Visceral and Cutaneous Leishmaniasis Recommendations for Solid Organ Transplant Recipients and Donors

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VISCERAL AND CUTANEOUS LEISHMANIASIS IN SOLID-ORGAN TRANSPLANT RECIPIENTS

Epidemiology and Risk Factors

Leishmaniasis is a protozoan disease transmitted through the bite of infected female sandflies of the genera Phlebotomus (Old World) and Lutzomyia (New World). Infection with *Leishmania* species (Figure 1) may cause cutaneous, mucocutaneous, or visceral leishmaniasis (VL). Cutaneous leishmaniasis (CL) is characterized by single or multiple skin ulcers, satellite lesions, or nodular lymphangitis and is associated with multiple species (Figure 2). Mucocutaneous leishmaniasis (MCL) is often caused by *L. braziliensis* and *L. panamensis*, and leads to metastasis of the disease to the mucosal tissues of the mouth and upper respiratory tract via lymphatic or hematogenous dissemination (Figure 3). VL in the New World is caused by *L. infantum* (= *L. chagasi*).[1,2] In this form, the parasite can infect internal organs, such as the liver, spleen, and bone marrow, causing life-threatening diseases.[3,4] However, in immunocompromised hosts, such as organ transplant recipients, the clinical presentation of this disease and the response to treatment can be greatly altered.[5-8]

Annually, there are 1.3 million new cases of leishmaniasis worldwide, predominantly in tropical and Mediterranean regions, where the disease is endemic. Over 1 000 000 new cases of CL and 200 000 to 400 000 new cases of VL are reported annually.[9,10] Brazil has a high burden of both VL and CL. In 2014, 3453 cases of VL were reported (0.41 cases per 10 000 population at risk), and the total number of CL cases was 19 402 (1.46 cases per 10 000 population at risk). The incidence of CL was highest in Nicaragua, Panama, and Suriname and was higher in men (35.48, 27.32, and 18.08 per 10 000 population at risk, respectively) than in women (18.08, 13.02, and 9.20 per 10 000 population at risk, respectively).

Reported cases of leishmaniasis in solid-organ transplant (SOT) recipients have been predominantly VL; CL is rarely reported among these patients.[5] It remains unclear whether this difference occurs because SOT leads to a greater susceptibility to VL, because fewer organ transplants are performed in areas highly endemic for CL or because of a publication bias. In a recent study, VL prevalence among SOT recipients ranged from 0.1% to 0.5% in endemic countries.[11]

In the New World, leishmaniasis is predominantly a zoonotic disease, but the reservoirs vary by parasite species (from sylvatic to domestic animals) and location. CL was formerly considered an occupational disease related to outdoor activities, such as timber harvesting, mining, agriculture, military operations, and road construction. Occupational exposure remains important, but widespread deforestation has led to a rapid increase in cases and to peridomestic, periurban, and even urban transmission. Particularly in Brazil, VL is concentrated in periurban areas, where domestic animals serve as reservoir hosts.[1]

The factors causing infected individuals to develop clinical disease are only partially understood; however, parasite virulence, nutritional status, age, and host genetic and response

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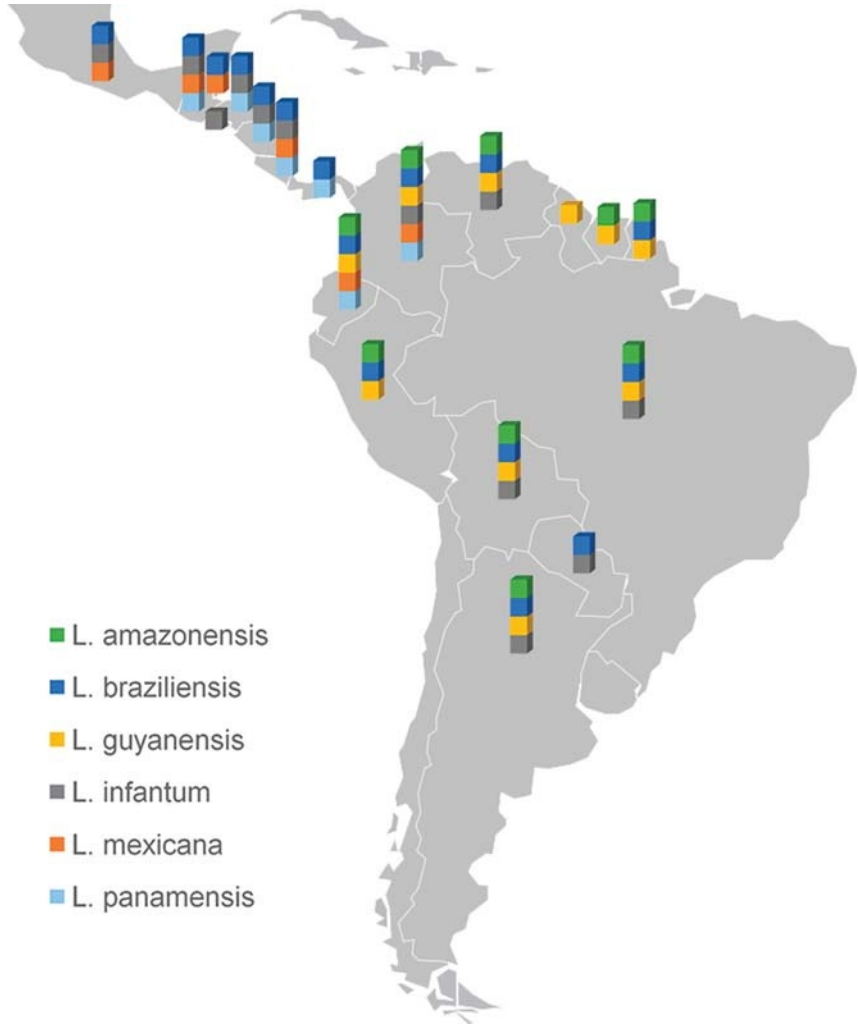

FIGURE 1. Leishmania species distribution in Latin America.

factors are known to contribute to the development of clinical disease.[8] Seventy percent of individuals can be asymptomatically infected in highly endemic areas, depending on the geographic location and detection technique used.[12] In healthy, immunocompetent hosts, T helper cells kill Leishmania protozoa. However, in immunosuppressed patients, the T-cell response is inadequate, thus increasing the susceptibility of these patients to develop clinical disease or more severe disease and leading to higher rates of relapse.[13] In organ transplant recipients, the risk factors for developing leishmaniasis have been poorly studied. Immunosuppression, especially due to the use of high-dose steroids, may play a role in the development

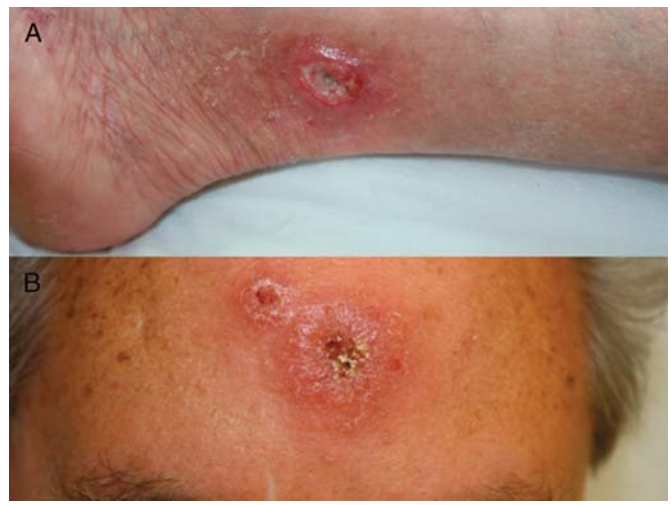

FIGURE 2. Cutaneous leishmaniasis. An ulcerated lesion on the leg (A) and on the face (B).

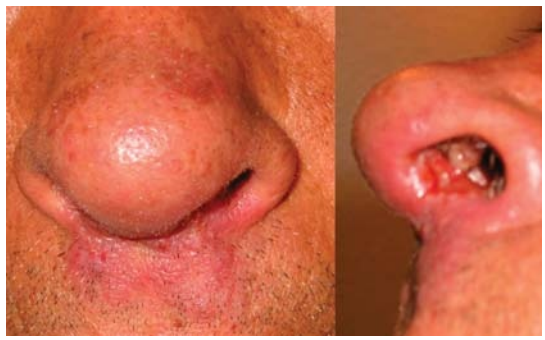

FIGURE 3. Mucocutaneous leishmaniasis. An ulcerated lesion on the face.

of disease.[11] Leishmaniasis is frequently described in renal transplant recipients. This finding may be attributed to the higher number of renal transplants compared with other organs or to a publication bias; although, it is conceivable that renal failure or dialysis may increase the risk of developing leishmaniasis via an as-yet-unknown mechanism.[5,14,15]

Transplant patients can develop leishmaniasis by (i) primary infection via a vector, (ii) reactivation of a latent infection, or (iii) donor-derived infection (organ or blood).[16,17] Leishmaniasis should be suspected in transplant recipients from endemic areas or in those who have traveled to endemic areas, even if they did so many years before transplantation.[3] Leishmaniasis can occur at any time after transplantation; although, most infections present in the first year posttransplant.[5,11,18] There is evidence linking the intensity of endemicity in an area with early infection after transplantation.[11]

Clinical Manifestations

VL

VL is the most severe form of leishmaniasis and is characterized by prolonged fever, weight loss, splenomegaly and hepatomegaly, progressive anemia or pancytopenia, and hypergammaglobulinemia.[19,20] Fever is the most common symptom of VL in SOT recipients,[5] whereas organomegaly may be less frequent in SOT recipients than in immunocompetent individuals.[21] Disease presentation in SOT can be atypical; only one-third of patients exhibit the triad of fever, visceromegaly, and cytopenia.[11] Although VL predominately affects organs of the reticuloendothelial system, in cases of severe immunosuppression, amastigotes may disseminate through all tissues, including the intestines, oral cavity, skin, and lungs.[22] Cutaneous manifestations can occur before, during, or after the VL episode, with postkala-azar dermal leishmaniasis being more common in immunocompromised patients.[8] Secondary infection with bacteria or cytomegalovirus[11] is also common. Disseminated mycobacterial infections, histoplasmosis, and lymphoma (posttransplant lymphoproliferative disorder) should all be considered in the differential diagnosis of VL.[8]

CL and MCL

CL can manifest as a self-limiting cutaneous lesion or can be so severe as to cause disfiguring mucocutaneous ulcerations.[23] Although the clinical presentation of CL in immunocompromised patients will often be like that in immunocompetent individuals, atypical features include parasite dissemination with multiple lesions, clinical polymorphism and visceralization, even with species thought to only cause cutaneous disease. Patients with nonhealing skin lesions and a history of travel to an endemic region should be evaluated for CL.[24] Because the recommended treatment for CL varies by parasite species, species identification should be pursued.[8]

Diagnosis

VL

Direct Examination

The confirmatory diagnosis of VL is based on the demonstration of Leishmania parasites by microscopic examination or culture. This approach requires invasive procedures, such as spleen or bone marrow aspiration (BMA). Splenic aspirate cytology has excellent sensitivity, exceeding 95%, but has been associated with potentially fatal hemorrhage in inexperienced hands.[25] BMA sensitivity varies from 53% to 86%, depending on personal expertise. Culture isolation remains the reference method for parasite identification at the species level, but it is labor intensive and requires up to 4 weeks.[3,19,20,26,27]

Serology

Unlike in patients with human immunodeficiency virus (HIV), serological test sensitivity in SOT recipients appears to be like that for immunocompetent individuals.[8] The most widely used serological techniques are the indirect fluorescent antibody test, enzyme-linked immunosorbent assay, and rapid tests, such as immunochromatographic and direct agglutination tests.[20] Sensitivity and specificity vary per the methods and antigens used. In Brazil, it has been reported that RDT with rKE16-based products appears to perform less well than rK39 products. This difference in performance may be partially explained by the fact that rKE16 tests are based on a recombinant antigen from *Leishmania donovani*, whereas rK39 is based on Leishmania infantum.[28] Antigens that are more specific, such as rK39, have been used in both enzyme-linked immunosorbent assays and rapid tests, improving the performance of these assays. Serology limitations include the potential for lack of agreement between methods, the inability to distinguish previous exposure from active infection and potential cross-reaction with other protozoa.[11] Diagnosis based on positive serology without confirmation by direct examination should be supported by clinical correlation.

Molecular Diagnosis

Molecular Diagnosis techniques present high sensitivity and specificity, and may enable species identification[5,20,29]; the use of peripheral blood samples for polymerase chain reaction (PCR) testing offers the advantage of being a noninvasive method with a sensitivity and specificity like those of bone marrow aspirate.[30] Additionally, quantitative PCR can be used for monitoring response to treatment. Conventional Leishmania PCR tests that use blood samples will present negative results soon after the beginning of treatment, and the reappearance of a positive PCR result can indicate relapse.[8] However, asymptomatically infected individuals may present a positive PCR test without any further disease development; thus, a positive PCR result does not always indicate disease.[31] Additionally, a positive PCR result may be recovered from scar tissue many years after adequate treatment.[32]

Various regions of the Leishmania genome, such as ribosomal DNA (ITS-1 and SSU rDNA), kinetoplastid minicircle DNA, splice leader mini-exon, tryparedoxin peroxidase gene

and heat-shock protein 70 genes, have been targeted for molecular assays. The choice of target is related to the different applicability of each assay: an assay targeting the kinetoplastid minicircle DNA may be used for diagnosis due to its sensitivity, whereas assays targeting ITS-1 are more specific and may be used for species identification.[33] False-negative results can occur due to either degradation of the protozoa during cell necrosis and lysis or to technical errors during DNA extraction.[34]

Finally, despite the unquestionable superiority of methods able to identify species, species identification is laborious and performed only in reference laboratories; thus, this approach is not always practicable for routine use.

Antigen Detection

Leishmanial antigens can be detected in serum and urine samples with widely varying sensitivity and specificity.[26] The usefulness of this detection method in the SOT recipient population remains to be determined.[8]

Cell-Based Tests

A recent study[35] demonstrated the production of immunological markers (IFN-γ, TNF-α, granzyme B, IL-5 and IL-10) by soluble Leishmania antigen–stimulated peripheral blood mononuclear cells; these markers could be used to indicate exposure, especially for induced immunosuppressed patients.

CL

Direct Examination

The criterion standard for CL is the demonstration of parasite presence by microscopy or molecular methods. Material from the ulcer margin usually has the highest yield for histopathological examination. Parasite culture tends to present low sensitivity and to provide variable results.[4] PCR is particularly useful when the parasite burden is low[24] and enables species identification. This characteristic is important because multiple species can coexist in each area, and the choice of treatment and patient response are species dependent.[29]

Histopathology and Immunohistochemical Examination

Histopathological findings depend on the stage of development of the lesion, the species of Leishmania, the response of the host, and the degree of cellular immunity. The initial lesion begins as circumscribed papules (like an insect bite), which may enlarge to form nodules or plaques and often become ulcerated. Acute lesions usually present with dense dermal infiltrate; with time, tuberculoid granulomas may replace the infiltrate. Many parasites indicate anergy, whereas necrosis and granulomatous lesions represent a robust immune response.[36,37] Immunohistochemical examination is useful as a supplementary tool for confirming a diagnosis based on hematoxylin-eosin staining. Limitations of this method result from ground staining, an inadequate selection site for tissue sampling and cross-reactions with other protozoa.[34,38]

Immunological and Serological Tests

The Montenegro skin test is an indirect method to detect a previous exposure to leishmaniasis and is often used in epidemiological studies to assess disease prevalence. This test has limited diagnostic utility in endemic areas, as positive results may be obtained in patients without active or cicatricial lesions.[23] Furthermore, this skin test can result in a false negative if anergy is present. Overall, serological testing is not reliable because of the poor humoral response provoked by infection.[4]

Recommended Diagnosis Approach

Ideally, the combination of multiple methods is recommended for leishmaniasis diagnosis.[8] Therefore, some authors suggest adapting a diagnostic approach per the level of invasiveness by considering sequential testing.[33] However, in the transplant setting, a flowchart for leishmaniasis diagnosis has not yet been proposed. For CL, the MST is not routinely conducted aside from usually providing negative results in immunocompromised individuals. Therefore, if microscopy is negative, PCR, which has the advantage of species identification, could be used. For VL, if clinical and epidemiological evidence suggests disease, serological tests may be performed; if these tests are negative, a bone marrow biopsy should be conducted, although PCR can be considered, even in peripheral blood samples. The usefulness of monitoring the parasite load with PCR to predict relapses or treatment failure has not been established. PCR monitoring can be helpful for patients with a partial response to treatment or after the first relapse.

Therapy

VL

The therapies for VL in SOT recipients are diverse and depend on various factors, such as patient characteristics (eg, age, immune status and renal/liver function), Leishmania species, disease extent, drug availability, concomitant infections and previous treatments.[39] Therapeutic options may include different formulations of amphotericin B, pentavalent antimonials, miltefosine, and paromomycin, among others.[40,41] Immunosuppressant dose reduction has been recommended by some experts for SOT recipients developing VL, but such decisions must be made on an individual basis.[8]

Liposomal Amphotericin B

Currently, liposomal amphotericin B (LamB) is considered the first-line treatment for VL, and it is the only approved drug for VL in many countries.[5,7] Recent guidelines and a panel of experts have proposed LamB as the preferred therapy for SOT recipients.[8,11,40-43] The World Health Organization recommends the following schedule for immunosuppressed patients (both HIV and non-HIV) with VL: 3 to 5 mg/kg per day on days 1 through 5 and on days 10, 17, 24, 31, and 38.[3,44,45] Some authors even recommend secondary prophylaxis.[46] LamB is much safer than traditional deoxycholate amphotericin B. Nevertheless, the possibility of developing adverse effects, namely, back pain during infusion, electrolyte disturbances, infusion reactions or nephrotoxicity, must be considered.

Pentavalent Antimonials

Two drugs are available from this group: sodium stibogluconate (100 mg Sbv+/mL) and meglumine antimoniate (85 mg Sbv+/mL).[43] These drugs have traditionally been considered first-line treatments for VL and are still considered as such in many regions of the world.[39] However, these drugs present potentially severe adverse effects when systemically administered (cardiotoxicity manifesting as potentially lethal arrhythmias and severe pancreatitis). Another drawback of pentavalent antimonials is that resistance has developed in some areas. In our opinion, these drugs should be considered

second-line treatment options for SOT recipients developing VL and should be reserved for those intolerant or unresponsive to LamB or for those SOT recipients in areas where LamB is not available.[47]

Miltefosine

This drug has been used in India as a first-line therapy for VL for more than a decade,[39,43] but high rates of clinical failures have been reported in recent years.[48] The standard dose of miltefosine for VL is 150 mg/d for 28 days in adults with a body weight over 50 kg. This drug has an acceptable toxicity profile, with gastrointestinal symptoms as the main adverse effect. The published evidence regarding the use of this drug for the treatment of immunosuppressed patients is scarce.[49] No trials in SOT recipients have been published, but in a recent small cohort, miltefosine was used in 6 SOT patients (5 kidney transplants and 1 lung transplant) who experienced VL relapse after LamB treatment. All these patients showed initial improvement, but 5 of the 6 patients developed a new episode of VL after treatment.[50] Future studies might explore the utility of combining treatments, including both miltefosine and LamB, or of using miltefosine as a transitional tool to a long-term phase of secondary prophylaxis. Thus, no experience using combination therapy or secondary prophylaxis with miltefosine in SOT recipients has been reported.

Paromomycin

This second-line drug has limitations, including suboptimal effectiveness and the potential for irreversible toxicity. In a comparative clinical trial, this drug was demonstrated to be as active as pentavalent antimonials and deoxycholate amphotericin B against *L. donovani* leading to VL in Bihar (India) and Africa (Kenya and Sudan).[43] The adverse effects of this aminoglycoside include ototoxicity and renal toxicity. No data are available regarding its use in the Mediterranean region or in the Americas. No accounts of using paromomycin for the treatment of VL in SOT recipients have been published.

Other Drugs

Anecdotal reports have communicated the successful administration of itraconazole plus miltefosine for VL in immunocompromised subjects after the failure of standard therapy.[51] Older reports described the use of meglumine antimoniate plus allopurinol for the treatment of recalcitrant VL in patients infected with HIV.[52]

CL

The therapeutic options for CL, including MCL and postkala-azar dermal leishmaniasis (PKDL), in SOT recipients are diverse and depend on various factors, as is the case for VL.[39,53-61] Drugs with activity against CL and PKDL include amphotericin B, pentavalent antimonials, miltefosine, pentamidine, and paromomycin. Immunosuppressant dose reduction has been recommended for SOT recipients developing CL, although such decisions must be made on an individual basis in this context.[62]

Treatment for CL among immunocompetent individuals depends on the number and size of skin lesions. Topical treatment (cryotherapy, thermotherapy, intralesional antimonials or surgical excision) has been advocated in cases involving a limited number of small lesions.[37,63-68] Anecdotal cases of topical treatment for CL in immunosuppressed patients by treatment with TNF-α antagonists have been communicated.[68] No experiences regarding the use of any of these types of topical treatments as the sole therapeutic measure for CL in SOT recipients have been reported. Therefore, systemic treatment (as used for the treatment of VL) is recommended for CL in SOT recipients by this panel and by others.[7,8,39,53,62,69-71]

LamB has shown high cure rates for CL, even for mucosal leishmaniasis.[72] The usefulness of miltefosine has yet to be elucidated. The susceptibility of cutaneous Leishmania species to miltefosine is lower than that of *L. donovani*. Clinical trials in Colombia and Nicaragua have shown variable efficacy of miltefosine that seemed to correlate not only with the Leishmania species but also with geographical heterogeneity within the same species. The response rates for pentamidine isethionate are like those of antimonials for CL, mainly in areas where *L. guyanensis* is more prevalent.[73] Table 1 summarizes the treatment options available, regarding clinical forms and Leishmania species involved.

Prevention and Prophylaxis

Value of Screening Both Donors and Candidates

Although both CL and VL may reactivate in the setting of organ transplantation, the data available to determine whether screening potential organ transplant recipients would be beneficial is lacking.[7,8,18] However, patients known to be seropositive at the time of transplant should be monitored closely for signs and symptoms of reactivation. Additionally, given the limited data on donor-derived infection, donor screening is not recommended.[7,20,74]

Risk of Relapse, Utility of Secondary Prophylaxis and Preemptive Treatment

Patients with known or suspected CL and VL pretransplant have been reported to develop recurrent disease post-SOT. Relapsed VL was diagnosed in 24% to 35% of SOT cases as early as 1 month and as late as 5 years posttransplant.[5,11,75,76] The successful use of secondary prophylaxis has been reported in cases of VL in SOT recipients, and different regimens have been used in this context, including weekly amphotericin B or daily fluconazole and monthly meglumine antimoniate.[11,72,77,78] Because relapse is common in the presence of continued immunosuppression, secondary prophylaxis may need to be continued for prolonged periods. Patients with known previous CL or VL, or recipients of organs from donors with VL should be clinically monitored for evidence of infection after organ transplantation, especially during the first year after transplantation, as failure and relapse occur commonly during this period.

Protective Measures to Prevent Exposure

When visiting endemic areas, transplant recipients should minimize outdoor activities, especially during dusk hours, when sand flies generally are the most active. These individuals should also wear protective clothing, apply insect repellent (ie, N,N-Diethyl-meta-toluamide or diethyltoluamide [DEET]) to exposed skin, use pyrethroid-treated bed nets, and spray dwellings with residual-action insecticides.[79]

TABLE 1.

Summary of Leishmaniasis in SOT recipients in Latin America

Clinical form	Species involved	Presentation	Diagnosis	Treatment[a]
VL	*L. infantum*	Prolonged fever, weight loss, splenomegaly and hepatomegaly, progressive anemia or pancytopenia, and hypergammaglobulinemia. Disease presentation in SOT recipients can be atypical; only 1/3 of patients exhibit the triad of fever, visceromegaly and cytopenia	Ideally, a combination of methods. Direct examination: - microscopy (Sensitivity BMA: 53 to 86%; Spleen > 95%). - molecular: variable per technique. Serology: should be supported by clinical correlation.	LamB[b] Second-line treatment: Pentavalent antimonials
Localized CL	Multiple species of both the Leishmania and Viannia subgenera	Single or multiple skin ulcers, satellite lesions, or nodular lymphangitis and association with multiple species	Direct examination: - microscopy: criterion standard. - molecular method: useful if parasitic burden is low. Positive PCR can be observed in scar tissue. Culture: enable species identification.	LamB[b] Second-line treatment: Pentavalent antimonials, miltefosine
Disseminated CL	*L. braziliensis*, *L. panamensis*, *L. guyanensis,* and *L. amazonensis*	Extensive, numerous nodular or ulcerated lesions infections with or without mucosal involvement.		
Diffuse CL	*L. mexicana* and *L. amazonensis*	Usually no mucosal lesions. The condition does not heal spontaneously. Initially, responds to standard treatment but relapses and becomes unresponsive to further treatment.		
MCL	*L. braziliensis* and *L. panamensis* Similar conditions caused by other species have been reported in immunosuppressed patients.	Mucosal tissues metastasis of the mouth and upper respiratory tract by lymphatic or hematogenous dissemination.		

[a] Consider secondary prophylaxis for VL. The first-line drug for secondary prophylaxis is LamB (3 mg/kg) administered in a single dose every 3 or 4 weeks. The optimal duration of secondary prophylaxis has not been defined.
[b] Standard dose of LamB: 3-5 mg/kg/day on days 1 through 5 and on days 10, 17, 24, 31, and 38.

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