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Mucosal Injuries by Tegumentary Leishmaniasis: A Systematic Review

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Abstract: American Tegumentary Leishmaniasis (ATL) it's the name given to the amount of infection diseases that cause immunological and polymorphic changes on the skin and mucosa. Caused by the contamination of protozoa of the genus Leishmania, the pathogenesis in question can manifest itself in the Tegumentary (mucosa and cutaneous) and in the visceral form, depending on the parasite and the host. The aim of this study was to collect the scientific knowledge produced about the Mucosa Tegumentary Leishmaniasis, presenting the epidemiological, clinical, diagnostic and therapeutic relations available in the researched literature. It was applied the Muños Protocol (2002) in published articles between 1981 and 2018 and indexed in the database of the Health Virtual Library (HVL) that was selected for this review study. The research strategy used was: "Tegumentary Leishmaniasis" and "Mucosa", including, too, the following limits: articles in Portuguese, English and Spanish, available. The works present interfaces of Mucosa Tegumentary Leishmaniasis, stating epidemiological, clinical, diagnostic and therapeutic data of the pathology. It is evidenced the importance of the realization of studies about this theme to the development of new medical treatments. It is noticed that there is still a limited number of researches in this field, becoming necessary new studies about the theme.

Keywords: Mucosal injuries. Leishmaniasis. Infection diseases.

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Introduction

The American Tegumentary Leishmaniasis (ATL) is a zoonosis of wild animals, mainly rodents, being transmitted by certain species of sand flies of tropical forests (Amato, 1996). This infectious and non-contagious disease presents manifestation polymorphic on the skin and mucosa caused by many protozoan of the genus Leishmania, being the most common in Brazil the Leishmania (Viannia) guyanensis, L. (Viannia) braziliensis, and L. (Leishmania) amazonensis (Murback 2011). Those are transmitted for the sting of insects of the genus Lutzomya, and who develops the form of promastigotes, while in the mammal host its morphology corresponds to the amastigote, parasite intracellular macrophage (Telmo, 2012).

The disease can be presented in the located cutaneous (LC) form, cutaneous disseminated (LCD), cutaneous diffuse (LCD) and mucosa (LM), with or without injuries on the skin. The Mucosa Leishmaniasis (ML) occurs in a percentage that varies in three to 5% of the infectious cases by L. (V) braziliensis; it is graver and can leave sequels (Velozo, 2006). In order of frequency, the mucosa injuries manifest themselves, mainly, on the nose, hard palate, pharynx and larynx, where can present itself with erythematous-infiltrated, granulose, ulcerated or polypoid aspect, with roughly shrouded surface (Neto, 2008). Can be complicated for infections as rhinitis, sinusitis, meningitis and bronchopneumonia, being this last the principal responsible for the obit (Marsden, 1986). This commitment can leave to the perfusion of the nasal septum, destruction of the nasal mucosa, labial, soft palate, pharynx and larynx (Silva, 2007).

The lymphatic metastasis or hematogenous of local cutaneous parasites of inoculation for the nasopharyngeal mucosa is considered the subjacent cause of the mucosa disease (Figueroa, 2009). The association of the infection by L. braziliensis with this form of the disease suggests that, beside the host, related factors to the parasite be relevant for the development of the mucosa disease (Lessa 2007). Previous studies has been calling attention to that constitute themselves risk factors to the mucosa leishmaniasis development the presence of injuries above the pelvic waist, cutaneous ulcers of a big size and inappropriate treatment to the cutaneous Leishmaniasis (Carvalho, 1994).

The condition of the skin and the auricular cartilage occurs for being a place with a lower temperature, conducive to the leishmaniasis growth, besides being an exposed area to the inoculation of the vectors (Ecco, 2000). The association of lower temperature with

leishmaniasis can be, in part, be explained for the documentation in vitro that the macrophages cultivated in the temperature of 29° Celsius with a minor capacity of destructing leishmaniasis than the macrophages cultivated in 33° Celsius (Scott, 1985). The specific destruction of nasal cartilage can also indicate autoimmune reaction, what would explain why some patients attend with intense tissue destruction meanwhile others just present the mucosa impairment decades later (Marsden, 1986). The cartilage commitment of the epiglottis and the arytenoids can occur like in the cartilaginous septum, in a bigger or smaller intensity, making the swallowing extremely painful, by the established perichondritis in these circumstances (Lessa, 1999).

The mucosa Leishmaniasis diagnosed are limited by the invasiveness and limited sensibility of the methods of biopsy and histopathology, as well the fact that these methods require qualified medical specialists (Figueroa, 2009). Thus, this work objectives to reunite the scientific knowledge produced about the Mucosa Tegumentary Leishmaniasis, presenting the epidemiologic, clinical, diagnostic and therapeutic relations, available in the researched literature.

Methodology

Published articles between 1981 and 2018 and indexed in the database of the Health Virtual Library (HVL) were selected for this review work. The research strategy used was: “Tegumentary Leishmaniasis” and “Mucosa”, being included, also, the following limits: portuguese, english and spanish articles, available in full. Were excluded revision articles, as well literature comments, editorials, communications and letters to the editor. The research period of the articles occurred between october 20th of 2018 and november 1st of 2018.

The articles selection was realized by two evaluators and, in the case of disagreements, the third examiner was summoned for the final consent. Each article was read in full and its information were disposed in a spreadsheet, including the publication year, authors, database and periodic. Then, the works were summited to three relevance tests composed by objective questions, that analyze the article relation with the proposed objectives for the consonant research descript by Muñoz et al., 2002.

The first relevance test consisted in the following questions: Does the study agree with the investigated theme? Was the published study stipulated in the project? Was the study

published in the language stipulated in the project? Does the study approach the solution of the problem that it is being investigated? Was the study included in?

The second test objectives to verify the methodology finality used for the study, having the following questions: Is the research problem clear? Do the objectives of the study have relation with the studied question? Is the methodology descript with clarity and approach all the objectives? Are the results compatible with the used methodology? There is accuracy in the employed results? Was the study included in?

In the relevance test, were extracted detailed information of each selected article, distributing them in a spreadsheet with the following questions: (a) Main theme; (b) Research type; (c) Study sample; (d) Adopted Methodology; (e) Statistical Analysis; (f) Results; (g) Conclusion. For the data studies, the following stage involved the information division obtained starting from the lecture of each one of the works in three categories: epidemiology, clinic and therapeutic.

Results

Among the 79 articles identified initially in the electronic search, only 24 articles were included in the final sample after the relevance tests and criteria analyze fully (Figure 1). The obtained references describe clinic evolutions, therapeutic methods and epidemiologic analyzes about mucosa injuries by Tegumentary Leishmaniasis (Table 1).

Figure 1. PRISMA diagram with methodological search results

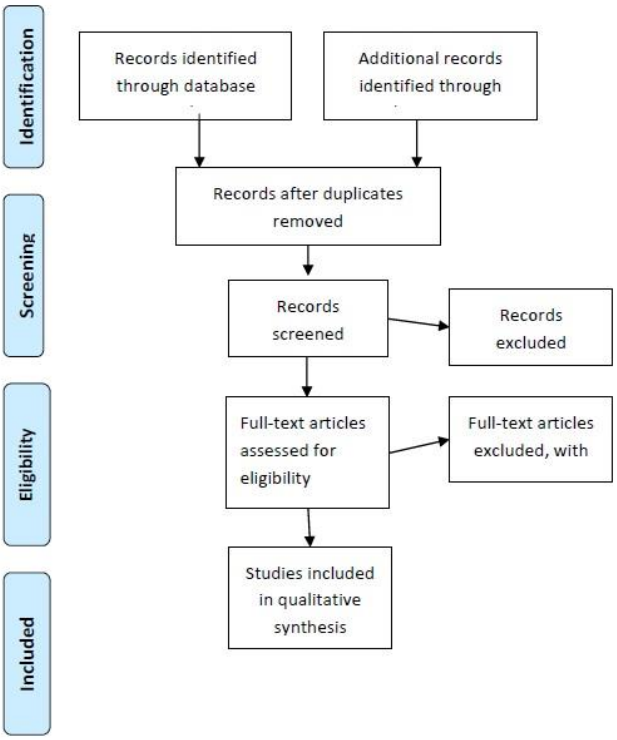


Table 1. Results by selected article

Author and year	Magazine	Objective	Methodology	Results	Conclusion
Padilha; Albuquerque;Pedrosa, 2010.	Pan-Amazônica Health Magazine	Evaluate the dinamic of the endemy and to plan measures of control, objecting lowing its impact on the population.	The epidemiologic indicators of the American Tegumentary Leishmaniasis of the Health Ministry, collected in a timeline of 10 years, has been quantified and evaluated.	There was the surging of 1.338 new cases where among them, 1.097 of the involved patients possessed age equal or bigger than 10 years. About the sex, 525 patients were from the feminine sex and 811 were from the masculine sex. In 2007 there was a peak of the disease where it was diagnosed in 969 patients in its cutaneous form. It was realized, then, 625 dermic reactions of Montenegro, obtaining, in 2008, the maximum value of 88,1% of the cases.	In Alagoas it was detected a bigger prevalence of the disease in men older than 10 years old. Besides, the cutaneous form was the most founded. Knowing the situation of the Leishmaniasis in Alagoas, helps the decision taking in public health in the State.
Oliveira, 2011.		To evaluate the genetic diversity of Leishmaniasis, analyzing directly the injuries in individuals with leishmaniasis, including individuals coinfected by the immunofeciscienc e human virus.	Analisou-se um total de 38 amostras de pacientes através de reações de cadeia de polimerase (PCR).	The presence of DNA of the parasite was evidenced in all of the samples analyzed, making possible the specific diagnosis. In samples of patient collected at the same time in the mucosa, oral and nasal, there wasn't a divergence in the genetic profile founded, while that the genetic profiles of collected samples in different times in the same location were different.	The genetic and statistic analysis made possible to affirm that the genetic diversity in the level of intrapatients is lesser than the observed among the patients.
Oliveira, 2011.		To characterize the epidemiologic profile of the american tegumentary leishmaniasis in the city of Rio Branco – Acre,from the period of 2000 to 2008.	It was analyzed 2671 cases of ATL in the city of Rio Branco. The data were obtained through the National Grievance of Notification System – SINAN.	It was verified that there was a growth in the occurrence of the leishmaniasis in urban habitants of the city. The biggest occurrence of the cases was in individuals from the masculine sex and the age range most impaired was the economically active of 15 to 49 years with 67,0% of the cases. The majority of the patients with ATL presented the cutaneous clinical form.	The leishmaniasis in the city of Rio Branco it characterizes itself as a transmission disease mainly rural, in the latter years the was a growth of the number of notifications in the urban field of the city.
Murback et., 2011.	Brazilian Dermatology Anais	Avaliar clínica, epidemiológica e laboratorialmente pacientes com Leishmaniose Tegumentar Americana, atendidos no Hospital Universitário Maria Aparecida Pedrossian, Universidade Federal de Mato Grosso do Sul, Brasil.	Foram avaliados dados de pacientes suspeitos de Leishmaniose Tegumentar Americana, de 1998 a 2008, e encaminhados ao Laboratório de Parasitologia/ para complementação diagnóstica.	Predominated men with more than 45 years, with a cutaneous form, with lesser than six months. The commitment of the mucosa was crescent with the growth of the age and bigger in patients that searched later treatment.	The association of parasitological and immunologic exam makes the laboratorial diagnosis more secure.
Braga, 2012.		Evaluate the ear functions of the patients with the mucosa form of ATL to verify the frequency of the tubal/otitis dysfunction medium with effusion and to describe the factors associated to it.	The patients were submitted to the otorhinolaryngology and speech-language pathology evaluations in the pre-treatment consults and until a month later the conclusion of the treatment or even the normalization of the alterations.	It was included 17 patients, being 15 of them from the masculine sex and 2 of the feminine sex. The age varied from 30 to 77 years. 23,5% presented curve B or C in the immitanciometric test, and from these, 2 presented retraction of the tympanic membrane and a conductive type audiometric curve.	These results made visible the importance of the realization of an otoscopic evaluation and audiometric and immitanciometric exams before and after the treatment of patients with mucosal leishmaniasis

Viana et al., 2012.	Medicine Magazine of minas Gerais	To know the patients' profile with cutaneous leishmaniasis in the city of Montes Claros – MG.	It was realized a data collect in the files of the Grievance and Notification of the National System of the patients with cutaneous leishmaniasis, in the period of 2002 to 2010.	The notifications were from 446 patients, being 283 men and 163 women. The age of the patients varied between 1 and 90 years. The clinical form predominant was the cutaneous, being registered new cases of the disease. In the diagnosis, the intradermic reaction of Montenegro presented positive cases in 281 patients in 308 realized tests.	It was concluded that thecutaneous leishmaniasis are in growth in the city and that there is the necessity of creating a conscientization program of the population about the expation of the disease in the last years. .
Dorta et al., 2012.	Experiment al Parasitology	To compare the efficiency of the methods of isolation of parasites ex vivo and in vivo.	Biopsy fragments of cutaneous injuries or mucosa were inoculated in the middle of cultures or in the rat's paw. It was evaluated 114 samples using both methods independently.	Patient samples with LC had an isolation rate higher in ex vivo cultures than in in vivo. However, almost twice the number of LM injury isolated was isolated using a rat model in comparation with isolated ex vivo cultures.	Use of genetically modified rats can improve the isolation of parasites. Isolation and stocking of parasites, are critical to evaluate the genetic diversity of the parasite, as well to study the host-parasite interactions to identify biological markers of Leishmaniasis.
Oliveira, 2013.		To describe the nutritional status of adult and senior patients with american tegumentary leishmaniasis.	It was realized a study with 68 adult and senior patients with ATL in the period of 2009 to 2012. The nutritional evaluation was realized through the weight, height, Corporal Mass Index and serum albumin.	Most of the samples were composed by men, adults with a grade of instruction of fundamental incomplete. The predominant form of ATL was the cutaneous and 39% presented comorbidities. The clinic and nutritional complications were reduced recently in the ingestion of food, nasal obstruction, oral ulcer and anorexia.	The serum albumin diminution affected negatively the injury healing, suggesting that a nutritional intervention could increase the efficacy of the ATL treatment.
Vanconcellos, 2013.		Describe the efficiency and the security of the meglumine antimoniate administrated by intralesional way, for the treatment of cutaneous leishmaniasis.	It was realized a study with patients attended in the Vigilance Lab in Leishmaniasis from the Clinic and Research Institute Evandro Chagas – FIOCRUZ from 2002 until july of 2011 that has been treated for cutaneous leishmaniasis with intralesional application of meglumine antimoniate.	The meglumine antimoniate administrated intralesional way had minimum adverse effects. Not having necessity of changing the drug to others with a harder administration and high cost, and without developing the mucosa injuries.	Patients with cutaneous leishmaniasis presented good therapeutic response to the meglumine antimoniate administrated by intralesional way.
Ruas, 2014.		Describe the vocal alterations in LM and evaluate the speech therapy effects in the rehabilitation of the disease.	In the first article it was realized a study with 26 patients with LM in activity, accompanied in the Clinic Research Institute Evandro Chagas – Fiocruz, in the period from 2010 to 2013. In the second article, was realized an intervention speech therapy study between 2010 and 2012, in 16 patients that presented favorable answer to the treatment for LM in the Vigileish between 2005 and 2009.	The middle ages were the 55 years being 81% from the masculine sex. The injuries founded itself distributed in the nasal, oral, pharynx and larynx cavity. The main complain referred was nasal obstruction followed by dysphonia, odynophagia and dysphagia.	Even after LM drug treatments, approximately 70% of the patients remain with vocal alterations, suggesting that exclusive drug treatment may not be sufficient for voice reestablishment.

Costa, 2014.		Evaluate the frequency of occurrence of oral injuries of ATL to describe its clinical, laboratory, therapeutic peculiarities.	A study was carried out using data obtained from medical records and clinical examination of the mucosa of the upper aerial-digestive tracts of 206 patients with Mucosa Leishmaniasis, assisted at IPEC – Fiocruz between 1989 and 2013.	There was a prevalence of the male gender among the patients with the mucosal form. It was possible to determine that the most affected mucosal site is nasal, followed by oral, pharyngeal and laryngeal mucosa.	Considering the worse therapeutic results associated with the presence of oral injuries, it is suggested that injuries at this location represent a worse prognostic factor for LM.
Galdino et al., 2014.	BMC Infectious Diseases	Evaluate the expression. Of IL-32 in cutaneous and mucosal injuries, as well as in peripheral blood mononuclear cells exposed to Leishmania braziliensis.	IL- 32, tumor necrosis factor and IL-10 protein expression. Were assessed by immunohistochemistr y in cutaneous and mucosal injuries and compared to healthy specimens.	Expression of IL-32 mRNA, in particular IL-32y, was also upregulated in injuries of patients with cutaneous or mucosal leishmaniasis.	These data suggest that IL-32 plays an important role in the inflammatory process caused by Leishmania sp. Or that IL-32 is crucial for controlling infection by Leishmania sp.
Martínez-Valencia et al., 2017.	PLoS Negl Trop Disease	To investigate clinical and parasitological parameters associated with the presence and viability of Leishmania after treatment and resolution of LC.	70 patients who were treated with meglumine antimoniate or miltefosine and cured were included in this study. The persistence and viability of Leishmania were determined by detection of DNA and RNA transcripts respectively before, at the end of treatment and 13 weeks after initiation of treatment in injuries and smears of nasal and tonsillar mucosa.	70% of the patients had evidence of persistent Leishmania at the 13th week after initiation of treatment. An earlier episode of LC has been shown to be a protective factor for the detectable persistence of Leishmania. DNA genotyping could not discern differences between persistent parasite populations and those isolated in the diagnosis.	Leishmania persists in the tissues of the skin and mucosa in a high proportion of patients who have achieved therapeutic cure for CL. This finding stimulates the evaluation of the contribution of persistent infection in the transmission and endemicity of CL, and the reactivation of disease and protective immunity.
Amato et al 1995	Journal of the Brazilian Society of Tropical Medicine	Evalute the utility of pentamidine when there is mucosal involvement in American cutaneous leishmaniasis	10 patients with ACL, who had mucosal injuries, were treated with pentamidine isethionate at a dose of 4mg/kg, every other day, intravenously.	The healing of the injuries occurred in 9 (90%) of the patients who completed the treatment. There was no relapse in the follow-up period of 1 to 24 months (mean of 7, 7 months).	Pentamidine isethionate is effective in wound healing, but there is a need for a better evaluation of its value in the prevention of relapses.
Brown, D.R. et al 1996	The Journal of Experiment al Medicine	To assess the need for NK1.1 Beta 2-microglobulin-dependent + T lymphocytes type 2.	It was used 2 mices with deficiency of beta 2m on both BALB/c and C57BL/ 6 backgrounds were used to check their ability to react by Th2 cells after a series of antigens stimulated by various pathways.	It was found by immunization with antigens that Beta 2m deficient mice developed Th2 functional responses similar to wild-type mice.	The results indicate that beta 2m-dependent T lymphocytes are not required for the development of Th2 in vivo.
Enciso et al 2000		To verify the osteo-facial impairment of human populations of ancient Peru by Leishmania Tegumentary of mucosa form.	First, a pathological pattern of LTA of a mucosal form in the human skull was defined i patients treated at the Evandro Chagas Hospital Research Center (FIOCRUZ), with a clinical History of	The rate of 2.07 for mucosal injuries compatible with ACL may suggest the high prevalence in a prehispanic era.	There was therefore confirmation of the hypothesis and indirect antecedents.

			destruction of the facial mass, mainly the oro-nasal cavity. Then there was the archaeological review of 241 skulls from the Inca cementery of Makat-tampu, Lima, Peru.		
Bevenuto, 2000		To better understand the epidemiology of American Cutaneous Leishmaniasis in the State of Espirito Santo.	Study of the number of cases occurred in the period from 1989 to 1998 by municipality. Using some types of analysis, the map projections were done year by year categorizing according to the parameters used by the FNS to classify Low, Medium, High and Very High Rates and to study the spatial behavior of the LTA by municipality.	The incidence in the period studied varies from 23/100.00 in 1989, increasing to 33.09 in 1993, falling progressively to 8.7 in 1996 and rising again to 20.41 in 1998, which indicates that the state has been maintained in most of the years studied, in the incidence range high.	In the time series studied, it was observed that there was no defined seasonality, an apparent cyclicity that needs further investigation has been noted.
Castro et al 2002	Journal of the Brazilian Society of Tropical Medicine	To know the epidemiological profile of cutaneous leishmaniasis in the Northern region of Paraná.	Survey of 316 cases of the disease in 35 municipalities of Paraná between 1993 and 1998.	Male subjects (61,2%), aged 15 to 49 years (70,8%) accounted for the majority of cases of ACL. 67% of the patients presented single injuries, 31% multiple injuries and 2% mucosal injuries.	The ATL in the state of Paraná is characterized as endemic. As an area of endemism it is observed that the conditions in which transmission occurs remain stable.
Serra et al 2003	Public Health Notebook	To describe the occurrence of LT in dogs from the town of Morada das Aguias (Tiririca Mount), Maricá, State of Rio de Janeiro, Brazil.	Eighty-three dogs were evaluated through clinical, serological and parasitological examination. Sera of 11 (13.2 percent) animals were reactive to indirect immunofluorescence (IFI) and 30 (36.1 percent) to the enzyme-linked immunosorbent assay (ELISA)	Cutaneous and / or mucosal ulcers were observed in 18 (n = 83; 21.7 percent) of the animals. Leishmania was isolated from 11 dogs.	The occurrence of the disease and occupation of the locality are discussed.
Garcia et al 2005	Brazilian dermatology anais	To compare the results of the Montenegro intradermalimetry (MRI), presence of leishmania in biopsy (Bc), indirect immunofluorescence reaction (Rifi), DNA sequencing and PCR-RFLP (-restriction fragment lenght polymorphism) for the diagnosis of ACL.	Was studied 152 patients with ACL. For PCR in Bc, specific primers were used for sequence of 120bp of the mini circle kDNA common to all species of leishmaniasis. The PCR product, used for sequencing and enzymatic restriction with Hae III, was compared to L. (L.) amazonensis and L. (V.) braziliensis cultures.	There was a predominance of male, white and urban professionals. The age ranged from three to 77 years. The majority was from the State of São Paulo, with the cutaneous form prevailing. The MRI was positive in 73.4 percent, and the Rifi in 59.7 percent, while the Bc showed presence of leishmania in 30.6 percent. PCR was positive in 81.6 percent, and PCR-RFLP identified L. (V.) braziliensis as the predominant species, which also occurred with sequencing. Comparing PCR-RFLP and sequencing, there was agreement between the results, showing significance of PCR-RFLP for L. (V.) braziliensis.	MRI and PCR were statistically equivalent as subsidiary methods for the diagnosis of LTA, PCR-RFLP and sequencing were also found in the identification of leishmania species, the first presenting lower cost and execution time compared to DNA sequencing.
Oliveira-Neto, Mattos, 2006	Journal of the Brazilian Society of Tropical Medicine	To propose an alternative antimonial scheme to be used in cutaneous leishmaniasis when high doses of	Use of intramuscular intravenous meglumine antimonia ampoule every day until clinical cure in a series of 40 cases. The total dose used per	Of the 40 patients studied, 36 are still under follow-up, with an average time of 10.7 ± 7 months and an average of 9 months. There were no recurrences or mucosal lesions.	The scheme was well tolerated, easy to apply and comparable to the WHO-officially recommended regimen, which is a

		antimony are undesirable	patient ranged from 1,822.5 to 12,150 mg of pentavalent antimony and the treatment time from 3 to 10 weeks with efficacy of 86 percent.		valuable alternative for cases with potential antimony toxicity or whose application of daily injections represents an obstacle to treatment.
Meneses, 2007		To describe the epidemiological, clinical, laboratory, therapeutic and evolutionary patterns (including sequelae) of the mucosal or cutaneous mucosal forms of American Cutaneous Leishmaniasis (ACL)	A total of 132 medical records were selected from patients attending the Otorhinolaryngology Clinic of the Evandro Chagas Clinical Research Institute (IPEC) / Fiocruz, Rio de Janeiro, between January 1, 1989 and December 31, 2004. The diagnosis was established based on epidemiological criteria , clinical and laboratory tests, including response to Montenegro intradermalimoration (IDRM), LTA serology, histopathology and culture.	The nasal cavities were affected in 92.4 percent of the cases. The most frequent aspect of lesions was mucosal infiltration. The ulcer was the active cutaneous lesion predominant in the cutaneous-mucosal form.	Of the patients that performed IDRM, 97.4 percent had a strong reaction. Indirect immunofluorescence serology titers declined steadily over two years posttreatment. In the histopathology, the predominant aspect was the chronic granulomatous inflammatory infiltrate, without the presence of amastigotes.
Lindoso et al 2009	British Journal of Dermatology	Describe a series of patients co-infected with Leishmania and HIV.	Analysis of medical records of patients by demographic data, clinical manifestations, diagnoses, treatments and results	15 cases of AIDS / LT were found. Several manifestations have been found, ranging from ulcer to polymorphic lesions. Mucosal lesions were present in 80% and cutaneous lesions in 73% of the patients. All received anti-Leishmania therapy and 53% relapsed. 67% received highly active antiretroviral therapy but did not show differences in results compared to those who did not. 40% died during the study period.	Clinical manifestations of LT in patients with HIV are diverse. The study emphasizes possible common manifestations of the disease in seropositives, especially in severe cases.
Figueroa et al 2009	Journal of infectious diseases	Detection of Leishmania in the unaffected mucosae of patients with leishmaniasis caused by Leishmania (Viannia).	The presence of Leishmania in the mucosa of 26 patients with cutaneous leishmaniasis and 2 with mucocutaneous leishmaniasis was evaluated. Samples of the nasal, tonsil and connective mucosa were analyzed using the polymerase chain reaction with LV-B1 primers and Southern blot hybridization.	2 patients with mucocutaneous leishmaniasis and 21 of 26 patients with cutaneous leishmaniasis had kinetoplast (kDNA) present in mucous membranes. KDNA was detected in the mucosa of patients with cutaneous disease.	The presence of asymptomatic parasites in the mucous membranes may be common in patients with Leishmania infection (Viannia).

Source: Research Data

Discussion

Epidemiology

The American Tegumentary Leishmaniasis (ATL) is a polymorphic disease on the skin and/or the mucosa that provokes ulcerated injuries, nodular, unique or multiples, caused by protozoa of the genus Trypanosomatidae. The presented disease presents a wide distribution in the country, with registers of cases in all of the brazilian regions. (Viana. G. et al., 2012) The ATL constitutes a Public Health problem. Its importance resides not only in its high incidence and wide geographic distribution, but also in the possibility of taking forms that can determine destructive injuries, disfiguring and also incapacitating, with a big repercussion in the psychosocial field of the individual. (Gontijo and Carvalho, 2003) The World Health Organization (WHO) includes the American Tegumentary Leishmaniasis among the six infectious diseases and priority parasite for control actions.

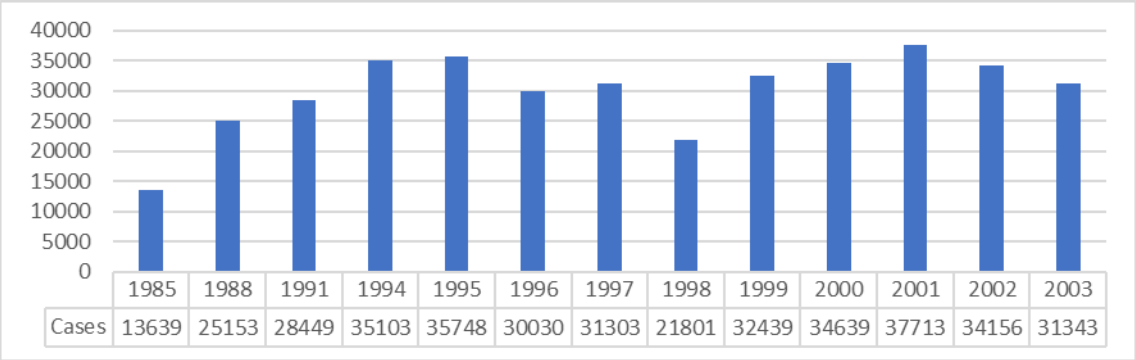
Human beings are always susceptible, not doing habitually part of the placement chain, can acquire the disease when unbalance, in an intentional way, the primitive forestall ecosystem, in which coexist the reservoir mammal, the vector insects and etiologic agent. (Furtado, 1989) The etiologic agent is a protozoa of the Leishmania genus, transmitted through the sting of insects known as sand flies (Meneses, 2007) The most prevalent species are Leishmania (V.) braziliensis and Leishmania (Leishmania) amazonensis (Cupolillo et al., 2003, Guerra et al., 2011, Lindoso and Linsoso, 2009).

After the transmitting, the evolution can vary from subclinical infections until grave and mutilating mucosa forms, depending on some factors. (Meneses, 2007) The type of the infection is determined by the genus Leishmania, factors of virulence and immunity answer, may result in cutaneous injury, cutaneous or visceral mucosa. The Mexican Leishmania complex and braziliensis are responsible for cutaneous injuries. The subgenus Vianna species is particularly important for the propriety of causing mucosa-cutaneous injuries. (Ameen, M., 2010)

The WHO stipulates, ordinarily, 12 million of Leishmania infections, being about 1,5 million of cases of cutaneous leishmaniasis in the world. From the 80's decade, in Brazil, it is verified the growth in the number of the cases of ATL registered, varying from 3.000 (1980) to 35.748 (1995). It is observed transmission peaks in each five years, presenting tendency in the growth of the number of the cases, starting from 1985, when it solidifies

the implantation of vigilance actions and the control of ATL in the country. (Oliveira, 2011).

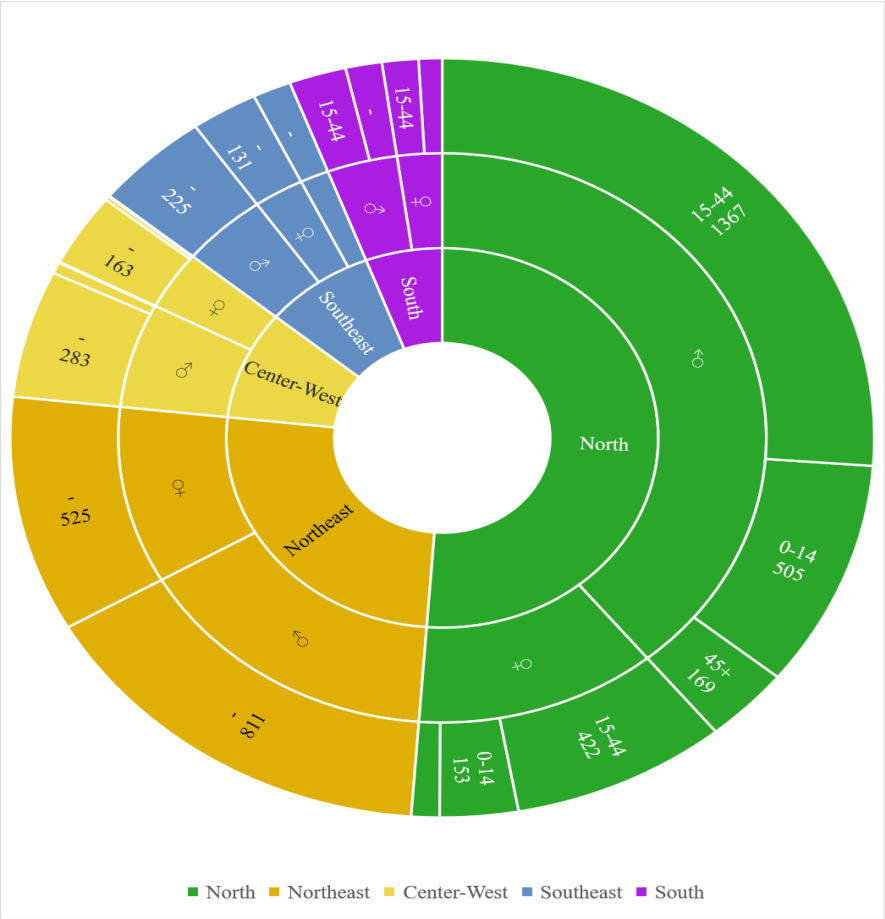
Figure 2. Number of cases of detection of autochthonous cases of ATL Brazil – 1985 to 2003; reproduced of the American Tegumentary Leishmaniasis atlas.



	1985	1988	1991	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
Cases	13639	25153	28449	35103	35748	30030	31303	21801	32439	34639	37713	34156	31343

The leishmaniasis prevails more in urban than the rural zones, with a suggestion of bigger occurrence in poor ambient and near to forest. (Meneses, 2007 Oliveira, 2011, Viana A. G. et al., 2012) It must be emphasized the occurrence in the peri-urban profile of transmission, it is related with the lack of basic sanitation, the precarious economic situation, the population migration for the peripheral of the cities, the inappropriate construction materials and the socializing with badland animals or even domesticated that serve as new reservoir of the disease, allied to the growth of the rate population that concentrates in the “deposit” of trash in these areas. (Basano and Camargo, 2004) The occurrence of high numbers of ATL cases between men and adults suggests more extradomiciliar transmission in economically active population, while the occurrence between woman and child suggests the transmission intra and/or peri domiciliary (Viana A. G. et al., 2012).

Figure 3. Chart with the epidemiologic prevalence of leishmaniosis cases studied in relation to region, gender and age, accordingly to the articles included on results.



Clinic and Diagnosis

American Tegumentary Leishmaniasis (ATL) is the name given to the infectious set that causes immunological alterations and polymorphic alterations on the skin and mucosa. Caused by the contamination with the protozoa in the genus Leishmaniasis, the pathogen in question can manifests itself in the tegumentary forms (mucosa and cutaneous) and in the visceral form, depending on the parasite and the affected host (Oliveira, 2011; Padilha; Albuquerque; Pedrosa, 2010).

There is in the American continent, more than 11 types of responsible species by the surging of the disease. In Brazil the dermotropic species more frequently founded are L. braziliensis, L. amazonensis and L. guyanensis, respectively. The cutaneous form of the

disease can be classified in located, disseminated and diffuse, varying accordingly with the local and with the amount of existent injuries (Braga, 2012).

The Located Cutaneous Leishmaniasis (LCL) is characterized by the appearing of papules with the evolution for the painless injuries with high borders well delimited, that appears generally in location of easy access to the transmitter insect. Besides that, the commonly ulcer presents rounded and reddish aspect and grainy coarse and can regress in the absence of treatment in a period of 15 months after its emergence (Oliveira et al., 2016; Murback et al., 2011).

In the Disseminated Cutaneous Leishmaniasis (DCLi), the injuries appear in bigger amount and spreads for all the cutaneous surface in a disorder form, simulating an aspect of unique injury. The Diffuse Cutaneous Leishmaniasis (DCL) it is differentiated of the other cutaneous forms because besides being rarer, it will present, with the disseminated injuries, the presence of infiltrations and tubercles in body areas very extended. Besides, the DCL possess a bad answer to the existent treatments, differently from the LCL and DCLi (Costa, 2014; Dorta et al., 2012).

Accordingly, to Martínez-Valência et al. (2017) and with Gomes et al. (2014), the most important characteristic of Mucosa Leishmaniasis (LM) is the appearing of invasive injuries in the respiratory paths. These, generally, are associated to the deformity and the destruction of facial structures, mainly septum nasal and most rarely mucosa on the mouth, pharynx and larynx. The LM tends to affect individuals that don't treat correctly the LC and it is associated to the lymphatic dissemination of the parasite. The patients commonly complain of symptoms with nasal obstruction, total sensibility, epistaxis, dysphagia, and others. It is important to salient that the existent injuries in the mucosa form of the disease are progressive and rarely regress spontaneously.

The diagnosed of Leishmaniasis is characterized as laboratorial, clinic and epidemiologic, seen that in the progress of diagnose must be observed, besides the clinical and laboratorial signs, if the patient resides or frequent recently endemic areas of the disease. The confirmation of the disease it is given through the realization of parasitological exams that permits to observe the presence of the parasite (RUS, 2014). There is a big number of laboratorial exams employed actually in the diagnosed of ATL like it is possible to observe in the Table 2.

Table 2: Most used laboratory tests, specifying their principles, methodologies, percentage of effectiveness and occurrence of cross-reaction (Ministry of Health, 2017).

Laboratorial Diagnosis				
Test	**Via**	**Methodology**	**Eficacy**	**Cross reaction**
Biopsy	Parasitological	Removal of cellular material or a tissue fragment from a living being for analysis.	89%	Absent
Culture	Parasitological	Culture in vivo.	95%	Absent
ELISA	Sorological	Teste imunoenzimático que permite a detecção de anticorpos específicos.	90%	Common
IFI	Sorological	A technique that allows the visualization of antigens through the use of specific antibodies labeled with fluorochrome, capable of emitting light at a certain wavelength, allowing their observation under a fluorescence microscope.	90%	Common
PAAF	Parasitological	The practitioner inserts a fine needle in the region and removes some cells that will be sent to the laboratory and analyzed.	89%	Absent
PCR	Molecular	Amplification of the parasite DNA in different types of samples.	94%	Absent
Lesion scraping	Parasitological	Microscopic visualization of the evolutionary forms of the parasite after scraping of the lesion.	80%	Absent
RIDM	Immunological	Immune response developed after contact with the protozoan.	80% - 100¨%	Absent
Western-Blot	Sorological	This technique uses gel electrophoresis to separate the native proteins from the parasite.	100%	Unusual

Vaconcellos (2013) affirms that the fundamental diagnostic of leishmaniasis consists in the realization of pathological exams, immunological and molecular. Among the parasitological tests more commonly realized, stand out the biopsy accompanied by histopathology conventional or immunohistochemica, scraping injury and aspired by fine needle (PAF), these permits the direct visualization of the parasite and therefore are the tests of first choice.

The immunological tests, act in an indirect form because it possibilities the visualization of immunological answer existents in the disease. The intradermic reaction of Montenegro (IRM) it is the most known exam and most realized, followed by serological exams of ELISA and indirect immunofluorescence. The IRM permits the answer visualization of the later hypersensitivity against the antigens of the

Leishmaniasis, while the serological tests evidence the existent antibodies against the parasite in question (Cerutti et al., 2017; Menezes-Souza et al., 2015).

The molecular diagnostic made by the chain reaction of polymerase (CRP) is considered the most sensible and effective, therefore its high cost and methodology more complicated don't permit that it is widely realized (Ferreira; Gomes; Pereira-Chioccola, 2015).

Therapy

In the treatment for ATL with impairment of the mucosa the antimonies pentavalents are the first-choice treatment indicated by the Health Ministry. The patients with mucosa injuries must utilize 20mg Sb5+ /kilo/day for 30 days, respecting the maximum limit of 3 dailies ampoules. The use of these drugs has been associated to adverse effects, mostly in the most elevated age range, and in the mucosa form. As second line medicaments it is indicated Anfotericine B and Pentamidine when there is no possibility of the use of antimonies or when the answer with the utilization of this isn't satisfactory. (Costa et al., 2014)

Studies from Velozo et al. (2006) approached a relate of a child's case with the age of 5 years impaired with ATL and mucosa, nasal and oral injuries, submitted to the initial treatment with the antimony pentavalent of 20mg SbV/kg in alternate days (23 days) by Pediatrics. With the surging of new injuries, it was administrated amphotericin B liposomal in the total doses of 517 mg, presenting growth in the urea and creatinine, decay of a general state and aggravation of the injuries, afflicting nose, lips, hard and soft palate, periorial region and right malar. The patient ended being afflicted for secondary infections, being taken to sepsis and obit. The author didn't consider satisfactory the treatment with the antimony pentavalent, however incomplete, being recurrence documented even after the patronized treatment. As the amphotericin B, he considered, even with applied adequate doses, that there are many therapeutic flaws.

In the researches of Amato et al. (1996) made with 10 patients impaired with mucosa injuries, being five of the patients compromising the nasal cavities, four of the nasal cavities and oropharynx and one of the palate caused for ATL, interned in the Division of Infectious and Parasitic Diseases from the Hospital of Clinics, of the Medicine College of the University of São Paulo and in the Public Server Hospital of the State "Francisco Morato de Oliveira", and treated with isethionate of pentamidine in the dose of 4 mg/kg in

alternate days intravenous way, 90% of the patients that finalized the treatment have had complete cicatrization of injuries without recurrence in the period of accompaniment from 1 to 24 months. The isethionate of pentamidine is well absorbed and stays, after a unique dose, detectable in the blood only during a short period being excreted slowly for the kidneys, presenting restrictions only with relation to the tolerance of the patients. Against this the precarious answers of the antimonies with relation to the impairment of the mucosa referred by the author, he pointed out the necessity of a better evaluation of pentamidine in the treatment of the mucosa injuries of ATL, mainly, to verify if it produces less recurrence than the antimonies.

The application of the treatment with pentavalents antimonies in 4 related cases of patients from the equatorial coast with ATL and mucosa injuries, mostly nasal and oral, by Ronquillo et al. (2012) shows itself satisfactory, being the response evaluated with the disappearing of activity signs, ulceration, erythema and, finally, fibrous cicatrization with permanent sequels. The pentavalent antimonies were considered, a therapy of choice.

In the studies of Costa et al. (2014), 78 patients impaired with ATL and oral mucosa affected were evaluated, being 93,7% treated with antimonies of meglumine, 3,4% with amphotericin B and 2,9% with other drugs. It was observed a bigger number of recurrences and lesser frequency of finalization and healing until a year later the treatment in these patients with buccal commitment. The presence of an oral injury in ATL also has been associated to a high alimentary deficit, with consequent malnutrition and difficulty in the healing of the injuries. The use of small doses of antimoniate of meglumine presented itself efficient in the treatment of patients with an oral localization. However, the results of these studies suggested that the oral involving in ATL is relate to worsts therapeutic results and may be considered as a factor of worst prognosis in its mucosa form.

Meneses et al. (2007 related a study with 128 patients, that realized a treatment in the Leishmaniasis Reference Center – IPEC/ Fiocruz,, with mucosa form of ATL, being 92,4% of the cases with the nasal cavity impaired. 86% of the patients were treated with a lower doses of antimoniate of meglumine (5mg Sb5+/ kg/day), with a good response to the treatment and lesser adverse effects, including the cases re-treated by recurrence and therapeutic flaw, being 79 submitted to the continuous scheme treatment, application for 30 days uninterrupted, and 31 to the scheme in series of 10 days with equal breaks without application. The majority of the adverse effects was soft and transitory or absents, mainly in the patients submitted to the continuous treatment. It is suggested that the use of high doses for the treatment of the mucosa form of ATL, as is regulated for the WHO, is

responsible for the most problematic adverse events, because in this study the majority of the submitted patients to lower doses didn't present meaning side effects.

In the studies of Ruas et al. (2014) in the Clinical Research Institute Evandro Chagas (IIPEC) with 16 treated patients of ATL associated to diverse mucosa injuries, mostly nasal (93,8%), 11 patients were impaired with vocal alterations, suggesting that the exclusive medicated treatment can be insufficient to the reestablishing of the voice. The number of sessions of speech therapy varied from 1 to 18, being 81% has frequented between 2 and 10 sessions. 6 patients presented significant general improvement; the rest of the patients stayed with some functional alteration though with a lower grade of intensity. The speech therapy rehabilited 71% of the patient's sequels. It is pointed out the necessity of a strategy implantation of speech therapies intervention in the post-treatment of the patients with mucosa injuries accordingly to this study.

Studies from Guedes et al. (2014) with rats BALB/c immunized intranasally with serine protease partially purified starting from extracts of soluble promastigotes (LaSP-Sol) and extracellular (LaSP-Ex) of amazonensis Leishmania before the infection by L. amazonensis, considering an effective form and non-invasive of inducing the active immunity against infectious agents, that enters the body through the mucosa, the local tolerance and the peripheral to antigens, showed that an antigen more defined, protease serine extracellular of L. amazonensis, is protector by intranasal way encouraging additional searches in this second generation vaccine. And in the relates of Seyed et al. (2016) the reverse vaccinology shows itself as a prophylaxis form more promising because through the genomic comparative or subtractive field it reduces the time to the development of attenuated live attenuated vaccines, once there is an availability of the genomic sequences of pathogenic cepes e non-pathogenic.

Researches of Hugentobler et al. (2012) realized with rats BALB/c using the oral immunization with live Lactococcus lactis co-expressing LACK and IL-12 showed protection against the Leishmania major subsequent. This vaccination induced to the antibodies production in the mucosa and answers T H 1 specific and systemic of LACK. This protection showed as a prophylactic promising form for relating itself with the generation of the answer T H 1 specific against the Leishmania.

Conclusion

The Tegumentary Leishmaniasis represents an expressive problem of world public health. In this vies, the epidemiologic studies descript referred that the prevalence of LT is notoriously related to the socioeconomic conditions of the populations, expressing the necessity of the development of jurisprudences that intensifies the care with the public health.

So, it's indispensable the conception and application of measures that strengthen the universal access to the health public services and the progress of education projects in health. Beyond that, the standardization of therapeutic procedures with the election of easy administration chemotherapeutics and low risk and cost for the ill. It is appropriated also the intensifying the governmental aids to the research and for the development of new antiparasitic drugs, beyond the epidemiologic analyzes studies that possibilities the planning and professional actuation in front of the TL.

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