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Review

Perspectives and recommendations towards evidence-based health care for scorpion sting envenoming in the Brazilian Amazon: A comprehensive review

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A R T I C L E I N F O

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A B S T R A C T

Although underreported across the Amazon region, scorpion stings are very prevalent in some areas and can be potentially life-threatening, especially in children. The most vulnerable populations are those living in locations far from the capitals, hence having limited access to the health system where the appropriate structure for the treatment of severe cases is found. An abundant and diverse fauna of scorpions is found in the region, but few studies have been conducted to decipher the clinical characteristics and therapeutic response of the available antivenoms in envenomings caused by the various species. Antivenom underdosage as well as delayed medical assistance are common among indigenous populations, resulting in poor outcome rates. An in depth understanding of the epidemiological, clinical and therapeutic aspects of scorpion sting envenomings in the Amazon is necessary to improve the outcome of these cases.

1. Introduction

Approximately two billion people live in risk areas for scorpion envenoming with annual estimates reaching over a million cases worldwide (Chippaux and Goyffon, 2008). These occur predominantly in countries with tropical and subtropical climates (Dabo et al., 2011), especially in the warmer season (Chowell et al., 2006; Hui Wen et al., 2015). Developing countries from Africa, the Middle East region, Southern India, Mexico, Brazil and other Latin American countries within the Amazon region present the highest prevalence of severe cases. In Brazil, scorpion stings are an emerging and neglected public health problem, with an increasing number of cases being reported yearly. A total of 124,077 cases were reported in 2017, which represents an incidence of 59.7 cases/100,000 inhabitants (Ministério da Saúde/ SVS, 2019).

Most medically important scorpion species in South America belong to the buthid genus *Tityus* (Borges and Graham, 2016). This genus comprises the most diverse group of scorpions in South America (Wil-son R. Lourenço, 2002a, 2002b). In Brazil, the main species of med-ical interest belongs to the genus *Tityus*, which, in addition to their dis-tribution in natural habitats, has a high adaptive capacity to colonize anthropic environments (Ministério da Saúde do Brasil- Fundação Nacional de Saúde (FUNASA), 2001). In the Brazilian Amazon, tax-onomical and distribution information is available for four subgenera

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comprising 27 *Tityus* species (Limeira-de-Oliveira et al., 2006; Lourenço, 2017, 1981a; 1979; Lourenço et al., 2005; W R Lourenço, 2002c; Lourenço, 2008, 2006; 2005, 1997; 1988, 1986; 1984, 1981b; Lourenço and Leguin, 2008; Lourenço and Pézier, 2002; Lourenço and Ramos, 2004; Lourenço and Silva, 2007; Mello-Leitão, 1945; Pinto-da-Rocha and Lourenço, 2000) (Table 1). Outside the Amazon region, *T. bahiensis*, *T. serrulatus* and probably *T. costatus* and *T. stigmurus* are the major causative agents of scorpion stings, resulting in high severity and lethality rates (Lourenço, 2015; Ministério da Saúde do Brasil- Fundação Nacional de Saúde (FU-NASA), 2001).

The clinical presentation of scorpion stings may vary from mild lo-cal symptomology as pain, paresthesia, mild edema, erythema, sweat-ing, piloerection and burning sensation to severe systemic neurotoxicity, which may lead to autonomous nervous system imbalance, further caus-ing uncoordinated neuromuscular activity, myocardial depression, respi-ratory failure and multiorgan failure (Isbister and Bawaskar, 2014).

The effects caused by scorpion stings do not have a typical charac-teristic that discriminates them from injuries caused by other arthropods and *vice versa*. Envenoming diagnosis may be very inaccurate, especially in cases presenting no systemic signs. This fact can lead even to the un-necessary use of antivenom in the case of assistance to be carried out by an inattentive professional.

Clinical manifestations related to local envenoming should be treated with parenteral analgesic agents and anesthetic nerve block to relief local pain. Supportive intensive care treatment for autonomic distur-bances, acute pulmonary edema and cardiogenic shock often includes the use of inotropes and vasodilators (Isbister and Bawaskar, 2014). On the other hand, the evidence for the effectiveness of antivenom treat-ment recommended for scorpion envenoming is variable, and the fre-quency of antivenom use, as well as antivenom dosage, varies according to the species causing the sting, the availability of the product, and the clinical effects of envenoming.

An uncertain scenario regarding the epidemiology, main causative species, clinical presentations and proper access diagnosis and treatment access turns scorpion sting into a major public health problem in many countries from Latin America since there is a shortage of studies on the subject, especially in the Amazon region. Therefore, in order to syn-thetise the current knowledge regarding scorpion sting in the Amazon region, we comprehensively reviewed the literature of scorpion sting in the Brazilian Amazon region. We further provide recommendations to confront pending issues, such as incomplete epidemiological and clinical information, limitations in the access to effective treatment, lack of diag-nostic and therapeutic guidelines adapted to the local contexts, and lim-ited preclinical and clinical knowledge on the efficacy of existing scor-pion antivenoms against venoms from Amazonian species. The follow-ing sections outline these aspects.

2. Estimating scorpion stings burden in the Amazon region

In the Amazon Region, a pattern of increased incidence is notable from 2000 to 2017, especially in the states of Pará, Tocantins, Maranhão and Mato Grosso (Fig. 1). Scorpion stings were found to be unevenly distributed in the Brazilian Amazon, ranging from 9.2 to 200 cases/ 100,000 habitants in certain areas (Figs. 2 and 3) (Ministério da Saúde/SVS, 2019).

Scorpion stings represent a potential occupational health problem for rural populations (Queiroz et al., 2015). Cases were found to oc-cur predominantly in males (63.9%), living in rural areas (56.6%), be-ing classified as work-related accidents in almost half the cases (38.7%). The most common occupational group was farmer/fishermen (72.4%), and the most affected age group was 21–30 years old (19.7%). Stings occurred mostly in the upper (47.9%) and lower limbs (46.5%),

Table 1
Tityus scorpions recorded in the Brazilian Amazon.

Species	Distribution	Study Reference	Incriminated in human envenomings
Tityus (Archaeotityus) subgenus			
Tityus bastosi Lourenço (1984)	Western Brazilian Amazon region, reaching Peru, Equador and Colombia	Lourenço (1984)	Yes
Tityus clathratus Koch, 1844	Roraima state. Guyana Shield and Venezuela.	Lourenço (1984)	No
Tityus maranhensis Lourenço, Jesus-Júnior & Oliveira, 2006	Caxias, state of Maranhão.	Limeira- de-Oliveira et al. (2006)	No
Tityus mattogrossensis Borelli, 1901	Open areas of Mato Grosso and other areas of Central Brazil.	Lourenço (1979)	No
Tityus silvestris Pocock, 1897	From the French Guyana and Amapá and Pará states to the Peruvian Amazon. Most of the area of Amazonas.	Lourenço (1986)	Yes
Tityus (Tityus) subgenus			
Tityus canopensis Lourenço and Pézier (2002)	Tarumã Mirim, Manaus, state of Amazonas.	Lourenço and Pézier (2002)	No
Tityus carvalhoi Mello-Leitão (1945)	Pará. Barra do Tapirapés. Eastern Mato Grosso.	Mello-Leitão (1945)	No
Tityus gasci Lourenço, 1981a,b	French Guiana. Amazon Basin in Brasil and Peru.	Lourenço (1981a)	No
Tityus marajoensis Lourenço and Silva (2007)	Marajó Island, state of Pará.	Lourenço and Silva (2007)	No
Tityus nelsoni Lourenço (2005)	São Gabriel da Cachoeira, state of Amazonas.	Lourenço (2005)	No
Tityus raquelae Lourenço (1988)	Rio Preto da Eva, Itacoatiara and Tefé, state of Aamzonas.	Lourenço (1988)	No
Tityus strandi Werner, 1939	Amazonas and Pará states, along the Solimões and Amazonas rivers.	Lourenço (1981b)	No
Tityus sylviae Lourenço (2005)	PNJ Seringalzinho, state of Amazonas.	Lourenço (2005)	No
Tityus thelyacanthus Mello-Leitão, 1933	Tocantins. Ilha do Bananal. Goiás and Mato Grosso.	Mello-Leitão (1945)	No
Tityus (Atreus) subgenus			
Tityus apiacas Lourenço (2002c)	Northern Mato Grosso. Rondonia. Southern Amazonas.	(W R Lourenço, 2002c)	Yes
Tityus dinizi Lourenço (1997)	Rio Negro-Anavilhanas, state of Amazonas.	Lourenço (1997)	No
Tityus elizabethae Lourenço and Ramos (2004)	Pacaraima, state of Roraima.	Lourenço and Ramos (2004)	No
Tityus generaltheophiloi Lourenço (2017)	Roraima. Serra da Mocidade National Park.	Lourenço (2017)	No

Table 1 (*Continued*)

Species	Distribution	Study Reference	Incriminated in human envenomings
Tityus matthieseni Rocha & Lourenço, 2000	Amazonas and Roraima.	Pinto-da-Rocha and Lourenço (2000)	Yes
Tityus metuendus Pocock, 1897	Most of the area of Amazonas and Roraima states. Areas of Pará, Amapá and Acre states. Peruvian Amazon.	Lourenço (1988)	Yes
Tityus neblina Lourenço (2008)	Amazonas. Neblina Peak, Venezuelan border.	Lourenço (2008)	No
Tityus obscurus Pocock, 1897	Large area of the Pará and Amapá states. French Guyana. Suriname.	Lourenço and Leguin (2008)	Yes
Tityus tucurui Lourenço (1988)	Pará. Eastern state.	(W R Lourenço, 2002c)	No
Tityus unus Rocha & Lourenço, 2000	Santa Isabel do Rio Negro, state of Amazonas.	Pinto-da-Rocha and Lourenço (2000)	No
Tityus (Brazilotityus) subgenus			
Tityus adisi Lourenço and Pézier (2002)	Tarumã Mirim, Manaus, state of Amazonas.	Lourenço and Pézier (2002)	No
Tityus lokiae Lourenço et al. (2005)	Tarumã Mirim, Manaus, state of Amazonas.	Lourenço et al. (2005)	No
Tityus rionegrensis Lourenço (2006)	Amazonas. Rio Negro region, Neblina Peak vicinity, Venezuelan border.	Lourenço (2006)	No

and most of the cases received medical assistance within the first 3h af-ter the sting (69.6%) (Queiroz et al., 2015). Intra-domiciliar scorpion stings are also important, especially to children.

The incidence of scorpion stings is directly affected by the rainfall and increased river levels, with a higher occurrence in rainy months, probably due to rainfall flooding of the natural habitats of scorpions, which forces them to seek refuge in locations close to human dwellings. This seasonal profile is not evident in some states, probably because their lower proportion of areas under influence of watercourses (Fig. 4).

Surveillance is a critical aspect in this manner. The local topograph-ical complexity is a burden to increase surveillance efficacy once trans-portation within rural amazon is performed mainly through the river. In-dividuals with mild stings in inaccessible areas rarely reach health units, whereas severe cases often die on their way. Even in Manaus, the cap-ital city of the state of Amazonas, in which the population exceeds 2 million people and transportation occurs mainly by car, around 10% of the scorpion stings are not reported to the official surveillance system. Therefore, the real prevalence of scorpion stings is expected to be much higher in riverine and indigenous communities (unpublished data).

The topographical scenario, by itself, hampers precise assessment of the burden of this disease in remote areas, which consists as a crucial challenge in the Amazon (Hui Wen et al., 2015). Increasing surveil-lance sensitivity, therefore, is a critical step for good estimates of scor-pion stings.

2.1. Recommendations

1. To estimate the underreporting burden of scorpion stings in the in-digenous and riverine populations, through population- and hospi-tal-based field studies in remote areas.
2. To estimate the costs associated to scorpion sting envenomings in the health system and from a more general societal perspective.

3. Agents of scorpion stings in the Brazilian Amazon

Among the *Tityus* genus, only few species are generally subject of attention to health professionals managing scorpion stings. It is highly likely that several of these species possess highly toxic venoms and prob-ably are implicated in human envenomings (Lourenço, 2016). From the *Tityus* genus, six species have been formally associated with human envenomings so far: *T. bastosi* (Costa et al., 2016) *T. silvestris* (Costa et al., 2016; Monteiro et al., 2016), *T. apiacas* (da Silva et al., 2017), *T. matthieseni* (Costa et al., 2016), *T. metuendus* (Costa et al., 2016) and *T. obscurus* (P. P. O. Pardal et al., 2014; Torrez et al., 2015). The geographic distribution and other available information are described in Table 1.

A major concern today is the possibility of introduction of the highly anthropized scorpion species *T. serrulatus* to the Amazon region. Due to the household habits and the often-severe nature of envenomings, it is responsible for most of the scorpion stings in Brazilian urban regions. Previously restricted to Minas Gerais, due to its good adaptation to ur-ban environments and its rapid and great proliferation, today its distrib-ution has expanded to Bahia, Ceará, Mato Grosso do Sul, Minas Gerais, Espírito Santo, Rio de Janeiro, São Paulo, Paraná, Paraíba, Alagoas, Per-nambuco, Sergipe, Piauí, Rio Grande do Norte, Goiás, Distrito Federal and some records from Santa Catarina, Tocantins, Rio Grande do Sul, Mato Grosso and Rondônia (Bortoluzzi et al., 2007; Lourenço and Cloudsley-Thompson, 1996). The species has a rare feature among scorpions, which is parthenogenesis, that is, the ability to reproduce without fertilization. This allows a single specimen transported to a new location to readily reproduce and develop a colony. It is believed that the spreading of this species is being supported by road network, the main transportation system in Brazil.

Fig. 5 shows the major scorpion species responsible by envenomings in the Brazilian Amazon region, and *T. serrrulatus*, the major noxious scorpion species outside the Amazon region.

3.1. Recommendations

1. To carry out field works in urban, rural, forested and transitional ar-eas to describe the scorpion fauna composition, as well as behavioral patterns such as diet, reproduction, and activities, in order to estab-lish phylogeny patterns for identifying risk factors of envenomings; and to identify how ecological alterations are affecting scorpion pop-ulation distribution,
2. To enable the Amazonian municipality to register, capture and con-trol scorpion species that pose risks to human health, as well as the State for the supervision, follow-up and organization of these actions;
3. To identify urban and rural areas in which environmental factors favor the proliferation of scorpions, such as cemeteries, stormwater banks, canals, wastelands, potteries, civil constructions, warehouses, silos, open sewage, home infestation ratings and to develop surveil-lance campaings in these localities;
4. To implement surveillance of the introduction of exotic species highly adapted to the anthropic environment in the Amazon Region,

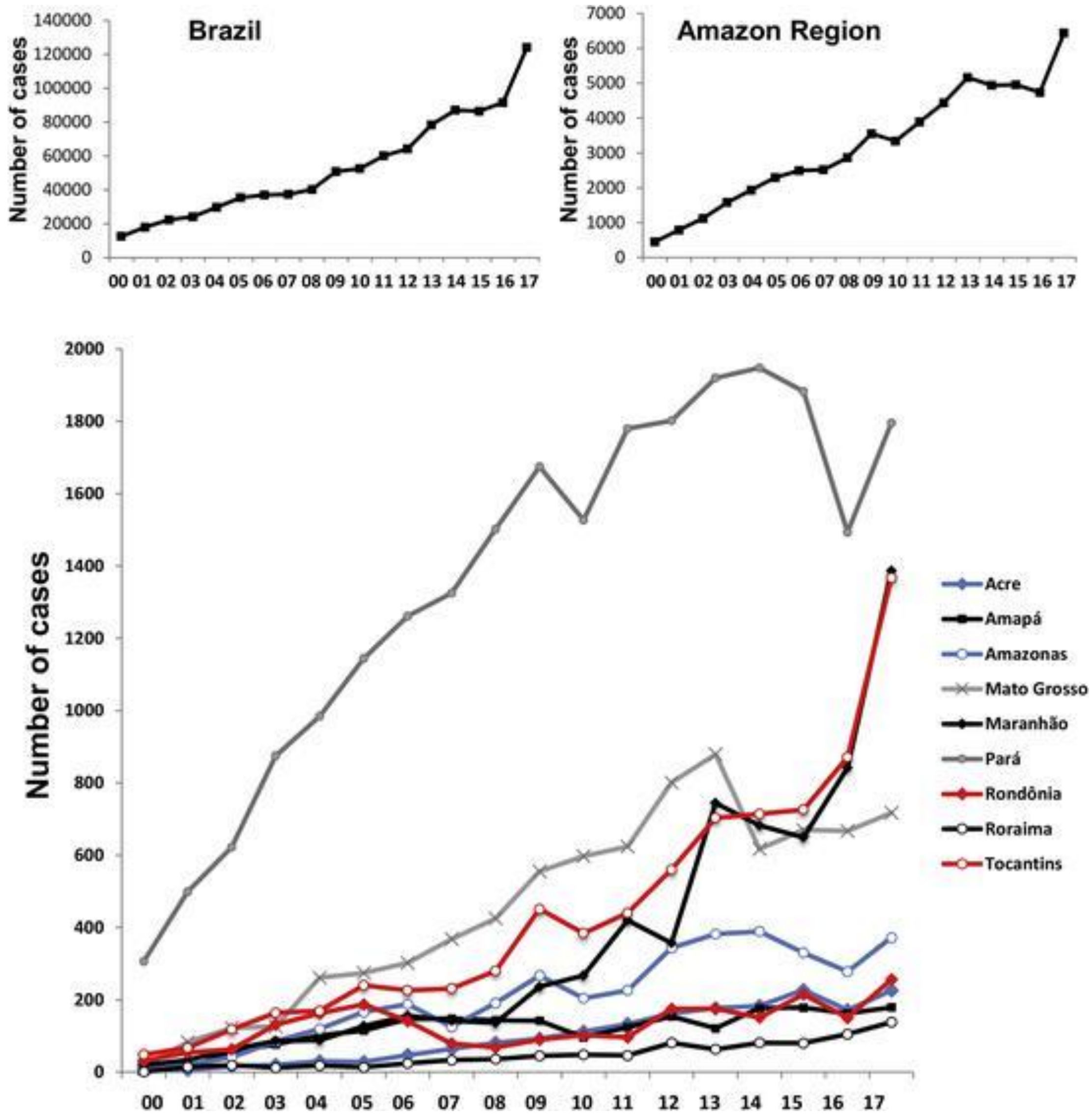

Fig. 1. Time distribution of scorpion stings in Brazil, Brazilian Amazon and states located in Brazilian Amazon region, from 2000 to 2017.

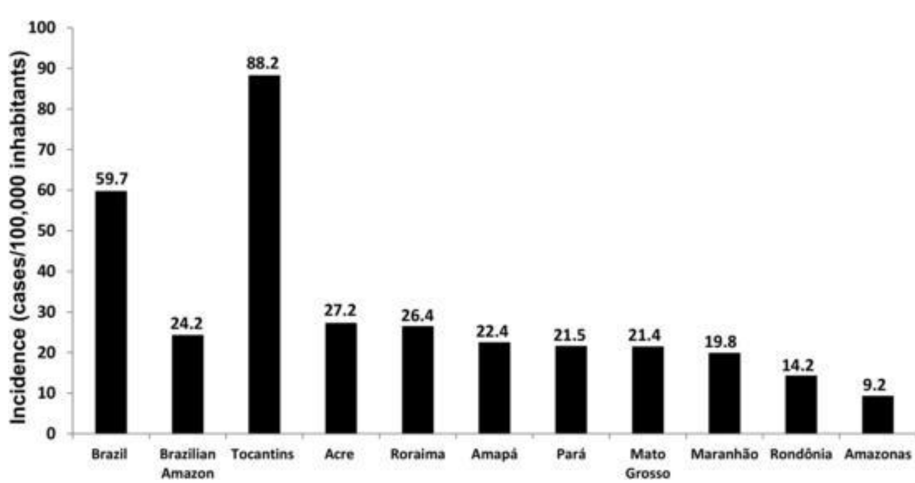

Fig. 2. Incidence of scorpion stings in Brazil, Brazilian Amazon and states located in Brazilian Amazon region, in 2017.

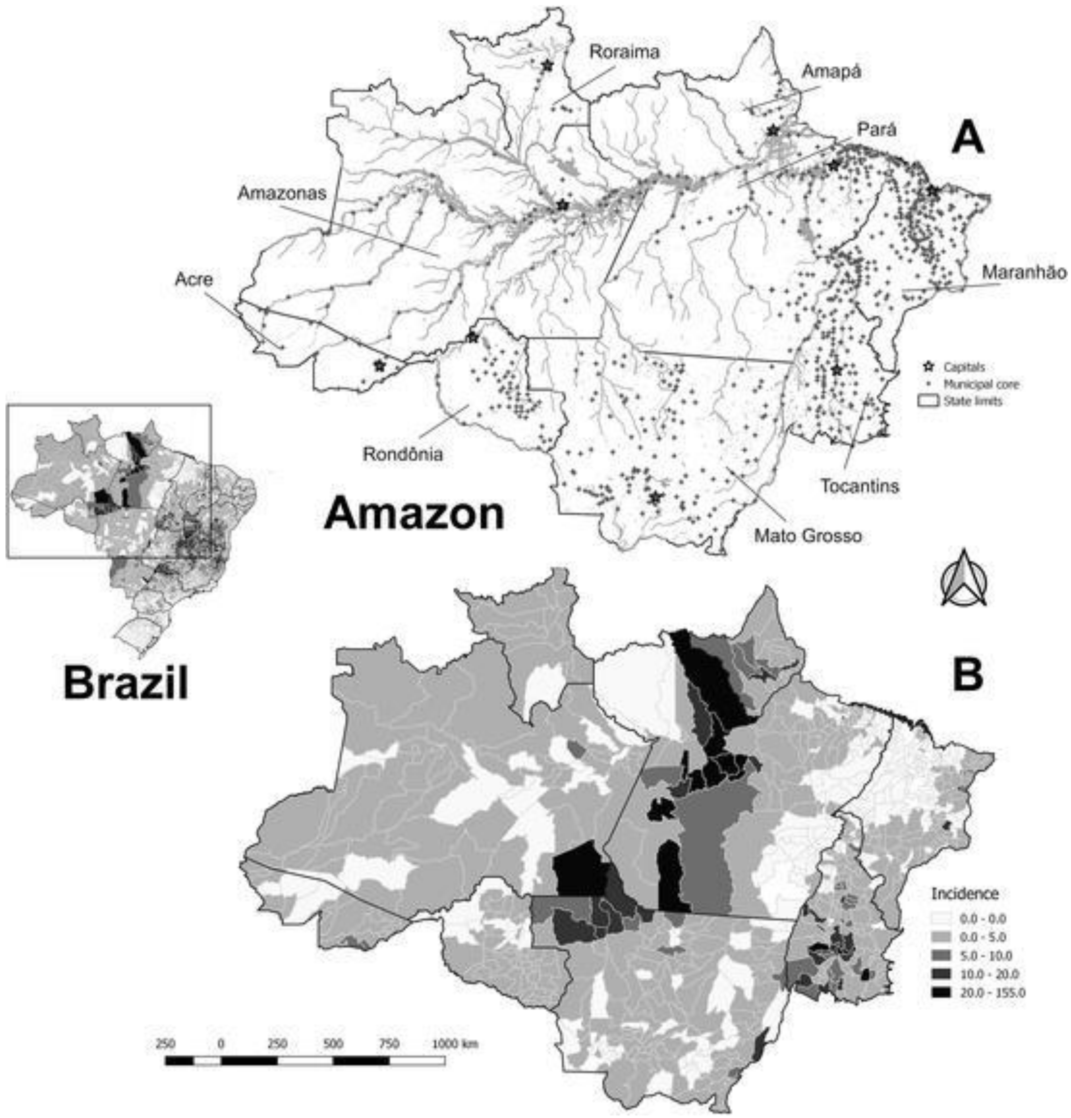

Fig. 3. Scorpion stings incidence map highlighting Amazon region in Brazil: (A) Amazon States, capitals and municipalities and their straight relationship with the main Amazon Basin rivers. Transportation at these municipalities is predominately carried out by vessels and is very time-consuming; (B) Incidence rates within municipalities prevailing in a range that goes from Southern Amapá, the Northern and Central Pará, Southern Amazonas and Northern Mato Grosso. High incidence also occurs at Southern Tocantins State.

especially *T. serrulatus*, which represents an imminent threat to increase the burden of this disease.

4. Clinical aspects of scorpion stings in the Amazon region

The major clinical effect of scorpion stings in the Amazon is local pain of variable intensity (Coelho et al., 2016; P. P. O. Pardal et al., 2014; Torrez et al., 2015), which is consistent with what has been described in other regions of Brazil (Bucaretchi et al., 2014). Cases of scorpion stings in the Brazilian Amazon have been mostly classified as mild, with only 5–7% presenting severity criteria such as profuse and uncontrollable vomiting, intense sweating, severe drooling, prostration, convulsions, coma, bradycardia, heart failure, acute pulmonary edema and shock (da Silva et al., 2018; Ministério da Saúde/SVS, 2019). In the Eastern Brazilian Amazon, age <10 years and stings occurring in the rural area were independently associated with the risk of developing severity; lethality rate among children ≤10 years was 1.3%, being four-fold higher than the overall lethality in the general population (0.3%) (Ministério da Saúde/SVS, 2019).

The severity of scorpion stings has been graded according to classification developed by the Scorpion Consensus Expert Group (Khattabi et al., 2011), which consists of four classes, ranging from 0 to 3, based on characteristics of the sting and clinical manifestations. Nonetheless, it's applicability to *Tityus* sp. envenomings may be of dubious value, since no evidence based clinical classification is available from countries from the amazon region presenting *Tityus* sp. scorpions. Nonetheless, such classification may be of use since clinical presentation resemble those described in the concesus for other scorpion species. Moreover, more studies are needed to better characterize and classify the clinical presentations of *Tityus* sp. envenomations.

In general, knowledge on scorpion stings in this region is based on information generated from epidemiological surveillance. The available clinical characteristics come from a few studies from the Amazon region presenting confirmed cases from different species. These are summarised in Table 2. In general, clinical manifestations appear to be homogenous across Tityus species. Nonetheless, it is notable the increased severeness of systemic manifestations in cases presenting *T. obscurus* stings. Local and systemic clinical manifestations are presented in Figs. 6 and 7, re-spectively.

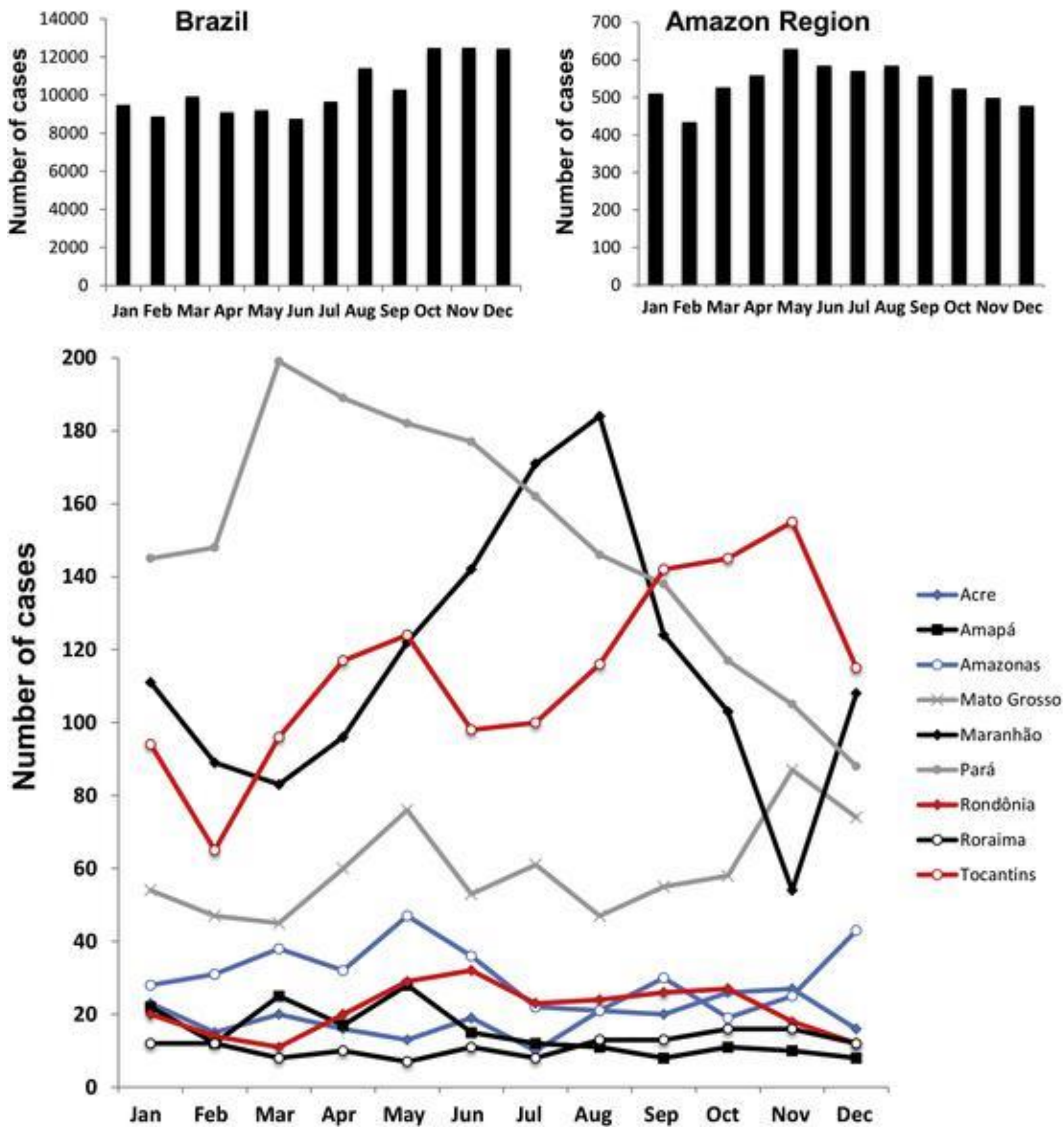

Fig. 4. Monthly distribution of scorpion stings in Brazil, Brazilian Amazon and states located in Brazilian Amazon region, in 2017.

Cases presenting mild clinical manifestations involving other scorpion genera, such as *Ananteris*, *Brotheas* and *Rhopalurus*, are possible but scarcely registered in the Amazon. In Alter do Chão, state of Pará, a patient stung by *Rhopalurus amazonicus* reported local pain immedi-ately after the scorpion sting in his right thumb, which rapidly spread throughout his arm, together with paresthesia, remarkably numbness, tingly sensations, mild swelling and severe itching from the hand to the arm (Souza et al., 1995).

Recommendations:

1. To describe clinical characteristics and complication rates associated with envenomings caused by different scorpion species occurring in the Amazon;
2. To better differentiate clinical presentation in children, in which evaluation needs to consider the duality between systemic maniestations and terror, pain and distress from the envenomationt;
3. To identify risk factors associated to clinical complications;
4. To identify the effectiveness of health facilities located in the countryside municipalities to manage of scorpion envenomings and their possible complications.

5. Venom research: biochemistry and pathophysiology

Few studies have addressed the association between scorpion venom composition and pathophysiological mechanisms of envenomations from specimens of the *Tityus* genus in the Amazon region, with most of them in animal and cultured-cell models. These are summarised al-most exclusively in the characterization of the composition of *T. ob-scurus* venom. Of note, *T. obscurus* was the first name given to this scorpion and it is now more used in the literature. Nonetheless, *T. cambridgei* and *T. obscurus* are the same species, with both names be-ing used indistinctly. Toxins were described to have near 50% iden-tity with toxins from other Brazilian scorpions of the *Tityus* genus and showed activity mainly on sodium and potassium channels (Batista et al., 2000, 2002b). One of them, Tc49b (recently renamed To1), was lethal to mice, affecting Na(+)-channels of rat cerebellum granular cul-tured cells. Other peptides were identified to also affect Na(+)-chan-nels (Batista et al., 2004; Borja-Oliveira et al., 2009)(57,58) and present selective activity against K(+)channels of T lymphocytes rather than Shaker B K(+)-channels (Batista et al., 2002a, 2002b). One of

Fig. 5. Major scorpion species responsible by envenomings in the Brazilian Amazon, and *T. serrrulatus*, the most important venmous scorpion species outside the Amazon region. A) *Tityus metuendus* (Pocock, 1897), female adult (90mm length) darkish-red coloration, almost black, Purus river, Amazonas state; B) *Tityus metuendus* (Pocock, 1897), male adult (100mm length), black and darkish-red in coloration with males presenting bulkier body structures than female specimens, from Reserva Liberdade, Acre state; C) *Tityus apiacas* (Lourenço, 2002c), female adult (90mm), reddisch-brown colorations with some yellowish zones on the sternites, Juruena National Park, Mato Grosso state; D) *Tityus silvestris* (Pocock, 1897), male adult (45mm) presenting yellowish coloration with scattered dark spots in general, Moa river, Acre state; E) *Tityus obscurus* (Gervais, 1843), female adult (100mm), of dark, blackish coloration, females having less slender pedipalps and metasomal segments compared to male specimens, Santarém, Pará state; F) *Tityus serrulatus* (Lutz & Mello, 1922), female adult (60mm) with general yellowish coloration and blackish lateral and ventral metasomal segments I to V, from Guararapes, São Paulo state. Length measured from pedipalp to telson structures. Pictures: Paulo Bernarde. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

these peptides (Tc48b) was shown to affect Na(+)-channel permeability in pituitary GH3 cultures cells in a similar fashion to those reported in α-scorpion toxins, contrary to most of the New World scorpion toxins, which are β-toxins (Borja-Oliveira et al., 2009).

Detailed analysis of To1 and To4 (first named Tc54) revealed that these toxins enhance more negative potentials of human NaV 1.3 and 1.6, of the insect channel BgNaV1 and of arachnid VdNaV1 channel, supporting their classification as β-toxins (Duque et al., 2017; Tibery et al., 2019). Also, molecular cloning of the putative Na(+)-channel scorpion toxins from *T. pachyurus* and *T. obscurus* venom glands iden-tified new putative Na(+)-channel toxins from both venoms and indi-cated a clear geographic separation between scorpions of *Tityus* genus inhabiting the Amazonian and highland Andes regions and those distrib-uted over the southern of the Amazonian rainforest (Guerrero-Vargas et al., 2012).

Transcriptomic investigation of the venom glands corroborated by a shotgun proteomic analysis of the venoms of *T. obscurus* and *T. serrulatus* revealed high abundance of metalloproteinases sequences followed by sodium-potassium channel acting toxins. Several putative venom com-ponents such as anionic peptides, antimicrobial peptides, bradykinin-po-tentiating peptide, cysteine rich protein, serine proteinases, cathepsins, angiotensin-converting enzyme, endothelin-converting enzyme and chy-motrypsin-like protein, proteinase inhibitors, phospholipases and hyaluronidases were also identified (De Oliveira et al., 2018). Although venom composition of these two allopatric species of *Tityus* genus are similar in terms of the major classes of proteins syn-thesized and secreted, their individual toxin sequences are considerably divergent, which may be reflected in different epitopes for the same pro-tein classes in each species.

The effects of *T. obscurus* and *T. serrulatus* venoms were compared in rats and demonstrated that *T. obscurus* venom caused hemorrhagic patches in the lung parenchyma but did not lead to pulmonary edema and changes in the occurrence and intensity of induced convulsions or hippocampal neuronal loss. Moreover, *T. obscurus* venom induced lower edematogenic and moderate nociceptive activity in mice compared to *T. serrulatus* venom (de Paula Santos-da-Silva et al., 2017). In mice, *T. obscurus* and *T. serrulatus* venoms was found to change Na+ and K+ channel permeability but only *T. obscurus* venom was shown to act di-rectly on skeletal muscle. This finding calls for further studies on *T. ob-scurus* venom to identify the toxin responsible for its direct inotropic activity as it may have clinical applications (Borja-Oliveira et al., 2009).

Characterization of *T. metuendus* venom revealed the presence of metalloproteinases, hyaluronidases, endothelin and angiotensin-con-verting enzymes, bradykinin-potentiating peptide, allergens, other en-zymes and other proteins and peptides, also indicating the presence of Na+ and K+ channel acting toxins (Batista et al., 2018). The au -

Table 2
Description of local and systemic manifestations according to Tityus species.

Species	Local manifestations	Systemic manifestations
T. obscurus	Local and radiating pain, paresthesia, edema, erythema, sweating, piloerection and burning (Asano et al., 1996; Martins et al., 2002; P. P. de O. Pardal et al., 2014; P. P. O. Pardal et al., 2014; Pereira De Oliveira Pardal et al., 2003)	Neurological symptoms (paresthesia, ataxia, dysarthria, myoclonus, dysmetria, and electric shock-like sensations throughout the body) (P. P. O. Pardal et al., 2014). Acute cerebellar dysfunction, abnormal neuromuscular manifestations and skeletal muscle injury (Torrez et al., 2015)
T. silvestris	Pain, paresthesia, erythema and edema (Asano et al., 1996; Coelho et al., 2016)	Malaise, nausea, vomiting, prostration and somnolence (Coelho et al., 2016). Generalized muscle spasms (Monteiro et al., 2016)
T. apiacas	Local edema, erythema, pain and sensation of electric shock (almost immediately after the sting) (da Silva et al., 2017)	Mild and not life-threatening systemic manifestations (da Silva et al., 2017)
T. metuendus	There are no detailed data on clinical manifestations caused by this species (Souza et al., 1995)	Electrocardiographic alterations
T. bastosi and *T. matthieseni*	No clinical description is available (Costa et al., 2016)	

thors also showed that the venom contains both α- and β-scorpion toxin types, which were lethal to mice.

5.1. Recommendations

1. To study the chemical composition of all medically-relevant Amazon-ian scorpion venoms, including “omics” technologies;
2. To define the predominant pathophysiological mechanisms and modes of action of venoms of different populations of scorpions in the Amazon region, considering the possibility of intra-species varia-tions;
3. To verify the association between the chemical composition of all medically-relevant Amazonian scorpion venoms and clinical presen-tations.

6. Therapy issues and antivenom spectrum efficacy

6.1. Antivenom manufacturing, composition and major concerns

Scorpion antivenom is produced by immunizing horses with a pool of venoms from different scorpion species. In Brazil, this is composed of 50% of *Tityus serrulatus* venom and 50% of *T. bahiensis*, none of which are prevalent in the Amazon region (Wen et al., 2015). These are animal plasma-derived immunoglobulins, which are F(ab’)2 fragments. Two types of scorpion antivenoms are available in Brazil: *Tityus* scorpion antivenom and a polyvalent antivenom against spiders (*Loxosceles* and *Phoneutria*) and scorpions from the *Tityus* genus.

The composition of *T. obscurus* and *T. serrulatus* venoms are consider-ably similar in terms of the major classes of proteins, although their indi-vidual toxin sequences are considerably divergent. These differences at the amino acid level may have implications in terms of the predominant epitopes for the same protein classes in each species, explaining the basis for the poor recognition of *T. obscurus* venom by the antivenom raised against other species (de Paula Santos-da-Silva et al., 2017). Some evidence suggests variations in toxicity resulting from the diversity of *T. obscurus* venom in different Amazonian regions (De Oliveira et al., 2018). The western blotting analysis of these venoms using a horse anti-*Tityus serrulatus* antivenom showed that some *T*. *obscurus* venom components are not antigenically similar to those of *T*. *serrulatus*.

6.2. Neutralization efficacy

Cross-neutralization studies against Amazonian scorpion venoms of the current *Tityus* antivenom available in Brazil are scarce. Nishikawa et al. showed a significant in vivo toxicity variation, measured by the Median Lethal Doise (LD_{50}) for mice (et al., 1994). *T. obscurus* venom cross-reacted in immunoelectrophoresis and immunoblotting tests using horse anti-*T. serrulatus* antivenom, but neutralization of the lethal activ-ity of *T. obscurus* venom was not investigated.

Human envenomings by *T. obscurus* (P. P. O. Pardal et al., 2014) showed minor systemic features, varying from nausea, dizziness and sweating to myoclonus, electric shock-like sensations, dysarthria, ataxia and dysmetria. Benzodiazepines and scorpion antivenom were adminis-tered to patients presenting myoclonus. Apparently, scorpion antivenom did not shorten the intensity and duration of the neurological mani-festations of Class II patients; the duration of their hospital was more prolongued than that of patients showing Class II severity grade

Fig. 6. Local manifestations of scorpion sting in the Amazon Region. A) Male patient of 4 years old from Manaus, stung by *Tityus metuendus* in the fifth right finger, presenting very intense pain, with relief after truncal block with infiltration of 2% lidocaine in interdigital space. No other apparent alteration at the site of the sting. B) One-and-a-half-year-old female patient from Manaus, stung by *Tityus metuendus* in the external hindfoot face, presenting intense pain, treated with analgesics. A mild edema is also observed in the region of the sting. C) Female patient of 38 years old from Cruzeiro do Sul, stung by *Tityus metuendus* in the right side of the back, presenting moderate pain, burning sensation and erythema possibly exacerbated by scratching, and small circular induration at the sting site. D) 37 years-old male patient from Cruzeiro do Sul, Acre, stung in three points on the right ankle by a *Tityus silvestris* specimen that got into his boot during a walk in the forest. The patient reported moderate pain for about 2h. The arrows show the 3 hyperemic points of the stings. No systemic manifestations were present in these cases.

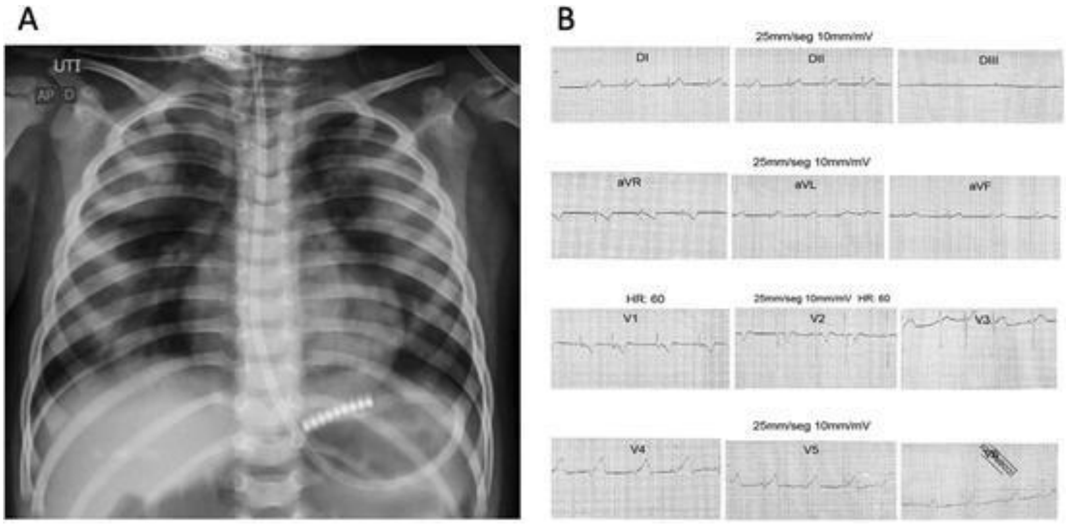

Fig. 7. Severe cases of scorpion stings with multiorgan involvement in children in the Amazon region. A) Chest X-Ray showing diffuse pulmonary infiltrates and also depicting the en-dotracheal tube from a two-year-old female patient weighting 11kg, from Borba, a city 215km far from Manaus and only accessible by boat or airplane. The patient was stung by *Tityus metuendus* on the plantar region of the right foot. Local health care referred the patient to the capital. She arrived at the hospital in Manaus after 29h of the accident and was immediately transferred the ICU. Only at hospitalization the patient received antivenom serum (six vials). She was pale, presented cyanosis in extremities, breathless and non-responsive to any stimulus when convulsions started. She was immediately sedated and intubated. She developed shock, arrhythmias, renal and respiratory failure. Patient clinical status progressed, and she was discharged after eleven days of hospitalization. B) ECG of a five-year-old male patient from Manaus, stung by *Tityus metuendus* in the left foot, showing a pattern suggestive of subepi-cardial ischemia in the anteroseptal wall. Laboratory findings showed an increase in the activity of serum lactate dehydrogenase (524 U/L), alkaline phosphatase (600 U/L) and creatine kinase (924 U/L). Other signs and symptoms included uncontrollable vomiting, dehydration, psychomotor agitation, sialorrhea, and abdominal cramps. The patient needed antivenom and intensive care support, being discharged after a week without complaints.

with sympathetic signs and symptoms. Similar findings were shown by Torrez et al. (2015), which described two presumed *T. obscurus* cases with myoclonus, dysarthria, visual changes and decreased conciosness level, with evident failure of antivenom in reversing systemic envenom-ing manifestations, even though both patients had been treated early on in the course of envenoming with scorpion antivenom intravenously; in these cases, signs and symptoms persisted for at least three days. For *T. silvestris*, another Amazonian scorpion, Monteiro et al. (2016) described persistent and generalized muscle spasms despite antivenom treatment, whereas Coelho et al. (2016) suggested a similar clinical improvement of mild intensity of systemic symptoms with or without scorpion antivenom. These clinical findings raise doubts on the efficacy of the currently available scorpion antivenoms in the control of clinical manifestations in envenomings by some Amazonian scorpions.

6.3. Antivenon therapy indications

Antivenom is indicated in cases of envenomings with signs of sys-temic toxicity within the first hours after the sting. This is based on *T. serrulatus* severity grade, which is the species related to most of severe cases and deaths in Brazil (Cupo et al., 2007).

Using enzyme-linked immunosorbent assays for detection of *T. ser-rulatus* venom antigen and of horse anti-*T. serrulatus* venom antibod-ies (Rezende et al., 1995, 1998), it has been shown that specific an-tivenom cleared circulating venom antigens in patients, although car-diorespiratory manifestations, profuse sweating and vomiting did not disappear promptly after antivenom therapy. These studies supported the Brazilian scorpion sting guidelines, in which antivenom treatment is recommended for cases presenting systemic manifestations, although considering that, when severe manifestations were already present, an-tivenom treatment may have limited efficacy. The need for a rapid ad-ministration of antivenom in cases presenting systemic manifestations is explained by the mismatch between venom toxicokinetics and an-tivenom pharmacokinetics. Owing to the low molecular mass of scor-pion venom neurotoxins, they are able to rapidly reach extravascular targets.

In other American countries, antivenom is also recommended for *Centruroides* sp systemic envenoming, based on large studies perfomed in Mexico (Osnaya-Romero et al., 2001) and the USA (Boyer et al., 2013). However, clinical protocols and guidelines do not mention neu-rological aspects of envenoming caused by Amazonian scorpions. As a result, there is conflicting evidence of antivenom effectiveness for res-olution of symptoms and survival for all scorpion envenomings in the Amazon region.

It is recommended that all patients stung by scorpions should be observed up to 4–6h in the first-line care facility or emergency room, with a special attention to children under 10 years old. Besides early antivenom administration, patients with severe envenoming should be maintained in an intensive care unit (ICU) to prevent or treat cardiovas-cular and/or respiratory collapse or neurological dysfunctions. Support-ive treatment is crucial and includes mechanical ventilation for patients with respiratory failure, vasoactive drugs for myocardial depression and benzodiazepines for muscular spasms.

There is a tendency to overtreat patients stung by scorpions in Ama-zon region, even those with just local envenoming. Table 3 shows dif-ferent experiences from observational studies in scorpion antivenom uti-lization, according to region and prevalent species (Benmosbah et al., 2013; Bucaretchi et al., 2014; da Silva et al., 2017, 2018; De Roodt et al., 2003; Otero et al., 2004; P. P. O. Pardal et al., 2014; Ribeiro et al., 2001; Torrez et al., 2015). These findings bear serious implications in terms of the cost for antivenom acquisition, waste of this precious drug, and the risk of adverse reactions to animal-derived im-munoglobulins. However, early adverse reactions to scorpion antivenom are less frequent in patients with adrenergic manifestations after *T. ser-rulatus* stings than in those without these clinical features (Amaral et al., 1994).

Recommendations:

1. To carry out preclinical assessments of the efficacy of existing an-tivenoms against the venoms of scorpio species from the Amazon re-gion.

Table 3

Antivenom administration, according to site, perpetrating species and severity grading, South America.

Study	Site	Sample size	Antivenom use rate (%)	Number of vials	Perpetrating species	% of severe cases (Class III)	Lethality (%)	Study Reference
1	São Paulo, Brazil	1,323	2.3	4.7 (mean)	*T. bahiensis* (85.8%) and *T. serrulatus* (14.2%)	1.9	0.0	Ribeiro et al. (2001)
2	8 provinces, Argentina	511	91.4	Unknown	*T. trivitattus* 100%	0.0	0.6	De Roodt et al. (2003)
3	10 towns, Colombia	129	14.7	1-2 vials (moderate), 2–4 vials (severe)	*T. pachyurus* (39.5%), *Centruroides gracilis* (24.0%), *T. astenis* (5.2%) and *T. fuehrmanni* (22.5%)	3.1	0.0	Otero et al. (2004)
4	Cayenne, French Guiana	253	Unknown	Unknown	Unknown	1.6	0.0	Benmosbah et al. (2013)
5	Pará state, Brazilian Amazon	48	31.2	3.0 (mean)	*T. obscurus* (100%)	0.0	0.0	(P. P. O. Pardal et al., 2014)
6	Campinas, Brazil	1,327	5.2	4.0 (median)	*T. bahiensis* (28.0%), *T. serrulatus* (19.3%) and unknown (52.6%)	1.8	0.1	Bucaretchi et al. (2014)
7	Santarém, Pará, Brazilian Amazon	58	91.4	Unknown	*T. obscurus* (8.6%) and unknown (91.4%)	25.8	0.0	Torrez et al. (2015)
8	Belém, Pará, Brazilian Amazon	13	7.5	2.0 (mean)	*T. silvestres* (100%)	0.0	0.0	Coelho et al. (2016)
9	Apuí, Southern Brazilian Amazon	4	100.0	2 vials each	*T. apiacas* (100%)	0.0	0.0	da Silva et al. (2017)
10	Upper Juruá, Acre, Brazilian Amazon	148	68.9	1-3 vials (61.1%), 4–6 vials (38.9%)	Unknown	7.6	0.0	da Silva et al. (2018)

2. To perform multicenter studies aimed at the standardization of clini-cal protocols for assessing antivenom efficacy and defining objective criteria for recommending antivenom administration and dosage;
3. To undertake phase IV studies for adverse reactions under antivenom pharmacovigilance.

7. Network of scorpion envenoming assistance and professional training in the Amazon

7.1. Possible causes of the higher lethality in the Amazon region

Even though envenomings caused by *T. serrulatus* are generally con-sidered to be more severe than those caused by other species, data from the official surveillance system shows that lethality from scorpion stings in the Brazilian Amazon is significantly higher compared to other re-gions in Brazil. From 2000 to 2017, 122 deaths from scorpion stings, among 57,360 cases, were reported in the Amazon (case fatality rate of 0.21%); while in other regions, 1,111 deaths were recorded from 893,177 scorpion sting cases (case fatality rate of 0.12%) [OR =1.71 (IC95%1.42–2.06), p<0.0001] [11]. Higher odds for lethality are found in the states of Rondônia, Amazonas, Mato Grosso, Pará and Maranhão (Table 4). A high lethality rate due to scorpion stings may re-sult from challenges found in small remote towns in the Amazon region related to experience of health personnel, appropriate antivenom ther-apy and quality of care, with the latter being dependent on equipment from health facilities (particularly resuscitation equipment). Therefore, in these towns located far from reference centers, investment in training health professionals in the initial management of the patient and follow up of possible complications of scorpion stings is essential (Queiroz et al., 2015).

Table 4

Differential lethality risks from scorpion stings in Brazilian Amazonian states compared to Extra-Amazonian regions.

Area	Number of cases	Number of deaths	Lethalithy (%)	OR (IC95%)	p
Extra-Amazonian states	893,177	1,111	0.12	…	…
Amazonian states	57,360	122	0.21	1.71 (1.42–2.06)	<0.001
Acre	1,783	0	0.00	…	…
Amapá	2,143	0	0.00	…	…
Amazonas	3,735	13	0.35	2.80 (1.62–4.85)	<0.001
Maranhão	6,434	15	0.23	1.88 (1.13–3.12)	0.014
Mato Grosso	8,103	21	0.26	2.09 (1.35–3.21)	0.001
Pará	24,342	55	0.23	1.82 (1.38–2.38)	<0.001
Rondônia	2,326	13	0.56	4.49 (2.59–7.76)	<0.001
Roraima	857	0	0.00	…	…
Tocantins	7,759	5	0.06	0.52 (0.21–1.25)	0.135

7.2. Countryside infrastructure and care accessibility

Currently, most of the municipalities of the Amazon Region have the facilities to maintain antivenom stocks, i.e. cold chain, in at least one hospital in their urban area. This is reflected by the similar propor-tion of antivenom administration in patients treated in the capital Man-aus and in countryside municipalities (Fig. 8). Despite that, it is noted

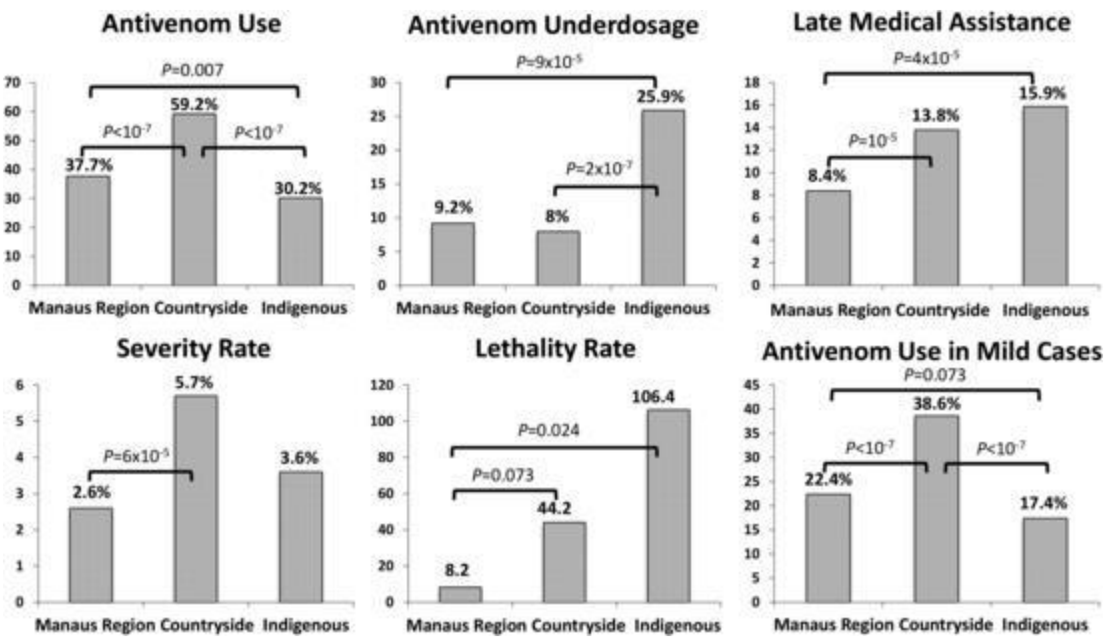

Fig. 8. Comparison between antivenom use, antivenom underdosage, late medical assistance, lethality and severity levels in Manaus region, countryside and indigenous population in the Amazonas state, for scorpion stings recorded in the state of Amazonas, Western Brazilian Amazon.

that the time to medical care is significantly higher in patients from the countryside, particularly in the case of patients from indigenous communities. Similarly, severe cases and deaths are also more frequently recorded in these populations as compared to patients reported in the capital. In indigenous communities, other complicating factors are the high proportion of patients receiving less antivenom than the recommended dosage and the paths by which patients try to reach proper medical attention. When a patient from an indigenous community seeks care with the village's Indigenous Health Agent, this professional can re-fer the patient to the nearest urban center, and in severe cases, articu-late the referral to the state capital or another larger city. In many other cases, these patients will seek the *shamans* and local healers after tradi-tional medicine, being referred to the official health system only after the case evolves to severity.

7.3. Intensive care availability in the Amazon region

One of the aspects that should be considered in the treatment of cases of severe scorpion envenomings is the access to health facilities with intensive care unit (Fan and Monteiro, 2018), especially for the pe-diatric population. In this sense, the official numbers suggest that the Amazon Region presents a major bottleneck in the treatment of this type of patient. In 2016, there were 1,961 hospitals with 41,741 ICU beds in Brazil. Of these, 66.4% are for adult care and only 10.3% are destined to the pediatric population. The Amazon region contributes only with 1,237 ICU beds for adults (4.5%) and 352 beds for pediatric ICU (8.0%). Comparing to other regions of the country, the rate of ICU beds calculated by the population of the Amazon region is the low-est, or 1.7 ICU beds versus 4.1/10,000 habitants in the more developed Southeast region. In addition, a situation of inequality within the re-gion itself also exists, with a huge concentration of beds in the capitals. While in the capitals of the states of the Amazon region the rate of ICU beds per 10,000 inhabitants is 3.1, in the countryside this rate is only 0.4. Of the 352 pediatric ICU beds available in the Brazilian Amazon, only 69 (19.6%) are located outside of state capitals. The State of Ama-zonas, Amapá and Roraima do not have any ICU beds in the countryside (Brasileira, 2016).

7.4. Medical training

Despite the high incidence of envenomings from bites and stings of venomous animals, there is a lack of systematic professional training on the diagnosis, specific therapy, and clinical management of compli-cations. Thus, antivenom misuse is frequently seen, either in quantity (number of ampoules administered) or the specific antivenom selected for the treatment. Current training programs seek to link medical knowl-edge with snakes' and scorpions' biology and surveillance. However, this approach often does not reflect the need for professional diagnosis algo-rithms and coherent and responsive case management. Thus, adherence to medical training and courses in this area has been a major challenge. Furthermore, there is a high turnover of health professionals in small Amazonian cities, hence calling for a regular periodic scheme of train-ing. Although communication technologies that greatly facilitate knowl-edge dissemination have proliferated in the area, these are still barely harnessed for training of health staff in the subject of envenomings. The use of electronic media for training professionals in the management of envenomings is increasing and may be an alternative to classroom courses in the future.

7.4.1. Recommendations

1. To organize programs for systematic training for all health professionals, including nurses who are critical in the initial management of the patients and in the follow up of possible complications;
2. To systematically update all relevant diagnosis and treatment guide-lines;
3. To encourage the use information and communication technologies and diverse electronic media in training programs and distance learn-ing.

8. Final remarks

The incidence of scorpion sting envenomings is increasing in the Brazilian Amazon, with high incidence rates in some regions. Envenomings by *Tityus* sp. in this region show distinct epidemiological and clini -

cal aspects, which show differences when compared to envenomings caused by *T. serrulatus*, the most important causative agent of scorpion stings in other regions of Brazil. Moreover, climate changes and defor-estation are likely to alter the geographical distribution and epidemio-logical profile of scorpion stings in the near future. The differences de-scribed between *T. obscurus* and *T. serrulatus* venoms, and the conse-quent variations in the pathophysiology of envenomings may have im-plications in terms of health policies, including antivenom design and availability, as well in the development of treatment guidelines adapted to the Amazon region.

Moreover, our knowledge of Amazonian scorpion venom composi-tion and mechanisms of action has large gaps that demand renewed re-search efforts. It is necessary to develop cooperative and integration ef-forts throughout the Brazilian amazon region, a huge and diverse geo-graphical area, in order to consolidate a local multi-disciplinary network centered on scorpion envenoming assistance and training. It is expected that the major issues highlighted in this review contribute to the devel-opment of such integrative initiative.

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Embora subnotificada na Região Amazônica, as picadas de escorpião são muito prevalentes em algumas áreas e podem ser potencialmente fatais, principalmente em crianças. As populações mais vulneráveis são aquelas que vivem em locais distantes das capitais, tendo, portanto, acesso limitado ao sistema de saúde, onde é encontrada a estrutura apropriada para o tratamento de casos graves. Uma fauna abundante e diversificada de escorpiões é encontrada na região, mas poucos estudos foram realizados para decifrar as características clínicas e a resposta terapêutica dos antivenenos disponíveis nos acidentes causados pelas várias espécies. Subdosagem de antiveneno e assistência médica tardia são comuns entre as populações indígenas, resultando em taxas de gravidade e óbito maiores nessa população. Uma compreensão aprofundada dos aspectos epidemiológicos, clínicos e terapêuticos dos ambientes de picadas de escorpião na Amazônia é necessária para melhorar o resultado desses casos.

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