

# Leishmaniose Tegumentar no Estado do Mato Grosso: Características Sociodemográficas e de Saúde Associados com Reações Adversas Laboratoriais e Eletrocardiográficas

## Tegumentary Leishmaniasis in Mato Grosso State: Socio-Demographic and Health Characteristics Associated with Laboratory and Electrocardiographic Adverse Reactions

Déborah Cláudia Denis de Souza Caetano<sup>a\*</sup>; Cristina Eunice Okuyama<sup>a</sup>; Susana Nogueira Diniz<sup>ab</sup>; Márcia Regina Machado dos Santos<sup>a</sup>; Audrey de Souza Marquez<sup>ac</sup>; Regina Mara Silva Pereira<sup>b</sup>

<sup>a</sup>Universidade Anhanguera de São Paulo, Programa de Pós-Graduação Stricto Sensu em Farmácia. SP, Brasil.

<sup>b</sup>Universidade Anhanguera de São Paulo, Programa de Pós-Graduação Stricto Sensu em Biotecnologia. SP, Brasil.

<sup>c</sup>Universidade do Norte do Paraná, Centro de Pesquisa em Ciências da Saúde. PR, Brasil.

\*E-mail: [deborah.claudia.caetano@gmail.com](mailto:deborah.claudia.caetano@gmail.com)

### Resumo

Este estudo identificou características da população associadas com reações adversas laboratoriais e eletrocardiográficas em pacientes durante o tratamento de leishmaniose tegumentar. Os efeitos adversos foram monitorados em prontuário médico de pacientes em Hospital Universitário no Brasil. Os resultados mostraram que dos 470 prontuários analisados, 367 (78,09%) eram homens, 249 (52,98%) dos pacientes tinham educação fundamental incompleta e 438 (93,19%) se identificaram como pardos. O efeito adverso mais frequente foi a alteração no eletrocardiograma (85,48%). As variáveis mais prevalentes associadas com os efeitos adversos foram idade acima de 60 anos (RP = 9,79/IC95% = 5,86 – 16,34), leishmaniose mucosa (RP = 2,45/IC95% = 1,55 – 3,86), doenças pré-existentes (RP = 5,44/IC95% = 3,52 – 8,40), uso de anfotericina B (RP = 18,31/IC95% = 9,26 – 36,21) e pentamidina (RP = 25,51/IC95% = 15,08 – 43,14) como tratamento de primeira escolha. Entre os indivíduos com doenças pré-existentes, 74,03% (n=57) foram hipertensos e 24,59% (n=14) dos pacientes com hipertensão tinham algum tipo de efeito adverso. O conhecimento do perfil da população com leishmaniose tegumentar é importante para o desenvolvimento de novas estratégias para prevenção e redução das reações adversas, levando a um tratamento mais efetivo e rápido.

**Palavras-chave:** Efeitos Adversos. Anfotericina B. Pentamidina. Antimonial Pentavalente.

### Abstract

*This study identified population characteristics associated with laboratory and electrocardiographic adverse reactions in patients during the treatment of tegumentary leishmaniasis. Side effects were monitored in patients' medical record in the University Hospital, Brazil. The results show that of the 470 records analyzed, 367 (78.09%) were from males, 249 (52.98%) of the patients had incomplete elementary education and 438 (93.19%) identified themselves as brown skinned. The most frequent was alterations in the electrocardiogram (85.48%). The most prevalent variables associated with adverse effects were age above 60 years old (PR = 9.79/CI95% = 5.86 – 16.34), mucosal leishmaniasis (PR = 2.45/CI95% = 1.55 – 3.86), pre-existing diseases (PR = 5.44/CI95% = 3.52 – 8.40), use of amphotericin B (PR = 18.31/CI95% = 9.26 – 36.21) and pentamidine (PR = 25.51/CI95% = 15.08 – 43.14) as first treatment choice. Among individuals with pre-existing disease, 74.03% (n=57) are hypertensive and 24.59% (n=14) of patients with hypertension had some type of adverse effect. In conclusion, although the treatments have achieved high rate of cure, this study identified socio-demographic and health characteristics associated with adverse effects in patients leishmaniasis treatment. Knowledge of the population profile with tegumentary leishmaniasis is important for the development of new strategies for prevention and reduction of adverse reactions.*

**Keywords:** Adverse Effects. Amphotericin B. Pentamidine. Pentavalent Antimonial.

### 1 Introduction

Leishmaniasis is an infection disease caused by several species of protozoan *Leishmania* (L.) with various clinical manifestations. According with World Health Organization (WHO) it has been still on the list of neglected diseases and it is a serious public health problem. WHO and Pan American Health Organization (PAHO) estimates that the disease exposes 350 million people worldwide and there are approximately 2 million new cases of different clinical forms, per year (WHO; PAHO, 2019). In 2017, out of 22,145 new cases notified to WHO, 20,792 (94%) occurred in seven countries, including Brazil, which is amongst the nine countries where tegumentary leishmaniasis (TL) prevails (WHO, 2018).

In Brazil, autochthonous cases of TL have already been reported in all states (ANVERSA *et al.*, 2018; TELES,

FONSECA, GONÇALVES, 2019; DETONI *et al.*, 2019). Due to the high incidence and wide geographical distribution, TL deserves special attention because it can lead to disfiguring and disabling destructive lesions, with impacts in the psychosocial aspects of people affected by the disease (TORRES-GUERRERO *et al.*, 2017; BORGES, GOMES, RIBEIRO-DIAS, 2018).

Until today, pentavalent antimonials is considered the first line of drugs used in the treatment of the leishmaniasis. The development of pentavalent antimonials enabled a reduction in treatment toxicity and have been used in the cure of tegumentary and visceral leishmaniasis (SUNDAR; CHAKRAVARTY, 2015). Other drugs applied as a second choice have been used, such as amphotericin B and pentamidine (ULIANA, TRINCONI, COELHO, 2017). Currently, still there is no efficient vaccine to treat leishmaniasis (ANDRADE-NETO *et*

*al.*, 2018).

The pentavalent antimonial has a clinical cure rate of up to 80% when used in tegumentary leishmaniasis treatment (SAHEKI *et al.*, 2017; CATALDO *et al.*, 2018), however this drug display important limitations such as parenteral administration, high toxicity, high cost and long periods of treatment (MARQUES *et al.*, 2019). Antimony therapy is often accompanied by severe side effects that include cardiotoxicity, pancreatitis and hepatotoxicity (SADEGHIAN; ZIAEI; SADEGHI, 2008; LYRA *et al.*, 2016). Adverse reactions that arise during treatment of the disease may compromise patient's quality of life, increase patient length of stay, medication consumption and costs (EID RODRÍGUEZ *et al.*, 2019). Thus, data collection capable of identifying risk groups associated with severe adverse reactions is important in the management of leishmaniasis treatment. In the present study aimed to identify population characteristics of the Midwest region of Brazil (endemic area) that help prevent or reduce adverse effects, contributing to the therapeutic success of patients.

## 2 Material and Methods

### 2.1 Study design and procedures

This research is a descriptive cross-sectional study conducted in patients diagnosed with leishmaniasis, treated at the University Hospital (UH) in the city of Cuiabá, in Mato Grosso state, Brazil, in the period of 2009 to 2014. The UH has an Infectious Disease Center that serves the entire urban and rural population of the state and is considered the main health facility in the region.

The therapeutic protocol of tegumentary leishmaniasis was indicated according to the clinical form, supported by the laboratory diagnosis and following the criteria established for each situation. For treatment initiation the confirmation of diagnosis is required by clinical or laboratory criteria or, where it is not possible, by epidemiological criteria. Thus, for cutaneous clinical forms, the dose ranged from 10 to 20mg Sb<sup>+5</sup>/kg/day for adults and children administered for 20 consecutive days. And in all clinical forms involving mucosal, the dose used was 20mg Sb<sup>+5</sup>/kg/day for 30 consecutive days (BRASIL, 2013).

The diagnosis, treatment and monitoring of patients with leishmaniasis were performed compulsorily by the public health services. We assessed the medical records of these patients for data gathering. The index terms used for this research were prevalence of leishmaniasis, practices of treatment, adverse reactions, association between patients in treatment of leishmaniasis, which had side effects, and preventative measures. The determining of sample number was randomly conducted.

### 2.2 Criteria for inclusion and exclusion of the population

Patients from both sexes included in the survey were those with medical records consistent with leishmaniasis in the database of UH. We excluded all incomplete medical records and the requests and prescriptions from other divisions of the hospital that not the Reference Center of Infectious Diseases.

### 2.3 Study variables

The socio-demographic data were collected, considering the age, sex and level of education of the patients. It was evaluating the association of adverse reactions in patients under treatment of leishmaniasis in the UH, during the referred period. In the treatment of leishmaniasis one or more adverse effects may occur, promoted by the medicines administered. The adverse effect most frequently are arthralgia, myalgia, anorexia, vomiting, abdominal pain, edema, acute renal failure. However, the most severe adverse effects were evaluated separately from questionnaires, and them also considered as a variable. Accordingly, the following outcomes were evaluated: alterations in the electrocardiogram, hyperglycemia, alteration of renal function, increased transaminase enzymes through laboratory tests that assess the progress of heart and kidney disease caused by prolonged use of treatment.

### 2.4 Ethical Statements

The survey was approved by the Ethics Committee of the University Hospital Júlio Müller (Certificate of Presentation for Ethical Appreciation – CAAE, number 44516415.7.0000.5541 and protocol number 1.046.361/2015). The identities of prescribers, patients and others involved in this research were protected and the identification used only to control data collection, to ensure confidentiality of all information taken from the records, as well as the notification form and the database of National System of Reportable Diseases (SINAN) in Brazil.

### 2.5 Statistical analysis

Bivariate and multivariate descriptive analysis were performed. Tables show absolute and relative frequencies of categorical variables. In bivariate analysis was verified the association between independent variables (socio-demographic characteristics) with the dependent variables (initial drug treatment, drug used in treatment failure, pre-existing diseases). For further analysis of categorical variables, it was used the Chi-square method of Mantel-Haenszel or Fisher's exact test. In multivariate analysis it was applied Poisson regression, adjusted for interfering variables. Epi Info 7.0 and STATA 11.0 statistical packages were used to perform the analysis. A P-values < 0.05 ( $\alpha=5\%$ ) were considered statistically significant.

### 3 Results and Discussion

#### 3.1 Characteristics of patients in treatment

In this study, were evaluated 470 medical records of patients from both sexes, aged 8 to 65 years and various ethnicities. There was a prevalence of male patients (78.09%; n=367), with elementary school – incomplete (52.98%; n=249), identified themselves as brown skinned (93.19%; n=438) and urban inhabitance (77.61%; n=357) individuals. The demographic information of the participants is shown in Table 1.

**Table 1** - Socio-demographic characteristics of patients admitted to the University Hospital, for treatment of leishmaniasis, between 2009-2014 (n = 470)

Socio-Demographic Characteristics	N	%
<b>Sex</b>		
Feminine	103	21.91
Masculine	367	78.09
<b>Age group</b>		
< 10 years	14	2.98
10 – 19	29	6.17
20 – 29	53	11.28
30 – 39	87	18.51
40 – 49	96	20.43
50 – 59	92	19.57
60 e +	99	21.06
<b>Schooling</b>		
Illiterate	16	3.40
Elementary school – incomplete	249	52.98
Elementary school – complete	66	14.04
High school – incomplete	23	4.89
High school – complete	48	10.21
Higher education – incomplete	5	1.06
Higher education – complete	35	7.45
Unknown	28	5.96
<b>Race/Color</b>		
White	23	4.89
Brown	438	93.19
Indigenous	5	1.06
Unknown	4	0.85
<b>Inhabitance*</b>		
Urban	357	77.61
Rural	101	21.96
Periurban	2	0.43

\*Missing data.

Source: Research data

In the present study, although the incidence of male patients was higher, the results did not find an association between gender and adverse reactions. The higher frequency

of leishmaniasis in men is probably due to outside labor activities and exposition to agricultural areas, which are closer to the vector habitat, data also observed in other studies (BRILHANTE *et al.*, 2017; GOSCH *et al.*, 2017; TELES; FONSECA; GONÇALVES, 2019). Cutaneous and mucous-cutaneous leishmaniasis related to labor has been described in agricultural or forestry workers in endemic areas and in other specific situations of occupational exposure as, for example, in research and clinical analysis laboratories (TORRES-GUERRERO *et al.*, 2017). Regarding the age of patients, was identified ages ranged from 8 to 65 years and the prevalence was of adult individuals aged over 30 years. This is because individuals are generally more productive in this age group (TELES; FONSECA; GONÇALVES, 2019), increasing the risk of contracting leishmaniasis due to work activities, especially in the fields of agriculture and extractivism (TORRES-GUERRERO *et al.*, 2017).

Concerning schooling, the results show that more than half of the patients had incomplete elementary degree (52.98%). In Cavalcante and Vale (2014) study, that took place in the state of Ceará (Brazil), it was also found a low level of education among the cases of adults affected by leishmaniasis: approximately 6.5% were illiterate and 57.5% had incomplete elementary school. The education level, income and health are the pillars to calculate the human development index of a region. Education acts as a tool for the promotion of health, empowering individuals on disease prevention, appropriate means of hygiene and healthy nutrition (KHATOON *et al.*, 2017).

In addition, low education probably leads to lack of understanding and the higher exposure to the vector, for being more involved in field-related activities (GOSCH *et al.*, 2017; TORRES-GUERRERO *et al.*, 2017). Moreover, it is not possible to exclude the possibility of these individuals to engage in leisure activities such as fishing, hunting, camping, swimming in lakes and rivers, exposing them to environments compatible with the mode of transmission classically attributed to leishmaniasis infection (GOSCH *et al.*, 2017).

Another variable examined in this study was race/color, in which brown was the predominant result (93.19%). This data can be reinforced by the Brazilian Institute of Geography and Statistics (IBGE, 2017), that indicates a brown population of 46.7% in the overall resident population.

Table 2 demonstrates the characteristics of patients and the types of injuries reported in SINAN (National System of Reportable Diseases) notifications. The results show a higher incidence of leishmaniasis in cutaneous clinical form (72.34% of cases), followed by mucosal manifestations (27.66%). The new cases (individuals who first contracted leishmaniasis) were the most frequent (96.17% of patients). The majority of the patients presented weight inferior to 90 kg (85.56%). It was also noted that patients who had no pre-existing diseases had a higher prevalence of leishmaniasis (83.62%).

**Table 2** - Characteristics of the patients with leishmaniasis admitted in University Hospital from 2009 to 2014 (n=470)

Characteristics of the Disease	N	%
<b>Clinical form</b>		
Cutaneous	340	72.34
Mucosal	130	27.66
<b>Hospital admission*</b>		
New case	452	96.17
Recurrence	14	2.98
Transference	2	0.43
<b>Pre-existing diseases</b>		
Yes	77	16.38
No	393	83.62
<b>Work-related*</b>		
Yes	175	41.08
No	247	57.98
<b>Weight* (Kg)</b>		
< 90	322	86.56
> 90	50	13.44
<b>Initial Drug prescribed</b>		
Pentavalent Antimonial	403	85.74
Amphotericin B	11	2.34
Pentamidine	44	9.36
Another drug	12	2.55
<b>Drug used in case of initial treatment failure*</b>		
Amphotericin B	12	2.57
Pentamidine	10	2.14
Others	6	1.28
Not applicable	439	94.00
<b>Clinical Course*</b>		
Cure	399	85.26
Abandonment	15	3.21
Transference	44	9.40

\*Missing data.

Source: Research data

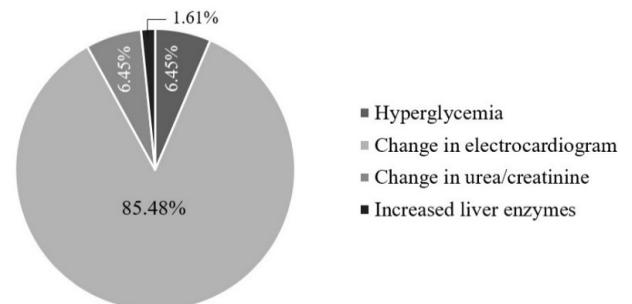
Regarding patient's treatment, pentavalent antimonial (Glucantime®) was the most drug prescribed (85.74%). The cure of these patients overcame to 85.26% rate, so the use of a second-choice drugs was rarely necessary (Table 2).

As for the clinical evolution, there was 85.26% prevalence of cure. The cure criteria of leishmaniasis is based on clinical aspects and it is recommended up to 12 months of regular monitoring. In the mucosal form of the disease, the cure criteria is defined by the regression of all lesions and confirmed by otorhinolaryngological physical examination, until six months after the conclusion of the therapeutic scheme (BORGES; GOMES; RIBEIRO-DIAS, 2018).

The drug of first choice for the treatment of leishmaniasis is pentavalent antimonials (Sb<sup>5+</sup>). The WHO recommends the use of two types of pentavalent antimonials, N-methylglucamine antimoniate and sodium stibogluconate, the latter not being marketed in Brazil (BRASIL, 2013). However, following WHO recommendations, 10 – 20mg Sb<sup>5+</sup>/kg/day (for 20 continuous days) and 20mg Sb<sup>5+</sup>/kg/day (for 30 continuous days) of meglumine antimoniate were used to treat

cutaneous and mucosal leishmaniasis, respectively. Although antimonials display important limitations such as high cost (EID RODRÍGUEZ *et al.*, 2019), toxicity and long periods of treatment, the pentavalent antimonial has a clinical cure rate of up to 80% when used in tegumentary leishmaniasis treatment (CATALDO *et al.*, 2018; WHO; PAHO, 2019), similar cure rate was observed in the present study.

Among patients that underwent leishmaniasis treatment, 13.19% (n=62) showed treatment-related adverse reactions. The most frequent side events was electrocardiogram alteration (85.48%; n=53), as showed in the Figure 1.

**Figure 1** - Adverse reactions observed in patients during treatment of tegumentary leishmaniasis in UH (n=62)

Source: Research data

Adverse reactions of medicines are unfavorable events associated with the time and the use of a medicine (OLIVEIRA *et al.*, 2011; EID RODRÍGUEZ *et al.*, 2019). In the review of the adverse effects of cutaneous leishmaniasis treatment performed by Oliveira *et al.* (2011) it is shown that the most frequently reported clinical adverse effects were myalgia, gastrointestinal disturbances, headache, anorexia, asthenia/fatigue, fever, cutaneous reactions and cardiovascular alterations.

Alterations in the electrocardiogram were observed in 85.48% of the patients with adverse reactions, in the present study. Electrocardiographic adverse effects such as flattening, or inversion of T wave or long QT interval are cardiac effects associated with the duration of the therapeutic treatment and the daily dose of Sb<sup>5+</sup> (OLIVEIRA *et al.*, 2011). Electrocardiogram changes were evaluated in patients under treatment with systemic meglumine antimoniate. The most common change in the meglumine antimoniate treated patients was prolongation of QT interval (SADEGHIAN, ZIAEI, SADEGHI, 2008; OLIVEIRA *et al.*, 2011). Laboratory adverse effects described less frequently are changes of the renal function and elevated levels of liver enzymes with increased serum levels of urea and creatinine (OLIVEIRA *et al.*, 2011; BERBERT; DE MELLO; WOLF NASSIF, 2018).

### 3.2 Characteristics associated with adverse events during treatment

After socio-demographic and health characteristics survey of the patients with tegumentary leishmaniasis, statistical analyzed was realized to found association with adverse

reactions during treatment. Table 3 describes the association of socio-demographic variables with adverse reactions in patients receiving treatment for leishmaniasis. In the present study, nor gender or race showed significant statistical differences when related to adverse effects. Nevertheless, individuals aged 60 years old or more showed the highest prevalence of adverse reactions (45%), PR = 9.79 (CI95% = 5.86 – 16.34),  $P < 0.001$ . It was found that patients with 60 years or older suffer more side effects. This can be justified by the clinical conditions of the patients. It is known that the elderly can present compromised liver enzyme system, processes of

absorption and kidney function that facilitates the appearance of adverse effects. In addition, the elderly can often exhibit polypharmacy behavior which increase the chances of drug interaction leading to various adverse reactions (CASTILHO *et al.*, 2018; TATUM *et al.*, 2018).

In addition, patients who have studied up to the incomplete elementary school and those living in rural areas also had a significant but weak association with adverse effects during treatment (PR = 0.19 (CI95% = 0.10 – 0.34) /  $P < 0.001$ ) and (PR = 0.45 (CI95% = 0.21 – 0.96) /  $P = 0.028$ ), respectively (Table 3).

**Table 3** - Prevalence of socio-demographic characteristics associated with adverse reactions in patients on treatment of leishmaniasis in University Hospital (2009 – 2014)

Variables	n/N	Prevalence (%)	PR	(CI 95%)	P-value
<b>Sex</b>					
Feminine	19/103	18.45		1.00	
Masculine	43/367	11.72	0.63	(0.38 – 1.04)	0.074
<b>Age Group</b>					
< 60	17/370	4.52		1.00	
> 60	45/100	45.00	9.79	(5.86 – 16.34)	<0.001
<b>Weight*</b>					
< 90	1/50	2.00		1.00	
> 90	11/322	3.42	0.58	(0.07 – 4.43)	1.000
<b>Schooling</b>					
Other educational degrees	49/199	24.62		1.00	
Elementary - incomplete	13/271	4.80	0.19	(0.10 – 0.34)	<0.001
<b>Race/Color**</b>					
White	03/23	13.04		1.00	
Brown	58/438	13.24	1.01	(0.34 – 2.99)	1.000
Indigenous	0/5	-	-	-	1.000
<b>Inhabitation*</b>					
Urban	55/359	15.32		1.00	
Rural	7/101	6.93	0.45	(0.21 – 0.96)	0.028

\*Missing data. \*\*Fisher's exact test. PR - prevalence ratio; CI - confidence interval.

Source: Research data

The leishmaniasis recurrence did not affect the presence of adverse reactions in these patients. The treatments started with amphotericin B (PR = 18.31 (CI95% = 9.26 – 36.21),  $P < 0.001$ ) and pentamidine (PR = 25.51 (CI95% = 15.08 – 43.14),  $P < 0.001$ ) showed statistically significant associations

with the adverse effects. However, when these drugs were used as second choice, in the cases of initial treatment failure, this association was not observed. Other variables such as weight and clinical course did not show significant prevalence of adverse reactions (Table 4).

**Table 4** - Prevalence of health characteristics associated with adverse reactions in patients on treatment of leishmaniasis in University Hospital (2009 – 2014)

Variables	n/N	Prevalence (%)	PR	(CI 95%)	P-value
<b>Clinical Form</b>					
Cutaneous	32/340	9.41		1.00	
Mucosal	30/130	23.08	2.45	(1.55 – 3.86)	<0.001
<b>Hospital admission†</b>					
New Case	60/462	13.27		1.00	
Recurrence	1/14	7.14	1.85	(0.27 – 12.46)	1.000
Transference	1/2	50.00	7.00	(0.67 – 72.86)	0.241
<b>Pre-existing Diseases</b>					
No	30/393	7.63		1.00	
Yes	32/77	41.56	5.44	(3.52 – 8.40)	<0.001

<b>Work-related*</b>					
No	39/247	15.79		1.00	
Yes	14/175	8.00	0.50	(0.28 – 0.90)	0.017
<b>Initial Drug prescribed*</b>					
Pentavalent antimonial	14/403	3.47		1.00	
Amphotericin B	7/11	63.64	18.31	(9.26 – 36.21)	<0.001
Pentamidine	39/44	88.64	25.51	(15.08 – 43.14)	<0.001
Other drugs	2/12	16.67	4.79	(1.22 – 18.80)	0.073
<b>Drug used in case of initial treatment failure*</b>					
Amphotericin B	5/12	41.67		1.00	
Pentamidine	7/10	70.00	1.68	(0.76 – 3.67)	0.230
Others	4/6	66.67	1.60	(0.66 – 3.84)	0.619
<b>Clinical Course*</b>					
Cure	53/399	13.28		1.00	
Abandonment	4/15	26.67	2.00	(0.83 – 4.82)	0.137
Transference	2/44	4.55	0.34	(0.08 – 1.35)	0.144

\*Missing data. †Fisher's exact test. PR - prevalence ratio; CI – confidence interval.

**Source:** Research data

Some variables such as clinical form of leishmaniasis, pre-existing diseases and work-exposure presented a higher likelihood of developing adverse effects during treatment (Table 4). Patients with mucosal form of leishmaniasis presented association of PR = 2.45 (CI95% = 1.55 – 3.86),  $P < 0.001$ ) with adverse reactions. And those with pre-existing diseases the association with adverse effects was PR = 5.44 (CI95% = 3.52 – 8.40),  $P < 0.001$ ). The pre-existing diseases identified in this survey were: hypertension, diabetes, human immunodeficiency viruses (HIV), psoriasis vulgaris and rheumatoid arthritis, as shown in Table 5. Among individuals with pre-existing disease, 74.03% (n=57) are hypertensive, 12.99% (n=10) are diabetics and 5.19% (n=4) are hypertensive/diabetics. Taking in consideration all adverse effects observed, 93.75% occurred in hypertensive patients (Table 5). In addition, data analysis shows that 24.59% (n=14) patients with hypertension and one with hypertension/diabetes had some type of adverse effect. Adverse effects observed during treatment of patients with previous diseases include blood glucose change, amylase increase, cardiotoxicity, electrocardiogram abnormalities, herpes zoster, renal failure and drug allergy.

**Table 5** - Pre-existing disease and laboratory and electrocardiographic adverse effects in patients on treatment of leishmaniasis in University Hospital (2009 – 2014)

Pre-existing diseases	n	Prevalence of Adverse Effects, n(%)
Hypertension	57	14(24.56)
Diabetes	10	0
Hypertension/diabetes	4	1(25.00)
HIV/AIDS	4	0
Psoriasis vulgaris	1	0
Rheumatoid arthritis	1	0
Total	77	15

**Source:** Research data

The pentavalent antimonials are drugs commonly used in the treatment of cutaneous and muco-cutaneous leishmaniasis. However, treatment with these drugs is expensive and can cause serious adverse effects (CARVALHO *et al.*, 2019). The present work showed the prevalence of adverse side effects associated with patients with pre-existing diseases. This suggests that the altered physiological conditions favor patient's onset of side effects during treatment. Hypertension was the most frequent comorbidity. Similar data were also presented by Amato *et al.* (2009), who evaluated 140 patients with mucosal leishmaniasis and observed that 42.86% were hypertensive. When analyzing data from patients with pre-existing disease, it was observed that hypertensive patients have a higher risk of adverse effects. No reports of association between pre-existing hypertension and adverse events were found in leishmaniasis patients. Thus, additional studies with a larger number of patients with pre-existing diseases, especially hypertension, should be performed to verify this relationship.

Amphotericin B and pentamidine are drugs usually used as second choice in the treatment of leishmaniasis (TORRES-GUERRERO *et al.*, 2017). In the current study, the initial treatment with amphotericin B as well as pentamidine showed significant association with the adverse effects (Table 4). The association of these drugs with adverse events observed in leishmaniasis patients may probably be due to the toxicity of these drugs (LANIADO-LABORÍN; CABRALES-VARGAS, 2009; OLIVEIRA *et al.*, 2011). In the study, some of the patients were treated with either amphotericin B or pentamidine because they had changes in the electrocardiogram were over 60 years old. This indicates that the adverse reactions may be associated with the patients age and their pre-existing diseases, as well as with the toxicity of the drugs.

The multivariate analysis through Poisson's regression final model was applied in order to check the combined

effect of the side-effects and the set of variables in patients undergoing treatment for leishmaniasis. With this analysis, it was found that the interaction between the initial drug prescribed (PR = 13.30 (CI95% = 7.07 – 25.02),  $P < 0.001$ ) and pre-existing diseases (PR = 2.03 (CI95% = 1.26 – 3.27),  $P = 0.003$ ) presented statistically significant association with adverse reactions. This shows that the presence of these variables represents a catalyzing effect for the development of adverse reactions.

Leishmaniasis is a mandatory reporting infection according to SINAN. However, it should also be remembered that, in this study model, underreporting of information can occur, as is the case with individuals who have difficulties in seeking medical help and the more detailed inclusion of analyzes during the treatment period. The absence of this information limits the studies, as these data are important and can contribute to a more in-depth assessment of the adverse effects of the drugs used.

#### 4 Conclusion

Although the treatments have achieved high rate of cure, this study demonstrated that it comes with adverse reactions that are particular to each type of medication used, the age and overall state of health of individuals. Knowledge about socio-demographic and health characteristics of the leishmaniasis population associated with adverse reactions is important for the development of new prevention strategies. Reduction of adverse reactions can lead to effective and prompt treatment. These data reinforce the need for further studies to minimize the toxic effects of drugs, especially in patients with more debilitating conditions.

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