Cutaneous and Mucocutaneous Leishmaniasis

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KEYWORDS

• Leishmaniasis • Cutaneous • Mucosal • Diagnosis • Antimonial • Amphotericin B

KEY POINTS

- Tegumentary leishmaniases are characterized by diversity of the species of *Leishmania*, of reservoirs and vectors occurring in sylvatic or peri-domestic environment and of clinical manifestations.
- Tegumentary leishmaniases prevail in tropical and subtropical areas but the human mobility makes them a medical problem also in non-endemic areas.
- Clinical manifestations may comprise cutaneous and mucocutaneous forms that may be localized, disseminated or diffuse in distribution and may differ in Old and New World.
- The process of diagnosis and treatment is intricate due to the diversity of *Leishmania* species involved, and to varied clinical manifestations.
- Leishmaniases in HIV-infected patients may present atypical clinical manifestations and augment the difficulty in the diagnosis and treatment.

Leishmaniases are diseases that are caused by protozoa of the genus *Leishmania*, which are prevalent in tropical and subtropical areas, and which consist of both visceral and tegumentary forms. The estimated incidence of tegumentary leishmaniasis is 1.5 million cases per year in 82 countries, with 90% of cases occurring in Afghanistan, Brazil, Iran, Peru, Saudi Arabia, and Syria.[1,2]

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During its life cycle, *Leishmania* are present in the phlebotomine sandflies as promastigotes (elongated forms of the protozoa with an external flagellum) and in the vertebrate host as amastigotes (round forms without any external flagellum).[3] In **Fig. 1**, both zoonotic (red arrows) and anthroponotic (black arrows) cycles of the *Leishmania* are shown. Infected female sandflies inject promastigotes into the skin of the vertebrate sylvatic or human hosts. Within vertebrate hosts, the parasites are phagocytized by macrophages in which they differentiate into amastigotes. The vertebrate hosts become reservoirs of the parasite that transmit it to the sandflies during blood feeding. The reservoirs may or may not present skin lesions.

Parasites causing tegumentary leishmaniases belong to the order Kinetoplastida, family Trypanosomatidae, genus *Leishmania*, subgenus *Leishmania* or *Viannia*. Approximately 15 different species are known: (1) *Leishmania* (*Leishmania*) *major*, *Leishmania* (*Leishmania*) *tropica*, *Leishmania* (*Leishmania*) *aethiopica*, and some strains of *Leishmania* (*Leishmania*) *infantum* in Asia, Africa, and Europe; (2) *Leishmania* (*Viannia*) *braziliensis*, *Leishmania* (*Leishmania*) *amazonensis*, *Leishmania* (*Viannia*) *guyanensis*, *Leishmania* (*Viannia*) *panamensis*, *Leishmania* (*Leishmania*) *mexicana*, *Leishmania* (*Leishmania*) *pifanoi*, *Leishmania* (*Leishmania*) *venezuelensis*, *Leishmania* (*Viannia*) *peruviana*, *Leishmania* (*Viannia*) *shawi*, and *Leishmania* (*Viannia*) *lainsoni* in the New World, mainly Latin America, with more diversity found in the Amazon region. *L* (*V*) *braziliensis* is the more prevalent followed by *L* (*L*) *amazonensis* and *L* (*V*) *guyanensis*.[2,3]

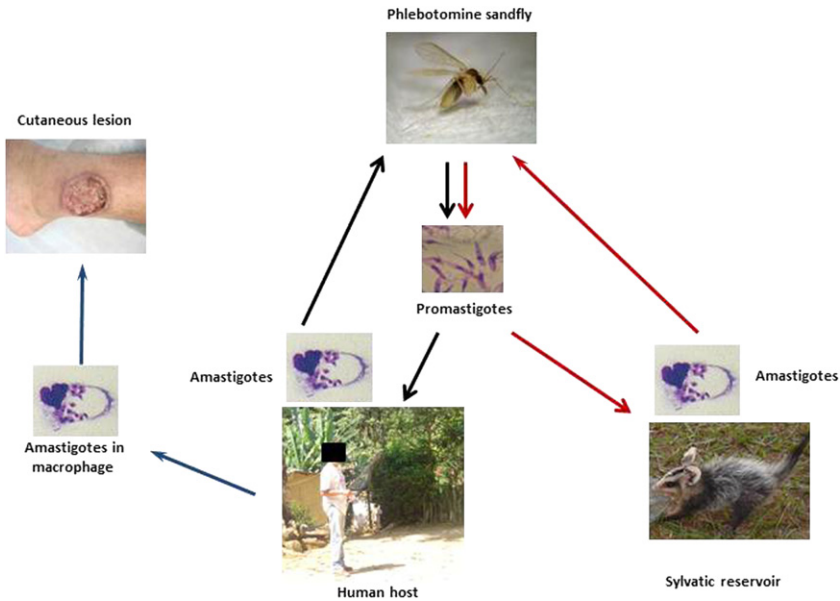

Fig. 1. Lifecycle of *Leishmania*. *Leishmania* is transmitted by phlebotomine sandfly (female *Lutzomyia whitmani* is shown), which inject promastigotes into the skin of the vertebrate sylvatic host or human host. Within vertebrate hosts, the parasites are phagocytized by macrophages in which they differentiate into amastigotes. Zoonotic cycle (*red arrow*). Anthroponotic cycle (*black arrow*). In humans, the infection can cause tegumentary lesions (*blue arrow*). (*Courtesy of* Eunice A.B. Galati from Faculdade de Sáude Pública-USP (sandfly photograph) and Roberto Hiramoto from Instituto Adolfo Lutz-São Paulo (sylvatic host photograph.)

Most leishmaniases are zoonotic diseases; the exceptions are those leishmaniases that are caused by *L* (*L*) *tropica* and *Leishmania* (*Leishmania*) *donovani*, which are considered to be anthroponotic.[2,3] The transmission of dermotropic species of *Leishmania* involves reservoirs and sandfly vectors of the order Diptera, family Psychodidae, subfamily Phlebotominae and genera *Phlebotomus* in the Old World or *Lutzomyia* in the New World.[4] The transmission cycles of each *Leishmania* species are diverse and involve different reservoirs and species of phlebotomine sandflies. The transmission can be predominantly peridomestic or sylvatic, as in the following examples. In the transmission of *L* (*V*) *braziliensis* in Brazil, peridomestic animals as equines and dogs (putative reservoirs), and sandflies *Lutzomyia intermedia* and *Lutzomyia whitmani* adapted to peridomestic habitat[5] are involved. In the transmission of *L* (*V*) *guyanensis* in the Amazon region of Brazil, sylvatic animals such as sloth *Choloepus didactilus*, and the sandfly *Lutzomyia umbratilis*, which are found in the forest canopy,[5] are involved.

Understanding the transmission cycles of *Leishmania* species in an area, the circadian and seasonal density of the vectors, feeding time of the vectors, the reservoirs, and the vector competence for transmission may aid in the prevention of the disease. Control and prevention measures are thus primarily directed at avoiding contact between man and phlebotomine sandflies.[4,6] Neither a vaccine nor prophylactic drugs are available for leishmaniasis. Contact with sandflies can be minimized by using garments to protect the body, including long-sleeved shirts and long trousers that are preferably white or light in color to facilitate the visualization of the insects. In addition, the use of repellents and a bed net that is impregnated with an insect repellent is advisable in high-risk areas.[4,6] It is also important to avoid the feeding period of the specific vectors; for most species, this period occurs at dusk and early night, although some vectors are active at dawn.[5]

LEISHMANIASES IN NONENDEMIC AREAS AND IN TRAVELERS

Leishmaniases are nowadays a concern in nonendemic areas, given the high global human mobility. Adventure tours and ecotourism place tourists in close contact with environments that can contain habitats that are reservoirs for vectors of leishmaniasis. In addition, Latin America and countries in the Old World are popular travel destinations.[7,8] Furthermore, cutaneous leishmaniasis caused by *L* (*L*) *tropica* is anthroponotic in Asia,[9] and there is an increase in vectors that are becoming more adapted to environments in periurban areas.[5] Among the dermatologic diseases that can occur in travelers, tegumentary leishmaniasis is frequent, and, in a survey of the GeoSentinel Surveillance Network covering a 10-year period (1997–2006), it represented 3.3% of 4594 patients.[7] Thus the prevention measures mentioned earlier have to be considered depending on the travel destination.

CLINICAL PRESENTATION

Tegumentary leishmaniases comprise various clinical forms that depend on the *Leishmania* species and strain that is involved as well as the host response. The initial lesion is in the site of the vector bite in the form of a macule, which from 2 weeks to 3 months onward may present as a small, pruritic, erythematous papule and/or nodule and may involve draining lymph nodes. The lesion may develop into a granuloma with a progressive increase in the nodule that may progress to a plaque.[10,11] This lesion may resolve spontaneously or may develop into a characteristic ulcer; some lesions may then develop into other chronic forms. Although some evidence suggests a correlation between the clinical features and the species and strains of *Leishmania*,[12,13] this

relationship remains unclear, particularly in regions in which many different species coexist. Studies to address this question are needed but are difficult to perform, because these approaches are not easily available for processing the clinical specimens.

In general, dermotropic species from the Old World cause fewer clinical manifestations than New World species.[2,14–16] Viscerotropic *Leishmania* species can cause cutaneous lesion as well.[2,14,15] Post–kala-azar dermal leishmaniasis (PKDL) is caused by *L* (*L*) *donovani*,[17] and cutaneous leishmaniasis is caused by some zimodemes of *Leishmania* (*Leishmania*) *infantun* in Europe and Africa.[18] Based on their differing clinical presentations, tegumentary leishmaniases are classified as localized cutaneous leishmaniasis (LCL), diffuse cutaneous leishmaniasis (DCL), disseminated leishmaniasis, leishmaniasis recidiva cutis (LR), and mucosal leishmaniasis. This article briefly describes the main features (see Refs.[2,14–16] for detailed descriptions).

LCL is the most prevalent form and is caused by all of the dermotropic *Leishmania* species. The most common lesion type is characterized by an ulcer and can vary from 1 to 10 lesions that are localized in an exposed area of the body (**Fig. 2**A). Usually, the ulcer is painless, pink, and round, with well-delimited and raised edges, an indurated base, and a clean bottom where a central crust that may bleed can sometimes appear. A spontaneous resolution may occur, leaving a hypopigmented, smooth, thin scar. However, some cases evolve to other forms of the disease.

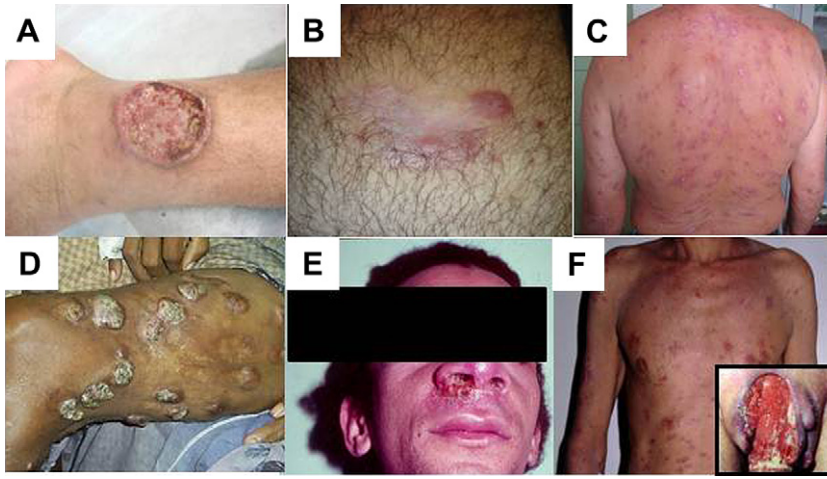

Fig. 2. Clinical forms of tegumentary leishmaniasis. (*A*) LCL presenting a single ulcer on the leg. (*B*) Leishmaniasis recidiva cutis presenting papules and vesicles around the healed lesion of cutaneous leishmaniasis on the leg. (*C*) Disseminated cutaneous leishmaniasis presenting numerous small ulcers on the back. (*D*) DCL presenting tumoral lesions and nodules associated with crusts and several scars from previous injuries on the left thigh. (*E*) Mucocutaneous leishmaniasis lesion in the nose and infiltration in nasal mucosa. (*F*) Atypical cutaneous leishmaniasis in a patient infected with human immunodeficiency virus presenting multiple macules on the chest and abdomen. (Insert in *F*) Extensive ulcer on the penis of a patient with acquired immune deficiency syndrome. ([*A*] *Courtesy of* Luiza K. Oyafuso, Instituto de Infectologia Emilio Ribas, São Paulo, Brazil; [*B*] *Courtesy of* Maria Edileuza Brito, Centro de Pesquisas Aggeu Magalhães, Fundação Oswaldo Cruz, Brazil; [*C*] *Courtesy of* Edgar M. Carvalho, Universidade Federal da Bahia, Brazil; [*D*] *Courtesy of* Jackson ML. Costa, Centro de Pesquisas Gonçalo Muniz, Fundação Oswaldo Cruz, Brazil.)

LR is more prevalent in the Old World (associated with *L* (*L*) *tropica* infection) but has also been observed in the New World. The lesion is characterized by an active lesion at (or near) the edge of the healed lesion or a scar (see **Fig. 2**B) that develops with or without treatment after a variable period of time. In the New World, LR is associated with *L* (*V*) *braziliensis* and *L* (*L*) *amazonensis* in Brazil[19] and *L* (*V*) *panamensis* in Ecuador.[20]

Disseminated leishmaniasis (DL) is characterized by the appearance of multiple (10–300) pleomorphic lesions in 2 or more noncontiguous areas of the body (see **Fig. 2**C), which are likely caused by hematogenous or lymphatic spread. The lesions are acneiform, ulcerated, and papular, and the mucosa is affected in 29% of cases. In Brazil, this presentation is attributed to *L* (*V*) *braziliensis*, although other species cannot be excluded.[21]

DCL is the anergic form of tegumentary leishmaniasis; thus, the lesions are full of parasites. DCL is a rare condition that is reported in South America, Central America, and Ethiopia. It evolves progressively from LCL; is characterized by multiple nodules, papules, or tubercles with diffuse cutaneous infiltration and no ulceration; and is localized primarily on exposed areas of the body (see **Fig. 2**D). The principal species involved include *L* (*L*) *mexicana* and *L* (*L*) *amazonensis* in the New World and *L* (*L*) *aethiopica* in the Old World.[2,22]

Mucosal leishmaniasis (ML) can occur simultaneously with a cutaneous manifestation (mucocutaneous leishmaniasis); however, ML usually occurs months or years after the cutaneous leishmaniasis. ML primarily affects the nasal mucosa (see **Fig. 2**E), but the oral mucosa can also be affected. The initial symptoms are nonspecific, making the diagnosis difficult. The symptoms can include itching in the nose that progresses to crust formation and bleeding. Initially, nasal inflammation and congestion are observed on a nostril examination; however, ulceration and perforation of the septum can slowly ensue. Parts of the face, soft palate, pharynx, and larynx may be affected. *L* (*V*) *braziliensis* is the primary species that is involved in New World mucosal leishmaniasis, although *L* (*V*) *panamensis*, *L* (*V*) *guyanensis*, and *L* (*L*) *amazonensis* can also be involved.[16] In the Old World, *L* (*L*) *major* and viscerotropic *L* (*L*) *infantum* are common.[23] The frequency of ML varies based on the geographic location. In Brazil, the incidence can range from 0.4% to 2.7%[16]; in Andean countries, the average incidence is 7.1%.[24]

Clinical manifestations of leishmaniasis in cases of human immunodeficiency virus (HIV)/*Leishmania* coinfection may present with different characteristics (see **Fig. 2**F). In the Old World, PKDL is reported in HIV-infected patients.[25] In the New World, the manifestations can vary from those that are similar to the symptoms that are found in non–HIV-infected patients to unusual manifestations. A wide variety of lesions, such as papules, nodules, plaques, and ulcerations, can occur, and some lesions can also affect the genital organs (see **Fig. 2**F, insert).[26] In the mucosa of the palate, a diffuse infiltration has been observed.[26] Tegumentary leishmaniasis may be the manifestation of an immune reconstitution inflammatory syndrome with newly disseminated lesions appearing or worsening while a recovery of the CD4+ T cell count and a decrease in viral load on antiretroviral treatment are detected.[27]

Some manifestations of infectious or noninfectious dermatologic diseases can be considered in the differential diagnosis and can include pyogenic skin infections, pyoderma gangrenosum, cutaneous mycobacterium infection, leprosy, syphilis, blastomycosis, chromoblastomycosis, sporotrichosis, sickle-cell anemia–related ulcers, idiopathic midline granuloma, sarcoidosis, Kaposi sarcoma, squamous cell carcinoma, basal cell carcinoma, B-cell cutaneous lymphoma, seborrheic keratosis, venous stasis, and traumatic ulcers.[16,28]

DIAGNOSIS OF LEISHMANIASIS
Laboratory Tests for Diagnosis

Parasite or parasite-related molecule detection

The presence of the parasite in the lesion is essential for diagnosis. Antigen-related or parasite-related molecules are occasionally detected, and these can serve as definitive markers in the diagnosis of leishmaniasis. The methods include a direct microscopic examination of a sample (**Fig. 3**A) that is taken from the lesion (by scraping, fine-needle puncture, or biopsy), an in vitro culture of a lesion sample to recover the parasite (see **Fig. 3**B), and immunohistochemistry to detect *Leishmania* antigens in the tissues (see **Fig. 3**C). The sensitivity of these methods is low and can be up to 58% using culture,[29] or 88% by immunohistochemistry.[30] The sensitivity can also depend on the clinical form; diffuse leishmaniasis lesions present with a high parasite density, whereas chronic lesions such as in ML and DL have few parasites. These methods can detect the parasite, but cannot identify the *Leishmania* species, which is possible only in reference laboratories that use recovered parasites from the lesion in culture and do tests for identification using *Leishmania* species–specific monoclonal antibodies[31] or by analyzing the isoenzyme profiles using electrophoresis.[32]

For etiologic diagnosis, alternatives include molecular approaches to detect *Leishmania* DNA using polymerase chain reaction (PCR) –based methods and can (1) detect the genus *Leishmania* to confirm leishmaniasis (as with other parasitologic methods) or (2) identify *Leishmania* species. The most commonly addressed targets are extrachromosomal DNA kinetoplast minicircle DNA (kDNA) and ribosomal RNA such as

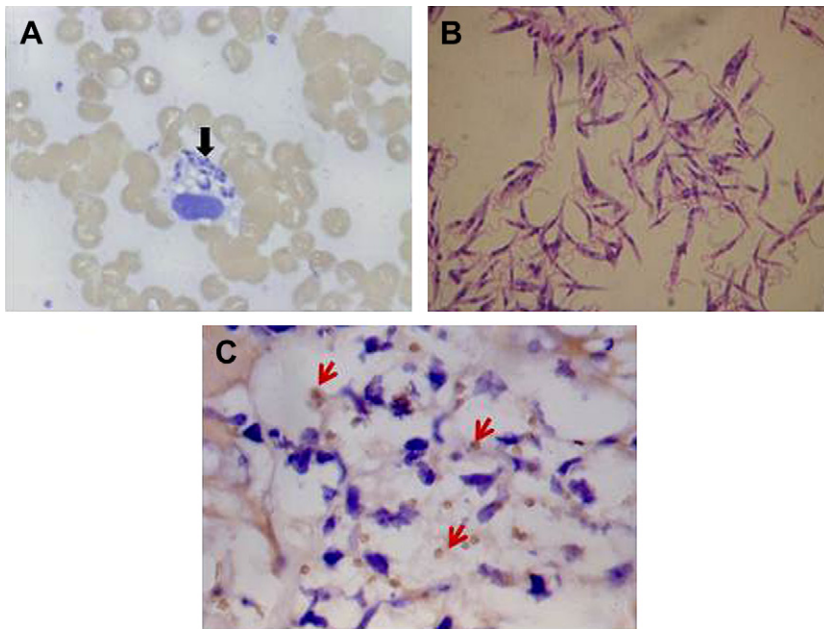

Fig. 3. Laboratory tests for the diagnosis of tegumentary leishmaniases. (*A*) Presence of *Leishmania* amastigotes within macrophages (*black arrow*) in smear from cutaneous lesion. (*B*) Presence of *Leishmania* promastigotes in culture. (*C*) Detection of *Leishmania* antigen (*red arrows*) by immunohistochemistry using polyclonal anti-*Leishmania* antibodies. 100×.

small subunit rRNA.[33] However, to be useful as a reference method, the protocols need to be standardized and optimized, and the sensitivity and specificity need to be evaluated in different centers to be considered comparable and reliable.

The identification of *Leishmania* species constitutes a challenge, and the available approaches are designed to analyze directly the genes for glucose-6-phosphate dehydrogenase,[34] mannose isomerase,[35] or restriction enzyme length polymorphism of kDNA, ribosomal internal transcribed spacer, heat shock protein 70,[36] or glycoprotein of molecular mass 63 (GP63)[37] gene products. Real-time PCR (qRT-PCR) has recently been evaluated as well for the diagnosis and identification of *Leishmania* species.[38]

Immunologic assays for diagnosis

Alternative or complementary approaches for diagnosis include the evaluation of indirect parameters using immunologic assays such as (1) anti-*Leishmania* delayed-type hypersensitivity (the Montenegro test or the leishmanin skin test) and (2) anti-*Leishmania* antibody assays.

Montenegro or leishmanin skin test At 48 or 72 hours after the injection of *Leishmania* antigen in the forearm, local induration is evaluated and considered positive when larger than 5 mm. This Leishmanin skin test is used in the diagnosis, but it can reveal both present and past infections,[39] even in infected asymptomatic individuals. Therefore, it is more appropriately used in epidemiologic studies to determine disease prevalence or for diagnosis in travelers who live in nonendemic areas and have no prior exposure to infection. In patients, only those who present with DCL test negative. One hundred percent of patients who present with ML or DL test positive, and 82% to 89% of patients with LCL test positive.[40]

Serologic diagnosis Indirect immunofluorescence assay (IIFA) and enzyme-linked immunosorbent assay (ELISA) are the methods that are commonly used in the diagnosis of leishmaniasis; however, in tegumentary leishmaniases, the sensitivity is considered to be low. In chronic lesions such as LR, MC, and DL, the sensitivity may be higher. In the case of ML (in which it is difficult to detect the parasite), positive serology may be the only criteria for diagnosis.[2] In addition, because the antibody level decreases after treatment,[41] a positive result may indicate a current infection.

In HIV/*Leishmania* coinfection, a diagnosis of leishmaniasis is difficult because of the varied clinical manifestations. A positive serologic test may help to provide an accurate diagnosis. In the Mediterranean region, serologic tests had low sensitivity in HIV/*Leishmania*-infected individuals,[42] but in Brazil, the sensitivity was higher, reaching 77%.[26] This finding might be explained by some patients having severe manifestations and/or a previous exposure to *Leishmania* in endemic areas and therefore likely having *Leishmania*-specific committed memory cells preserved, even in the face of immunosuppression from the HIV infection.

TREATMENT

For the definition of cases for treatment, see the flowcharts for cutaneous (**Fig. 4**A) and mucocutaneous leishmaniasis (see **Fig. 4**B), in which the contributions of each parameter are depicted.

Drug therapy for tegumentary leishmaniasis has not significantly changed since the beginning of the twentieth century, when it started. However, knowledge regarding the differences in the drug responses of the *Leishmania* species that are prevalent in different geographic areas and their clinical manifestation is slowly increasing. In

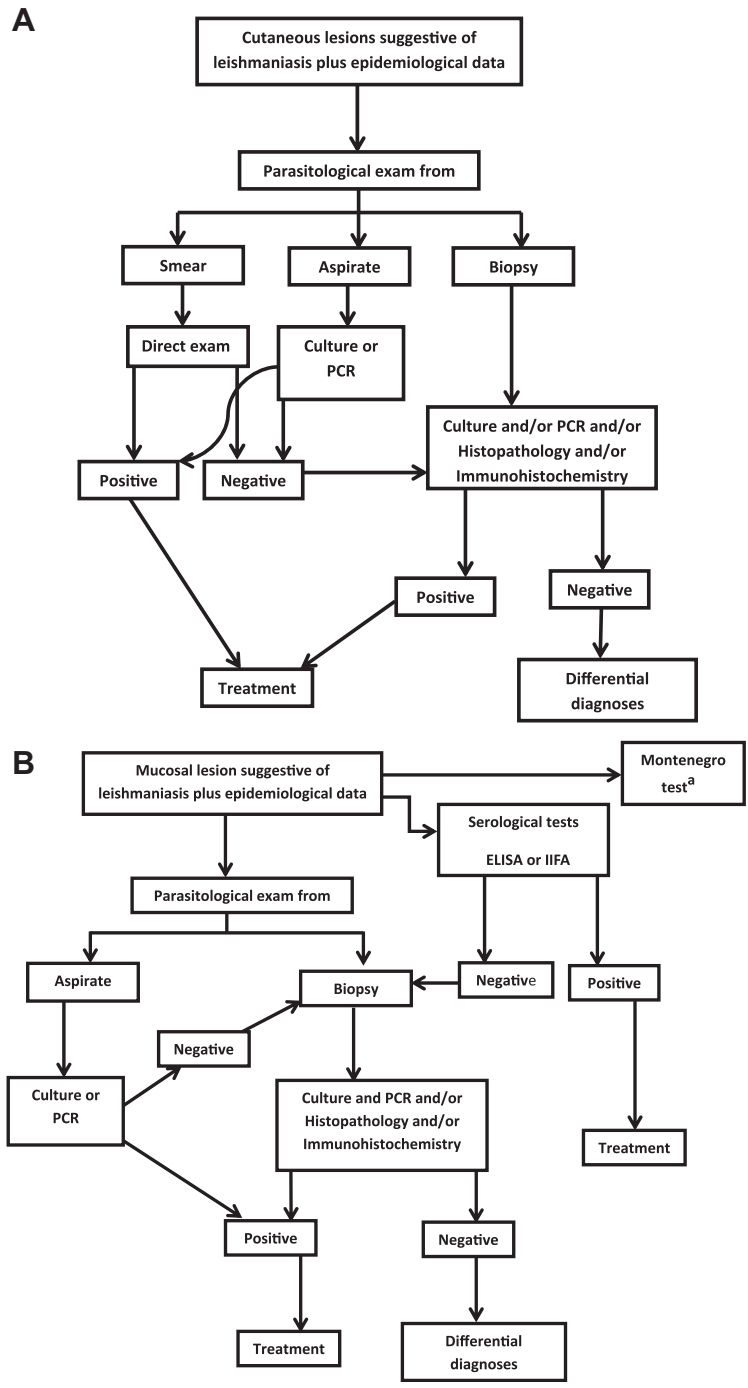

Fig. 4. Flowchart for the diagnosis of cutaneous (*A*) and mucocutaneous leishmaniasis (*B*). [a] Positive Montenegro test indicates present or past *Leishmania* infection; however, in a patient living outside an endemic area who presents a lesion that suggests leishmaniasis, it can be a criteria for definition of leishmaniasis.

addition, studies of resistance to drugs and the leishmaniases in immunosuppressed patients have been reported. However, in general terms, because the same drugs are used in both the Old World and New World, there is an urgent need to develop a more rational use of available treatments and to develop novel drugs.

On establishing a diagnosis, the treatment may be either local or systemic. There is growing evidence regarding the efficacy of local treatment in cutaneous leishmaniasis in the Old World, but less is known in the New World, which suggests the need for better designed studies there. Choosing systemic therapy instead of local therapy (which is more common in the New World) can minimize the potential risk for developing ML, which exists in the New World and has a more prolonged disease course[14,15] However, there is no conclusive study showing that systemic treatment is effective in preventing a severe outcome.[43] Therefore, in localities where the prevalence of this severe form is low (such as Venezuela and Colombia[24]), local treatment may be considered.

Recently, a report of the meeting of the World Health Organization (WHO) Expert Committee on the Control of Leishmaniases was published,[2] and the treatment recommendation was based on the grade of evidence, of geographic distribution, clinical manifestation, and *Leishmania* species. For the Old World *L* (*L*) *major* LCL, the following criteria to recommend local treatment were set: proven or strongly suggested *L* (*L*) *major* as the infecting agent; up to 4 lesions; the diameter of the lesions less than 5 cm; no potentially disfiguring or disabling lesion; no immunosuppression; and the possibility for follow-up. As summarized in **Table 1**, when indicated, the options for local therapy include the use of 15% paromomycin plus 12% methylbenzethonium chloride ointment or intralesional antimonials plus cryotherapy or thermotherapy. These procedures can cause discomfort, and many require local anesthesia.[2,44] For other conditions, systemic treatment should be chosen, with the use of fluconazole or pentavalent antimonials plus pentoxifylline for 10 to 20 days.[2,44]

To treat Old World LCL that is caused by *L* (*L*) *tropica*, *L* (*L*) *aethiopica*, or *L* (*L*) *infantum*, the local treatment mentioned earlier with intralesional antimonials alone, thermotherapy, or perhaps cryotherapy alone is recommended. In particular cases in which systemic treatment is indicated, the use of the pentavalent antimonials plus oral allopurinol is recommended when the disease involves *L* (*L*) *tropica* causing LR; pentavalent antimonials plus intramuscular paromomycin are indicated when the disease involves *L* (*L*) *aethiopica* causing DCL.[2,44]

In the New World, local treatment is considered in some situations, including the use of 15% paromomycin and 12% methylbenzethonium chloride ointment, thermotherapy (sometimes requiring 3 applications), or intralesional antimonials for all species.[2,45]

In the New World, systemic treatment is better established, and the efficacy depends on the *Leishmania* species that is involved. To treat LCL that is caused by *L* (*L*) *mexicana*, the use of ketoconazole or miltefosine is recommended. To treat LCL that is caused by other *Leishmania* species, pentavalent antimonials are commonly used. Alternate drugs for *L* (*V*) *guyanensis* and *L* (*V*) *panamensis* include pentamidine or miltefosine. For *L* (*V*) *braziliensis*, alternate drugs include amphotericin B deoxycholate or liposomal amphotericin B. To treat LCL that is caused by *L* (*L*) *amazonensis*, *L* (*V*) *peruviana*, or *L* (*L*) *venezuelensis*, the recommended initial treatment is exclusively based on pentavalent antimonials.[2,45]

Episodes of relapse are common in the New World, and this can be followed by amphotericin B deoxycholate, pentavalent antimonials plus topical imiquimod, or liposomal amphotericin B.

The only option for treating ML is systemic, sometimes using a higher dosage or prolonged treatment. The recommended drugs are (1) prolonged (30 days) pentavalent

Table 1
Local and systemic treatment regimens for tegumentary leishmaniasis

Local Treatment

Therapy	Doses/Regimens	Period	Clinical Form	*Leishmania* Species
15% Paromomycin plus 12% Methylbenzetonyl chloride	Twice daily	20 d	CL	All species
Intralesional pentavalent antimonial	1–5 mL/session	Every 3–7 d, 1–5 sessions	CL	All species
Cryotherapy (liquid nitrogen: -195°C)[a]	Every 3–7 d	1–5 sessions	CL	*Leishmania* from Old World
Thermotherapy	50°C for 30 s	1–3 sessions	CL	All species
Imiquimod[b]	Every other day	20 d	CL	*Leishmania* from New World

Systemic Treatment

Drug	Doses	Period	Clinical Form	*Leishmania* Species
Pentavalent antimonial	20 mg sb^{5+}/kg/d (IV or IM)	20 d	CL	All species
	20 mg sb^{5+}/kg/d (IV or IM)	30 d	ML	All species
Amphotericin B deoxycholate	0.7 mg/kg/d (IV infusion)	25–30 doses	CL	*L* (*V*) *braziliensis*
	0.7–1 mg/kg/d (IV infusion)	25–40 doses	ML	All species
Liposomal amphotericin B	2–3 mg/kg/d (IV infusion)	Total dose: 20–40 mg/kg	CL	*L* (*L*) *aethiopica*, *L* (*V*) *braziliensis*
	2–3 mg/kg/d (IV infusion)	Total dose: 40–60 mg/kg	ML	All species
Pentamidine isethionate	4 mg salt/kg/d, every other day (IM)	3 doses	CL	*L* (*V*) *guyanensis*, *L* (*V*) *panamensis*, *L* (*L*) *mexicana*
Miltefosine	2.5 mg/kg/d (oral) (maximum dose: 150 mg/d)	28 d	CL	*L* (*V*) *guyanensis*, *L* (*L*) *mexicana* *L* (*V*) *panamensis*
	2.5–3.3 mg/kg/d (oral) (maximum dose: 150 mg/d)	28 d	ML	*L* (*V*) *braziliensis* from Bolivia
Fluconazole	200 mg/d (oral)	6 wk	CL	*L* (*L*) *major*
Ketoconazole	600 mg/d (oral)	28 d	CL	*L* (*L*) *mexicana*
Pentoxifylline[b]	400 mg/every 8 h (oral)	10–20 d	CL	*L* (*L*) *major*
	400 mg/every 8 h (oral)	30 d	ML	All species
Allopurinol[b]	20 mg/kg/d	30 d	CL	*L* (*L*) *tropica*
Paromomycin[b]	15 mg (11 mg base)/kg/d (IM)	≥60 d	CL	*L* (*L*) *aethiopica*

Abbreviations: CL, cutaneous leishmaniasis; IM, intramuscular; IV, intravenous; ML, mucosal leishmaniasis.
[a] Could be used alone or in association with intralesional antimonial.
[b] Used only in association with other drugs.

antimonial treatment, (2) pentavalent antimonials plus oral pentoxifylline, (3) amphotericin B deoxycholate, or (4) liposomal amphotericin B.[2,45] In Bolivia, miltefosine can be used to treat ML that is caused by *L* (*V*) *braziliensis*.[2,46]

In HIV-infected patients, relapses of tegumentary leishmaniasis are more frequent; thus, only systemic drug treatment is indicated. Because of more frequent side effects that are associated with pentavalent antimonial use in HIV-infected patients, amphotericin B is the drug of choice (at the same dose and duration as in non–HIV-infected patients). No secondary prophylaxis is indicated for patients with tegumentary leishmaniasis who also have acquired immune deficiency syndrome.[47]

A detailed description of the drug actions and the efficacy of other drugs are provided in a recently published review by Goto and Lindoso[16] and in the report of the meeting of the WHO Expert Committee on the Control of Leishmaniases.[2] Briefly, among the antileishmanial drugs, pentavalent antimonials (including sodium stibogluconate and meglumine antimoniate) are most commonly prescribed. Varied efficacy among the different species, but also within the same species, has been observed. For example, in ML, the cure rates range from 30% to 90%, depending on the geographic area and the dose of the drug.[48,49] Another example is the failure rate for treating *Leishmania* (*V*) *braziliensis* versus *Leishmania* (*V*) *guyanensis*, which is higher for the former in Peru[50] and lower for the former in Brazil.[51] Various dosages have been studied, and doses other than the recommended dose are occasionally used; however, such a decision must be based on structured studies within the same area and with the same *Leishmania* species.[52,53] Contraindications for the use of pentavalent antimonials include pregnancy and renal, heart, or hepatic failure.

Amphotericin B is found in 4 different formulations: amphotericin B deoxycholate, liposomal amphotericin, cholesterol dispersion amphotericin, and lipid complex amphotericin. They all present similar efficacy but differ in side effects. Renal injury is more frequent with amphotericin B deoxycolate.[54]

Pentamidine presents the same efficacy as antimonials[55] in cutaneous leishmaniasis caused by *L* (*V*) *panamensis* or *L* (*V*) *guyanensis* in Brazil, Colombia, French Guiana, and Suriname, but less with *L* (*V*) *braziliensis*. Hypoglycemia and hyperglycemia are its main adverse effects.[54]

Using miltefosine, cure rates of 75% and 88%, respectively, were reported in Bolivia and Brazil, in LCL caused by *L* (*V*) *braziliensis*,[56,57] and 71.4% was reported in LCL caused by *L* (*V*) *guyanensi*.[58] Its use is contraindicated during pregnancy.

Azoles such as fluconazole, ketoconazole, and itraconazole have shown cure rates between 55% and 79% in the Old World.[59] In the New World, ketoconazole has shown efficacy against *L* (*L*) *mexicana* and *L* (*V*) *panamensis* and is recommended to treat LCL in Guatemala and Panama.[45]

As shown earlier, pentoxifylline, an immunomodulatory drug inhibitor of TNF-α, has been used in conjunction with antimonials to treat mucosal and cutaneous leishmaniasis and led to a reduction in healing time.[60,61] Conversely, immunotherapy using *Leishmania* antigen alone or in combination with bacille Calmette-Guérin has been used with partial success in Brazil and Venezuela, although it is not in routine use.[62,63] Regarding the use of immunomodulatory drugs or immunotherapy, it is important to better understand the immunopathogenesis of cutaneous leishmaniasis and ML, because immunotherapy can increase the immune inflammatory process that may interfere with the manifestations of cutaneous and mucosal leishmaniasis that are caused by hypersensitivity rather than immunosuppression,[64] with the exception of DCL.

On treatment, it should be emphasized that the criteria of cure are only clinical because neither parasitologic nor laboratory parameters meet this purpose. In cutaneous

leishmaniasis, the criteria of cure are total epithelialization of the lesion and the disappearance of the induration at the base of the ulcer that should occur up to 3 months after treatment. In ML, cure is total regression of clinical signs that should ensue within 6 months after treatment. If clinical cure according to these criteria is not achieved, it is considered as relapse and new treatment should be provided with the same or an alternative regimen.[47]

SUMMARY

Tegumentary leishmaniasis is a disease characterized by an extreme diversity of the various species of the causal agent, their different geographic distribution, diverse reservoirs, and diverse vectors occurring in sylvatic or peridomestic environments and varied clinical manifestations. Global human mobility, climate changes, civil wars, and HIV infection have increased the complexity of an already multifaceted disease in recent years. These characteristics complicate the process of diagnosis and treatment. This article provides an overall guide to assist patients with tegumentary leishmaniasis.

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