazili*, and *L. muta* [8].

Bothrops atrox is the most important snake in the Amazonia, causing 80–90% of snake envenomings in the region [9]. This species is widely distributed in the Amazon and is the most abundant venomous snake in this region. The size of adult specimens ranges from 1 to 1.72 m. This species is present both in forested areas and in anthropized areas, such as pastures, crops, and urban areas. *B. atrox* is especially active during the night, when adults are often seen on the ground for hunting, while juveniles hunt on the vegetation (up to heights of 1.5 m). Regarding food preferences, this snake is a generalist, feeding on centipedes, fish, amphibians, lizards, other snakes, rodents, marsupials, and birds [10]. Juveniles prefer ectothermic animals (frogs, lizards, and centipedes) and adults prefer endothermic animals, mostly rodents, for food. As a viviparous species, this snake may give birth to between 11 and 43 offspring of 28–35 cm, found between December and February [11]. This snake is known by different common names according to the region (in Brazil, it is known as *jararaca*, *surucucu*, *surucucu-do-barranco*, *boca-podre*, and *comboia*; in Spanish-speaking countries, it is known as *grage*, *jergón*, *mapanare*, *mapaná*, and *equis*; in French, it is known as vipère, serpent, grage petits carreaux, …) [12, 13]. However, a possible confounding factor in snake identification by the local population exists since both *Bothrops atrox* and *Lachesis muta* receive the same popular name "*surucucu*" in certain Amazonian areas [9].

Epidemiology

Bolivia

Scarce information has been published on snakebites in Bolivia. A study based on health facilities records and community surveys has shown that around 700 bites are reported each year in Bolivia, with an annual incidence of eight bites per 100,000 people in the country. A significant inverse correlation was observed between snakebite incidence and altitude, i.e., the incidence is very low (< 1 snakebites/100,000 population) in the high mountain region, but exceeds 50 bites per 100,000 population in the Bolivian Amazon [14]. The annual case fatality rate estimated from community surveys is 0.4/100,000 population (40 deaths per year) [14]. The extrapolation of case fatality rate from household survey data lacks precision and reliability, but the country official surveillance system information on mortality has only been partial by [15]. Snakebites' official surveillance began in 1996, was interrupted between 2001 and 2009, and reinstated after 2010 [15].

Brazil

In Brazil, 28,842 cases of snakebites were reported in 2018, of which 9523 occurred in the Amazon region. These data show an unequal distribution of the problem across the country, as despite having a population of only 8.7% of the country's total, 33% of snakebite cases occurred in the Amazon region, which amounts to incidence rates that are five times higher than in the rest of the country [16]. It is noteworthy that the incidence of snakebites has been increasing since 2000, and this increment is more evident in the Amazon. In this region, snakebites appear among the most important type of envenoming by animal bites or stings, with the highest incidence (52.6/100,000 population per year). In the northern states of Roraima, Eastern Pará, and Amapá, incidences higher than 100 cases per 100,000 population have been reported [17]. These increments in snakebite incidences are associated with the rainy season. In conditions of heavy rainfall, snakes tend to seek for drier shelters, generally closer to human settlements in rural areas. In addition, urban expansion along with deforestation causes a major impact on the natural habitat of these animals, exerting pressure for animal migration and consequently increasing the likelihood of encounters between humans and snakes [18–20].

In the Brazilian Amazona, victims of snakebite are predominantly men, of working age, rural residents, riverine, and indigenous. Snakebite is an occupational hazard in this region, because many of these people work in agriculture, hunting, and forest activities, as in the case of rubber tappers [17, 21–23]. A study conducted with indigenous and riverine populations showed that 13% of them had experienced snakebites during their lifetime [21]. The Amazon region has a low coverage of highways and roads, with much of the human displacement taking place through river transportation, leading to delays in accessing medical care. Time delays of more than 6 h to reach healthcare facilities have been associated with poor outcomes in terms of severity and mortality. Other risk factors associated with poor outcomes are older age and bites related to work activities [17].

Colombia

Only a few studies about the epidemiology of snakebites have been reported in Colombia. The first evidence found of snakebites as a major health problem in the country dates from the 60s, when Marinkelle (1966) described 71 deaths caused by *B. atrox* envenomings during 1962–1966, and highlighted that few of the victims went to hospital [24]. Later on, significant morbidity and mortality from snakebites was described in the Amazonian and Orinocan regions of Colombia [25]. From 2006 to 2010, snakebites were the most frequent envenomings reported by toxicology centers from all over Colombia (47%) [26]. Data from the official reporting system, available online since 2009, shows a mean annual number of snakebites of around 4150 (8.5/100,000 population), resulting in about 35 deaths (0.8%; 0.08/100,000 population). It is of note that incidence was higher in the Amazonian departments [15].

Ecuador

In Amerindian communities, annual incidence and mortality from snakebites were estimated in 1500 and 130 per 100,000 population, respectively [27, 28]. A study of 142 patients in the Province of Morona Santiago reported a case fatality rate of 2.9% [29]. A high rate of mortality was also observed among 294 hospitalized snakebite patients in Eastern Ecuador (5.4%) [30]. Despite the low human population density, national health statistics show that the annual incidence in the Amazon region exceeds 120 envenomings per 100,000 population, almost ten times more than in the highly populated coastal area [31]. In Ecuador, the most affected population is represented mainly by males aged 10–54 years and cases are more often recorded in the rainy season, from January to April, when snakebite incidence is twice as high as in the dry season [31]. The case fatality rate from snakebites was estimated at 0.6% (mortality rate: 0.05/100,000 population), thus indicating that mortality is low in Ecuador, which can be explained either by good management of the envenomings or, conversely, the underreporting of fatalities, particularly in the Amazonian region, where health facilities are scarce [31]. Even with the possibility of underreporting, incidence and mortality were higher in the Ecuadorian Amazon than in other regions of the country [31].

French Guiana

Since case notification of snakebites is not mandatory in French Guiana, no territory-level statistics are available [32•]. Of the 283 snakebite envenomings attended in the Cayenne Hospital from 2007 to 2015, 43 (15.8%) were severe, and four resulted in death (1.4%) [32•]. This case fatality rate is among the highest in Latin America, just after Panama, Bolivia, and Guyana. However, these figures could be underestimations because snakebite numbers remain imprecise due to a large population of gold miners with irregular migratory status, living in the Amazonian forest, some of whom may have died from snakebites without medical assistance [32•].

Guyana

According to statistics released by the Public Health Ministry of Guyana, in the years 2010–2014, a total of 1190 persons (32 cases/100,000 population) were victims of snakebites, of which 95 proved fatal (8% case fatality rate), with a high predominance of men in the age of 30–40 years [33]. This high fatality rate is explained by the absence of antivenoms until recently. Since there is no compulsory notification of snakebites at the national level, the statistics are based on the information of Georgetown's reference hospital. However, snakebites in the Amazon region are certainly greatly underestimated, partly because it was likely that few patients attend the health facilities and, on the other hand, because of the near nonexistent evacuation possibilities to Georgetown [15].

Peru

Scarce information about snakebites has been reported in Peru. Chippaux described that, between 2000 and 2015, on average, 2150 snakebites occurred each year in this country (7.2/100,000 population), resulting in about 10 deaths (0.043/100,000 population) [15]. The departments with the highest incidences (> 50/100,000 population) were Loreto and Ucayali, in the Amazon region, while the incidences in the coastal region and the south of the country were lower.

Suriname

No information on the burden of snakebites in Suriname was found in the literature. Notification of snakebites is not mandatory in the country, and estimates obtained from the neighboring territory of French Guiana are taken as approximations for Suriname: an incidence of 25 snakebites/100,000 population and a mortality rate of 0.9/100,000 population [15]. It is likely that the majority of these cases occur in the Amazon region of the country.

Venezuela

In Venezuela, during the years of 1996–2004, a total of 53,792 snakebites were reported by the Ministry of Health and Social Development (5976 cases average per year; 24.5 cases/100,000 population/year) [34]. The state of Amazonas presented the highest annual median incidence, with 70.9 cases/100,000 population. Nevertheless, the incidence was likely to be underestimated, as compared to data from the Amazon region in other neighboring countries, which could be due to limitations of the case reporting system [15]. Epidemiological data from the Ministry of Health show that there were 266 reports of death due to snakebite between 1995 and 2002 (33 per year), mostly males (79.7%). The mortality rate by age showed an age-dependence, with higher rates in older age groups [35].

Pathology and Pathophysiology of Envenomings

Proteomic studies of *Bothrops* snake venoms indicate that the predominant components playing a role in toxicity are zinc-dependent metalloproteinases, phospholipases A_2, and serine proteinases. In addition, other components include vasoactive peptides, disintegrins, L-amino acid oxidases, cysteine-rich secretory proteins (CRISPs), and C-type lectin-like components [36]. There are important regional differences in the composition of the venoms of *B. atrox* along the Amazon, which are likely to have implications in the pathophysiology and clinical manifestations of envenomings [36–38].

Local Effects

Bothrops sp. venoms induce prominent local tissue damage, characterized by hemorrhage, myonecrosis, dermonecrosis, and blistering, in addition to a pronounced edema [39]. Hemorrhage occurs as a consequence of the action of zinc-dependent metalloproteinases on the integrity of the microvasculature. Specifically, these proteinases are able to cleave proteins of the basement membrane, particularly type IV collagen, thereby weakening of the mechanical stability of the capillary wall, followed by its disruption leading to bleeding [40]. Metalloproteinases are also responsible for the degradation of the dermal-epidermal interface, with the formation of blisters [39]. P-I and P-III metalloproteinases causing hemorrhage and dermonecrosis have been characterized from *B. atrox* venom [41, 42]. Myonecrosis is the consequence of the direct damage of the muscle fibers by the action of myotoxic phospholipases A_2 and phospholipase A_2-homologs. These toxins disrupt the integrity of the plasma membrane, leading to irreversible cell damage [39]. In addition, the vascular alterations described cause tissue ischemia, which contributes to muscle necrosis. Edema, in turn, occurs as a consequence of the action of a wide variety of inflammatory mediators, which are released or synthesized in the tissues upon the onset of venom-induced issue damage. Some of these endogenous mediators are also responsible for the excruciating local pain that characterizes these envenomings [43]. Inflammatory mediators released as a consequence of venom-induced tissue damage may play a role in the overall local tissue pathology [44].

Systemic Effects

In addition to local tissue damage, *Bothrops* sp. venoms induce systemic pathophysiological alterations whose main manifestations are systemic bleeding, coagulopathies, hemodynamic alterations, and acute kidney injury [45]. Hemorrhage is the consequence of the action of venom metalloproteinases in the systemic microvasculature. In addition, venom-induced consumption coagulopathy results from the action of coagulant venom metalloproteinases and serine proteinases, as well as from toxins that induce thrombocytopenia [46]. Procoagulant enzymes induce the formation of microclots and the consumption of clotting factors, resulting in alterations in blood clotting tests and defibrinogenation. These effects, added to the action of other venom toxins on platelets, contribute to the systemic bleeding initiated by the metalloproteinases [45, 46]. Envenomings by neonate *B. atrox* specimens are more likely to induce coagulopathies than bites by adult specimens [47]. When extensive, bleeding, together with systemic increments in vascular permeability, causes hypovolemia and hemodynamic disturbances that may end up in cardiovascular shock and multisystem organ failure. *Bothrops* sp venoms also cause acute kidney injury, a phenomenon of multifactorial origin resulting from the combination of renal ischemia, direct nephrotoxic action of toxins, formation of microclots in the renal vasculature, and deposition of myoglobin and hemoglobin in the renal tubules [45].

Clinical Manifestations

Bothrops envenoming occurs in most cases among young and healthy persons, predominantly in rural settings, but also in urban contexts. Bites occur predominantly on the feet (70–75%) and hands (20–25%) and result in a syndrome involving local effects and systemic manifestations. Unclottable blood is the most common hemostatic disorder followed by systemic bleeding. Local effects vary from local pain to edema, blistering, hemorrhage, and myonecrosis. Systemic manifestations including bleeding, circulatory shock, and renal failure, which have been strongly associated with fatal *Bothrops* snakebites [32•, 48•]. According to clinical manifestations, three grades of envenoming are reported to classify patients and the severity of envenomation (I: mild, II: moderate, III: severe) (Table 1) [48•]. Table 2 summarizes the main clinical signs recorded after *Bothrops* sp. snakebites in various studies. This pattern of clinical manifestations is common to the majority of *Bothrops* sp. envenomings, although the severity varies. *B. atrox*, which can inject a large volume of venom, is more prone to inflict severe bites than minor species.

Local Manifestations

Bothrops venom-induced local complications include pain, edema, erythema, local hemorrhage, and blistering [46, 49–51] (Fig. 2). Additionally, severe local complications may be observed including necrosis, secondary infection, and compartment syndrome [52–54].

After bites by *Bothrops*, local swelling is usually detectable within 2–4 h and can extend rapidly to peak on the second or third day. Blistering appears within 2–12 h, and tissue necrosis becomes obvious within 1 day of the bite. Sloughing of necrotic tissue and secondary infections, including osteomyelitis

Table 1 Classification of the clinical signs and symptoms of *Bothrops* snakebites [48•, 78]

		Grade		
		I (mild)	II (moderate)	III (Severe)
Local signs	Pain	+	+	+
	Swelling	Not exceeding elbow or knee	Exceeding elbow or knee	Beyond the root of the limb
	Blister	–	+	+
	Necrosis	–	–	+
Coagulation disorder (WBCT20 or other coagulation laboratory tests)		+ or −	+	+
Local or systemic bleeding		–	+	+
Other systemic manifestations Hemodynamic alterations, acute kidney injury, disseminated intravascular coagulation, multisystemic failure		–	–	+

WBCT20 20-min whole blood clotting test

(infection of underlying bone), develop during subsequent weeks or month [52]. Compartmental syndrome in *Bothrops* snakebite envenomings is rare, usually occurring early after the snakebite [52–54]. It may result in necrosis of muscle mass

Table 2 Clinical manifestations recorded after *Bothrops sp* snakebite in the Amazon region (expressed as percentage of cases)

Author	de Oliveira et al.	Roriz et al.	Mutricy et al.	Alves et al.	Personal data
Reference	[46]	[49]	[51]	[50]	Unpublished
Region	Manaus	Western Amazon	French Guiana	Western Amazon	French Guiana
Year	2016–2017	2008–2010	2007–2015	2014–2016	2016–2018
No. of cases	100	92	273	186	94
Clinical severity of envenomation					
Mild	27	23.9	–	43	47.9
Moderate	59	26.1	–	49	25.5
Severe	14	50	–	8.1	26.6
Local manifestations					
Swelling/edema	99	97.8	23.1	100	97.9
Pain	97	94.6	–	86	98.9
Bleeding from fang punctures	45	66.3	–	46.8	8.5
Ecchymosis	20	–	–	–	3.2
Blistering	4	12	8.1	–	13.8
Necrosis	1	–	4.8	4.8	11.7
Systemic alterations related to hemostasis					
Unclottable blood	54	–	–	66.1	100
Thrombocytopenia[a]	10	–	15.4	–	37.2
Renal injury	–	10.9	7	12.9	16
Dialysis	–	–	2.6	2.2	8.5
Systemic bleeding	20	–	–	–	18.1
Any systemic bleeding	14	–	–	8.6	1.1
Gingival	9	–	–	8.6	6.4
Macrohematuria	7	33.7	–	31.7	2.1
Hematemesis	3	–	–	–	2.1
Hemoptysis	2	–	–	–	3.2
Conjunctival	1	–	–	–	2.1

[a] Thrombocytopenia: platelet count < 150 G/L

Fig. 2 Local manifestations of *Bothrops* snakebites. **a** A 65-year-old male patient, hospitalized 6 h after bite, presenting edema in the right whole hand. **b** A 43-year-old male patient, hospitalized 2 h after bite, presenting edema in the right whole hand and bleeding from fang marks. **c** A 13-year-old female patient, hospitalized 7 h after bite, presenting mild edema and ecchymosis around punctures in the internal side of the left foot. **d** A 50-year-old male patient, hospitalized 6 h after bite, with blisters of bloody content in the back of the left foot. **e** A 24-year-old female patient, hospitalized 14 h after bite, presenting moderate edema and necrosis of the second and third toes of the right foot, 4 days post-admission. **f** A 43-year-old male patient, hospitalized 1 h after bite, presenting edema and blisters of serosanguinolent content in the perilesional region in the middle finger of the right hand. **g** A 38-year-old male patient, hospitalized 10 h after bite, presenting edema and blisters of bloody content in the internal side of the right foot, and blisters of purulent content in the right calf. **h** A 55-year-old male patient, hospitalized 13 h after bite, presenting extensive area of cellulitis from secondary bacterial infection 6 days post-admission. **i** A 40-year-old male patient, hospitalized 8 h after bite, presenting an abscess with sero-purulent content in the internal ankle region of the right foot, being aspirated, 7 days after bite. **j** A 31-year-old female patient, 10 days after hospital admission, with severe *Bothrops* bite in the right hand, presenting extensive necrosis and secondary bacterial infection with culture positive for *Morganella morganii.* **k** Same previous case, after wound surgical debridement. **l** A 34-year-old male patient, hospitalized 10 h after bite, presenting compartment syndrome, after fasciotomy suture

as well as neuropathy and may lead to amputation if not dealt with. Diagnosis is difficult and based on the clinical findings and the measurement of increased intra-compartmental pressure, which helps to determine whether fasciotomy is indicated [52–54].

Systemic Manifestations

Coagulopathy and bleeding (Fig. 3) develop within a few hours after *Bothrops* snakebite and can persist for 3 to 4 days in untreated patients. Hemodynamic shock can develop secondary to hypovolemia. Renal injury is an infrequent complication of bothropic syndrome. It can lead to renal failure needing dialysis in some cases.

The mechanism of coagulopathy has been widely explored in the literature [45]. Indeed, hypofibrinogenemia is a major systemic complication from *Bothrops* snakebites, affecting more than 80% of the patients [55]. This condition results from the action of serine proteinases having thrombin-like activity, which converts fibrinogen to fibrin, and also to the procoagulant activity of metalloproteinases, which activate factors II and X of the coagulation cascade, resulting in the formation of endogenous thrombin [56]. The action of these venom enzymes causes a consumption coagulopathy.

Coagulopathy is very well established using the 20-min whole blood clotting test (WBCT20) [47, 48•, 57]. The WBCT20 is a bedside, simple, and fast test which has been used for victims of snakebites to determine whether they have a significant coagulopathy [47, 48•, 57]. It can also be used to assess the efficiency of antivenom on coagulopathy [58]. The incoagulability of the blood generally indicates a marked fibrinogen deficiency, with a close relationship between the results of the WBCT20 and the corresponding plasma fibrinogen concentrations. Other laboratory tests, such as prothrombin time and partial thromboplastin time, are also used to monitor clotting alterations. In addition, *Bothrops* sp. venoms induce thrombocytopenia [46] and platelet hypoaggregation.

Systemic Bleeding

Systemic bleeding is one of the hallmarks of the *Bothrops* envenomation, with unclottable blood and thrombocytopenia as its associated major risk factors [46]. It commonly arises in case of microvascular damage by proteolytic degradation of

Fig. 3 Systemic bleeding in *Bothrops* snakebites. **a** A 22-year-old male patient, hospitalized 10 h after bite, presenting bilateral conjunctival hemorrhage, more intense on the left side. **b** Urine of a 59-year-old male patient, hospitalized 7.5 h after bite, presenting macro-hematuria. The same patient also presented gingival bleeding and hemoptysis. **c** A 31-year-old male patient, hospitalized 3.5 h after bite, presenting extensive area of ecchymosis along the whole left lower limb. Fang marks were observed in the leg. **d** A 27-year-old male patient, hospitalized 2 h after bite, presenting gingival bleeding and hemoptysis. **e** Bloody sputum of the same previous patient

basement membrane [41]. The involved enzymes are PI and P-III snake venom metalloproteinases (examples are batroxase [59], Atroxlysin-Ia [60], and Batroxrhagin [42]). Systemic bleeding observed in *Bothrops* snakebites was reported in 3.6–15.3% of patients [55, 61]. It includes gingival bleeding, subconjunctival hemorrhage, hematuria and, in severe cases, cerebral hemorrhage. Unclottable blood and thrombocytopenia on admission were independently associated with systemic bleeding during hospitalization [46].

Acute Kidney Injury

Renal injury following *Bothrops* bite is reported in 7–16% of cases [50, 51]. Its severity varies from biological renal impairment to anuric renal failure requiring dialysis (2–8% of cases) [50, 51]. Renal injury following *Bothrops* bite can be explained by (a) the action of nephrotoxic components of the venom, (b) the ischemia resulting in the kidneys from hemodynamic failure, (c) the toxicity induced by the precipitation of hemoglobin and myoglobin in the kidney tubules, (d) the action of metalloproteinases in the basement membrane of the glomeruli, and (e) thrombotic microangiopathy [1••, 62, 63].

Hemodynamic Shock

Early-onset hemodynamic shock following snakebite in the Amazonian region can be explained by hypovolemia secondary to intravascular fluid loss (which moves to the interstitial space because of extensive edema), or to hemorrhagic syndrome because of coagulopathy and vascular wall alterations. It can also be explained by the importance of vasoplegia secondary to the inflammatory reaction induced by the venom. Late-onset hemodynamic shock is of septic origin in most cases [52].

Management

The management of snakebite envenomings in the Amazonia is often complicated by the difficulties people have to reach health facilities, especially in remote regions inhabited by indigenous communities. In addition, the lack of public health posts in many of these regions, as well as the lack of antivenoms in some areas, further complicates the timely management of envenoming cases [64]. Delays in the access to medical care are directly associated with poor outcomes in these envenomings [17]. Depending on the country, the availability and accessibility of antivenoms is highly variable, as well as the cold chain conditions to keep liquid antivenoms. All these circumstances constitute significant challenges for public health authorities in the region [65, 66].

Upon admission of patients at health facilities, complete clinical examination as well as laboratory tests needs to be carried out. Examination begins with an assessment of the airway, breathing, and circulation (ABCs). Airway patency and security are evaluated first. Once the airway is secured, ventilation is assessed, and circulation and end-organ perfusion are evaluated. A detailed account of the signs and symptoms of each case is required in order to determine whether the patient is envenomed and the degree of severity, as well as to identify the type of envenoming (bothropic, crotalic, elapid) and to select the appropriate antivenom.

Antivenom Therapy

Several antivenom manufacturing laboratories exist in Central and South America which produce antivenoms effective in the treatment of envenomings by viperid snakes of the Amazon region. These include bothropic, crotalic, lachetic, bothropic-crotalic, bothropic-lachetic, and bothropic-crotalic-lachetic antivenoms. Some of these antivenoms are made of $F(ab')_2$ antibody fragments, whereas others consist of whole IgG molecules (see details in Fan et al. [66]). Preclinical studies underscore the efficacy of various antivenoms, produced using different mixtures of viperid venoms, for neutralizing the venoms of *B. atrox* and of other Amazonian species [67, 68]. Moreover, the efficacy of the bothropic and bothropic-lachetic Brazilian antivenoms, as well as other bothropic and polyvalent antivenoms manufactured in Ecuador and Colombia, has been demonstrated in clinical trials in envenomings by *B. atrox* in the Amazon region [8, 47, 61]. However, in the Amazon, the availability of antivenom is limited to some areas due to problems with distribution, causing patients to travel long distances to receive antivenom treatment [66]. Access to health centers in a relatively short time, and availability of referral hospitals or appropriate medical centers, is not always achieved [64, 69]. In addition, there are differences between countries in terms of availability of antivenoms and access to medical care in the Amazon. Studies are needed in the region to check for differences in side effects, good manufacturing practices, and potential of scaling up production.

Mode of Administration

For optimal efficacy of treatment, administering antivenom must begin early, within 6 h following the onset of envenoming. If administered early enough, antivenoms have proven highly effective in the control of systemic envenoming [69]. Continuous and optimal monitoring of blood pressure and heart rate should be started immediately. Methods of administration need to be optimized, especially in the most vulnerable groups: elderly, children, and pregnant women. Antivenoms are administered intravenously, diluted in saline solution. The volume of antivenom administered depends on the type of antivenom, as the neutralizing potencies vary between products. The antivenom dose should be adjusted to the severity of envenoming.

Adverse Effects to Antivenom Administration

A percentage of patients receiving antivenom develop early adverse reactions (EARs). These usually appear within the first hour of antivenom infusion and can be mild, i.e., characterized by cutaneous manifestations only (urticaria, pruritus), or severe, i.e., characterized by systemic manifestations such as bronchospasm, hypotension, tachycardia, and shock. Most of these reactions are non-IgE mediated. They are treated with subcutaneous adrenaline and intravenous anti-histamines and steroids. Some patients develop late adverse reactions 1 to 2 weeks after antivenom administration. This corresponds to serum sickness, characterized by urticaria, pruritus, arthralgia, and fever, and is treated with corticosteroids. In the Brazilian Amazon, early adverse events after AV therapy were observed in 19.8% of the patients. The most common were urticaria (13.8%), pruritus (11.2%), facial flushing (3.4%), and vomiting (3.4%). All adverse events were mild, and all signs and symptoms of early adverse reactions ceased within 48 h from management [70].

Adjuvant Treatments

Essential adjuvant treatments include different therapeutic classes. First of all, treatment with level 2 or even 3 analgesics must be quickly initiated. Pain monitoring is done using the visual analog scale, the aim being to achieve a score less than 3 (VAS < 30). Verification of the immune status against tetanus and administration of tetanus toxoid, if necessary, should be carried out. All patients whose vaccinations are not up to date should therefore receive their boosters as well as a dose of tetanus antitoxin.

Antibiotics

Preemptive antibiotic administration in snake-bite patients should be considered only in those with severe local signs of envenomation, and in those having local or general signs of infection, regardless of the degree of envenoming [71]. The most appropriate antibiotics to be provided on an empirical basis are third-generation cephalosporins. Empirical amoxicillin-clavulanate should no longer be used in this context [71, 72]. These recommendations follow bacteriological studies of the oral microbiota as well as the wound of patients envenomed by *Bothrops* snakes [73, 74]. The latter revealed the recurrent presence of the following bacteria: *Aeromonas hydrophila*, *Morganella morganii*, *Klebsiella pneumoniae*, *Bacillus* spp., and *Proteus mirabilis* [73].

Debridement of Necrotic Tissue and Fasciotomy

Necrotic tissue should be debrided under general anesthesia, and abscesses have to be drained. Fasciotomy is indicated as an emergency measure; surgical opinion for discharge aponeurotomy is recommended in case of compartmental syndrome secondary to compressive edema [75]. There is a need to perform proper investigations and comprehensive serial examination of the patient using whatever modalities may be available at the treatment facility, in order to avoid the unnecessary and commonly disabling effects and further complications of fasciotomy [54].

Other Therapeutic Interventions

In case of hypovolemia resulting from systemic hemorrhage and increments in vascular permeability, the administration of plasma expanders and fluid replacement must be considered, taking care of volemia monitoring (central venous pressure, echocardiography) in order to avoid a fluid overload. When shock develops, adequate fluid resuscitation and inotropic drugs are used to restore cardiac output, systemic blood pressure, and renal perfusion. In case of acute kidney injury, characterized by increment in serum creatinine concentration and drop in urine output, administration of isotonic saline or a diuretic has to be considered. In more complicated cases, dialysis is required.

Prognosis

The prognosis of snakebite cases in the Amazon is directly related to the time needed to reach medical attention. Likewise, other factors associated with severe cases are older age and belonging to indigenous communities, because of the usual remoteness of these populations and the lack of rapid transportation to reach health facilities [76]. In addition, the prognosis of cases is related to the volume of venom injected by the snake, the anatomical site of the bite (bites in head and trunk tend to be more complicated), and the presence of patient co-morbidities. Clinical manifestations of *Bothrops* envenoming may completely resolve in 3 to 10 days or may progress to local and systemic complications or death in some cases [15, 32•]. Complications include local or systemic infection, acute kidney injury, cerebrovascular accident, and extensive necrosis requiring amputation in some cases and leading to permanent functional loss [1••, 52]. Physical and psychological sequelae secondary to these complications represent a significant burden, which demands more attention from health authorities and civil society organizations. The mortality rate resulting from *Bothrops* snakebites in the Amazon region vary from 0.032 to 0.274 deaths/100,000 population/year [32•].

Concluding Remarks

Snakebites constitute a relevant public health problem in the Amazon region. This neglected tropical disease is complicated in this region of South America by a combination of factors: (a) the abundance of *B. atrox*, a snake which can inject a large volume of venom and therefore inflict severe envenomings; (b) the difficulties in transportation in many regions, resulting in delays to reach health facilities; (c) the existence of human groups, particularly indigenous communities, located in regions far away from medical facilities, and sometimes cultural beliefs and practices that interfere with medical treatment; (d) the scarcity of public health posts in some of these regions; (e) the difficulties, in some countries, to provide antivenoms to these regions, including a poor cold chain infrastructure in some cases; and (f) the deficit in the number of health professionals that can attend remote regions in the Amazonia. The relative weight of each of these issues varies between countries and between regions in a country, making this a complex public health problem that requires an integrated attention by the health systems and the communities alike.

The fact that the Amazon comprises regions of several countries, sharing similar ecological features and snake species, particularly *B. atrox*, calls for coordinated international efforts at the public health level. This would facilitate the standardization of effective and coordinated intervention policies with the aim of providing rapid medical attention to people suffering snakebite envenoming. This includes the strengthening of public health systems; the provision of antivenoms to urban centers, as well as in remote health posts in the Amazon; the permanent training of health staff in the correct management of these envenomings; and the development of prevention campaigns at the community level, with the commitment of local organizations of the civil society. The concerted distribution of antivenoms between countries in the Amazon, under the coordination of the Pan American Health Organization (PAHO) and the ministries of health, is an aspect that should be improved. Likewise, there is a need to develop regional international workshops to exchange experiences and to draft protocols for prevention, diagnosis, and treatment of envenomings, under an interdisciplinary perspective. Such an integrated approach is aligned with the WHO strategy to prevent and control snakebite envenomings [77], and with the concerted participation of the health authorities of Bolivia, Brazil, Colombia, Ecuador, French Guiana, Guyana, Peru, Suriname, and Venezuela. This endeavor would be an example of international cooperation which could provide impetus for similar efforts in other regions of the world.

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