LUMEN ET VIRTUS
ISSN: 2177-2789

AMERICAN TERGUMENTARY LEISHMANIASIS: BIOLOGICAL CHARACTERISTICS, PATHOPHYSIOLOGY, DIAGNOSIS AND TREATMENT

ASPECTOS BIOLÓGICOS DO PARASITO, FISIOPATOLOGIA, DIAGNÓSTICO E ESTRATÉGIAS TERAPÊUTICAS DA LEISHMANIOSE TEGUMENTAR AMERICANA

ASPECTOS BIOLÓGICOS DEL PARÁSITO, FISIOPATOLOGÍA, DIAGNÓSTICO Y ESTRATEGIAS TERAPÉUTICAS DE LA LEISHMANIASIS TEGUMENTARIA AMERICANA

https://doi.org/10.56238/levv16n50-031

Submitted on: 06/07/2025 **Publication date:** 07/07/2025

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ABSTRACT

American Tegumentary Leishmaniasis (ATL) is a zoonosis of significant epidemiological relevance, caused by protozoa of the Leishmania genus and transmitted by phlebotomine sandflies. This study presents a narrative literature review aimed at analyzing diagnostic and therapeutic advances in ATL, incorporating biotechnological innovations and identifying gaps in clinical management. The databases PubMed, SciELO, and Medline were consulted, covering publications from 2014 to 2024. Polymerase chain reaction (PCR) has emerged as a sensitive and specific method for early diagnosis. In terms of treatment, drugs such as miltefosine and liposomal amphotericin B have shown greater clinical efficacy and lower toxicity compared to traditional pentavalent antimonials. Adjunct therapies, including immunomodulators and photodynamic therapy, are also being explored. However, the genetic variability of Leishmania and its genomic plasticity contribute to treatment resistance, posing challenges to effective disease control. The findings demonstrate promising advances, although genetic resistance remains a significant barrier to effective ATL management, underscoring the need for new therapeutic strategies based on a deeper understanding of the parasite's genetics and biology.

Keywords: Cutaneous Leishmaniasis. Laboratory Diagnosis. Pharmacological Treatment. Genetic Variability. Parasitic Resistance.

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RESUMO
A Leishmaniose Tegumentar Americana (LTA) é uma zoonose de importância epidemiológica, causada por protozoários do gênero Leishmania e transmitida por flebotomíneos. Este estudo apresenta uma revisão narrativa da literatura, com o objetivo de analisar os avanços diagnósticos e terapêuticos da LTA, incorporando inovações biotecnológicas e identificando lacunas no manejo clínico. Foram consultadas as bases PubMed, SciELO e Medline, considerando publicações entre 2014 e 2024. A reação em cadeia da polimerase (PCR) destaca-se como método sensível e específico para diagnóstico precoce. No tratamento, fármacos como miltefosina e anfotericina B lipossomal mostram maior eficácia clínica e menor toxicidade em comparação aos antimoniais tradicionais. Terapias adjuvantes, como imunomoduladores e fotodinâmica, também vêm sendo investigadas. No entanto, a variabilidade genética do Leishmania e sua plasticidade genômica contribuem para a resistência aos tratamentos, dificultando o controle da doença. Os achados demonstram avanços promissores, embora a resistência genética continue sendo uma barreira significativa ao controle efetivo da LTA, reforçando a necessidade de novas estratégias terapêuticas baseadas no conhecimento genético e biológico do parasita.

Palavras-chave: Leishmaniose Tegumentar. Diagnóstico Laboratorial. Tratamento Farmacológico. Variabilidade Genética. Resistência Parasitária.

RESUMEN
La leishmaniasis cutánea americana (LCA) es una zoonosis de importancia epidemiológica, causada por protozoos del género Leishmania y transmitida por flebótomos. Este estudio presenta una revisión narrativa de la literatura, con el objetivo de analizar los avances diagnósticos y terapéuticos en LTA, incorporando innovaciones biotecnológicas e identificando brechas en el manejo clínico. Se consultaron las bases de datos PubMed, SciELO y Medline, considerando publicaciones entre 2014 y 2024. La reacción en cadena de la polimerasa (PCR) se destaca como un método sensible y específico para el diagnóstico precoz. En el tratamiento, fármacos como la miltefosina y la anfotericina B liposomal muestran mayor eficacia clínica y menor toxicidad en comparación con los antimoniales tradicionales. También se están investigando terapias adyuvantes, como inmunomoduladores y fotodinámicas. Sin embargo, la variabilidad genética de Leishmania y su plasticidad genómica contribuyen a la resistencia a los tratamientos, dificultando el control de la enfermedad. Los hallazgos demuestran avances prometedores, aunque la resistencia genética sigue siendo una barrera importante para el control efectivo de la LCA, lo que refuerza la necesidad de nuevas estrategias terapéuticas basadas en el conocimiento genético y biológico del parásito.

Palabras clave: Leishmaniasis cutánea. Diagnóstico de laboratorio. Tratamiento farmacológico. Variabilidad genética. Resistencia parasitaria.

INTRODUCTION

American Cutaneous Leishmaniasis (ATL) is a non-contagious infectious disease that affects the skin and mucous membranes, caused by protozoa of the genus *Leishmania* and transmitted to humans by the bite of infected female sandflies. In Brazil, ATL represents an important public health problem due to its wide geographical distribution and high incidence (VASCONCELOS et al., 2018).

According to data from the Ministry of Health, approximately 21,000 new cases of ACL have been registered per year in Brazil in the last five years, with an average incidence coefficient of 8.6 cases per 100,000 inhabitants. The regional distribution of these cases is uneven, with a greater concentration in the North, Northeast, and Midwest regions of the country (BRASIL, 2024).

From a biological point of view, ATL has a digenetic life cycle, alternating between the invertebrate host (sandfly) and the vertebrate host (humans and other mammals). The pathophysiology of the disease involves an intense T-cell-mediated immune response, which contributes to tissue destruction and the formation of ulcerated lesions on the skin and mucous membranes. In some cases, the exacerbated inflammatory response can progress to more severe forms of the disease, such as mucocutaneous leishmaniasis (REGO et al., 2023).

The clinical manifestations of ATL can occur in different forms. The most common cutaneous form begins with erythematous papules or nodules that progress to ulcers with raised borders and a granular fundus. These lesions can heal spontaneously after months or years, often leaving permanent scars. The mucosal form, on the other hand, can appear late, months or years after the initial skin infection, compromising the mucous membranes of the nose, mouth, and pharynx, with symptoms such as nasal congestion, bleeding, and ulceration, which can lead to deformities and functional impairment (SANTOS et al., 2019). In rarer cases, the diffuse or disseminated form of the disease is observed, characterized by multiple non-ulcerated skin lesions, associated with a deficient immune response and greater difficulty in treatment (DIAS et al., 2024).

Given the relevance of ATL in the context of Brazilian public health, it is essential to deepen knowledge about its biological aspects, pathophysiological mechanisms, diagnostic methods, and therapeutic approaches. In this sense, this literature review aims to analyze the characteristics of the parasite, the pathogenic processes of the infection, the available diagnostic strategies, and the most effective therapeutic options, with emphasis on the advances and challenges faced in the clinical management of the disease.

METHODOLOGY

This study is a narrative review of the literature, whose objective was to analyze the main biological, pathophysiological, diagnostic, and therapeutic characteristics of American Cutaneous Leishmaniasis (ATL), with emphasis on scientific and clinical advances published between 2014 and 2024. The narrative review is characterized by allowing a broader and more interpretative approach to the available literature, being useful for the construction of theoretical syntheses and identification of gaps in knowledge, without necessarily following the rigorous protocols of systematic reviews (CASARIN et al., 2020. ROTHER, 2007).

The search for studies was carried out in widely recognized scientific databases, including PubMed, Scopus, Web of Science, SciELO, and Google Scholar. Controlled and uncontrolled descriptors were used, combined by Boolean operators "AND" and "OR". Among the terms used, the following stand out: *"American tegumentary leishmaniasis", "Leishmania", "pathophysiology of leishmaniasis", "diagnosis of leishmaniasis"* and *"treatment of leishmaniasis".* In the PubMed database, the corresponding MeSH (Medical Subject Headings) terms were used to increase the sensitivity of the search. The research was conducted in Portuguese, English and Spanish.

The inclusion criteria included: original articles, systematic reviews, and clinical studies that directly addressed ATL. publications between 2014 and 2024. availability of the full text in the consulted databases. and relevance to at least one of the thematic categories: biological aspects, pathophysiology, diagnosis, or treatment. Articles that did not specifically address ATL, conference abstracts, dissertations, editorials, and papers not available in full were excluded.

The selection process involved screening by title and abstract, followed by full reading when necessary. Data extraction and analysis followed a thematic approach, with the findings organized into the following categories: biological characteristics of *Leishmania*. pathophysiology of the infection. diagnostic methods. and therapeutic approaches. The analysis sought to identify recurring patterns, contradictions, and gaps in knowledge, as well as to point out possible paths for future investigations.

This narrative review aims to offer a critical and accessible synthesis of current knowledge about ATL, contributing to the improvement of clinical management and public policies related to the disease.

DISCUSSION OF LITERATURE RESULTS

BIOLOGICAL CHARACTERISTICS OF LEISHMANIA

The genus *Leishmania* comprises digenetic protozoa of the family *Trypanosomatidae*, with a life cycle that alternates between two main forms: promastigotes and amastigotes. Promastigotes are elongated, extracellular forms, with a free flagellum and developed kinetoplast, which multiply in the digestive tract of the sandfly vector. Amastigotes, in turn, are intracellular, spherical forms without free flagellum, adapted to replication inside mammalian host macrophages (ROCHA et al., 2021).

These parasites have wide genetic and physiological variability, which contributes to the diversity of clinical manifestations of leishmaniasis, which can range from self-limiting skin lesions to severe and potentially fatal visceral forms (ROCHA et al., 2021).

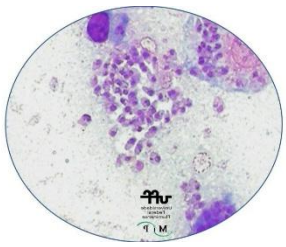

Figure 1

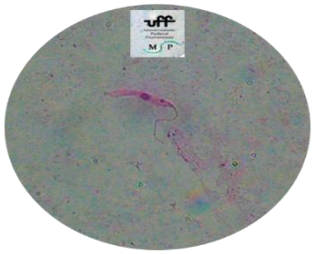

Figure 2

Figure 1. Protozoan Amastigote of Leishmania. Intracellular form of the parasite, with no free flagellum**.**
Figure 2. Protozoan Promastigote of Leishmania. Extracellular form of the parasite, presence of a free flagellum.

Source: adapted images. Virtual Atlas of Parasitology Uff, 2016.

The biological success of *Leishmania* is directly related to its ability to evade the host's defense mechanisms. The parasite interferes with essential processes of the immune system, such as inhibition of phagosome-lysosome fusion, modulation of cytokine signaling, and reduction of the inflammatory response, allowing its survival and replication in the intracellular environment (AGUIRRE-GARCIA et al., 2018).

In addition, the parasite is able to tolerate the oxidative stress imposed by the activated macrophages. This resistance is mediated by antioxidant enzymes, such as superoxide dismutase and trypanothione reductase, which neutralize reactive oxygen and nitrogen species generated as part of the immune response (FERREIRA. PEREIRA-CHIOCCOLA, 2016).

The parasite's metabolic plasticity also favors its persistence. *Leishmania* is able to use different sources of nutrients — such as amino acids, lipids, and glucose — and

manipulate cell signaling pathways to inhibit the apoptosis of infected macrophages, prolonging their stay in the host (AGUIRRE-GARCIA et al., 2018).

GENETICS AND SPECIES DIVERSITY OF *LEISHMANIA*

The genetic diversity of species of the genus *Leishmania* is manifested at different levels, including intraspecific (variation within the same species) and interspecific (variation between distinct species) diversity. The classification of species is based on life cycle characteristics, morphology and genetic markers. Among the most prevalent are *Leishmania infantum*, *Leishmania major*, *Leishmania tropica,* and *Leishmania braziliensis*, which are associated with different clinical forms of the disease, such as visceral, cutaneous, and mucocutaneous leishmaniasis (SANTI & MURTA, 2022).

The Leishmania *species complex* presents a remarkable genetic diversity, with variations both between species and within the same species. At the interspecific level, for example, there are significant genomic differences between *L. major* and *L. tropica*, both responsible for cutaneous leishmaniasis, but with different epidemiological and molecular profiles. At the intraspecific level, regional strains of *L. braziliensis* demonstrate wide genetic heterogeneity, with variants isolated in the Amazon genetically differentiating from strains from southeastern Brazil, which can influence pathogenicity and response to treatment (SANTI & MURTA, 2022).

Molecular studies, including microsatellite analysis, have been fundamental to investigate the genetic variability of *Leishmania* populations. These studies demonstrate that genomic diversity directly impacts the parasite's adaptability to different vectors (sandfly mosquitoes) and vertebrate hosts, including humans, in addition to affecting its virulence and drug resistance (SANTI & MURTA, 2022).

Advances in Leishmania *genomics* have provided important insights into host-parasite interactions and the molecular mechanisms associated with treatment resistance. The genome of *Leishmania* has relevant functional particularities, such as the polycistronic organization of genes—in which several genes are transcribed into a single messenger RNA—, the absence of typical promoters, and the predominantly post-transcriptional regulation of gene expression. In addition, the parasite has a highly specialized mitochondrial genome (kinetoplast), which contains essential information for its survival in adverse environments, such as those found inside macrophages (LLANES et al., 2022).

Genetic variability also contributes to the parasite's ability to escape the host's immune response. Modification of surface antigens, favored by genetic mechanisms, allows *Leishmania* to avoid detection and destruction by immunological mechanisms. In addition,

the parasite has high genomic plasticity, which gives it the ability to adapt to different environmental conditions, resist oxidative stress and tolerate the action of drugs used in the treatment of leishmaniasis (PACHECO & CARVALHO, 2014).

DIAGNOSIS OF LEISHMANIASIS

Clinical-epidemiological diagnosis

Clinical-epidemiological diagnosis, based on the typical signs and symptoms of ATL, is widely used in endemic regions. However, due to the clinical similarity with other dermatological diseases, this diagnosis must be complemented by laboratory tests to confirm infection. The use of clinical diagnosis alone can result in errors, since the clinical picture of ATL can be confused with other conditions (XIMENES. CHAVES, 2024).

Parasitological diagnosis

Among the parasitological methods, direct investigation of the parasite by means of slide smear, culture in specific medium and inoculation in animals are the most used. The direct examination of stained smears, despite being fast and inexpensive, may have limitations, especially when the parasite load is low, which can lead to false-negative results (NASCIMENTO, CARVALHO & ROCHA, 2019).

In addition, histopathological analysis can be crucial for differentiating between ATL and other diseases, such as leprosy. However, detection of the parasite in tissues is not always possible, which limits the effectiveness of this method. The interpretation of histopathological findings can be subjective, making it difficult to standardize the diagnosis (NASCIMENTO, CARVALHO & ROCHA, 2019).

Immunological diagnosis

Immunological tests, such as Montenegro intradermal and serological tests, are important in the diagnosis of ATL. The Montenegro intradermal test, for example, makes it possible to evaluate the host's immune response to the parasite. However, an important limitation of this test is that it cannot distinguish between active infection and previous exposure to the parasite (da Cruz et al., 2023).

A more promising alternative is serological tests based on recombinant proteins, such as chemiluminescent ELISA. The use of recombinant antigens, such as rK39 and rK28, has shown greater sensitivity and specificity, allowing a more accurate identification of the infection (LEITE, 2019).

Molecular diagnosis

Molecular diagnosis, especially by means of Polymerase Chain Reaction (PCR), has represented a significant advance in the diagnosis of ATL. PCR allows the direct detection of the parasite's genetic material, which increases the accuracy of diagnosis and reduces the possibility of false-negatives, especially in samples with low parasite load. Studies indicate that PCR is highly sensitive and effective, and is recommended for the diagnostic confirmation of ATL (DA SILVEIRA & SPENCER, 2019).

The integration of different diagnostic methods, such as parasitological, histopathological, immunological and molecular methods, is essential to ensure greater accuracy in the diagnosis of ATL. The use of multiple approaches allows for a more comprehensive evaluation and reduces the chances of diagnostic errors, in addition to offering greater possibilities of effective treatment. The continuous advancement of diagnostic techniques and the expansion of access to high-precision tests are essential for the control of ATL and for improving the quality of life of affected patients (CAETANO et al., 2019).

TREATMENT OF LEISHMANIASIS

The treatment of American Cutaneous Leishmaniasis (ATL) involves different therapeutic strategies, with pentavalent antimonials being the first line of intervention. Meglumine antimoniate and sodium stibogluconate are widely used, although they have significant adverse effects such as liver toxicity, cardiotoxicity, and nephrotoxicity. Traditionally, these drugs are administered systemically, but recent studies have evaluated intralesional therapy as a promising alternative, with lower toxicity and better tolerability (SILVEIRA, CANDIDO & FRANCISCATO, 2024).

In this sense, intralesional administration has shown good results in cases of localized lesions, reducing systemic side effects and increasing treatment adherence (SILVEIRA, CANDIDO & FRANCISCATO, 2024).

In addition, other therapeutic options include amphotericin B, especially indicated for refractory cases or in patients with contraindications to the use of antimonials. The liposomal formulation of this drug has been shown to be more effective and less toxic compared to the conventional version, as its release into the body occurs in a controlled manner, directing the action of the drug to infected cells and minimizing the toxic effects on healthy tissues. In addition, miltefosine, an oral agent, emerges as a viable alternative, providing greater convenience in administration and good therapeutic response rates.

Miltefosine works by inhibiting the synthesis of phospholipids in the parasite's membrane, affecting its viability and reproduction (SCARABELOT et al., 2023).

Thus, the choice of treatment should consider epidemiological factors, including the species of Leishmania involved, the anatomical location of the lesions, and the immune response of the host (Alencar & Figueiredo, 2019. Lima et al., 2024). In addition, the geographic variability of the infection influences susceptibility to drugs, making continuous epidemiological monitoring essential to define the most effective therapeutic strategies (LIMA et al., 2024).

Clinical studies indicate that the cure rate with pentavalent antimonials is around 70% to 90%, depending on the severity of the lesions and the species of *Leishmania* involved. Liposomal amphotericin B, on the other hand, has cure rates between 85% and 95% in refractory cases, being a more effective alternative with less toxicity compared to the conventional version. Miltefosine has demonstrated cure rates of 70% to 80% in oral treatments, being a promising option due to its ease of administration and proven efficacy (ISIDORO, et al., 2018).

Regarding adverse effects, pentavalent antimonials may lead to liver toxicity, cardiotoxicity, and nephrotoxicity, occurring especially with systemic administration. In the case of amphotericin B, although more effective, it can also cause adverse effects such as kidney dysfunction and liver toxicity. Miltefosine, on the other hand, despite being a more convenient oral alternative, has gastrointestinal disorders and liver toxicity as its main adverse effects, although to a lesser extent than antimonials (ISIDORO, et al., 2018).

Thus, new approaches have been studied, such as immunotherapies and natural compounds with leishmanicidal potential. These strategies seek to modulate the host's immune response to enhance the elimination of the parasite and reduce the rate of infection recurrence (SCARABELOT et al., 2023).

CONCLUSION

It is concluded that American Cutaneous Leishmaniasis (ATL) represents a significant concern for public health, due to the complex interaction between the parasite, the host and environmental factors. Its clinical manifestation varies according to the response

the individual's immunological impact, which directly impacts diagnosis and treatment. Although there has been an advance in the detection of the disease, there is still no single and totally accurate diagnostic method, which makes the combination of different techniques essential to increase the reliability of the results.

Conventional treatment, based on pentavalent antimonials, has limitations, such as adverse effects and resistance in some regions, highlighting the urgent need for new therapeutic approaches. In this context, targeted therapies, vaccines, and emerging technologies, such as genome editing, emerge as promising alternatives for the treatment of ATL.

However, it is important to emphasize that this review is based on a narrative analysis of the literature, which implies possible selection biases and the absence of a systematic critical evaluation. Therefore, continuous deepening of research is necessary, with a focus on innovative and more effective approaches.

Therefore, public policies that favor access to modern diagnostic methods, as well as the promotion of translational research focused on alternative therapies, are essential for the effective confrontation of ATL in the coming years.

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