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# A Review on Cutaneous Leishmaniasis

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***Authors' contributions***

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## ABSTRACT

Leishmaniasis is a vector-borne disease caused by flagellated protozoans belonging to the genus Leishmania. Cutaneous leishmaniasis (CL) is a parasitic disease transmitted by sandflies called phlebotomine that causes a variety of skin lesions. It has a wide range of clinical manifestations that are influenced by a number of unknown parasite and host factors. The disease can take many forms, ranging from self-limited and even self-healing cutaneous manifestations to fatal systemic disease. The standard treatment is pentavalent antimony. Pentavalent antimonials are the cornerstones of cutaneous leishmaniasis treatment, with novel oral and topical options on the horizon. Many lesions heal on their own and does not need to be treated. Antimonials are likely to cause a high number of reversible side effects. Other medications used in treatment include amphotericin B, pentamidine isethionate, paromomycin and antifungals. Although the cutaneous

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version of the disease is frequently self-limiting, it can leave considerable scarring and lead to more invasive mucocutaneous disease. As a result, treatment to prevent these problems may be considered. In endemic regions, leishmania parasites are frequently diagnosed clinically and, if possible, by microscopic inspection of lesion biopsy samples to visually confirm the aetiology. In non-endemic nations, the use of more advanced medical procedures that allow for species identification is mainly limited to research or therapeutic contexts. The application, use and adverse effects of drugs for systemic and topical treatment are also described.

*Keywords: Cutaneous leishmaniasis; diagnosis; treatment; pentavalent antimony compounds.*

## 1. INTRODUCTION

Leishmaniasis is one of the most complex vector-borne diseases caused by flagellated protozoans of the genus Leishmania [1]. The disease is found in 98 countries across Europe, Africa, Asia, and America and is most common in tropical and subtropical areas. However, more than 90% of new cases occur in nearly 13 countries. It is estimated that millions of people get to be infected each year, however only a small percentage of them develop the disease and 20,000–30,000 eventually die [2].

Leishmaniasis is a caused by various species of leishmania, a protozoan flagellate with unicellular kineto plastids [3]. The epidemiology and clinical features of the disease are highly variable due to the interaction of numerous factors in the parasites, vectors, hosts and environment involved. It manifests itself as a range of clinical syndromes, classified as cutaneous leishmaniasis (CL) and visceral leishmaniasis (VL) [4]. In CL, the parasites infect macrophages that lives in the skin. When the host cell becomes infected with parasites, it bursts, releasing amastigotes that infect nearby macrophages. In VL, however, the released amastigotes are spread through the bloodstream and infect cells of the liver, spleen, bone marrow, lymph nodes, and intestine's mononuclear phagocyte system (reticuloendothelial system) [2].

CL is the most common form of leishmaniasis, with million new cases reported each year around the world. It is classified into three forms: localised cutaneous leishmaniasis (LCL), diffuse cutaneous leishmaniasis (DCL), and mucocutaneous leishmaniasis (MCL) [5]. It can cause a wide range of cutaneous symptoms, ranging from small nodules and ulcers to extended plaques and disseminated forms [6].

## 2. EPIDEMIOLOGY

Leishmaniasis is found in more than 80 countries across Africa, Asia, southern Europe, and Latin America [7,4]. There are an estimated 12 million cases worldwide, and the number is rising, millions of new cases reported each year. The current form of leishmaniasis is emerging due to changes in the environmental and vector habitats due to deforestation, urban development and civil conflicts [7]. Although epidemics of the potentially fatal visceral form cause thousands of deaths, the disease is best known for its cutaneous form, which causes nonfatal, disfiguring lesions [8].

In established endemic areas, the prevalence of cutaneous leishmaniasis typically increases with age up to 15 years, after which it levels off, presumably due to the development of immunity [9]. The infection can cluster within households, owing to sandfly's short flight range, anthroponotic transmission, or genetic susceptibility [10,11]. Sex (e.g., sex bias usually points to behavioural patterns that increase vector exposure), age, construction material and household design, and the presence of domestic animals are all common risk factors for disease [12].

CL is a disease that occurs in returning travellers in North America and Northern Europe, such as among rural studies, tourists, and the militant community. Many infected persons are unfortunately unaware of their risks, do not take personal safety measures and experience late diagnosis and inappropriate treatment on return. The incidence of visceral disease is increasing in Southern Europe, with leishmaniasis at its end, usually in combination with HIV-1. Many of these patients are developing unusual cutaneous manifestations [13].

Although CL is widespread on a global scale, it is often quite dominant at local level due to the specific habitat requirements of the sandfly vector and its reservoir hosts. It is usually a zoonotic disease with a wide range of mammalian reservoirs, but in epidemics and urban environments, especially in Sudan, Afghanistan, and India, it can become anthroponotic [14]. In recent years, CL has emerged as a leading cause of morbidity and social stigma in war-torn countries such as Afghanistan [14,15].

## 3. PATHOLOGY

The promastigote form of the parasite is a motile form with an anterior flagellum that develops in the sandfly, insect vector. Over the course of about ten days, the promastigote form transforms into a metacyclic infectious form. With the bite of a sandfly, the parasite enters the human host and ingested by macrophages. Leishmania can survive the acidic lysosome environment and transform into amastigote forms. In humans, amastigote is the form that causes disease and it can adversely affect cellular immunity. This form will eventually be picked up by a sandfly while feeding, and it will develop back into the promastigote form within the insect [16]. Depending on parasite and host factors, the Leishmania parasites multiply and spread to other macrophages [4].

The infection in CL is usually limited to the skin and lymphatic system, but in DCL, it can spread to deeper tissues or recur in the mouth, nose, or pharynx in MCL. The immune response to CL is primarily mediated by T cells. In most cases, this results in a mixed inflammatory cell infiltrate at the infection site, with Leishman-Donovan bodies (amastigotes within macrophages) visible [4]. More chronic lesions with an intact immune response will have epithelioid granulomata and few parasites visible, whereas chronic lesions with a poor immune response will have a diffuse macrophage infiltrate and many parasites visible [17]. Predominant Th1 lymphocyte responses are related to greater outcomes than predominant Th2 lymphocyte responses, and are influenced by a number of well-known cytokines [18].

## 4. CLINICAL TRAITS

Several Leishmania species can cause CL in humans, though most infections are likely asymptomatic [9]. In children and adults, multiple species cause CL, primarily *L. major*, *L. tropica*, and *L. (L) aethiopica*; *L. infantum* and *L. chagasi* and *L. mexicana*, *L. (L) amazonenesis*, *L. braziliensis*, *L. (V) panamensis*, *L. (V) peruviana* [19]. After a bite from an infected sandfly, infection can develop to a papule that enlarges and ulcerates after a 12-week incubation period. Commonly occurring lesion is a painless ulcer with a necrotic base which is most often covered by an adherent crust of dried exudates [20]. The majority of patients have 1 or 2 lesions, typically in exposed areas, varying in diameter from 0.5 to 3 cm [21] Generally, half of those *L. major* or *L. mexicana* lesions will be cured within 3 months, while *L. tropica* lesions take longer, about 10 months, and *L. brazilinesis* lesions persist for much more time [22,23].

CL is most commonly found on the exposed parts of the body, such as the face, neck, arms, and legs. Furthermore, lesions are painless unless secondary infected, and the subject may present with a single or multiple lesions [24]. DCL is characterised by non-ulcerating lesions which spread to areas including the face and extending surfaces of the limbs locally and hematogenically, and which may also cause deep tissue destruction [25]. It can be transmitted, particularly in immunodeficient people [16].

Co-infection of the human immunodeficiency virus (HIV) with CL has been linked to unusual severe symptoms, higher rates of recurrence and reinfection, and lower cure rates with standard treatments. [26,27,28] Unusual severity of CL has also been reported in accordance with other causes of immunosuppression, such as steroid treatment [29] or immunosuppressant treatment after organ transplantation [30]. Patients infected with the HIV are highly susceptible [16].

CL complications include secondary infection and disfiguring scars. Secondary infections caused by skin commensals, coliforms, or invasive fungi should be treated as soon as possible to avoid prolonging the healing process. Because of the risk of local recurrence, disfiguring scars should not be considered for surgical revision until they have improved in appearance for at least 6 to 12 months [31].

## 5. DIAGNOSIS

The diagnosis and treatment are interlinked because the stage of disease progression and the accuracy of the diagnosis have a significant impact on treatment efficacy. To reduce parasite

transmission and CL increase, early and accurate diagnosis as well as effective patient management is required [32]. The combination of clinical history, data on epidemiology and laboratory confirmation is used for diagnosis of CL. Many diagnostic tools have been developed for diagnosing CL with huge variations in diagnostic accuracy [24]. A clinically typical lesion, combined with an appropriate history of exposure, is frequently used to make the diagnosis [20]. Differential diagnosis is essential because of the diseases with similar clinical spectrums to leishmaniasis (e.g., leprosy, skin cancers, tuberculosis, cutaneous mycoses) are common in leishmaniasis-endemic areas [33].

Due to its various clinical presentations, CL has a broad differential diagnosis [34]. The most of lesions appear within a few weeks of the sandfly bite, but they can take several months to appear. Certain entities for the differential diagnosis of CL are mentioned in Table 1 [35]. They must choose one of the laboratory methods to confirm the diagnosis [36].

**Table 1. Differential diagnosis of cutaneous leishmaniasis**

| | |
|---|---|
| Sporotrichosis | Ecthyma |
| Blastomycosis | Malignancy |
| Atypical mycobacterial infection | Sarcoidosis |
| Cutaneous tuberculosis | Tularemia |
| Lupus vulgaris | Yaws |
| Insect bite reaction | Cutaneous anthrax |

The most frequently used laboratory method, particularly in endemic areas, is the smear, an easy and inexpensive diagnostic tool [36]. The recent diagnostic tests are described in Table 2 [35].

## 5.1 Direct Microscopy, Histopathology, and Culture

The gold standard in leishmaniasis diagnosis has been and still is parasitological diagnosis, due to its high specificity. This is usually done through histopathologic examination of fixed tissue or parasite in vitro culture from suspected lesions. CL is diagnosed microscopically by identifying amastigotes in Giemsa-stained lesion smears from biopsies, scrapings or impression smears. Amastigotes have round or oval bodies that are about 2–4 m in diameter and have distinct nuclei and kinetoplasts. The material from the ulcer margin yields the highest yield [37]. Cultures obtained from an exudate, fine-needle aspirate or scraping also yield positive results [36]. The press-imprint-smear method is a simplified collection method. When compared to histopathology for the diagnosis of CL, PIS was positive in higher percent of study cases suspected of having CL, while histopathology was positive in only less percent. PIS is regarded as a quick and relatively sensitive method for diagnosing CL [37].

The culture of parasites in tubes containing Novy-MacNeal-Nicolle medium from suspected lesions is difficult, time-consuming, and requires significant technical expertise [37]. Culture has a low sensitivity and a wide range of variability. Mini- and micro-culture technologies, which have recently been developed, have the advantages of being less expensive due to the smaller volume of culture medium required, easier to use and more sensitive, even when parasite burdens are low. One disadvantage of micro-culture is that it does not allow the identification of additional species [38].

## 5.2 Leishmania Skin Test

The Leishmania intradermal skin test (LST), also known as the Montenegro skin test (MST), is a cellular immune response marker that is sometimes used to diagnose CL [37]. The LST is based on a delayed hypersensitivity response to total Leishmania promastigotes antigens [39]. Patients who have a negative LST but have other diagnostic confirmation tests are more likely to relapse or fail treatment. The LST or MST has several drawbacks, including the need for culture facilities to produce the MST antigen, the fact that different antigen preparations affect test sensitivity, and the fact that the test does not distinguish between past and present infections [37]. There is evidence that when LST data is combined with information on antigen-specific interferon-c (IFN-c) production, it may be easier to determine whether a suspected case has been exposed to Leishmania [40]. In contrast, it has been reported that the LST is significantly more sensitive than IFN-c levels in CL patients who have been cured [41].

## 5.3 Immunologic Diagnostic Methods

Antigens or anti-Leishmania antibodies found in serum or urine samples from patients are used to diagnose leishmaniasis [42]. The majority of current CL serologic tests are based on formats such as indirect fluorescent antibody, enzyme-linked immunosorbent assay (ELISA), western

blot, lateral flow assay, and direct agglutination test [43]. Cross-reactivity with other infectious diseases and false-positive results in some endemic areas are the major issues for immunological tests [39]. However, due to the poor humoral response elicited by the infection and the resulting low sensitivity, these formats are not widely used for the diagnosis of CL. Furthermore, the majority of currently available serologic tests are preliminary and rely on either a total parasite lysate or a whole promastigote, both of which result in atypical reactions [44].

To overcome these problems, new immunological tests are being developed, such as chemiluminescent ELISA to measure anti-galactosyl antibodies or the CL Detect Rapid Test, which targets the parasite's peroxidoxin antigen. Different antigen detection ELISA tests have been developed, and in a preliminary study using samples from VL patients from various endemic regions, they showed high sensitivity and specificity, as well as utility in monitoring treatment efficacy [45].

## 5.4 Polymerase Chain Reaction (PCR)

The widespread use of more sensitive molecular diagnostic tests has significantly changed sample collection, as well as the amount of time and reference laboratory support that were once standard [46] PCR, in particular, has been widely used as a single test, in a nested format, or as a quantitative assay. Over the last few decades, lots of new tests targeting a variety of gene sequences have been developed, with the ribosomal DNA internal transcribed spacer 1 sequence or sequences within the kinetoplast DNA of the Leishmania genus serving as the primary targets [37]. This is especially important in CL, where chronic lesions have lower parasite loads that microscopy cannot detect [45].

The approaches are based on the parasite's nuclear and mitochondrial genomes' coding and non-coding regions [47]. The PCR product focuses on a particular amplification of the target DNA evaluated on a conventional agarose gel, followed by downstream analysis, such as using restriction endonucleases, hybridization, or DNA sequencing, or by detecting and analysing fluorescent signals during amplification in a real-time PCR apparatus [47,48] Studies addressing inter-laboratory comparisons, in particular, are scarce, and the initiative by Cruz and colleagues, who proposed a protocol for inter-laboratory comparisons of conventional and real-time PCR methods, should be taken up [49].

**Table 2. Leishmaniasis diagnostic tests**

| | |
|---|---|
| Histology: Scraping, punch biopsy specimen, or aspirate | Easier and most commonly used method; demonstration of amastigotes on smear or biopsy sample, or promastigotes in aspirate |
| Culture: On Schneider Drosophila or NNN mediums | Unreliable, as organisms are difficult to isolate especially if lesions are old; results may take 1-3 wks. depending on parasite load |
| Molecular techniques: PCR<br><br>Antigen detection (using monoclonal antibodies) | Enables species identification; useful in monitoring patients after treatment; not widely available in endemic regions<br>Not widely available, expensive |
| Leishmanin skin test (Montenegro skin test) | Relies on delayed-type hypersensitivity response after injection of dead promastigotes intradermally; may produce positive results in 3 mo after appearance of lesions; result is considered positive if induration of >5 mm develops after 48 h. |
| Serologic tests: ELISA, IFA, DAT, rK39 ELISA, | Serum antibody detection can be useful in diagnosing visceral leishmaniasis but is of no use in cutaneous disease |

*PCR: Polymerase Chain Reaction*
*ELISA: Enzyme Linked Immuno Sorbant Assay*
*IFA: Indirect Immunofluorescence Assay*
*DAT: Direct Antiglobulin Test*
*rK39 ELISA: recombinant K39*

## 6. TREATMENT

Although CL is not fatal, it is treated to relieve the symptoms and prevent parasite spread (mucosal leishmaniasis) and relapse [9]. As a result, treatment to avoid these complications may be considered [50].

The primary goal of CL therapy is to reduce morbidity [51]. The clinical type, the involved species of leishmania and the geography of infection should be considered in the treatment [36]. The majority of lesions heal slowly without treatment; however, treatment should be considered when lesions are painful to the patient, the lesion(s) are complex, or there is a risk of mucosal disease [51]. The majority of currently available therapeutic options have significant toxicity and side effects. As a result, each CL patient must undergo a risk-benefit analysis by an experienced clinician, and in mild and indolent cases, a wait-and-see policy may be the best option. Furthermore, drug resistance is becoming a problem in the treatment of CL [52].

### 6.1 First-line Therapy

#### 6.1.1 Pentavalent antimony compounds (PACs)

These compounds are the gold standard for assessing the efficacy of new drugs because they are highly effective and the first-line treatment for most forms of leishmaniasis. Meglumine antimoniate and sodium stibogluconate are two PACs that are therapeutically equivalent. PACs are still the most toxic drug for most Leishmania species, considering up to 15% primary resistance being reported in different geographic regions [53]. Glucantime can be given intramuscularly or intralesionally (IL), while sodium stibogluconate can be given intravenously or intralesionally [36]. For intramuscular administration, the recommended dose is 20 mg/kg/day for 10–20 days [54]. Treatment failure is associated to the use of these drugs at doses below therapeutic levels and for short periods of time [55]. Their biochemical mechanism of action is unknown, but it may involve ATP synthesis inhibition [56].

### 6.2 Physical Treatments

#### 6.2.1 Cryotherapy

Cryotherapy has only been used in the treatment of CL in the Old World. In Turkey, for example, one session of cryotherapy with liquid nitrogen cured 90% patients being infected with *L. tropica* [57]. It can be used alone or in combination with intralesional or systemic PACs or paromomycin ointment to cure diseases. According to reports, combined therapies are more effective than cryotherapy alone [55]. A double freeze-thaw cycle of 10 to 25 seconds, with a 2-mm healthy area from the lesion border, is the most effective application method [58]. It is repeated two or three times in short intervals, leading to a total of 30-120 s. The whitening of the skin 2–3 mm outside the margins of the lesion indicates adequate application [59]. The main drawback of this treatment is its high relapse rate. Patients with darker skin may also experience permanent hypopigmentation [36].

#### 6.2.2 Thermotherapy

Another option is thermotherapy, has been studied in various of CL species and with a variety of heat delivery methods [60]. It requires specialised equipment and local anaesthesia [46]. In vitro studies have shown that Leishmania parasites do not multiply at temperatures above 39 ℃. Thermotherapy with radio-frequency waves has been the most extensively used [61]. Due to the high cost of the necessary devices and procedures, as well as the need for skilled health professionals to perform the treatment, this technique is not widely available [32].

#### 6.2.3 Treatment during pregnancy and lactation

Larger CL lesions with different and/or exophytic clinical presentations are common during pregnancy. There is no cure for it during pregnancy, but it has been observed that a postpartum cure is complete with treatment [36]. Since there is insufficient information on the safety of PACs and other drugs in pregnant or lactating women, systemic or intralesional anti-infective treatments are not advised. If treatment is required during this time, a physical method, such as cryotherapy or thermotherapy, can be used [53].

### 6.3 Oral Therapy

#### 6.3.1 Azoles

Oral imidazoles are yet another controversial CL treatment that may be considered for use in complex lesions and those with the potential to progress to MCL [62]. Leishmania parasites may

also be toxic to antifungal imidazole derivatives. The advantages are that it can be taken orally and it has fewer side effects [53]. Azoles block the Leishmania parasites from ergosterol synthesis. Several studies have used ketoconazole, itraconazole, and fluconazole to treat CL [62].

#### 6.3.2 Miltefosine

Miltefosine, a recent phosphocholine analogue, exhibited significant anti-leishmanial activity in vitro [50]. It has already been found to be as effective as PACs in treating Old World CL infections, particularly those caused by *L. major* . [53]. Miltefosine is administered at an oral dose of 2.5 mg/kg/day for 28 days. Advantages of miltefosine over PA include oral administration and less severe side effects [63]. It has been shown to be teratogenic and should not be given to pregnant women. More controlled trials with different species are needed before miltefosine can be recommended as a routine treatment for CL [50].

### 6.4 Parenteral Therapy

#### 6.4.1 Pentamidine

Pentamidine is a possible approach to PA and can be used as a first-line therapy. Following PA treatment failure, it is frequently used as a second-line therapy [63]. It is toxic to a variety of protozoa and fungi, and the mechanism of action is unknown [50]. When pentamidine was given intravenously, it had a higher efficacy than when it was given intramuscularly [51]. Before each injection, fasting glycemia, creatinine kinase, proteinuria and glycosuria in the urine, blood pressure, and heart rate must all be checked [36]. Pentamidine isethionate is also used to treat CL, particularly when caused by *L. guyanensis*, which appears to be less sensitive to antimony [57].

#### 6.4.2 Amphotericin B

Amphotericin B is an antifungal agent that is also effective against Leishmania species. It is commonly used in patients with PAC resistance or in the case of PAC contraindication. Amphotericin B is the only anti-Leishmania drug with no clinical resistance [64]. Amphotericin B, has a low therapeutic index, high acute toxicity, and must be administered via parenteral route. Liposomal amphotericin B, a new lipid-associated formulation of the original polyene amphotericin B, has been introduced to avoid these drawbacks. This formulation is better tolerated and has less infusion-related toxicity and nephrotoxicity than Amphotericin B, while maintaining the same efficacy [65].

## 7. CONCLUSION

CL is now recognised as a complex and highly variable disease in terms of epidemiology, pathology, and clinical features. Clinically, CL is characterised by self-healing noduloulcerative lesions on exposed parts of the body, but its unusual manifestations can mimic many other skin diseases and cause medication error, major diagnostic delays, and complications. The management of patients can be significantly improved by developing better approaches to case diagnosis and treatment. As a result, efforts must be directed toward rational investment in new therapies and treatment strategies against the disease in order to find therapies with fewer side effects, lower costs, and greater efficacy against these parasites.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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