Cutaneous Leishmaniasis

Updates in Diagnosis and Management

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KEYWORDS

- Cutaneous leishmaniasis • Antimony • Amphotericin • Miltefosine
- Leishmaniasis diagnostic testing

KEY POINTS

- Cutaneous leishmaniasis is a complex disease consisting of more than 20 *Leishmania* species that have varying pathogenicity and drug susceptibility.
- Molecular diagnostic tests are sensitive and specific; they require a small lesion specimen that permits less-invasive sampling methods.
- Several test methods should be done, using a lesion specimen, to maximize diagnostic yield.
- Systemic treatments may have significant toxicity and need to be carefully considered, taking into account *Leishmania* species, geographic region of acquisition, patient comorbid health status, extent/location of lesions, and previous treatments.

INTRODUCTION

Cutaneous leishmaniasis (CL) is a severely neglected tropical disease that has been significantly increasing in numbers affected over the past decades, with a change in global prevalence from 1990 to 2013 of +174.2%.[1] This sand fly bite–transmitted parasitic infection causes chronic skin lesions that heal with scarring, often on cosmetically obvious places, leaving those affected with some disfigurement.[2] CL is endemic in regions of most continents and recently areas in Thailand, Caribbean, and Ghana are reporting emerging foci of *L enriettii* complex causing human cutaneous and/or visceral infection.[3] Leishmaniasis acquired in parts of South America also may result, even years after the skin lesions heal, with mucosal destruction of

Disclosure Statement: N.E. Aronson and C.A. Joya have no commercial or financial disclosures. Disclaimer: The opinions and assertions expressed herein are those of the authors and do not necessarily reflect the official policy or position of the Uniformed Services University, the Department of the Navy, or the Department of Defense.

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Infect Dis Clin N Am 33 (2019) 101–117
https://doi.org/10.1016/j.idc.2018.10.004
0891-5520/19/Published by Elsevier Inc.
id.theclinics.com

the nose and pharynx (mucosal leishmaniasis [ML]). Over recent years, advances have been made in the diagnosis and treatment of CL, which are summarized in this article, with emphasis toward management approaches in North America.

DIAGNOSIS OF CUTANEOUS LEISHMANIASIS

The widespread use of more sensitive molecular diagnostic tests (such as polymerase chain reaction [PCR]) has radically changed both sample collection and the amount of time and reference laboratory support that were typical a decade ago (to confirm a leishmaniasis diagnosis). Another major advance is new antileishmanial treatments that drive more individualized therapies, which are often benefited by *Leishmania* species identification for prognosis and to direct management choices.

The first and most critical diagnostic step is for clinicians to consider a diagnosis of CL when assessing a chronic skin lesion(s) in a person with potential exposure in an endemic region (http://www.who.int/leishmaniasis/leishmaniasis_maps/en). The lesion(s) is often painless and purulence is uncommon; the location is typically on exposed areas, such as face and extremities. Appearances include ulcer (often with eschar or exudate overlying) and nodule/plaques most commonly, but lesions may also have sporotrichoid, verrucous, zosteriform, psoriasiform, eczematous, or erysipeloid features (**Figs. 1–4**).

Currently, there is no gold-standard single diagnostic test; clinical practice guidelines recommend performing several assays using a sample from an active-appearing skin lesion.[4] The sensitivity of the diagnostic assays depends on the

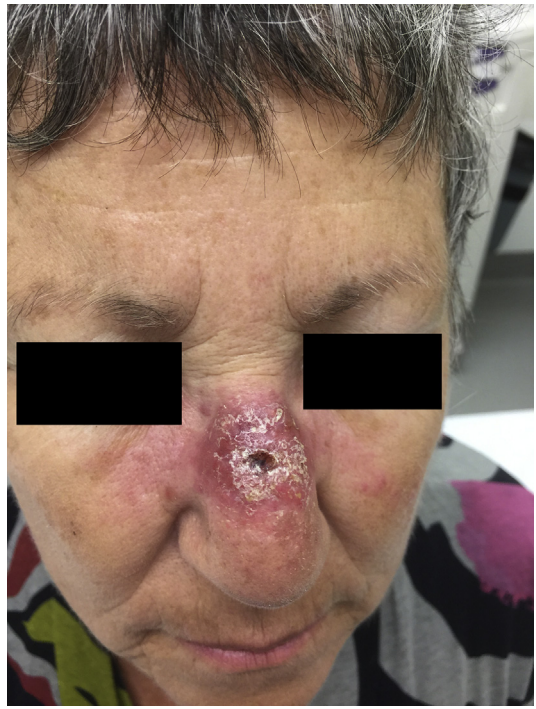

Fig. 1. Ulcerative lesion due to *L major* acquired in Morocco. (*Courtesy of* K. Billick, MD, Montreal, Canada.)

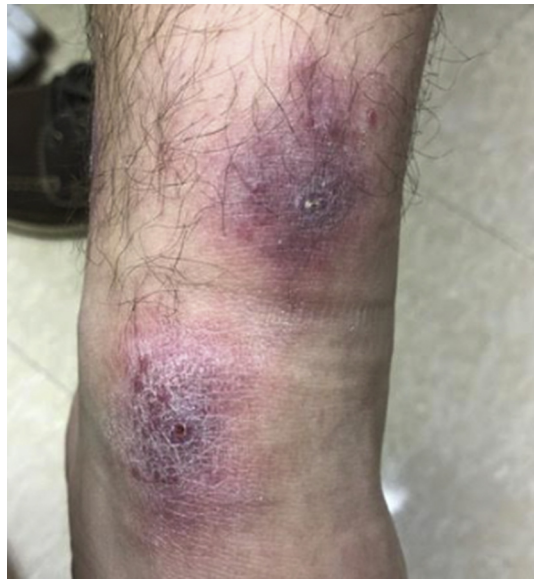

Fig. 2. Plaque-like lesions due to *L tropica* on the ankle, acquired in Syria. (*Courtesy of* S. Wood, MD, Bethesda, MD.)

number of parasites in the lesion (often equates with duration of lesion), *Leishmania* species, and type of lesion (ulcer often highest yield). There are national *Leishmania* diagnostic reference laboratories that generally provide services without charge; it is always preferable to contact them prior to obtaining samples (see **Table 3**).

Sample Collection

In CL, *Leishmania* parasites are found in the epidermis and upper levels of the dermis, so they are fairly superficial. In ulcerative lesions, the base has more parasites but also more tissue destruction; with assays, such as PCR and culture, the cleansed base is

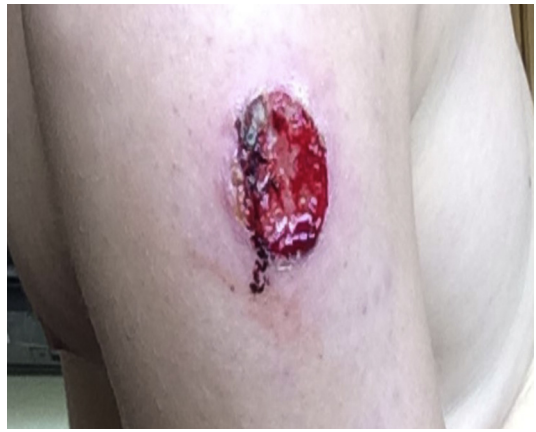

Fig. 3. Ulcerative lesion due to *L V panamensis*. (*Courtesy of* J.D. Malone, MD, San Diego, CA.)

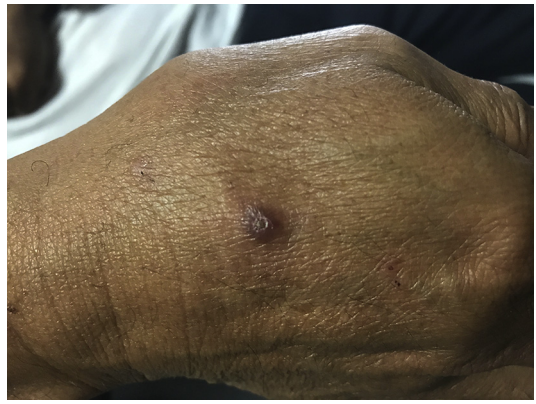

Fig. 4. Nodular lesion due to *L infantum* acquired in Sicily. (*Courtesy of* R. Maves, MD, San Diego, CA.)

the target collection site, but for histology, the less disrupted indurated border of the lesion is recommended. See **Table 1** for various sample collection techniques.

The preparation of a skin lesion for sampling is simple but key. The authors recommend the following:

- Thoroughly cleanse lesion with soap and water; rinse with water.
- Blot dry with gauze, removing any residual betadine if used.

Table 1
How to sample skin lesion for a *Leishmania* diagnosis[a]

Appearance	Methods[b]	Considerations
Ulcer	Swab using DNA collection swab, 10 times over ulcer[46]	Use for more sensitive molecular assays (eg, PCR)
	Tape strip disk, tape stripping[47]	Use for more sensitive molecular assays (eg, PCR)
	Cytology brush or dental broach[48]	For *Leishmania* culture or PCR, use for CL Detect assay
	Skin scraping with scalpel blade edge, sample about size of large rice grain[4]	Limit bleeding for best results, use local anesthesia, use 1 sampling each for smear, culture, and PCR
	Fine-needle aspirate generally from indurated border[4,48]	1-mL syringe with needle (20G–25G) with or without nonbacteriostatic saline; can be used for smear, culture, and PCR
	Shave biopsy	Use if other diagnoses under consideration as well
	4-mm punch biopsy of the indurated rim	Use if other diagnoses under consideration as well
	• Touch impression smears • Press imprint smears[49]	Use if less-invasive testing does not yield diagnosis
Nodule/plaque	Skin snip (like leprosy technique)	Smear, culture, PCR
	Fine-needle aspirate	Smear, culture, PCR
	4-mm full skin thickness punch biopsy	Smear, culture, PCR

[a] Not all-inclusive of methods.
[b] Choose an active looking lesion, débride if needed to ulcer base, cleanse with detergent and water, remove any residual betadine or soap, and blot dry.

- If pertinent, débride a portion of the exudate or overlying eschar down to clean ulcer base. Generally, this is painful, and local anesthesia should be considered. Limit bleeding because it may confound the smear.
- If parasite culture is planned, sterile technique should be used.

Full-thickness skin punch biopsies should not be the first diagnostic procedure for CL, both due to a more invasive nature and because they can be lower yield.[5,6] The median number of *Leishmania* parasites found at various skin tissue levels were epidermis, 42×10^6; superior dermis, 40×10^6; inferior dermis, 26×10^6; and subcutaneous tissue, 12×10^6.[6] The primary reason to perform a punch biopsy is to evaluate other diagnostic considerations, including histopathology, fungal, or mycobacterial etiologies: in this case, only a small amount of tissue is needed for leishmaniasis culture and PCR. It is also used when noninvasive studies yield negative results.

Types of Tests for Leishmaniasis Diagnosis

Globally, tissue microscopy (a smear, tissue imprint, or drop of tissue placed on a glass slide, stained with Giemsa, and evaluated under an oil immersion lens) is the most common leishmaniasis diagnostic test. Although less sensitive than others and requiring expertise in interpretation as well as a high-power microscope lens, its advantages are mainly low cost and readily available materials. The *Leishmania* amastigote seen in human tissues is a tiny, round to oval organism approximately 3 μm to 5 μm length, with a well circumscribed nucleus and a diagnostic rod-shaped kinetoplast; it can be intracellular or extracellular (**Fig. 5**). If the kinetoplast is not seen, then *Leishmania* cannot be distinguished from *Histoplasma* or even *Sporothrix* species.

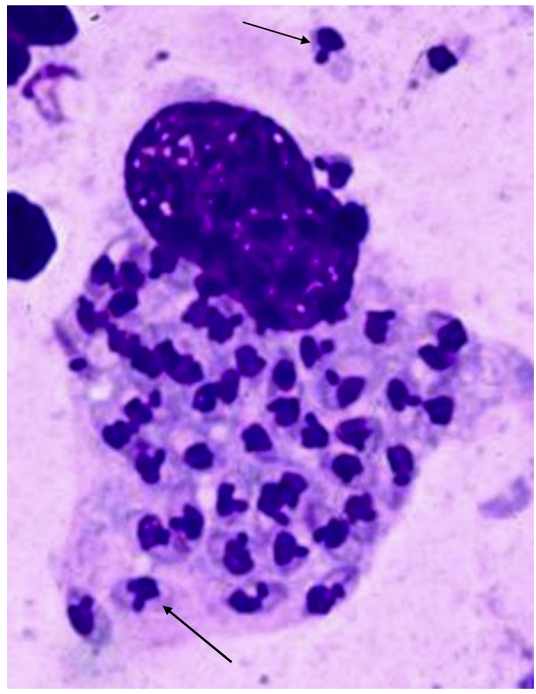

Fig. 5. Giemsa-stained skin scraping showing many intracellular amastigotes inside a mononuclear cell cytoplasm; note the rod-shaped perpendicular kinetoplast. *Arrows* indicate amastigotes. (Giemsa stain, original magnification ×250). (*Courtesy of* R. Neafie, Washington, DC.)

Histopathology is the least sensitive diagnostic method. A few practical pointers for the review of tissue histopathology for detection of *Leishmania* are to use oil immersion (100×), stain with hematoxylin-eosin but also stain sections with Brown-Hopps tissue Gram stain, resect to multiple 3-mm–thickness slices, and review areas of well-formed necrotizing and non-necrotizing granulomas carefully. Other consistent findings include an inflammatory plasma cell and lymphocyte infiltration, hypertrophied stratum corneum and necrotic ulceration, epidermal hyperplasia, parakeratosis, acanthosis, and intraepithelial abscesses.[7]

Table 2 reviews various techniques that are used for the detection of *Leishmania* parasites, concentrating on parasitologic diagnosis. The general categories of diagnostic approach are clinical, immunologic, and parasitologic. Clinical diagnosis (consistent clinical appearance and epidemiologic risk) is not considered sufficient and should always be confirmed with laboratory diagnostic testing. Immunologic diagnosis of CL is not included in **Table 2** except for the CL Detect test, because commercial serology is insufficiently sensitive to be clinically useful and the *Leishmania* skin test is not available in North America. Recent proteomic approaches may uncover more immunogenic and abundant antigens to improve serologic assays.[8] CL Detect is a Food and Drug Administration (FDA)-cleared, rapid immunochromatographic test detecting the peroxidin antigen of *Leishmania*, performed with skin lesion sampling collected with a dental broach.[9] It is particularly helpful for ulcerative lesions of recent onset (<4 months); any residual betadine interferes with assay results.

There are more than 20 *Leishmania* species associated with human infection. Unless a patient's travel history is circumscribed and there is only 1 known *Leishmania* species circulating there, species identification should be considered. Knowledge of the *Leishmania* species may allow better estimation of the risk of ML, time to healing, and response to various therapies. This is critical in immunocompromised hosts and those with medical comorbid conditions where significant risk benefit decisions must be made in treatment plans. Parasite identification has classically required parasite isolation with culture, expansion of the parasite, and then multilocus enzyme electrophoresis (so-called isoenzyme electrophoresis)[10,11] or multilocus sequence testing.[12] This testing is relegated to a few reference laboratories (**Table 3**). Because culture, albeit a definitive diagnostic test, is not highly sensitive; subject to contaminating skin flora overgrowth, nonviable organisms from transport, or finicky parasite in vitro growth; and slow (most laboratories holding cultures until 30 days before noting as no growth), this has an impact on whether species are identified (40% specimens) in a timeframe that is clinically useful.[13] Matrix-assisted laser desorption ionization (MALDI)–time of flight (TOF) mass spectrometry yields a protein spectral fingerprint of *Leishmania* species.[14–17] Although culture is required, this method has advantages of speed, and lesser cost, and, as more MALDI becomes available, this could be widely integrated into clinical laboratories. Lastly, nucleic acid amplification-based assays, such as PCR, have been developed to rapidly identify *Leishmania* species. There is great variability in gene targets, performance characteristics, methods/protocols, and a lack of commercial availability that currently limits the routine use of molecular testing for species identification. The miniexon PCR–restriction fragment length polymorphism (RFLP) genotyping has promise.[18,19]

There are 2 types of testing that are not clinically available but deserve notice: *Leishmaniavirus* coinfection and *Leishmania* drug susceptibility testing. *Leishmania* RNA viruses parasitize *Leishmania* parasites (multiple *Leishmania* species globally) and have a role in increased pathogenicity with associations with mucosal infection, lesion persistence, or increased relapse rates after treatment.[20–22] Although

Table 2
Cutaneous leishmaniasis: current diagnostic tests

Test	Considerations
Microscopy • Sample smeared on glass slide • Touch impression	• Rapid point-of-care test • Amastigote confirmed when organism with a distinct kinetoplast is seen (see Fig. 5) • Stain with Giemsa, Diff-Quik, Wright Giemsa, or Brown-Hopps stain • View with 100× oil immersion lens
Histopathology • Thin sections (3 mm) • Study slides for up to 1 h • 100× oil immersion	• Most organisms are superficial • Hematoxylin-eosin stain • Enhanced with Brown-Hopps tissue Gram stain • Not very sensitive
Parasite culture • Sterile collection without residual betadine on lesion • Reference laboratory, contact in advance (see Table 3) • Typical media is Schneider's with fetal bovine serum or NNN • Once in media, ship to laboratory at room temperature	• Prone to contamination with skin flora • Allows species identification (see narrative) ○ MLEE, MLST ○ Molecular methods, sequencing ○ PCR-RFLP ○ MALDI-TOF • Not all parasites expand well in vitro • Definitive diagnosis
Immunologic • CL Detect (InBios Seattle, WA) performed with tissue from lesion	• Point-of-care rapid test • FDA cleared • Avoid any residual betadine in sample
Recombinant polymerase amplification[50] • Lateral flow immunochromatographic strip • Targets kinetoplast DNA	• Point-of-care rapid test • Not readily available at this time
Loop-mediated isothermal amplification assay[51] • Pan–*Leishmania* spectrum • Role in resource limited settings where PCR may not be available	• Applied to boiled swabs as samples
PCR[48,52] • Multiple targets used • Multiple platforms used, real time PCR is preferred • Submit sample in high concentration ethanol (not formalin) • Can test paraffin embedded samples (lower sensitivity) • Sample can be dried onto filter paper and tested • DNA scraped off microscopy slides can provide sample • Tests vary laboratory to laboratory, comparative validation studies are needed	• Most sensitive assay • Relatively rapid • Methods allow species identification • Technique allows parasite quantitation

Abbreviations: MLEE, multilocus enzyme electrophoresis; MLST, multilocus sequence testing; NNN, Novy-MacNeal-Nicolle media.

clinical treatment failure may additionally be affected by factors other than drug susceptibility, the testing of *Leishmania* parasites for drug susceptibility remains relegated to research laboratories; although, as more therapeutic agents become available, there could be a role for testing.[23]

Table 3
Leishmaniasis diagnostic reference laboratories

Laboratory	Contact Information
National Reference Centre for Parasitology, Montreal, Quebec, Canada[a]	Momar Ndao, DVM, MSc, PhD Research Institute of the McGill University Health Centre 1001 Decarie Boulevard, Room E03, 5375 Montreal, Quebec H4A 3J1, Canada Telephone +1–514–934–8347 www. mcgill.ca/tropmed/nrcp
CDC, Atlanta, GA[b]	Marcos de Almeida, PhD CDC Division of Parasitic Diseases and Malaria SMB/STAT, Unit 52 1600 Clifton Road NE Atlanta GA 30329 Telephone 404-718-4175 DPDx@cdc.gov
Walter Reed Army Institute of Research, Silver Spring, MD[c]	Sheila Peel, MSPH, PhD WRAIR Leishmania Diagnostics Laboratory 503 Robert Grant Avenue Silver Spring, MD 20910–7500 Telephone 240-595-7353 http://www.wrair.army.mil/OtherServices_LDL.aspx
WHO Collaborating Centres	http://apps.who.int/whocc/List.aspx?cc_subject=Leishmaniasis

[a] Engagement of provincial public health laboratory to forward sample is preferred.
[b] Notify state public health laboratories when submitting to CDC.
[c] Restricted to US military and Department of Defense (DoD) civilian worker samples.

TREATMENT OF CUTANEOUS LEISHMANIASIS

The primary goal of CL treatment is to reduce morbidity (ie, preventing relapse and dissemination [mucosal disease]). A majority of lesions heal slowly without specific therapy; however, therapy should be considered, especially when lesions are distressing to the patient, the lesion(s) are complex (**Fig. 6**), or if there is risk of mucosal disease. Recently, clinical practice guidelines for the diagnosis and treatment of CL were published and are available on the Infectious Diseases Society of America web site (www.idsociety.org).[4]

Although a majority of these lesions are self-healing, without significant consequences, aside from disfiguring scar, some species of the subgenus *Viannia* (ie, *L V braziliensis*, *L V guyanensis,* and *L V panamensis*) are associated with ML, which can cause significant morbidity and even mortality. Treatment of leishmaniasis may resolve lesions more quickly (potentially reducing cosmetic consequences) and decrease mucosal metastases. There is no overall drug of choice treatment of CL, because the systemic treatments available have significant toxicities and are not equally effective against all species of *Leishmania*, and healing rates among the same species differ geographically. Host cell–mediated immunity is important in control of the infection. Therefore, the treatment of CL needs to be individualized to the patient, *Leishmania* species, and the geographic region where infection was acquired.

Parallel to an assessment as to whether CL is simple or complex, treatment decisions include observation with wound care versus local therapy to the lesion versus systemic therapy (see **Fig. 6**, **Box 1a**). Drugs available for the treatment of

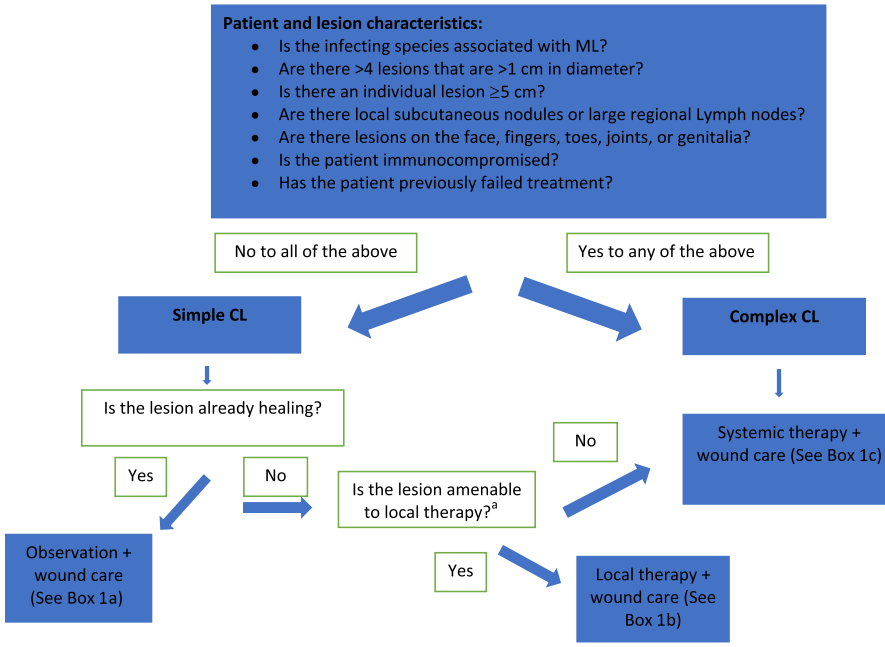

Fig. 6. Treatment algorithm for CL: a basic approach. Although CL treatment should be individualized to the patient, this is a generalized flowchart to describe a basic approach to therapy. All patients should be educated about the natural history of leishmaniasis and risks and benefits of treatment and agree to treatment plan. This does not address the treatment of pregnant patients, those with evidence of ML, or those with unusual syndromes of leishmaniasis (leishmaniasis recidivans, diffuse CL, or disseminated leishmaniasis). [a] Few lesions (<5), small lesions (<4 cm in diameter), lesions are not in a cosmetically important areas (ie, face), and not in functionally important areas.

CL are of limited availability and restricted in choices, and some have significant side effects. Historically, pentavalent antimonials (SbV) have been used for the treatment of CL; however, this treatment is not FDA approved, has some toxicity, cannot currently be given intralesionally in the United States, and there are concerns for resistance with increasing clinical failures.[23] Sodium stibogluconate (SbV) can be obtained through a Centers for Disease Control and Prevention (CDC)-sponsored investigational new drug (IND) protocol for intravenous (IV) use. Miltefosine is the only FDA-approved drug for the treatment of CL caused by *L V braziliensis*, *L V guyanensis*, and *L V panamensis*. Drugs that are used off-label in the United States are the azoles, liposomal amphotericin B (L-amB), and pentamidine; 15% topical paromomycin formulations can be compounded by individual pharmacies.

Local Therapy

For lesions that are simple and amenable to local therapy, and when a decision is made to treat, a local modality should be considered (**Box 1b**). Local therapy is generally first-line therapy for Old World cutaneous leishmaniasis (OWCL) and commonly used for New World cutaneous leishmaniasis (NWCL) that is not associated with ML (such as *LL Mexicana*). Local modalities include cryotherapy, thermotherapy, topical creams/ointments, and intralesional (IL) medications. The physical modalities

Box 1
Treatment dosing and indications for cutaneous leishmaniasis

a. Observation

Observation is reasonable in cases where all of the following apply:

- Lesions are consistent with simple CL (see Fig. 6).
- There is limited risk of mucosal metastasis (ie, infecting species is *L L mexicana,* an OWCL species, or, if species is unknown, the NWCL lesion was acquired north of Costa Rica).
- Lesions are already healing spontaneously at time of diagnosis.
- Patient is educated about the natural history of CL and the risks/benefits of treatment and agrees with the observation plan.

b. Local treatment

Local treatment is generally indicated for simple lesions (see Fig. 6)—there are a few, small lesions that are not in cosmetically or functionally important areas of the body.

Types and Administration of Local Therapy	Considerations
Cryotherapy • Usually performed by dermatologists • Liquid nitrogen applied for 15–20 s to lesion extending 1–2 mm outside of lesion, then allowed to thaw • Repeated 3 times per session • Treatment repeated every 3 wk until healing of lesion • Success dependent on skill of operator	• Appropriate for ◦ Simple lesions (see Fig. 6) ◦ There is no risk of mucosal metastasis ◦ Early lesions • Can be used in combination with SbV intralesional therapy • May consider in pregnant patients or others with contraindications to systemic therapy • Can cause permanent hypopigmentation at site
Thermotherapy • ThermoMed device (FDA cleared) • Local anesthesia is required • Heat of 50°C is applied for 30 s to lesion extending 1–2 mm outside of lesion. • Produces second-degree burn • Success dependent on skill of operator	• Appropriate for ◦ Simple small lesions (see Fig. 6) ◦ *L L major*, *L L tropica*, *L L mexicana*, and *L V panamensis* species • Not for use over superficial nerves, cartilage, eyelids, nose, or lips • Can be used in combination with systemic therapy • May consider in pregnant patients or others with contraindications to systemic therapy
Topical paromomycin • 15% paromomycin + 12% MBCL ointment ◦ Trade name: Leshcutan, Israel • 15% paromomycin cream is being developed by DoD ◦ May be approximated by compounding pharmacies ◦ Replaces WR 279,396 ◦ Apply to lesion bid for 20 d ◦ Currently IND only	• Appropriate for ◦ Simple lesions (see Fig. 6) ◦ Ulcerative lesions ◦ *L L major* and *L V panamensis* • Poor response rates in *L L tropica* and *L L aethiopica* infections • Not recommended if there is lymphocutaneous involvement • Can cause significant inflammation

Intralesional therapy • Sodium stibogluconate ○ Trade name: Pentostam ○ Not currently covered in CDC IND for parenteral therapy ○ Intradermal injection ○ 5 sites per lesion ○ 0.2–5 mL every 3–7 d until healing ○ Local anesthetic needed • Meglumine antimoniate ○ Trade name: Glucantime ○ Not available in the United States	• Appropriate for ○ Simple lesions (see Fig. 6) ○ OWCL, *L V panamensis, L L mexicana* • Improved efficacy when used in combination with cryotherapy

c. Systemic treatment

Systemic therapy can be used for all types of CL; however, treatment has toxicity and it should be carefully individualized based on patient characteristics. Systemic therapy can be used for simple lesions that are not amenable to local therapy, when there is risk of mucosal disease, when rapid healing is desired, and when lesion is in cosmetically or functionally important areas. It is generally the first choice for complex CL and for relapsed CL.

Types and Administration of Systemic Therapy	Considerations
Azoles • Fluconazole ○ Trade name: Diflucan ○ 200 mg po daily for 6 wk or ○ 400 mg po daily for 6 wk ○ Off-label use • Ketoconazole ○ Trade name: Nizoral ○ 600 mg po daily for 28 d ○ Off-label use • Itraconazole ○ Trade name: Sporanox ○ 100 mg po bid for 42–56 d ○ Off-label use	• Appropriate for ○ Lymphocutaneous CL, simple CL, and some complex CL ○ *L L infantum*, *L L donovani*, and *L L mexicana* showed cure rates of 80%–89%.[33] ○ May be used for *L L major*; however, higher doses may be needed if infection was acquired in Iraq or North Africa. ○ Ketoconazole has reported good cure rates for *L L mexicana*, *L L major* (from Iran), and *L V panamensis.* • Should not be used for *L V braziliensis*
Miltefosine • Trade name: Impavido • FDA approved for CL caused by *Viannia* species • Weight-based dosing • ≥45 kg body weight, 50 mg po tid for 28 d • Target dose is 2.5 mg/kg/d; however, limited by side effects when >150 mg/kg/d is taken • May be under-dosed in larger individuals	• Appropriate for ○ Simple and complex lesions ○ *L L major*, *L L tropica*, *L V panamensis*, *L V guyanensis*, and *L V braziliensis* (not acquired in Guatemala) • Expensive
Pentamidine isethionate • Trade name: Pentam 300 • Off-label use • 3–4 mg/kg every other day for 3–4 doses	• Exclusively used for *L V guyanensis*; however, generally second line due to adverse effects

SbV • Sodium stibogluconate ◦ Trade name: Pentostam ◦ Available from CDC under IND ◦ 20 mg SbV/kg/d IV for 20 d • Meglumine antimoniate ◦ Trade name: Glucantime ◦ Not available in the United States	• Appropriate for ◦ Complex lesions • Toxicity and increasing treatment failures due to resistance have relegated SbV to second-line choice in United States, Canada, and Europe
Amphotericin • Amphotericin deoxycholate ◦ Trade name: Fungizone ◦ 0.5–1.0 mg/kg IV daily or every other day for cumulative dose of 15–30 mg/kg ◦ Off-label use • Liposomal amphotericin ◦ Trade name: AmBisome ◦ Off-label use ◦ 3 mg/kg/d IV daily for d 1–5 and then d 10 or d 1–7 for cumulative dose of 18–21 mg/kg	• Appropriate for ◦ Complex lesions • Dosing is based off treatment of visceral leishmaniasis. • Optimal dosing for CL is not well defined. • L-amB is preferred due to less toxicity. • Higher doses and longer therapy are required for immunocompromised hosts. • Saline loading prior to dosing seems to partly protect against renal toxicity.

(cryotherapy and thermotherapy) may be of special use for patients who are restricted from use of systemic treatments, such as those during pregnancy and with other comorbid conditions, as well as for drug resistance.

Cryotherapy is generally well tolerated and readily available. A meta-analysis showed that cryotherapy has similar efficacy to IL antimony, with the proportion of patients cured per intention-to-treat analysis of 54% in the cryotherapy group and 68% treated with IL SbV.[24]

Thermotherapy is another option; however, it requires specialized equipment (such as ThermoMed, Thermosurgery Technologies, Inc, Phoenix, AZ) and local anesthesia. A meta-analysis showed a 73% cure rate overall for CL; however, it was somewhat less efficacious in *L V braziliensis*.[25] Most of the studies were done treating simple OWCL, although there are current trials planed in South America combining thermotherapy with miltefosine.[26]

Topical paromomycin is another local therapy that can be used for lesions that are ulcerated and due to *L L major*. A combination of paromomycin and gentamicin (WR 279,396) cream was used in a phase II clinical trial for treatment of *L V panamensis*, which showed greater efficacy in the combination therapy (87% vs 53%); a phase 3 trial in Tunisia for treatment of *L major* CL showed 81% efficacy in the paromomycin-gentamicin arm and 82% in the paromomycin arm.[27,28] A different product, 15% paromomycin in 12% methylbenzethonium chloride ([MBCL] Leishcutan), is made by Teva Pharmaceuticals (Petah Tikva, Israel).[29]

Intralesional antimony is a mainstay in many OWCL endemic regions of the world; however, it is unavailable in the United States. A recent systematic review of IL antimonials showed an overall efficacy of 75%.[30] The combination of cryotherapy and IL antimony was evaluated on systematic review and found cure rates of 82% versus 53% in IL antimony alone.[30,31] Intralesional amphotericin may bear further research as an alternative to SbV.[32]

SYSTEMIC THERAPY

If systemic therapy is necessary, the options are limited, and several have the potential for significant adverse effects. Therefore, the decision of which drug to use needs to be individualized, based on (1) the patient (ie, comorbidities, immunologic status, and if the patient is gravid, breastfeeding, or desires pregnancy in the near future), (2) the infecting species (ie, if the species is associated with ML or, if unknown, the infection was acquired in an area where ML is of concern [Bolivia, Brazil, or Peru]), and (3) the regionally observed drug susceptibilities (see **Box 1**).

For systemic therapy, the oral options are an azole (fluconazole, itraconazole, and ketoconazole) and miltefosine. Historically the azoles have reported variable cure rates; however, recent data support that they are less effective, especially for the *Viannia* subgenus. A meta-analysis showed a pooled efficacy for the azoles of 64% for the treatment of CL, with higher healing rates in *L L mexicana*, *L L infantum*, and *L L donovani*; however, the cure rates for *L L major*, *L V braziliensis*, and *L L tropica* were low.[33] In contrast, in a Cochrane systematic review of treatment of OWCL, itraconazole, 200 mg for 6 weeks to 8 weeks, was associated with healing in 85/125 (68%) subjects versus placebo 54/119 (45%).[34] A randomized controlled trial of high-dose fluconazole for *L V braziliensis* showed only a 22% cure rate on intention to treat analysis.[35] A nonrandomized study from Brazil showed that men with *L V guyanensis* infection treated with 450 mg of fluconazole daily had a 95% failure rate.[36] Azoles can have toxicity risks, including hepatotoxicity and QTc prolongation, which also need to be considered in treatment decisions.

Miltefosine is an FDA-approved oral option for the treatment of CL due to several *Viannia* species. Clinical response to the treatment of *L V braziliensis* has varied by geographic region, with port response in Guatemala and better response rates in Bolivia, Brazil, and Colombia.[37] Recent data from Colombia show a treatment failure rate of 16%; risk factors for failure were completing less than 1 month of therapy, being a child, having regional lymphadenopathy, prior meglumine antimoniate use, and adherence of less than 90%.[38]

Parenteral therapy for CL includes SbV drugs, pentamidine, and amphotericin (see **Box 1c**). SbV have been the standard of care for complex leishmaniasis for the early 20th century. Although areas of clinical antimonial resistance have been described, such as Bihar, India; national parks in Bolivia/southern Peru; and Bahia, Brazil, in other regions efficacy persists countered by toxicity and availability issues. When comparing IV treatment to intramuscular (IM) treatment using meglumine antimoniate for the treatment of *L L tropica* in Iran, there was a 95% cure rate; all of the failures were in the IM group.[39]

L-amB is one of the newer treatments for CL, its use extrapolated from is efficacy for visceral leishmaniasis with otherwise a weak supporting evidence base for CL therapy. A literature review of L-amB treatment of OWCL showed cure rates of 85%, yet the data were of poor quality and dosing regimens were variable.[40] There are fewer data for NWCL treated with amphotericin, consisting of case reports and case series with similar response rates of approximately 84%.[41,42] A retrospective analysis of returning travelers to Europe, however, showed only a 46% cure rate.[43]

In general, parenteral pentamidine is used exclusively for secondary treatment of *L V guyanensis.* Higher efficacy (85%) was seen when pentamidine was administered IV compared with IM (51%).[44] In Peru, CL treatment with 7 doses of pentamidine was inferior to SbV treatment (78% healing vs 35% in pentamidine).[45]

In addition to these treatments, all patients should have good wound care, including daily cleansings and petrolatum-based ointment. Secondary infection can complicate management and may slow the healing process.

SUMMARY

The complex nature of CL and limited treatment options that are well tolerated and effective highlight the need for further investigation. Treatment of special populations, such as, those during pregnancy, those who are HIV-infected, other immunosuppressed patients, and the elderly, can be more complicated and may require expert consultation. Approaches to CL diagnosis are focused on newer molecular methods, and the challenge is to standardize and have validated assays commercially available in the near future. As more people are traveling to or immigrating from endemic regions, CL has become a more frequently encountered diagnosis, and this article provides current information for the diagnosis and management of this neglected tropical disease.

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