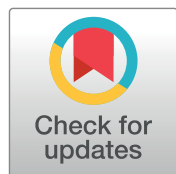




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REVIEW

Cutaneous leishmaniasis: immunological insights and clinical challenges

Leishmaniasis cutánea: perspectivas inmunológicas y desafíos clínicos

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Abstract

Cutaneous leishmaniasis is a neglected tropical disease caused by *Leishmania* species and transmitted through the bite of infected female sandflies. It primarily affects the skin and mucous membranes, with a broad spectrum of clinical manifestations that depend mainly on the host's immune response. The immune balance between Th1, Th17, and Th2 pathways plays a pivotal role in disease progression and outcome. Hyperergic responses (Th1/Th17) are associated with localized and mucosal forms, while anergic responses (Th2/Treg) underline disseminated and diffuse cutaneous forms. Despite its global prevalence, particularly in tropical and subtropical regions, cutaneous leishmaniasis remains underdiagnosed and mismanaged due to a lack of awareness of its immunopathogenesis, clinical diversity, and diagnostic limitations. Treatment continues to rely primarily on pentavalent antimonial compounds, which have significant toxicity, underscoring the urgent need for safer and more effective therapeutic alternatives. This narrative review aims to examine the immune response, clinical manifestations, diagnostic methods, and medical management strategies for cutaneous leishmaniasis. Understanding the complex interplay between immune responses and clinical manifestations is essential for improving diagnosis and treatment.

Resumen

La leishmaniasis cutánea es una enfermedad tropical desatendida causada por especies de *Leishmania* y transmitida a través de la picadura de moscas de arena hembras infectadas. Afecta principalmente la piel y las membranas mucosas, con un amplio espectro de manifestaciones clínicas que dependen principalmente de la respuesta inmune del huésped. El equilibrio inmunológico entre las vías Th1, Th17 y Th2 juega un papel fundamental en la progresión y el desenlace de la enfermedad. Las respuestas hiperérgicas (Th1/Th17) se asocian con formas localizadas y mucosas, mientras que las respuestas anérgicas (Th2/Treg) subyacen en las formas cutáneas diseminadas y difusas. A pesar de su prevalencia global, especialmente en regiones tropicales y subtropicales, la leishmaniasis cutánea sigue siendo subdiagnosticada y mal manejada debido a la falta de conocimiento sobre su inmunopatogénesis, diversidad clínica y limitaciones diagnósticas. El tratamiento continúa basándose principalmente en compuestos antimonials pentavalentes, que presentan una toxicidad significativa, lo que resalta la urgente necesidad de alternativas terapéuticas más seguras y efectivas. Esta revisión narrativa tiene como objetivo examinar la respuesta inmune, las manifestaciones clínicas, los métodos diagnósticos y las estrategias de manejo médico de la leishmaniasis cutánea. Comprender la compleja interacción entre las respuestas inmunitarias y las manifestaciones clínicas es esencial para mejorar el diagnóstico y el tratamiento.

Conflict of interest

None declared

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Authors contributions:

HSC and LKAP wrote the manuscript. Figures were created by HSC using the Biorender toolkit resources. CSL conducted a critical review and GO. All authors read and approved the manuscript

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Remark**1) Why was this study conducted?**

This study was conducted to examine how the host immune response shapes the clinical manifestations, diagnosis, and treatment of cutaneous leishmaniasis. Since the disease remains underdiagnosed and often mismanaged, the review aimed to clarify its immunopathogenesis and current clinical challenges..

2) What were the most relevant results of the study?

- The study highlights the central role of the balance among Th1, Th17, and Th2 responses in determining disease progression and clinical forms.
- Hyperergic responses (Th1/Th17) are associated with localized and mucosal disease.
- Anergic responses (Th2/Treg) underlie disseminated and diffuse forms.
- Diagnostic limitations persist and contribute to underdiagnosis.
- Treatment continues to rely on pentavalent antimonials, which have considerable toxicity.

3) What do these results contribute?

They provide a deeper understanding of how the host immune system determines the clinical expression and progression of cutaneous leishmaniasis. This insight is essential for improving diagnostic accuracy, guiding more appropriate therapeutic decisions, and emphasizing the urgent need for safer and more effective treatments. difference between groups showed borderline significance, larger studies may confirm these findings. The observed gender-related difference suggests IL-36 γ could be a potential biomarker. Future prospective studies with larger sample sizes should investigate IL-36 γ in pediatric allergic rhinitis, considering sex-related differences, to determine its clinical utility in assessing disease severity and guiding management.

Introduction

Cutaneous leishmaniasis is a neglected chronic granulomatous disease that affects the skin and mucous membranes. It is caused by at least 20 species of an obligate intracellular protozoan belonging to the genus *Leishmania*. It is transmitted by the bite of female sandflies of the genus *Phlebotomus* (Asia, Africa, and Europe) and *Lutzomyia* (the Americas) ¹⁻³. According to the World Health Organization (WHO), this disease is considered one of the seven most significant tropical pathologies globally. It is endemic in nearly 100 countries, with 90% of new cases concentrated in Afghanistan, Bangladesh, India, Bolivia, Brazil, Colombia, Iran, Peru, and Syria ⁴⁻⁶.

Over the past 20 years, approximately one million cases of cutaneous leishmaniasis have been reported worldwide, establishing it as a public health problem in tropical countries ⁷. This increase in disease burden is partially attributable to the lack of a gold standard for direct parasite detection, as well as limited awareness among healthcare professionals regarding the immune response, clinical characteristics, diagnostic techniques, and appropriate disease management. Therefore, this review aims to examine the immune response, clinical manifestations, diagnostic methods, and medical management strategies for cutaneous leishmaniasis.

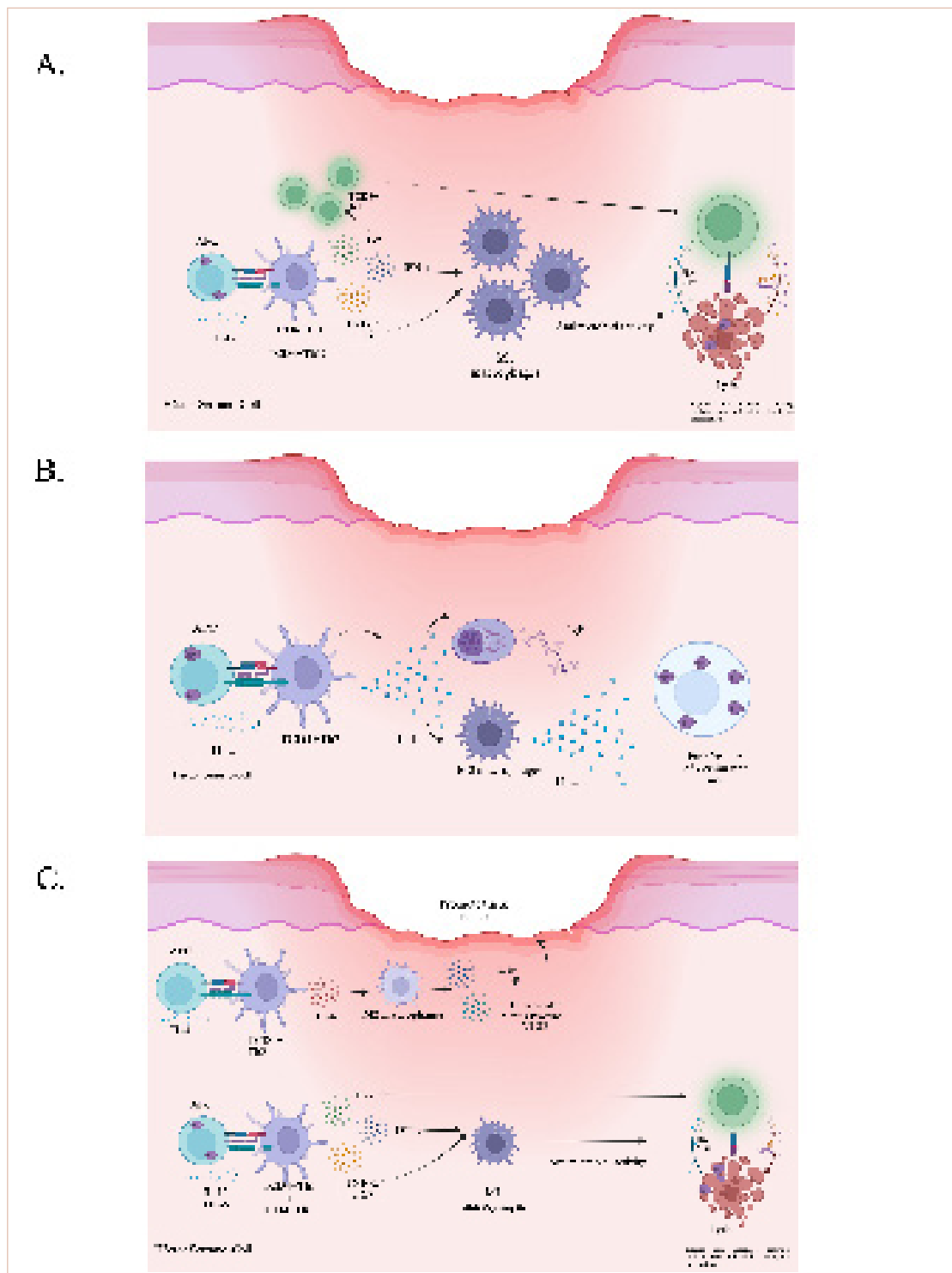


Figure 1. A-C. Immune response in cutaneous leishmaniasis. A. This figure illustrates increased CD4+ T cell activity with a Th1 and Th17 profile, leading to the release of pro-inflammatory cytokines such as IL-17 and TNF- α . These cytokines promote the recruitment of macrophages, which, under the influence of IFN- γ , differentiate into the M1 phenotype macrophages with high lytic and phagocytic capacity. Alongside the cytotoxic activity of CD8+ T cells, this response contributes to the destruction of *Leishmania* spp. but also causes collateral tissue damage. B. This figure depicts enhanced CD4+ T cell activity with a Th2 profile, promoting the release of anti-inflammatory cytokines such as IL-4. IL-4 drives the differentiation of macrophages into the M2 phenotype, which exhibits anti-inflammatory functions. Additionally, it promotes antibody isotype switching in B cells towards IgE, which has limited opsonization capacity and a reduced ability to induce antibody-dependent cytotoxic responses. This immune environment facilitates the proliferation of *Leishmania* spp. C. This figure highlights that the immunological balance between the aforementioned responses is critical for controlling the infection. On one hand, it promotes a Th1 and Th17 response by CD4+ T cells and a cytotoxic response by CD8+ T cells capable of destroying the parasite. On the other hand, a Th2 response drives the differentiation of M2 macrophages, which contributes to tissue repair.

Immune response in leishmaniasis

The adaptive immune response plays a central role in controlling cutaneous leishmaniasis. Traditionally, it has been postulated that in infections caused by intracellular microorganisms such as *Leishmania* spp., the Th1-mediated response is crucial for controlling the infection, while the Th2 response facilitates parasite proliferation. However, this statement is incomplete, as both Th1 and Th2 responses, together with the involvement of Th17 cells, are necessary for effective infection control⁸. During *Leishmania* infection, the balance between different T helper responses plays a crucial role in disease outcome^{9,10}. On one hand, Th1 and Th17 responses contribute to parasite elimination by enhancing phagocyte activation and promoting the production of inflammatory cytokines and cytotoxic molecules, which help control the infection¹¹⁻¹³. On the other hand, the Th2 response promotes a tissue-repair environment, facilitating patient recovery by reducing inflammation and supporting wound healing¹⁴. However, an excessive Th2 response may also contribute to parasite persistence by suppressing effective immune mechanisms.

Immune balance: The cornerstone of *Leishmania* control

In infections caused by intracellular microorganisms, such as *Leishmania* spp., the balance between immune responses (Th1 and Th17 versus Th2) is fundamental in controlling this infection¹⁵. An imbalance in these responses can lead to the development of leishmaniasis in its various clinical forms. Figure 1 A-C illustrates the immune response in a host infected with *Leishmania* spp.

The Th1 and Th17 patterns in CD4+ T lymphocytes play a crucial role in infection control by promoting the release of cytokines such as TNF- α ¹⁶. This, along with IL-17 released by Th17 CD4+ T lymphocytes, induces the recruitment of phagocytes such as neutrophils and macrophages¹⁶⁻¹⁹. Moreover, IFN- γ stimulates the differentiation of macrophages into their classical or M1 phenotype, characterized by high phagocytic activity against the parasite²⁰.

However, while this response is effective in initially eliminating the pathogen, its persistence can lead to a chronic pro-inflammatory state⁹. Sustained inflammation favors the chronicity of lesions and the development of more severe forms of the disease, such as localized cutaneous leishmaniasis and mucocutaneous leishmaniasis²¹.

Consequences of Th2 immune imbalance

On the other hand, if the host immune response against *Leishmania* spp. skews toward a Th2 effector pattern in CD4+ T lymphocytes, characterized by the release of IL-4 and IL-10²², several immunological consequences may ensue. One such consequence is the differentiation of macrophages into an alternative or M2 phenotype, characterized by anti-inflammatory activity mediated through the release of IL-10 and TGF- β ^{20,23}. These cytokines, especially TGF- β , play a crucial role in inducing the differentiation of some CD4+ T cells into regulatory phenotypes, such as Th3 and Tr1²³. Although the phenotypes involved in leishmaniasis-induced regulatory T cells are not yet clear, the study conducted by Brelaz et al.²⁴, demonstrated a higher expression of these cells in patients with active leishmaniasis. Therefore, we hypothesize that Th3 cells, driven by TGF- β , could regulate inflammatory responses and promote immune tolerance, creating an immunosuppressive environment that may facilitate *Leishmania* persistence^{22,25}. Additionally, Tr1 cells, characterized by IL-10 secretion, can help control excessive inflammation and prevent tissue damage, but may also contribute to chronic infection by suppressing protective immune responses. This immunosuppressive effect may hinder cellular immunity, allowing parasite proliferation and the development of severe forms such as disseminated or diffuse cutaneous leishmaniasis.

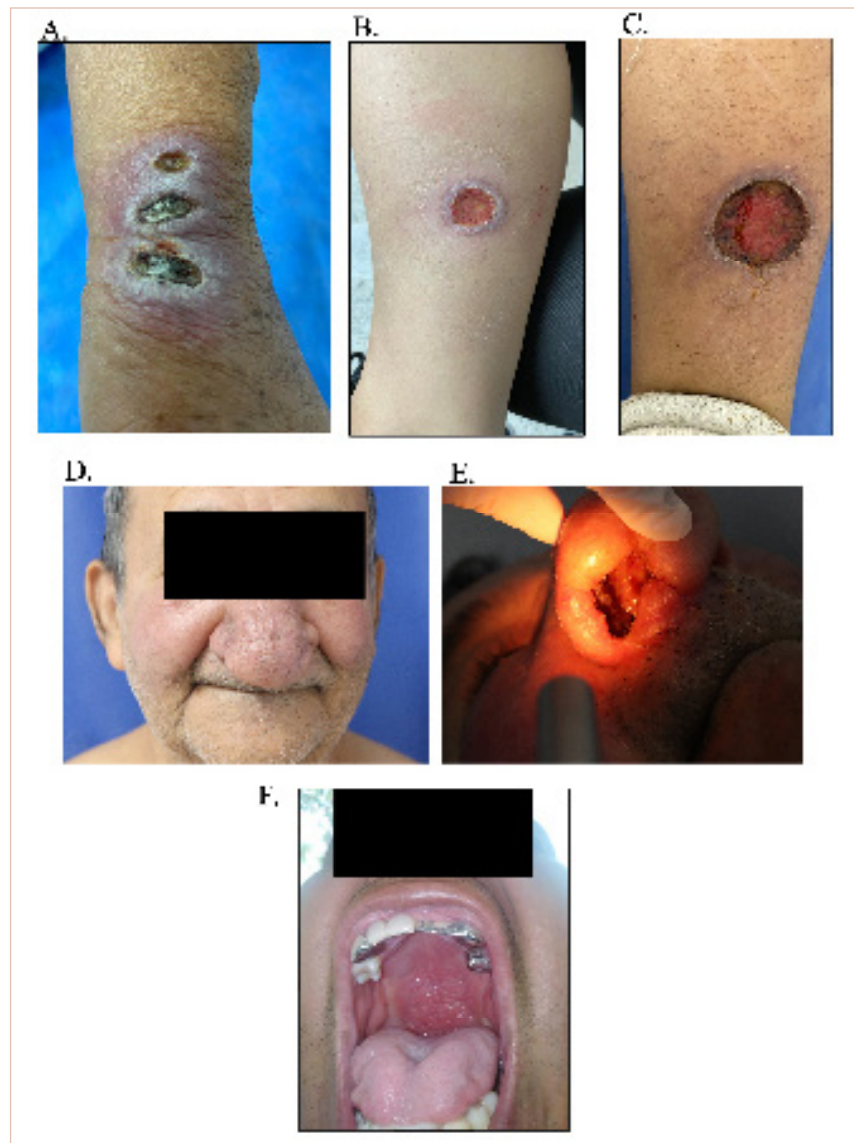


Figure 2. A-F. Cutaneous and mucosal leishmaniasis. A-C. These images depict typical lesions of localized cutaneous leishmaniasis, characterized by raised, well-defined edges and ulcerated, flat centers with granulated tissue. The lesions commonly appear on exposed areas such as the face and limbs and may be accompanied by regional lymphadenopathy. D-F. These images illustrate clinical features of mucosal leishmaniasis, including the characteristic tapir-like nose deformity due to cartilage destruction, perforation of the nasal septum, and a cobblestone appearance of the palate resulting from chronic inflammation and mucosal damage.

Immune regulation and disease control

Nonetheless, the balance between these effector patterns is crucial for controlling pathology. The presence of CD4⁺ T lymphocytes with Th1 and Th17 patterns promotes an effective cellular immune response against the microorganism^{23,26}. This is complemented by a cytotoxic response mediated by CD8⁺ Tc1 T lymphocytes, which release perforins and granzymes to induce osmotic lysis of *Leishmania*-infected cells²⁷. However, the cellular immune response mediated by CD4⁺ Th1, Th17, and CD8⁺ Tc1 cells must be balanced by a subset of CD4⁺ T lymphocytes with a Th2 profile^{9,28}, which promotes the activation of M2 macrophages²². These macrophages promote the repair of tissue affected by parasites and, over time, induce the action of induced regulatory T cells (iTregs), thereby modulating the activity of Th1 and Th17 cells as the lesion becomes chronic^{29,30}. Therefore, the long-term coexistence of these effector patterns is essential for infection control.

Clinical patterns of tegumentary leishmaniasis and their relationship with diagnostic tests

TL presents a broad spectrum of clinical manifestations, which vary according to the host's immune response to the parasite ³¹. Consequently, the clinical forms of localized cutaneous leishmaniasis and mucosal leishmaniasis predominantly display a hyperergic immune response. In contrast, cases of disseminated leishmaniasis and diffuse cutaneous leishmaniasis are characterized by an anergic immune response ¹⁰.

Hyperergic forms of tegumentary leishmaniasis

Localized cutaneous leishmaniasis. localized cutaneous leishmaniasis is characterized by a variable clinical pattern, ranging from a single lesion to multiple skin lesions ³². These lesions are typically papular, non-painful, and erythematous, commonly located in areas of the body exposed to the vector, such as the face, the auricular pavilion (widely known as “chiclero ulcer”), forearms, and legs ^{1,33}. The lesions often evolve into ulcerative forms, characterized by raised, thickened borders and friable granulation tissue, which may be accompanied by lymphadenopathy ³⁴. Figure 2 A-C illustrates the clinical characteristics of localized cutaneous leishmaniasis.

From an immunological perspective, this clinical form is predominantly mediated by effector CD4+ Th1 and Th17 cell responses ³⁵. Over time, this response induces a progressive reduction in the number of amastigotes. For this reason, in chronic forms of the disease, visualizing amastigotes becomes increasingly challenging, both in direct examination and in histopathological assessment ²¹. Therefore, after 12 weeks of disease progression, molecular detection plays a crucial role in identifying the parasite ³⁶. This clinical form, located at the most hyperergic end of the disease spectrum, is characterized by intense and prolonged proinflammatory activity mediated by Th1 and Th17 effector patterns. This sustained immune response causes mucosal tissue destruction and a reduction in the number of amastigotes, which complicates their visualization using traditional techniques such as direct examination and histopathology. In this context, molecular techniques play a crucial role in detecting this variant. Additionally, the Montenegro test is a delayed hypersensitivity skin test used to assess cellular immune response to *Leishmania* spp. ³⁷. It involves the intradermal injection of leishmanin and measuring induration after 48-72 hours ³⁸. A positive result indicates prior exposure and an active immune response but does not distinguish between past and active infection ³⁸. The test is useful in diagnosis and epidemiology and should be complemented with other methods, such as biopsy or PCR. A positive result can help keep this condition in diagnostic considerations.

Mucosal leishmaniasis. This form of leishmaniasis has a significant impact on patients' quality of life due to its physical sequelae and systemic involvement. The causative species of this condition belong to the *L. braziliensis* complex, which includes *L. braziliensis* and *L. peruviana* ³⁹. Clinically, it primarily affects the nasal and oral mucosa, accompanied by subtle and insidious symptoms, including local pain, epistaxis, and pruritus. Hematogenous or lymphatic metastatic spread can involve the nasopharynx, leading to septal perforation, destruction of the uvula, palate, larynx, and pharynx ^{1,5,33,39}. These complications result in dysphagia, severe odynophagia, and cachexia in the most severe cases, with potential involvement of the upper respiratory tract that can be fatal ^{1,5,33,39}. Moreover, this condition may be worsened by secondary bacterial infections ¹. Figure 2D-F illustrates the clinical features of mucosal leishmaniasis.

This clinical form, located at the hyperergic end of the disease spectrum, is characterized by intense and prolonged pro-inflammatory activity mediated by Th1 and Th17 effector patterns ^{10,40}. This sustained immune response leads to mucosal tissue destruction and a decrease in the number of amastigotes, complicating their visualization through traditional techniques such as direct examination and histopathology ⁴¹. In this context, molecular techniques play a crucial role in detecting this variant. Furthermore, the Montenegro test can be instrumental, as a positive result helps maintain this pathology within the diagnostic considerations ⁴².

Table 1. Clinical and paraclinical features

Clinical presentation	Predominant Immune Response	Montenegro Test	Direct Smear Microscopy	Molecular test	Histopathological
Localized Cutaneous Leishmaniasis	Th1, Th17	Positive	Yes	Only, after three negative direct examinations	Only, after three negative direct examinations
Mucosal Leishmaniasis	Th1, Th17	Positive	No	Yes	Yes
Disseminated Leishmaniasis	Th2	It could be positive	Yes	No	No
Diffuse Cutaneous Leishmaniasis	Th2	Negative	No	Yes	Yes

Anergic forms of cutaneous leishmaniasis

Disseminated leishmaniasis. disseminated leishmaniasis is a rare and endemic condition first described in the state of Bahia, Brazil, by Torres in 1920, where it remains endemic and neglected, particularly due to the high circulation of *L. braziliensis*⁴³. It has also been documented in other regions of Brazil, South America, Europe, and the Middle East⁴⁴. Clinically, it is characterized by the appearance of dozens to hundreds of generalized polymorphic lesions, which coexist as various types of skin lesions, including acneiform eruptions. These inflammatory papules may be eroded or crusted and may also be presented as nodules, ulcers, and, rarely, vegetative lesions, often with involvement of the nasal mucosa⁴⁵. Besides, the systemic manifestations include febrile peaks, asthenia, adynamia, and diaphoresis, suggesting a parasitic dissemination process through hematogenous spread^{21,46}.

From an immunological perspective, this clinical form is characterized by a predominance of the Th2 response in the host, which induces an anti-inflammatory environment and activates Treg cells that suppress the cellular immune response, thereby facilitating parasite proliferation^{9,21}. As a consequence of this immune response, tests such as the Montenegro test may yield ambiguous results, both positive and negative⁴⁶. However, since this form is typically more anergic, direct examination is especially relevant, allowing visualization of *Leishmania* amastigotes.

Diffuse cutaneous leishmaniasis. Diffuse cutaneous leishmaniasis is an uncommon, chronic, and progressive condition that affects large areas of the skin. It is characterized by multiple papular, nodular, or plaque-like lesions that lack ulceration and may resemble lepromatous leprosy^{47,48}. This condition is primarily associated with New World *Leishmania* species, such as *L. mexicana* and *L. amazonensis*, as well as *L. aethiopica*, which has been reported in countries like Ethiopia and Kenya⁴⁹.

The dissemination of skin lesions occurs due to a reduction in cellular immunity. Studies have shown that *Leishmania* amastigotes stimulate immunosuppressive activities, leading to anergy. This immunological dysfunction has been linked to HIV infection, highlighting the association of diffuse cutaneous leishmaniasis with immunosuppression in the context of co-infection^{1,49,50}.

Immunosuppression in these patients induces a pronounced anergic response, facilitating parasite proliferation⁵¹. Notably, this anergy prevents lesion ulceration, resulting in the presentation of nodules instead²¹. In this context, diagnostic tools such as the Montenegro skin test are ineffective⁵². Given the absence of ulcerated lesions, diagnosis relies on skin biopsy for histopathological and molecular studies (Table 1).

Medical management

Currently, the first-line treatment for cutaneous leishmaniasis involves the use of pentavalent antimonial salts (Sb5+), such as meglumine antimoniate or N-methylglucamine antimoniate (Glucantime®) and sodium stibogluconate (Pentostam®), administered at a dose of 20 mg/kg/day intravenously or intramuscularly, as a single daily dose for 20 days, with a maximum of 15 mL (equivalent to 3 ampoules per day)^{53,54}. The most common adverse effects of these drugs include acute inflammatory signs at the injection site, vomiting, abdominal pain, dizziness, fainting, myalgia, arthralgia, hepatotoxicity, nephrotoxicity, headache, and, in some cases, tachyarrhythmias and pancreatitis⁵⁵.

Alternative treatment regimens include:

1. 1. Miltefosine, administered orally at a dose of 1.5-2.5 mg/kg/day, with a maximum daily dose of 150 mg, for 28 days.
2. 2. Pentamidine isethionate, administered intramuscularly or intravenously at a dose of 3-4 mg/kg/day, given as 4 to 10 doses on alternate days.
3. 3. Liposomal amphotericin B, reserved for hospital use, is administered intravenously at a dose of 2-3 mg/kg/day, with a maximum daily dose of 250 mg. This formulation is preferred due to its lower nephrotoxicity compared to amphotericin B deoxycholate.
4. 4. The use of pentavalent antimonials in combination with an immunomodulator, such as oral pentoxifylline at 20 mg/kg/day for 30 days, combined with 400 mg of pentoxifylline every 8 hours for 28 days ^{21,55}.

Additionally, thermotherapy and/or cryotherapy, as well as intralesional infiltration with pentavalent antimonials, are reserved for specific cases. These include children under 10 kg and elderly patients with a single lesion smaller than 3 cm, not located in special anatomical sites, and always under the supervision of trained medical personnel ^{21,55}.

Emerging drug targets and therapeutic strategies for leishmaniasis include nanotechnology-based drug delivery systems and the exploitation of parasite-specific metabolic pathways. Liposomal encapsulation and nanoparticle formulations have shown great promise in enhancing the efficacy and bioavailability of antileishmanial drugs. For instance, challenges associated with the oral administration of pentamidine have been addressed by incorporating the drug into poly (lactic-co-glycolic acid) nanoparticles. These nanoparticles, prepared using a double-emulsion method, demonstrated successful *in vitro* and *in vivo* activity in *Leishmania*-infected BALB/c mice, offering a novel formulation with favorable pharmacokinetic and pharmacodynamic profiles. Similar nanoparticle-based strategies have also proven highly effective for the delivery of amphotericin B ^{56,57}. In parallel, the purine salvage pathway has emerged as a valuable metabolic target, given that *Leishmania* parasites lack the enzymatic machinery required for de novo purine nucleotide synthesis. Instead, they rely on the purine salvage system, which involves the uptake of purine bases from the host through specific nucleoside transporters. A key enzyme in this pathway, nucleoside diphosphate kinase, has been targeted by various compounds. Notably, an analog of a multitarget receptor tyrosine kinase inhibitor, as well as a pyrrole-indolinone compound, has been shown to bind to *L. major* nucleoside diphosphate kinase and exhibit significant *in vitro* antileishmanial activity. The latter compound demonstrated potency and efficacy comparable to that of amphotericin B, supporting its potential as a scaffold for the development of new nucleoside diphosphate kinase inhibitors against *Leishmania* spp ⁵⁶.

Immunotherapy as a key strategy in the treatment of cutaneous leishmaniasis

Immunotherapy may play a pivotal role in treating cutaneous leishmaniasis, as the parasite employs strategies to evade the host immune response. These include inhibition of the membrane attack complex (C5-9), disruption of pathways such as TLR2/TLR4 and JAK/STAT, and modulation of key cellular processes like phagosome-lysosome fusion and intracellular pH regulation ⁵⁸. Consequently, drugs like Pentraxin-3 and Semaphorin-3E, which promote the activation of Th1 and Th17 effector patterns ^{59,60}, could be valuable in addressing anergic forms of this disease, such as diffuse cutaneous leishmaniasis and localized cutaneous leishmaniasis. These agents are likely to enhance the host's cellular immune response against the parasite.

Ikeogu et al. ⁵⁹, and Gupta et al. ⁶⁰, demonstrated that *Leishmania major* infection is associated with a marked upregulation of long pentraxin-3. Deletion of the *PTX-3* gene in C57BL/6 mice resulted in enhanced resistance to *L. major* infection, as evidenced by reduced lesion

size and parasite burden. This improvement correlated with a significantly augmented Th17/IL-17 response. These findings suggest that neutralizing PTX-3 in infected individuals could potentially reduce disease severity. Supporting this, significantly higher pentraxin-3 expression has been observed in skin biopsy samples from patients with active lesions caused by *Leishmania braziliensis*, and chemotherapy has been shown to reduce pentraxin-3 expression in these individuals markedly.

On the other hand, Ikeogu et al.⁵⁹, showed that Semaphorin-3E (Sema3E), a host molecule involved in axon guidance, is upregulated at the site of *L. major* infection. Targeted deletion of the *Sema3* gene led to an enhanced Th1 response, which may explain the increased resistance observed in smaller lesion size and lower parasite burden following *L. major* infection. This study suggests that neutralization of Sema3E in infected individuals could potentially improve disease outcomes.

On the other hand, pentoxifylline could prove beneficial in mucocutaneous forms of leishmaniasis, as its anti-TNF activity reduces phagocyte recruitment and, consequently, inflammation driven by these cells. Additionally, Sales et al.⁶², conducted a randomized pilot clinical trial to evaluate the efficacy of an oral combination of miltefosine and pentoxifylline. A post hoc analysis from this study suggested a lower risk of adverse effects associated with this combination therapy.

In regions with a high burden of cutaneous leishmaniasis, immunoprophylaxis could play a crucial role in eradicating the disease. Currently, the following vaccines are in phase III clinical trials: Leishvaccine, Leishmune, CaniLeish, and Leish-Tec⁶¹. Advanced proteomics and cellular immunology techniques have been employed to identify promising vaccine candidates for *Leishmania*. Mou et al.⁶³, identified a dominant naturally processed peptide (PEPCK335-351) derived from *Leishmania* glycosomal phosphoenolpyruvate carboxykinase. This peptide, and/or its native protein, elicited strong CD4⁺ T cell responses in infected mice and humans. Similar to the peptide, recombinant glycosomal phosphoenolpyruvate carboxykinase or a DNA construct expressing full-length glycosomal phosphoenolpyruvate carboxykinase induced strong, long-lasting, cross-species protection in both susceptible and resistant mouse models.

However, we consider this approach challenging in the short term, as the efficacy of these vaccines will depend on the antigens used and their relation to the *Leishmania* species from which they were derived. Therefore, the success of these vaccines will be closely tied to our molecular epidemiological understanding of the *Leishmania* species present in endemic regions. However, we consider that this strategy could be complex in the short term, as the effectiveness of these vaccines will depend on the antigen used and its relationship with the *Leishmania* species from which it was derived. Therefore, the success of these vaccines will be closely linked to our knowledge based on the molecular epidemiology of the species present in our territories.

Conclusions and future directions

Despite advances in understanding the immune response to *Leishmania* spp., significant challenges remain in the clinical management of the disease. Among the most pressing issues are early diagnosis, particularly in chronic hyperergic forms, where direct examination and histopathology show reduced sensitivity, as well as the high toxicity of conventional antimonial treatments. Additionally, there are considerable barriers to accessing molecular diagnostics and effective treatment in low-resource settings, where leishmaniasis remains a neglected tropical disease. These limitations not only hinder therapeutic success but also severely impact the quality of life of affected patients, especially those with mucosal and disseminated forms.

The evidence presented in this review highlights the central role of immune balance, particularly among Th1, Th2, and Th17 responses, in determining the clinical outcome of tegumentary leishmaniasis. This understanding opens the door to novel therapeutic

approaches, such as immunotherapy with agents capable of modulating immune responses, including pentoxifylline, pentraxin-3, and semaphorin 3E. Additionally, ongoing vaccine development efforts, such as Leishmune and Leish-Tec, offer promising prospects for prevention. However, their success will depend on conducting clinical trials tailored to the local epidemiology of *Leishmania* species. This will require robust international collaboration to overcome health system gaps in endemic regions.

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