

Visceral Leishmaniasis: Clinical-epidemiological characteristics of cases and deaths in the state of Sergipe

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Leishmaniasis Visceral: Características clínico-epidemiológicas de casos y muertes en el estado de Sergipe

Matheus de Albuquerque Santos¹, Samuel Lucas Calmon Rodrigues¹, Aécio Lindenberg Figueiredo Nascimento¹, Janylle Souza Rodrigues¹, Marco Aurélio de Oliveira Góes¹.

¹Universidade Federal de Sergipe, Campus de Lagarto, SE, Brazil

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maogoes@gmail.com

ABSTRACT

Background and Objectives: Visceral Leishmaniasis (VL) is an endemic anthroponosis that occur in tropical areas, which has shown expansion and global increase in lethality. This study aims to characterize clinical and epidemiological aspects of VL, identifying factors associated with death. **Methods:** This is an observational epidemiological study, using data from the state database of VL cases living in the state of Sergipe, notified between 2007 and 2016 at the SINAN (Information System of Notifiable Diseases). **Results:** 577 confirmed cases of VL were reported, with concentration in the urban area (76.1%), with a general lethality of 12.3%. There was a predominance of males (69.5%), with higher lethality. The highest concentration of cases occurred in the first decade of life (38.5%). The lethality increased with each decade from the age of 40, reaching 39.3% in people aged 60 years or older. In both 5-year periods (2007 - 2011 and 2012 - 2016), it was observed that the mean incidence coefficient (MIC) in children under 10 years was similar between both genders and from that point on, it was always higher in males. The manifestations related to higher lethality were: hemorrhages (30.3%), jaundice (28.1%), infection (26.4%), edema (25.1%) and HIV coinfection (26,9%). **Conclusion:** Although Sergipe is an endemic VL transmission area, there have been changes in the epidemiological pattern, with an increase in the incidence in the population over 40 years, which may reflect the increase in lethality. The identification of this new scenario and the recognition of severity signs are very important for its early diagnosis and timely treatment.

KEYWORDS: Leishmaniasis, visceral. Epidemiology. Mortality.

RESUMO

Justificativa e Objetivos: A Leishmaniose Visceral (LV) é uma antropozoonose endêmica em áreas tropicais que vem demonstrando expansão e aumento global da letalidade. Este estudo objetiva caracterizar aspectos clínicos e epidemiológicos da LV, identificando fatores associados ao óbito. **Métodos:** Trata-se de um estudo epidemiológico observacional, utilizando-se os dados da base estadual dos casos de LV

residentes no estado de Sergipe, notificados entre 2007 e 2016 no SINAN (Sistema de Informação de Agravos de Notificação). **Resultados:** Foram notificados 577 casos confirmados de LV, havendo concentração na zona urbana (76,1%), com letalidade geral de 12,3%. Houve predomínio no sexo masculino (69,5%), com maior letalidade. A maior concentração de casos ocorreu na primeira década de vida (38,5%). A letalidade aumentou a cada década a partir dos 40 anos, chegando a 39,3% em pessoas com 60 anos ou mais. Em ambos os quinquênios (2007 – 2011 e 2012 – 2016), observou-se que o coeficiente de incidência médio (CIM) em menores de 10 anos é semelhante entre os dois sexos e a partir daí apresenta-se sempre maior no sexo masculino. As manifestações relacionadas a maior letalidade foram: hemorragias (30,3%), icterícia (28,1%), infecção (26,4%), edemas (25,1%) e a coinfeção com HIV (26,9%). **Conclusão:** Apesar de ser uma área de transmissão endêmica de LV, tem ocorrido mudanças no padrão epidemiológico com aumento da incidência em faixas da população maior que 40 anos, o que pode refletir no aumento da letalidade. A identificação desse novo cenário e o reconhecimento de sinais de gravidade são muito importantes para seu diagnóstico precoce e tratamento oportuno.

DESCRITORES: Leishmaniose visceral. Epidemiologia. Mortalidade.

RESUMEN

Justificación y Objetivos: La Leishmaniasis Visceral (LV) es una antropozoosis endémica en áreas tropicales que viene demostrando expansión y un aumento global de la letalidad. Este trabajo pretende analizar y caracterizar aspectos clínicos y epidemiológicos de la LV, identificando factores asociados al óbito. Método: Se trata de un estudio epidemiológico observacional, utilizando los datos de la base estadual de los casos de LV residentes en el estado de Sergipe, notificados entre 2007 y 2016 en el SINAN (Sistema de Información de Agravios de Notificación). **Resultados:** Se notificaron 577 casos confirmados de LV, habiendo concentración en la zona urbana (76,1%), con letalidad general del 12,3%. Se observó predominio en el sexo masculino (69,5%), con mayor letalidad. La mayor concentración de casos ocurrió en la primera década de vida (38,5%). La mortalidad aumentó cada década a partir de los 40 años, llegando al 39,3% en personas de 60 años o más. En ambos quinquenios (2007 - 2011 y 2012 - 2016), se observó que el coeficiente de incidencia medio (CIM) en menores de 10 años es similar entre los dos sexos ya partir de ahí se presenta siempre mayor en el sexo masculino. Las manifestaciones relacionadas con la mayor letalidad fueron: hemorragias (30,3%), ictericia (28,1%), infección (26,4%), edemas (25,1%) y coinfección con VIH (26,9%). **Conclusión:** Aunque de ser un área de transmisión endémica de LV, se han producido cambios en el patrón epidemiológico con aumento de la incidencia en franjas de la población mayor a 40 años, lo que puede reflejar en el aumento de la letalidad. La identificación de este nuevo escenario y el reconocimiento de señales de gravedad son muy importantes para su diagnóstico precoz y el tratamiento oportuno.

PALABRAS-CLAVE: Leishmaniasis visceral. Epidemiología. Mortalidad.

INTRODUCTION

Visceral Leishmaniasis (VL) is an endemic anthroponosis found in tropical areas, of which vector in Brazil is the phlebotomine of the genus *Lutzomyia*. It is a potentially fatal infectious disease considered by the World Health organization (WHO) as a priority disease among tropical ones, mainly due to its increased incidence and areas

of transmission. Classified as a neglected disease, VL affects mainly low-income populations in developing countries, being endemic in 75 countries.^{1,2}

Six countries (Bangladesh, Brazil, Ethiopia, India, Nepal and Sudan) account for 90% of cases of VL worldwide. In the Americas, human cases of VL are present in 12 countries, and approximately 14% of the world cases are reported in Brazil. Therefore, Brazil, as well as Argentina and Paraguay, are classified as countries with increasing transmission.^{1,3}

In Brazil, although it is a disease that originated in the rural areas, mainly in the Northeast of the country, it has disseminated and undergone an important epidemiological change since the 80's, starting to show an essentially urban and peri-urban characteristic in some regions. Environmental and climatic alterations, the discontinuation of control actions, disorderly occupation of urban space, vector adaptation, increase in the elderly and immunosuppressed populations, such as those infected by the human immunodeficiency virus (HIV), have collaborated to this change.^{3,4}

In addition to the VL expansion, there has been a tendency toward an increase in its lethality worldwide. Several factors may be involved in cases of death from VL, ranging from individual issues such as the patient's immunological status, as well as sociocultural aspects and timely access to diagnosis and treatment.

A recent study analyzing data from the 2016 Global Burden of Disease (GBD) study indicates that while age-adjusted DALY (disability-adjusted life-years) have shown a decrease for all neglected diseases, it has not occurred when dengue, visceral leishmaniasis and trichuriasis are assessed, of which occurrence has substantially increased. Moreover, age-adjusted DALY rates have decreased for most Brazilian states, increasing only in the states of Amapá, Ceará, Rio Grande do Norte, and Sergipe.^{2,3,4}

In the state of Sergipe, VL has occurred endemically and an increase in lethality has been described. Therefore, the aim of this study is to characterize clinical and epidemiological aspects of VL, identifying factors associated with death from 2007 to 2016 in the state of Sergipe, Brazil.⁴

METHODS

The study was carried out in the state of Sergipe, located on the northeast coast of Brazil. The state is subdivided into 7 regional health and has 75 municipalities, of which Aracaju is the capital city. According to the Brazilian Institute of Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística* - IBGE), its estimated population is

2,287,116 inhabitants (2017) living in an area of 21,910,354km², equivalent to 0.26% of the national territory. Its Human Development Index (HDI) is 0.665, ranking 18th in the country.⁵

This is an observational epidemiological study, based on secondary data recorded in SINAN (Information System of Notifiable Diseases), in the database of Sergipe Health Surveillance Directory of the State Health Secretariat.

The confirmed autochthonous cases of Visceral Leishmaniasis that occurred in the state of Sergipe from 2007 to 2016 were assessed. The population data were obtained from IBGE (*Brazilian Institute of Geography and Statistics*), based on the population estimates for the intercensitary period.

The socio-demographic variables (gender, age, ethnicity, regional health of residence, area of residence) as well as clinical-epidemiological ones were analyzed (type of health unit, time between symptom onset and diagnosis, signs and symptoms, coinfection with HIV, diagnostic methods, diagnostic confirmation criteria, medication used in treatment and clinical outcome).

The data were extracted from the SINAN database of the Sergipe State Health Secretariat, using the TABWIN (DATASUS) application, which were exported to the create a database using the Microsoft Office Excel program and performing the descriptive exploration of the data. For the analysis of the incidence by age group and gender, the Mean Incidence Coefficient was calculated for each 5-year period, 2007 - 2011 and 2012 - 2016, considering for the calculation the mean number of cases that occurred during that period for the population of each age group in the central year for each 5-year period, that is, the estimated population by IBGE in 2009 and 2014, respectively. The statistical analysis was performed using the free software BioEstat. Results were considered statistically significant when the p-value was <0.05, considering the 95% confidence interval.

The study used secondary data after authorization from the state of Sergipe Health Surveillance Directory, according to the recommendations of Resolution 466/2012 of the National Health Council for Scientific Research in Human Subjects.

RESULTS

During the study period (2007-2016), 577 confirmed cases of VL were reported in residents of the state of Sergipe, with a concentration of cases in the urban area (76.1%). Of these, 71 died, showing a lethality of 12.3%.

Table 1 shows the main demographic characteristics related to deaths and cases of Visceral Leishmaniasis. There was a predominance of cases in males (69.5%), in which there was a higher lethality (13.0%). The highest concentration of cases occurred in the first decade of life (38.5%), in which the lethality was significantly lower. Lethality increased with each decade, being significantly higher over 40 years of age, reaching 39.3% in people aged 60 years or over. There were cases in all regional state health departments, affecting 57 (76%) of the 75 municipalities. There was a concentration of 58.4% of the cases in the regional state health department of Aracaju, which is the city capital of Sergipe and accounts for 45.6% of the total number of cases.

Table 1 – Sociodemographic characteristics of deaths and cases of Visceral Leishmaniasis (VL) in Sergipe, 2007 to 2016.

Variable	N. of cases		N. of deaths		Lethality	RR
	N	%	N	%	%	(95%CI)
Gender						
Male	401	69.5%	52	13.0%	13.0%	1.2(0.73 – 1.9)
Female	176	30.5%	19	10.8%	10.8%	0.83 (0.51 – 1.37)
Age range						
0 - 9 yrs.	222	38.5%	11	5.0%	5.0%	0.29 (0.16 – 0.55) *
10 to 19 yrs.	74	12.8%	5	6.8%	6.8%	0.51 (0.21 – 1.24)
20 to 29 yrs.	68	11.8%	7	10.3%	10.3%	0.81(0.39 - 1.69)
30 to 39 yrs.	74	12.8%	11	14.9%	14.9%	1.25 (0.69 – 2.26)
40 to 49 yrs.	62	10.7%	14	22.6%	22.6%	2.03 (1.2 – 3.42)*
50 to 59 yrs.	49	8.5%	12	24.5%	24.5%	2.19 (1.27 – 3.79)*
60 or older	28	4.9%	11	39.3%	39.3%	3.59 (2.14 – 6.04)*
Ethnicity						
Caucasian	68	11.8%	8	11.8%	11.8%	0.95 (0.48 – 1.90)
Mixed-race	421	73.0%	52	12.4%	12.4%	1.01 (0.62 – 1.66)
Black	43	7.5%	6	14.0%	14.0%	1.15 (0.53 – 2.49)
Ignored	45	7.8%	5	11.1%	11.1%	0.90 (0.38 – 2.11)
Area of Residence						
Rural	138	23.9%	12	8.7%	8.7%	0.65 (0.36 – 1.17)
Urban	439	76.1%	59	13.4%	13.4%	1.22(0.86 – 2.79)
Regional Health						
Aracaju	337	58.4%	38	11.3%	11.3%	0.82 (0.53 – 1.27)
Estância	60	10.4%	7	11.7%	11.7%	0.94(0.45 – 1.96)
Glória	44	7.6%	4	9.1%	9.1%	0.72(0.28 – 1.89)
Itabaiana	20	3.5%	5	25.0%	25.0%	2.11 (0.96 – 4.66)

* *p* value < 0.05

Lagarto	17	2.9%	1	5.9%	0.47(0.07 – 3.19)
Propriá	33	5.7%	7	21.2%	1.80 (0.90 – 3.62)
Socorro	66	11.4%	9	13.6%	1.12 (0.59 – 2.15)
Cases of VL	577	100.0%	71	12.3%	

The mean incidence coefficient (MIC) was 3 cases per 100,000 inhabitants for the first five years (2007-2010) and 2.5 cases per 100,000 inhabitants for the second period (2012 - 2106). Table 2 shows the analysis of the mean incidence coefficient (MIC) of VL by gender and age group for the two analyzed 5-year periods. In both cases, it can be observed that the MIC in children under 10 years of age is similar between both genders and, from then on, it is higher in males. In the first 5-year period (2007 - 2011), it is observed that the highest MIC occurs in children up to 9 years of age (6.4 cases/100,000 inhabitants), with a decrease in other age groups in both genders. In the second 5-year period (2012-2016), despite the fact that the highest MIC was found in children under 10 years old (5.0 cases/100,000), it can be observed that males, after an initial decrease between 10 and 19 years old, progressively increase, showing a MIR of 5.3 cases/100,000 individuals aged 40-49 years and 6.0 cases/100,000 individuals aged 50-59 years.

Table 2. Mean incidence coefficient (per 100,000 inhabitants) by gender and age group and ratio between males and females (M / F), in 2007 – 2011 and 2012 – 2016.

Age range	2007 – 2011				2012 - 2016			
	Male	Female	General	M/F	Male	Female	General	M/F
0 - 9 years	6.4	6.3	6.4	1.0	5.0	4.9	5.0	1.0
10 - 19 years	4.0	0.9	2.4	4.6	1.8	0.9	1.3	2.1
20 - 29 years	2.9	1.0	2.0	2.8	2.4	0.6	1.5	4.1
30 - 39 years	4.3	1.2	2.7	3.7	3.1	0.6	1.9	4.8
40 - 49 years	3.7	0.3	1.9	11.1	5.3	0.7	2.9	7.5
50 - 59 years	4.3	0.5	2.3	8.5	6.0	1.0	3.4	6.0
60 or older	2.1	0.6	1.3	3.4	3.3	0.4	1.5	8.0
General	4.2	1.9	3.0	2.2	3.6	1.4	2.5	2.6

The diagnosis of VL was performed in the hospital network in 90.6% of the notified cases and the others in Basic Health Units. The confirmation criterion was the laboratory test in 536 (92.9%) of the cases. Among the laboratory tests, the Indirect Immunofluorescence Reaction (IFAT) was performed in 468 patients, with a positive result in 84.2%. The other methods performed were the rapid test rK39 and parasitological

research (in bone marrow aspirate), with positive results in 83.4% and 69.2%, respectively (TABLE 3). The diagnosis in 41 cases (7.1%) was based on clinical and epidemiological criteria.

Table 3. Distribution of laboratory test results in cases with a laboratory-based diagnosis of Visceral Leishmaniasis (VL) in Sergipe, 2007 to 2016.

Result	IFAT		rK39		Parasitological test	
	N	%	n	%	n	%
Negative	74	15.8	60	16.6	52	30.8
Positive	394	84.2	301	83.4	117	69.2
Total performed	468	100.0	361	100.0	169	100.0

IFAT = Indirect Immunofluorescence Reaction; rK39 = rapid qualitative test for detection of antileishmanial antibodies using recombinant K39 protein.

In most of the VL cases studied (66.4%), the time between symptoms onset and diagnosis was up to 30 days. The most frequent clinical manifestations were: fever (96.0%); splenomegaly (90.6%); hepatomegaly (81.2%); weakness (85.3%) and weight loss (80.4%). Some manifestations were significantly associated with higher lethality, such as hemorrhages (30.3%), jaundice (28.1%), infection (26.4%) and edema (25.1%). HIV co-infection occurred in 4.5% of cases, significantly increasing lethality (26.9%) in relation to the other cases (11.6%) (TABLE 4).

The medication initially used in 56.7% of cases was the pentavalent form of N-methylglucamine antimoniate, followed by amphotericin B deoxycholate (26.0%) and liposomal amphotericin B (14.9%).

Table 4. Clinical characteristics of deaths and cases of Visceral Leishmaniasis (LV) in Sergipe, 2007 to 2016.

Variables	Cases of VL		Deaths	Lethality	RR
	n	%	n	%	(95%CI)
Interval between symptom onset and diagnosis					
Up to 60 days	383	66.4%	49	12.8%	1.13 (0.70 – 1.81)
61 - 90 days	88	15.3%	6	6.8%	0.51(0.23 – 1.15)
> 91 days	106	18.4%	16	15.1%	1.29 (0.77 – 2.16)
Signs and Symptoms					
Coughing/diarrhea	367	63.6%	52	14.2%	1.57 (0.95 – 2.57)
Pallor	460	79.7%	61	13.3%	1.55 (0.82 – 2.93)
Splenomegaly	523	90.6%	68	13.0%	2.34 (0.76 – 7.19)

Infection	148	25.6%	39	26.4%	3.53 (2.30 – 5.42)*
Hemorrhages	109	18.9%	33	30.3%	3.73 (2.46 – 5.66)*
Hepatomegaly	469	81.3%	55	11.7%	0.79 (0.47 – 1.33)
Jaundice	121	21.0%	34	28.1%	3.46 (2.27 – 5.27)*
Fever	554	96.0%	70	12.6%	2.19 (0.42 – 20.01)
Weakness	492	85.3%	62	12.6%	1.19 (0.62 – 2.30)
Weight loss	464	80.4%	64	13.8%	2.23 (1.05 – 4.73)*
Edema	175	30.3%	44	25.1%	3.74 (2.40 – 5.84)*
HIV Coinfection					
Yes	26	4.5%	7	26.9%	2.32 (1.18 – 4.55)*
No	551	95.5%	64	11.6%	0.43 (0.22 – 0.85)*
Medication used					
Amphotericin B deoxycholate	150	26.0%	26	17.3%	1.64 (1.05 – 2.57)
Liposomal Amphotericin B	86	14.9%	15	17.4%	1.53 (0.91 – 2.58)
Pentavalent N- methylglucamine antimoniate	327	56.7%	16	4.9%	0.22 (0.13 – 0.38)*
Not used	14	2.4%	14	100.0%	
Cases of VL	577	100.0%	71	12.3%	

* p value < 0.05

DISCUSSION

Visceral leishmaniasis (VL) is an endemic disease in the state of Sergipe, located in northeast Brazil. VL cases have been recorded there since 1936, when Evandro Chagas described, in Aracaju, the first living patient with a diagnosis of the disease in Brazil. In the assessed decade (2007-2016), the state showed an annual average of 57.7 cases, higher than the average found in the previous decade, of 43.3 cases/year. Although the data show the concentration of VL in the metropolitan area (Aracaju Regional), there were cases of VL in 75% of Sergipe municipalities, distributed throughout the state, from the coastal region to the backwoods.^{6,7}

The predominance of males found in the study has been homogeneously verified by several authors, a fact that has been attributed to both hormonal factors and greater exposure of men in periurban and rural environments. In the pediatric age group, this disproportionality between the genders is not observed. The observed pattern of concentration of cases in the pediatric ranges, as seen in Sergipe, although classic in endemic areas, is no longer found in other studies, where young adults have been more

often affected. Local transmission characteristics can significantly influence the greater involvement of a given age group.⁸

When comparing the period of 2007 to 2011 with the period from 2012 to 2016, some differences are observed regarding the incidence distribution in the different age groups. It can be verified that, despite the persistence of the high incidence in individuals up to 9 years old, the second five-year period showed another peak of incidence, between 40 and 59 years, surpassing the MIC of VL in children. This fact may indicate the occurrence of changes in the pattern of transmission of this endemic disease in the studied area.⁸

VL has a wide spectrum of clinical manifestations, from asymptomatic forms (positive serology without clinical manifestations) to the classic form, with the presence of febrile hepatosplenomegaly, weight loss, pancytopenia and hypergammaglobulinemia, in addition to an important decline in the overall health status. The most frequently reported clinical manifestations were: fever (96%), splenomegaly (90.6%), weakness (85.3%) and hepatomegaly (81.3%), being the most often symptoms found in the literature. Factors related to the host and time of diagnosis can lead to variations in the frequency of the symptomatology.^{7,8,9}

Leishmania-HIV coinfection has shown large variations in several published samples, with the highest rates being found in some European countries, such as Spain (85%) and Italy (68.9%). In this study, Leishmania-HIV coinfection was present in 4.5% of the cases. Studies in Brazil have shown variations in the rates of this coinfection, finding lower rates in Tocantins (2.1%), Codó (Maranhão - 3%) and Fortaleza (6.6%). The identification of two endemic diseases in the territory has been the most important factor in determining the rates of coinfection.^{10,11,12}

HIV infection has been associated in some regions to the onset or increase in VL cases, since in addition to increasing the risk of becoming ill, it has been associated to a significant increase in lethality, as seen in this study, where lethality in cases of Leishmania-HIV co-infection was 26.9% ($p < 0.05$). The symptoms and evolution may vary in these patients, depending on the CD4 levels. The relevance of this prognostic factor probably arises from the induction of *Leishmania* replication by HIV, in addition to the fact that both induce a change in the Th1 response to Th2. It can be said that when in association, they mutually modulate their pathogens. In addition to HIV, studies have also shown there is an important association between VL and bacterial infections, in which cases their signs and symptoms may lead to an initial misdiagnosis.^{2,7,9,14}

The association of diagnostic methods may be necessary because, despite the high sensitivity of the serological methods, some VL cases are diagnosed based on nonspecific clinical and laboratory findings (pancytopenia, hypoproteinemia, albumin/globulin inversion). The diagnosis of 9.4% of the cases was based on clinical findings. The parasitological examination was performed in only 29.3% of the cases, with a positive result in 69.2%. The Indirect Immunofluorescence Reaction (IFAT) was the most often used test (81.1%), with a positive result in 84.2% of cases. This has been the most often used serological test for the diagnosis of VL in Brazil, with a sensitivity ranging from 55 to 96%, and specificity from 70 to 98%. Positive samples are those with titration starting at 1:80. The rapid test (rK39), which uses leishmaniasis antigen, besides being a noninvasive test, has shown good sensitivity (93%) and specificity (97%). In this study, the rK39 test was performed in 62.6% of the cases, with a positive result in 83.4% of cases.^{15,16}

Deaths from VL have been a matter of concern in several regions worldwide. In Brazil, a recent study shows that VL mortality and lethality rates have shown a significant increase in Brazil between 2000 and 2011, with different patterns between regions. In the study, the lethality found in Sergipe (12.3%) was higher than the national average (8.1%) and the one found in the northeast region (7.9%). Among the sociodemographic factors analyzed, only the age group significantly interfered with the evolution to death, with a gradual increase in lethality for each decade, being significantly higher after 40 years, reaching 39.3% in individuals aged 60 years or older. Older age brings a higher risk of mortality for many reasons, and one of the most important reasons is the association with chronic diseases and diagnostic delay. Despite the variations in lethality when the interval between symptom onset and the VL diagnosis was evaluated, reaching 15.1% in cases diagnosed after more than 90 days, there was no significant difference between the groups.^{4,13,17,18}

Some clinical features were strongly associated with a higher lethality, such as hemorrhage (30.3%), jaundice (28.1%), associated infection (26.4%) and edema (25.1%). In a recent meta-analysis, these manifestations have been identified as important predictors of fatal VL evolution. The presence of jaundice is associated with blood clotting disorders (thrombocytopenia) and suggests hepatic dysfunction, which can lead to important bleeding episodes. Therefore, the detection of bleeding at the time of the diagnosis or during the course of treatment is crucial for the identification of disease severity.^{13,14}

Pentavalent antimonials remain the most widely used drug worldwide for the treatment of VL, but several protocols have considered liposomal amphotericin as the drug of choice because of its greater leishmanicidal power and lower toxicity. The pentavalent antimonial was used in 56.7% of the cases, among which the lethality was 4.6%. The lethality was higher in patients who used the conventional (deoxycholate) and liposomal (approximately 17%) formulations. Corroborating the evidence, Brazil uses the pentavalent antimonial as the first line due to the lower cost, whereas the use of amphotericin is reserved for the severe forms, which already have a higher risk of death. The treatment follows the guidelines of the Brazilian Ministry of Health that recommend pentavalent antimony (SbV) as first-line therapy. Amphotericin B deoxycholate is recommended as the second-line drug, whereas the liposomal amphotericin B (LAmB) formulation is restricted to some special conditions (e.g., children <1 year and the elderly) and for the treatment of patients who have a contraindication or do not respond to the first- and second-line treatments. Because of the observational nature of this study, it is not possible to make inferences about the influence of the therapeutic option and lethality. Several authors argue that despite the higher costs, the superiority of liposomal amphotericin regarding efficacy, safety and time of treatment justifies its use as the first-line treatment.^{16,18,19}

An important limitation of the study is the use of secondary data, which came from the notification forms, and show variation regarding the quality of filled out data and limitation of the possibilities of variables to be explored.

The results of this study show, in addition to changes in the affected patients' profiles, that the high lethality of leishmaniasis constitutes a challenge for the state government. The timely identification of classic clinical manifestations (febrile hepatosplenomegaly), as well as those related to the worse prognosis, are important factors for the improvement of these results, together with increased access and favorable use of immunological and parasitological methods. Similarly, the therapy used in Brazil, which differs from that in other countries, also has an influence on the evolution of this disease, which was not demonstrated in this study because the use of liposomal amphotericin is reserved for the most severe cases. In addition to the care of human cases, for effective control of VL, prevention interventions should include vector control, reduction of infection in dogs and dissemination of knowledge about visceral leishmaniasis to the population, especially regarding the new transmission scenarios.

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