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Cutaneous Leishmaniasis: Current Treatment Practices in the USA for Returning Travelers

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Opinion statement

Leishmaniasis, a protozoal infection transmitted by sandfly bite, produces a clinical spectrum of disease ranging from asymptomatic infection to ulcerative skin and mucosal lesions to visceral involvement. Leishmaniasis is endemic in regions of Africa, the Middle East, south Asia, southern Europe, northern South America, and Central America. There has been an increase in imported leishmaniasis into developed, non-endemic countries due to increasing global travel. While pentavalent antimonials have been the mainstay of antileishmanial treatment for decades, newer therapeutic options have become available for all forms of infection, including liposomal amphotericin B, miltefosine, fluconazole, and ketoconazole. For the returning traveler with cutaneous leishmaniasis in the USA, treatment approaches are determined based on infecting species, initial presentation, extent and progression of disease, the advantages and drawbacks of available parenteral and oral drugs, and clinician-consultant experience.

Keywords

Leishmania; Leishmaniasis; Protozoa; Cutaneous; Diagnosis; Treatment; Travelers

Introduction

Epidemiology

Leishmania infection produces three clinical syndromes: visceral (VL), cutaneous (CL), and mucosal leishmaniasis (ML). The clinical epidemiology is divided into two distinct entities—Old World and New World disease—based on transmission geography. Infection is spread by blood-feeding *Phlebotomus* sandflies in the Old World and *Lutzomyia* sandflies in the New World. Rarely, infection is transmitted via other methods including blood transfusions [1].

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Leishmaniasis affects 12 million people worldwide (Fig. 1), primarily in remote rural regions [2]. There are an estimated 1.5–2 million new cases of CL each year; 90 % of which originate in ten countries: Afghanistan, Iran, Iraq, Saudi Arabia, Algeria, Ethiopia, Sudan, Syria, Brazil, and Peru [3]. CL is caused primarily by *Leishmania tropica*, *Leishmania major*, and *Leishmania infantum* in the Old World and by *Leishmania braziliensis*, *Leishmania guyanensis*, *Leishmania panamensis*, *Leishmania peruviana*, *Leishmania mexicana*, and *Leishmania amazonensis* in the New World [3].

Clinical presentation

CL typically manifests within several weeks of a sandfly bite with skin lesions developing on exposed body areas. New World CL (NWCL) produces variable clinical manifestations ranging from nodules to ulcerative skin lesions (Fig. 2) which may be accompanied by local lymphadenopathy. Old World CL (OWCL) presents similarly but can also produce plaque-like lesions [6]. The face, ear, and extremities are most frequently involved. Ulcers are typically painless and enlarge slowly with a granulomatous base and raised margins [7].

Depending on the species, CL infection also has the potential to disseminate hematogenously to mucosal surfaces of the nose, mouth, or pharynx and cause ML. ML may develop simultaneously with an initial skin lesion or months to years later, even despite apparently adequate treatment for CL. ML produces chronic nasal congestion and bleeding; ulceration of the nose, mouth, and pharynx; nasal septum perforation; and facial disfigurement. ML is most frequently seen in *L. braziliensis* infection, although it has also been reported in OWCL [8].

Diagnosis

Patients with non-healing skin lesions and a travel history to an endemic region should be evaluated for CL. Diagnostic confirmation may be made by culture but is principally achieved by direct microscopic detection of *Leishmania* amastigotes in skin biopsies (Fig. 3); serologic testing is not reliable. With high-level specificity for *Leishmania* DNA, polymerase chain reaction (PCR) testing of lesion specimens is particularly useful when parasite burden is low and is currently the most accurate method of diagnosis in CL [9].

Prognosis

CL is often self-limited, resolving within 6 months without therapy. However, non-healing skin ulcerations involving the face or limbs may cause significant morbidity. Since the complete eradication of viable organisms seldom occurs, lesions may recur despite prior clinical resolution, and therefore, “cure” is not generally assigned until 6 to 12 months after therapy (Fig. 3).

Prevention

Disease prevention is difficult for the traveler other than avoidance of outdoor activities in endemic areas. There is evidence that using insecticide-impregnated bed nets, curtains, and/or clothing may offer protection. There is currently no available vaccine, although some countries (e.g., Uzbekistan and Sri Lanka) still promote leishmanization, which involves the

direct inoculation of viable parasites into areas that are not cosmetically apparent (e.g., the buttocks) [10].

Treatment

Although attempts are now being made by European investigators [11, 12, 13•], the management of CL, an intrinsically diverse disease, has not been standardized for three reasons: (a) the basic heterogeneity of the disease given that multiple different species cause illness; (b) the fact that clinical manifestation, response to treatment, and outcome vary depending on the geographic region of acquisition; and (c) a general lack of high-quality clinical trials from which to draw guidance.

There are many important factors which play a role in the initial consideration of treatment, including the geographic region where infection was acquired, the species of *Leishmania* involved, and the extent and location of CL lesions. With patient willingness, observation alone (with adequate wound care) may well be satisfactory if there is evidence of spontaneous regression or well-localized infection caused by *L. major* (OWCL) and *L. mexicana* (NWCL). The latter approach is justifiable, as spontaneous healing (albeit with the likelihood of at least some scarring) occurs within 3 to 4 months in 70 and 88 % of localized infections caused by *L. major* and *L. mexicana*, respectively [13•]. Widely accepted indications for treatment in all forms of CL are listed in Table 1. Worldwide, the most frequently employed approach to localized CL is direct lesion treatment usually in the form of intralesional injections of antimony; cryotherapy, thermotherapy, and topical paromomycin have also been used (Table 2). In the USA, however, there has been little experience with direct lesion treatment. Furthermore, the goals of systemic treatment in the USA are aimed at attempting to accelerate control of infection to potentially reduce scarring, particularly in cosmetically important areas. The remainder of this review will focus on available systemic treatments used for CL in the USA. In short, these treatments include two parenteral agents, pentavalent antimony (in the form of sodium stibogluconate) and liposomal amphotericin B, and three oral agents, miltefosine and the azoles, fluconazole, and ketoconazole (Fig. 4). There is abundant data showing the efficacy of sodium stibogluconate and miltefosine in CL; clinical experience with liposomal amphotericin B and fluconazole or ketoconazole in CL is limited. Each of these agents has its own individual advantages and drawbacks.

Parenteral therapy

Pentavalent antimony (sodium stibogluconate)

- A group of compounds containing the heavy metal antimony; only available in the USA as sodium stibogluconate (Pentostam, GlaxoSmithKline).
- Remains the most standard antileishmanial treatment around the world for all forms of CL (as well as for ML and VL in many but not all regions).
- Not FDA-approved and only available (free of charge) via an investigational new drug (IND) protocol from the Centers for Disease Control and Prevention (CDC).

- Administered at 20 mg/kg via a 10-min intravenous (IV) infusion once daily, usually for 20 days in CL. A 10-day regimen has been used in *L. mexicana* infection [22].
- Clinical data for safety and efficacy far exceeds available data for all other therapeutic options in CL. The antimonials are generally considered to have high efficacy rates (approximately 80–90 % for most *Leishmania* species) with low rates of relapse [14].
- Produces numerous side effects and many patients have difficulty tolerating the full 20-day IV treatment course. As many as 25 % of patients require treatment interruption or discontinuation because of adverse effects including fatigue, fevers, headaches, arthralgias, abdominal pain, nausea and vomiting, pancreatitis, venous thrombosis formation, and phlebotoxicity at the infusion site [23].
- Rare but potentially life-threatening cardiac arrhythmias (including ventricular tachycardia, ventricular fibrillation, torsades de pointes) may occur, and EKGs should be performed once weekly [24].
- Other adverse signs include hyperamylasemia, elevated serum hepatic enzymes, thrombocytopenia, and leukopenia. Once-weekly blood testing (CBC with platelet count, chemistry profile with amylase) is therefore necessary, and therapy should be interrupted if the level of amylase reaches four times above the upper limit of normal.
- Antimony is contraindicated in pregnant women and should be avoided, if possible, in patients older than 55 years of age as well as in patients with preexisting cardiac, hepatic, or renal disease [13•]. Toxicity may also be increased in patients coinfecting with HIV.
- Since sodium stibogluconate is an investigational drug, approval by an institutional review board (IRB) is typically necessary, and it is often challenging to coordinate up to 20 days of IV treatment. Many home antibiotic infusion companies may not be willing to administer a non-FDA-approved drug, and insurance companies may decline to cover administration costs.
- Summary: Pentavalent antimony, in the form of sodium stibogluconate, is historically the most frequently used first-line therapy for CL, given its long clinical experience. It is administered at 20 mg/kg daily via IV infusion for 20 days. It frequently produces adverse reactions and is often difficult for patients to tolerate.

Liposomal amphotericin B

- Available as AmBisome (Astellas Pharma) and FDA-approved for VL but not for CL or ML.
- Based on safety, tolerance, and remarkably high-level efficacy in VL, the use of IV liposomal amphotericin B has been reasonably extrapolated to CL and ML [25••].

However, published clinical experience with treatment in CL and ML remains limited.

- The FDA-approved dosing regimen for VL includes a total dose of 21 mg/kg given IV over a 21-day period. Regimens in CL typically employ this same total dose (21 mg/kg), but the treatment period is usually abbreviated. One likely effective regimen consists of 3 mg/kg per day for seven consecutive days [26].
- Some clinicians administer a liter of IV saline prior to the 2-h infusion of liposomal amphotericin B in an attempt to reduce the likelihood of potential nephrotoxicity.
- Although usually well-tolerated, side effects of therapy include infusion-related fever and chills and may also include hypokalemia, anemia, and renal insufficiency. Blood counts and serum chemistries should be monitored twice weekly while on treatment.
- Liposomal amphotericin B is considered safe for use in pregnancy (category B).
- Liposomal amphotericin B treatment is expensive due to the cost of the drug itself in addition to the cost of IV administration. Insurance companies may decline to cover this treatment since CL is not one of the drug's FDA-approved indications.
- Summary: liposomal amphotericin B is highly effective therapy for VL, and its use has been extrapolated to CL. It is generally administered as a total dose of 21 mg/kg divided over seven consecutive days.

Oral therapy

Miltefosine

- Available as Impavido (Knight Therapeutics) and FDA-approved in 2014 as the first drug designated for the treatment of CL and ML in the USA. Also, FDA-approved for VL.
- A phospholipid compound developed in the 1980s for use as an anticancer drug; recent studies have also demonstrated some success in treating infections caused by free-living amoeba, including *Naegleria fowleri* and *Acanthamoeba* species [27].
- Clinical cure responses in NWCL range from 50 and 91 %, depending on the species involved and region of acquisition; experience in OWCL has demonstrated cure rates of 86–92 % [28].
- Available in 50-mg capsules and administered at 2.5 mg/kg/day (up to 150 mg/day) in two or three divided doses for 28 days [29••].
- Miltefosine is generally well tolerated; however, it regularly produces headaches, nausea, vomiting, and/or diarrhea in a significant percentage of patients, typically during the first week of treatment only [23].
- Hepatotoxicity and nephrotoxicity are unusual [30], but serum chemistry profiles should be tested weekly during therapy.

- Teratogenicity has been demonstrated in rats, and use in pregnancy (category D) or in breastfeeding is contraindicated. Effective contraception must be maintained during and for up to 3 months after treatment.
- Pricing for a 28-day course of miltefosine in the USA has not yet been established.
- Summary: miltefosine is a well-tolerated oral systemic therapy for CL and ML and is administered at 2.5 mg/kg/day (up to 150 mg/day) for 28 days.

Azoles (ketoconazole and fluconazole)

- These structurally related triazoles demonstrate antileishmanial activity in patients with both OWCL and NWCL. However, published clinical experience with these two agents is limited.
- There is some evidence to support the use of high-dose fluconazole for the treatment of OWCL caused by *L. major* [31•] and NWCL caused by *L. braziliensis* [32].
- Ketoconazole, at 600 mg once daily for 28 days, appears to be active in *L. panamensis* and *L. mexicana* infection acquired in Panama and Guatemala [33].
- Adverse effects for these azoles include gastrointestinal symptoms and hepatotoxicity [34•]. Serum chemistries should be monitored weekly for high-dose regimens.
- Summary: although reported clinical experience is limited, there is evidence to consider the use of high-dose fluconazole and ketoconazole as oral agents in the treatment of CL caused by selected species.

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Fig. 1. Geographic distribution of regions where cutaneous leishmaniasis (CL) is endemic (reprinted with permission from Reithinger, *Lancet Infectious Diseases*, 2007) [4].



Fig. 2. Clinical presentation of cutaneous leishmaniasis (CL). **a** Ulcerative face lesion in a traveler caused by *L. infantum* infection acquired in Malta. **b** Ulcerative *L. major* infection on leg in a traveler acquired in Israel. **c** Nodular *L. major* infection in a US soldier acquired in Iraq (figure reprinted from Murray, Lancet, 2005) [5]. **d** Disseminated *L. infantum* infection in a traveler acquired in Greece (courtesy of S. Haber, M.D.).

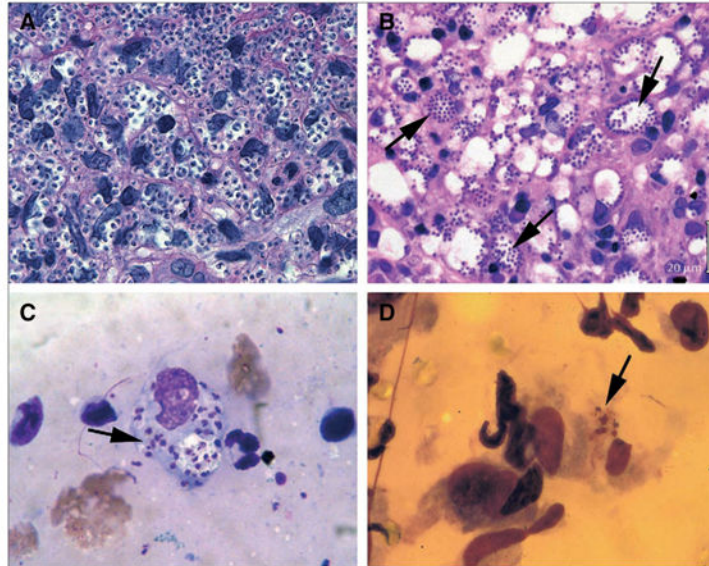


Fig. 3. Histologic diagnosis of cutaneous leishmaniasis in hematoxylin/eosin-stained skin lesion biopsies (**a**, **b**) and Giemsa-stained lesion scrapings and imprints (**c**, **d**). Arrows indicate amastigotes. **a**, **b** Biopsies show sheets of amastigotes in **a** *L. major* and **b** *L. mexicana* infection; in **b**, note large, parasite-laden macrophage vacuoles seen in *L. mexicana* infection. **c** Smear of lesion scraping in probable *L. panamensis* infection. **d** Impression smear in *L. mexicana* infection obtained by pressing glass slide to open ear lesion. Original magnification $\times 500$, except in **a**, $\times 1000$ (figure reprinted from Murray, Lancet, 2005) [5].



Fig. 4. Clinical outcome in treated cutaneous leishmaniasis (CL) in travelers returning to the USA. Images in *left column (a, c, e, g)* represent pretreatment lesions, while images in *right column (b, d, f, h)* are posttreatment. **a, b** Verrucous-like lesion on right chin caused by *L. major* infection acquired in Namibia, treated with IV pen-tavalent antimony (sodium stibogluconate), with no residual scarring. **c, d** *L. tropica* infection on elbow acquired in Egypt, treated with liposomal amphotericin B, with prominent posttreatment scarring. **e, f** *L. panamensis* infection on forearm acquired in Central America, treated with liposomal amphotericin B, with resolution and minimal scarring. **g, h** *L. major* infection on hand acquired in Morocco, responded clinically to initial miltefosine therapy but recurred 3 months later (**g**). Lesion responded to retreatment with fluconazole (**h**) and resolved with minimal scarring.

Table 1
Indications for treatment of cutaneous leishmaniasis

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- 1 Lesion size: 4 cm
 - 2 Lesion location: on body areas potentially disfiguring or disabling from scar formation (e.g., face, fingers, toes, ears, large joints)
 - 3 Number of lesions: 3 active lesions
 - 4 Lesion duration: present for >6 months
 - 5 Associated medical conditions: diabetes mellitus, pregnancy, immunosuppression (including HIV), and chronic comorbidities (e.g., congestive heart failure, moderate to severe liver disease, renal dysfunction)
 - 6 Age: 55 years
 - 7 Local spread or disseminated infection
 - 8 Geographic region where infection acquired: South America

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Table 2
Treatments for cutaneous leishmaniasis (CL) not available or seldom used in the USA

Therapy	Route	Comments	References
Pentamidine	IV	Use limited by adverse reactions. Used for infection caused by <i>L. guyanensis</i> (considered poorly responsive to pentavalent antimony).	[14••]
Amphotericin B deoxycholate	IV	Considered “rescue therapy” in refractory CL. Generally only used in regions where cost of liposomal amphotericin is prohibitive.	[15]
Meglumine antimoniate	IM	Another form of pentavalent antimony available as an intramuscular formulation in Europe (manufactured by Aventis)	[14••]
Paromomycin	Topical	Topical drug coformulated with methylbenzethonium appears to increase cure rates in both OWCL and NWCL using a regimen of twice-daily direct application for 21 days.	[16]
Imiquimod	Topical	Toll-like receptor immunomodulator (agonist) formulated as a 7.5 % cream. In CL in Peru, direct application every other day for 20 days in combination with pentavalent antimony reportedly more effective than antimony alone and may be useful in refractory disease.	[17]
Intralesional antimony	Local	Provides high concentrations of drug directly in the lesion with minimal toxicity. However, no uniformly accepted protocol for administration and satisfactory treatment requires clinical experience and technical expertise to achieve reasonable and consistent cure rates. Frequently used for localized CL in Europe and the UK, often in conjunction with cryotherapy.	[13•, 18]
Thermotherapy	Local	Radio frequency waves administered as up to three treatments of 50 °C for 30 s at 7-day intervals appear effective in OWCL and may be as effective as local antimony therapy in NWCL caused by <i>L. braziliensis</i> or <i>L. mexicana</i> .	[19, 20]
Cryotherapy	Local	Liquid nitrogen cryotherapy at –195 °C applied weekly to OWCL skin lesions for up to 6 weeks has been used for decades in many regions. In localized OWCL caused by <i>L. major</i> , the combination of superficial cryotherapy plus intralesional antimony may be more effective than either treatment alone.	[13•, 21]