

Cutaneous Leishmaniasis in Travellers: a Focus on Epidemiology and Treatment in 2015

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Abstract Imported cutaneous leishmaniasis (CL) is a growing problem with increasing global travel to endemic areas. Returned travellers seeking care encounter significant barriers to treatment, including diagnostic delays and difficult access to anti-leishmanial drugs. Treatment recommendations in non-endemic settings are a moving target, reflecting recent developments in *Leishmania* diagnostics and therapeutics. Accumulating experience with molecular-based species identification has enabled species-directed therapy. Clinicians are reevaluating more toxic traditional regimens in light of newly approved therapeutic agents and emerging data on local cutaneous treatments. Referral centers are implementing treatment decision algorithms designed to maximize efficacy while minimizing adverse events. Although management strategies continue to evolve, treatment of CL in non-endemic settings remains controversial. Persistent reliance on expert opinion reflects lack of research focused on travellers and limited randomized controlled trial evidence. We herein review the current epidemiology of cutaneous leishmaniasis in travellers and species-specific evidence for available therapies.

Keywords Cutaneous leishmaniasis · Leishmania · Travellers · Skin lesions

Introduction

Leishmaniasis is a protozoan parasitic infection endemic in 98 countries, with over 350 million people at risk globally and 0.7–1.3 million new cases per year [1]. Sandflies transmit the infection to humans by inoculating *Leishmania* promastigotes into exposed skin, resulting in cutaneous, mucocutaneous, or visceral disease syndromes. Clinical manifestations depend on causative *Leishmania* species and underlying host immunity. Although formerly limited to rural tropical and subtropical populations, cutaneous leishmaniasis is an increasing problem in travellers with the rise in adventure travel and ecotourism in the past decade [2••].

Guidelines for treatment of cutaneous leishmaniasis (CL) in returned travellers are evolving [3••, 4••]. Increasing availability of molecular diagnostics, including PCR-based assays, has enabled a shift towards species-directed treatment. Recent FDA approval of anti-leishmanial drugs such as miltefosine has expanded the range of therapeutic options [5]. With new data supporting local cutaneous treatments, clinicians are reevaluating the risks and benefits of systemic therapy. Referral centers are exploring novel algorithmic approaches to maximize cure rates while minimizing medication-related adverse events [6••].

Despite recent advances, optimal treatment of CL in travellers remains controversial. Clinicians lack evidence to inform decision-making, relying on small studies, personal experience, and expert opinion. Few studies focus on travellers. Extrapolation of data derived from *Leishmania*-endemic settings may inadequately reflect the natural history or treatment response in travellers, an immunologically naïve population

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with very different exposure rates and genetics. We herein review the epidemiology of CL in travellers and discuss major treatment options, integrating a species-specific approach.

Vector/Pathogen

Leishmania spp. are a diverse group of intracellular trypanosomid protozoans, with over 20 species causing human infection [7]. Although individual species have unique transmission patterns, local reservoirs, and predominant clinical features, *Leishmania* are broadly subdivided into Old World and New World species. Old World cutaneous leishmaniasis (OWCL) acquired in Africa, Asia, the Middle East, and Mediterranean/southern Europe is transmitted by sandflies of the genus *Phlebotomus*. Major causative species include *Leishmania major*, *Leishmania tropica*, *Leishmania infantum*, *Leishmania donovani*, and *Leishmania aethiopica*. In general, Old World species cause more indolent cutaneous disease without spread to mucosal sites. *L. infantum* and *L. donovani* also cause visceral leishmaniasis, but rarely concurrent with cutaneous disease.

New World cutaneous leishmaniasis (NWCL) is endemic throughout Latin America, ranging from Mexico to Argentina. Transmitted by sandflies of the *Lutzomyia* genus, two distinct New World subgenera have differing propensities towards complicated disease. Members of the *Viannia* subgenus including *Leishmania Viannia braziliensis*, *L. (V.) guyanensis*, *L. (V.) panamensis*, and *L. (V.) peruviana* may be locally aggressive and can progress to destructive mucocutaneous infection (mucocutaneous leishmaniasis (MCL)). The *Leishmania* subgenus includes *Leishmania (Leishmania mexicana)*, *L. (L.) amazonensis*, and *L. (L.) venezuelensis*, and almost never involves the naso- or oropharyngeal mucosa.

Epidemiology in Travellers

Imported CL is a growing problem due to increasing global tourism, adventure travel to remote destinations, and expanding military operations in endemic countries [8, 9]. CL was the third most common dermatologic diagnosis and the most frequent cause of cutaneous ulcer in a large series of patients presenting to GeoSentinel surveillance network clinics worldwide [2•]. The majority of returned travellers with CL were young and male and acquired infection in Costa Rica, Bolivia, and Afghanistan [2•]. Most North American civilian travellers acquire CL in Latin America, whereas Old World species predominate in European centers [2•, 6•, 8]. Infections occur in both short- and long-term travellers [10].

Exotic travel is not a prerequisite for infection, as travellers can acquire CL in common southern European tourist destinations. Most infections in a series of European travellers occurred during 1–3-week summer vacations in Spain, Italy, Malta, and Greece [10]. Destinations included the Balearic Islands, Sicily, and the Peloponnese, and *L. donovani* was the predominate species. Military activity in Iraq and Afghanistan has also led to an explosion of OWCL in coalition forces deployed to these areas. More than 1300 US army personnel in Iraq have acquired *L. major* infection since 2003, with additional cases of *L. tropica* from Afghanistan [11, 12].

Clinical Manifestations

CL in travellers classically presents as a painless cutaneous ulcer with a granulomatous base and raised violaceous borders, occurring at the sandfly bite site. Lesions typically begin as a small macule that evolves into an inflammatory papule, followed by a nodule that ulcerates over weeks to months [13]. Lesions may be single or multiple, and lymphocutaneous spread frequently occurs in travellers with *L. (V.) braziliensis* infection [7, 11, 14]. Depending on causative species and host immunity, CL can take on many different appearances including nodular, verrucous, psoriaform, zosteriform, and chancre-like lesions. Ulcers become painful with secondary bacterial or fungal infection.

The incubation period for cutaneous leishmaniasis is species and host dependent. US military personnel with CL due to *L. major* presented an average of 9 s±5 weeks after initial infection, although this represents an almost exclusively young, healthy, male population [15]. Time to presentation in other studies varied from week to months and rarely years, such that clinicians and patients may not associate the lesion with travel [13, 16•].

Risk of Mucocutaneous Leishmaniasis

Progression to mucocutaneous disease is the major feared complication of New World *L. Vianna* complex infections. Dissemination to nasal, oral, and hypopharyngeal mucosa manifests as destructive ulcerative or granulomatous lesions. Untreated MCL leads to serious sequelae including nasal septum and alae perforation and destruction, disfigurement, and rarely death related to airway compromise [13] MCL is rarely concurrent with the initial cutaneous infection, usually presenting 1–5 years after resolution, and occasionally as long as 35–50 years later [7, 17•, 18]. Intercurrent cutaneous and mucosal involvement may be more likely in travellers compared to MCL occurring in endemic populations. Early symptoms include nasal stuffiness and mild bleeding, with

associated mucosal erythema and edema progressing to ulceration. Hoarseness or dysphonia signal laryngeal involvement.

Risk of mucosal dissemination varies significantly with species and region of acquisition. Ninety percent of mucosal disease occurs in Bolivia, Peru, and Brazil, in particular with *L. (V.) braziliensis* and *L. (V.) peruviana* infection in high Andean regions [1, 17••]. Between 2 and 10 % of *L. (V.) braziliensis* infections in Brazil progressed to MCL, while rates approached 13 % in Peru, 12–14.5 % in Bolivia, and 6.9–7.7 % in Ecuador [16•, 17••, 69, 70]. By contrast, in Central America, mucosal involvement occurs in less than 1 % of *L. (V.) braziliensis* infections [14, 17••]. Risk factors for MCL identified in a major systematic review include multiple lesions, ulcer size >4 cm², head and neck localization, incomplete treatment course, and acquisition in high Andean countries, in particular Bolivia [17••].

MCL is rare in travellers and has not been systematically evaluated. In a pooled analysis of specialized travel clinics, 3 % (range 0–25 %) of patients had mucocutaneous involvement. However, selection bias strongly influenced these estimates, and data included immigrants as well as travellers [17••]. In the absence of high-risk factors (Table 2), immunocompetent travellers are thought unlikely to develop MCL [3••].

Diagnosis

A confirmed parasitologic diagnosis is essential in travellers. Parasite DNA amplification using PCR is now the preferred diagnostic approach, as PCR is highly sensitive and can provide species-level identification, particularly if paired with restriction fragment length polymorphism (RFLP) analysis or gene sequencing. PCR availability remains limited to major reference centers for tropical diseases [73–76]. *Leishmania* amastigotes may be identified on direct microscopy of thin smears or on histopathology of skin biopsies, though sensitivity of direct examination is limited. Amastigotes are best visualized under oil immersion using H&E or Giemsa staining, with tissue sections cut at 3–4 μm [11]. *Leishmania* spp. can also be cultured on specialized media such as Nicolle-McNeal-Novy (NNN) or Tobie's medium, but this process is slow, laborious, and technically challenging. Sensitivity of non-PCR-based techniques varies with lesion morphology and specimen quality and paradoxically decreases with longer duration of infection.

Traditional techniques for tissue specimen collection include lesion scraping, fine-needle aspiration, and biopsy. Punch-biopsies are most useful for non-ulcerative CL and when alternative diagnoses are likely. Recent advances in specimen collection include filter-paper-based techniques and cytology-brush scrapings [77, 78]. Both are painless, can be obtained in the setting of bacterial or fungal secondary infection, and are particularly helpful in children.

Treatment

Recommended first-line and alternative treatments in expert guidelines differ, reflecting experience at individual centers and limited data in travellers [3••, 4••, 6••, 13]. Even in endemic populations, there are comparatively few well-designed, adequately powered randomized controlled trials for CL. Treatment guidelines have shifted towards a species-based approach, made possible by molecular diagnostics [4••]. Although species-directed therapy can inform decision-making, treatment depends on multiple factors including risk of mucocutaneous spread, extent and location of lesions, host immune status, treatment toxicity, patient preference, and reliability of follow-up. Patients responding to treatment show clinical improvement within 4–6 weeks, achieve complete re-epithelialization of the ulcer base within 3 to 6 months, and ultimately develop an atrophic scar [9•]. A single treatment course is not always curative, particularly with extensive cutaneous involvement and immunocompromise [6••, 79]. Follow-up should continue for at least 1 year after treatment completion to monitor for relapse [3••]. In patients for whom causative species is known to be *L. (V.) braziliensis* or in patients who acquired their CL in high Andean regions, follow-up with annual rhinoscopic examination should continue for a decade after treatment (Table 1).

Local Cutaneous Treatments

Local therapies have significant advantages in returned travellers: they are convenient, inexpensive, and avoid systemic treatment toxicity. Potential options include wound care alone, intralesional antimonials (ILSb), cryotherapy, paromomycin creams, and thermotherapy. Local treatments are typically reserved for mild disease in immunocompetent patients. Most studies exclude patients with lesions >3–4 cm in diameter, more than three to five lesions, associated lymphadenopathy, and immunocompromise. Topical therapies are well established for OWCL and NWCL due to *L. mexicana* and may also be considered for *L. Viannia* species when risk of MCL is low (Table 2). Local therapy is unsuitable for sensitive areas including the genitalia, eye lids, and lips and is also discouraged for facial lesions.

1. Wound care, watchful waiting

The natural history for most CL is spontaneous resolution. Local wound care to promote healing and prevent secondary bacterial infection is effective for species that re-epithelialize over weeks to months. Single-lesion *L. major* resolved by 45 days in 20–45 % of patients, with 40–90 % cure by 3 months, and close to 100 % by 1 year [80, 81]. *L. tropica* is often more persistent, with 1 to 10 % resolving within 3 months, two thirds being cured by

Table 1 Treatment options for cutaneous leishmaniasis

Drug ^a (route/dose)	Curative efficacy	Adverse effects
Local therapy		
Cryotherapy+intralesional antimony 0.2–5 mL every 3–7 days ×5–8 treatments, or until healed	OWCL <i>L. major</i> , <i>L. tropica</i> : 89–100 % [19–22] <i>L. donovani</i> : 100 % [23]	Pain during injection Perilesional edema and erythema, blistering [20] Pruritus
Topical 15 % paromomycin/12 % MBCL (<i>Leshchutan</i>), OR 15 % paromomycin/0.5 % gentamicin (WR 279,396) BID × 10–20 days	NWCL <i>L. (L.) braziliensis</i> (ILSb alone): 70–80 % [24, 25] OWCL <i>L. major</i> : 41–82 % [26, 27–29] NWCL <i>L. (L.) panamensis</i> : 79–90 % [30, 31] <i>L. (L.) braziliensis</i> , <i>L. mexicana</i> : 91 % [32] <i>L. (Viannia)</i> spp. mixed: 79 % [33]	Local skin irritation, pain, edema
Thermotherapy Single treatment 50 °C for 30–60 min	OWCL <i>L. major</i> : 48–82 % [4, 12] <i>L. tropica</i> : 54–98 % [34–36] NWCL <i>L. mexicana</i> : 90–95 % [38] <i>L. (L.) panamensis</i> : 58 % [37] <i>L. (L.) braziliensis</i> : 58–64 % [37, 39]	Superficial second degree burns Pain at heat-application site (<1 week) [37]
Systemic therapy		
Pentavalent antimonials (sodium stibogluconate, meglumine antimoniate) 20 mg Sb/kg/day IV/IM × 20 days	NWCL Most species: 70–96 % [24, 39, 40, 41, 42] <i>L. (L.) guyanensis</i> : 55–90 %, region specific [41, 43] OWCL <i>L. major</i> : 54 %–81 % [12, 47, 48] 81 % with adjunctive pentoxifylline [49] <i>L. tropica</i> : 41–53 % [35, 41] <i>L. aethiops</i> ^b : 85 % [50]	Local anesthetic (e.g., lidocaine) required Fusidic acid ointment+ wound care post-treatment for infection prevention Prophylactic oral antibiotics used in some studies due to increased risk of bacterial cellulitis [39] Common: Arthralgia/myalgias (20–49 %), headache (24 %), fever (18–23 %), [44, 45] gastrointestinal disturbances (22 %), abdominal pain, fatigue (19 %), urticaria, local pain at IM administration site, phlebitis with IV administration [46] Laboratory abnormalities: mild to moderate transaminitis —reversible (43 %), elevated lipase (60 %), leukopenia (7 %), thrombocytopenia (7 %) [46] ECG alterations (30–60 %): QTc prolongation (16 %), ventricular repolarization disturbances (25 %), arrhythmia (3 %) [46] Rare: herpes Zoster, severe arrhythmias, fulminant hepatitis, pancreatitis, renal impairment, acute tubular necrosis, eosinophilic panniculitis, exfoliative dermatitis, peripheral neuritis [3, 17, 46]
Miltefosine [46] 2.5 mg/kg/day PO × 28 days (max dose: 150 mg/day) Formulation: 50 mg capsules 30–44 kg: 50 mg BID ≥45 kg: 50 mg TID Liposomal amphotericin B 3 mg/kg IV daily × 5–7 doses (preferred) OR Amphotericin B deoxycholate: 0.5–1.0 mg/kg IV every other day × 20–30 days (alternative)	NWCL: <i>L. (L.) panamensis</i> : 60–94 % [37, 40, 51, 52, 53] <i>L. (L.) braziliensis</i> : 33–88 % [40, 45, 52, 54] <i>L. (L.) guyanensis</i> : 71 % [44] <i>L. mexicana</i> : 60 % [52]	Teratogenicity, pregnancy category D, detectable in blood up to 5 months after treatment completion Common: nausea or vomiting (36–63 %), abdominal pain (23 %), headache (27 %), diarrhea (7–20 %), motion sickness (29 %), pruritus, cutaneous reactions Laboratory abnormalities: mild to moderate elevated creatinine (31 %), [13, 44] transaminitis, typically <2.5× upper limit of normal (5–10 %) [44, 45, 52]

Table 1 (continued)

Drug ^a (route/dose)	Curative efficacy	Adverse effects
Fluconazole 200–600 mg PO daily ×4–6 weeks	<p>OWCL: <i>L. major</i>: 81–88 % [48, 55] 80–90 % in non-randomized studies for both Old World and New World CL^b [56, 57, 58, 59]</p> <p><i>L. major</i>: 400 mg 81 %; 200 mg 44–79 % [60–62] <i>L. (f) braziliensis</i>^b: [63] 8 mg/kg/day: 100 % 6.5 mg/kg/day: 93 % 5 mg/kg/day: 75 % <i>L. (f) panamensis, L. (f) guyanensis</i>: >90 % [16, 41, 64, 65]; lower efficacy 60 % reported in some recent studies [43, 66] <i>L. (f) braziliensis</i>: 35–86 % [42, 67]</p>	<p>Rare: orchitis and decreased ejaculation, Stevens Johnson syndrome [5] Infusion reaction: fevers, rigors, flushing, dyspnea, chest/flank pain [57•] Local thrombophlebitis Nephrotoxicity Hypokalemia Transaminitis Cytopenias Prolonged QTc interval</p>
Pentamidine 2–3 mg/kg IV/IM daily or every other day ×4–7 doses		<p>Common: musculoskeletal pain (25 %), abdominal pain, nausea, vomiting, headache (15 %), fatigue (21 %), anorexia (27 %), fever (21 %), metallic or bitter taste (18 %), injection site pain (20 %) Laboratory abnormalities: elevated lipase, nephrotoxicity, transaminitis, hypoglycemia, hyperkalemia, QTc prolongation Rare: rhabdomyolysis</p>

^a For complete dosing schedules refer to The Medical Letter, Drugs for Parasitic Infections [68]

^b Observational evidence only

Table 2 Indications for systemic therapy for cutaneous leishmaniasis

General
Sensitive location: mucous membranes, genitalia, eyelids, overlying joints
Disfiguring lesions
Increased risk of local treatment failure: lesions >3–4 cm in diameter, > 3–5 lesions, immunocompromised host [13]
Local treatment failure
<i>L. Viannia</i> complex infections [17••]
Multiple lesions [69]
Size >4 cm ² [69, 71]
Upper extremity lesions [72]
Duration >4 months [71]
Acquired in high-Andean regions, particularly Bolivia [13, 14, 16•, 17••]
Immunocompromised host
Lymphatic involvement

1 year, and the remainder healing over 1 to 3 years [80, 82]. Among New World species, *L. mexicana* has high rates of spontaneous cure approaching 88 % at 3 months, but only 68 % at 6 months due to relapse [83]. Other NWCL species have more prolonged time to resolution. Six-month cure rates in endemic populations with *L. (V) braziliensis* were only 2–17 % [24•, 83].

Observation and wound care is effective in pre-selected travellers. Cleaning and wound dressing resulted in complete lesion re-epithelialization at 42–60 days in 92 % ($n=23/25$) of French returned travellers with low-risk limited disease, defined by the following criteria: four or fewer lesions; lesion size <4 cm; non-sensitive location; infection caused by *L. major*, *L. mexicana*, or other species showing signs of self-cure; and immunocompetent, non-diabetic host [6••]. Although this strategy avoids toxicity, watchful waiting is not universally acceptable to travellers, who often request active treatment [9•].

2. Intralesional antimonials plus cryotherapy

Combined intralesional antimonials (ILSb) and cryotherapy is the preferred first-line treatment option for OWCL in several European guidelines and can be considered in mild NWCL at low risk for mucosal involvement [3••, 4••]. Both treatments are individually effective for OWCL compared with placebo, but combination therapy resulted in significantly higher cure rates (89–91 %) compared with either cryotherapy (57–68 %) or intralesional antimony (56–75 %) monotherapy [19–21]. Major randomized controlled trials took place in *L. tropica*- and *L. major*-endemic areas, with minimal published efficacy data for other Old World species.

Clinicians in Latin America are increasingly using intralesional antimony for NWCL, although long-term risk of subsequent mucosal disease is not yet established. Intralesional antimony was effective for *L. (V) braziliensis* in two small studies. In an RCT including

80 Bolivian patients with small single-lesion CL, ILSb cured 70 % of patients at 6 months, compared with 20 % receiving cryotherapy, and 17 % in the placebo group [24•]. An older observational study of 74 Brazilian patients treated with ILSb revealed 6-month complete re-epithelialization in 80 % of patients. Three quarters were followed for at least 5 years, with no evidence of relapse or mucosal involvement [25]. Although there are no species-specific data evaluating intralesional antimony plus cryotherapy for other New World species, many experts consider this an option [4••].

Cryotherapy is readily accessible in dermatology clinics, but drug availability and lack of technical expertise in administration are major barriers to intralesional antimony treatment in North America [9•]. Cryotherapy and ILSb injections caused transient pain, as well as local erythema, edema, and vesicles [24•].

3. Paromomycin-containing ointments

Paromomycin is an aminoglycoside antibiotic active against *Leishmania* that can be locally applied to cutaneous ulcers. Less than 10 % of topical paromomycin is systemically absorbed, avoiding aminoglycoside-associated vestibular and renal toxicity [26••]. Mild to moderate skin irritation is common. More significant local inflammatory reactions occur when administered in methylbenzethonium chloride (MBCL) vehicle, occasionally requiring treatment interruption.

Topical 15 % paromomycin-12 % MBCL is a recommended first-line treatment for *L. major* in several guidelines [3••], but is not superior to placebo when delivered in alternate vehicles such as urea [22, 84]. Proposed hypotheses for differing vehicle-related efficacy are synergistic anti-leishmanial activity with MBCL, and improved skin penetration resulting from a heightened inflammatory reaction [84]. In meta-analysis, curative efficacy of topical paromomycin-MBCL for *L. major* was comparable to intralesional antimonials [84]. Paromomycin was also effective for *L. major* when co-formulated with 0.5 % gentamicin as the compound WR 279,396 [26••]. Both 15 % paromomycin-0.5 % gentamicin and paromomycin ointment cured 80–94 % of ulcerative *L. major* in Tunisia, compared with 58–71 % in the placebo group [26••, 27]. Although not systematically evaluated, topical paromomycin may be less effective for nodular lesions typical of *L. donovani* and *L. aethiopica* or hyperkeratotic forms of *L. tropica* [84].

Meta-analysis of small randomized controlled trials for NWCL suggests that topical paromomycin is superior to placebo, equivalent to intralesional meglumine antimoniate, and inferior to systemic antimonials [84]. Topical 15 % paromomycin-12 % MBCL and 15 % paromomycin-0.5 % gentamicin were both superior to placebo in several small studies of *L. (V) panamensis*, *L.*

(*V. braziliensis*, and *L. mexicana*. In *L. (V.) panamensis* infection, paromomycin combined with either 12 % MBCL or 0.5 % gentamicin achieved 79 to 90 % cure rates [30, 31]. In areas of Guatemala endemic for *L. (V.) braziliensis* (75 %) and *L. mexicana* (25 %), 15 % paromomycin-12 % MBCL cured 91.4 % of patients at 13 weeks compared with a 39.4 % in the placebo group [32]. Follow-up duration was insufficient to evaluate progression to MCL, and most studies took place in comparatively low risk areas of Central America [17••, 31].

Topical 15 % paromomycin-12 % MBCL is available in Israel under the trade name “Leshcutan,” but is not FDA-approved and difficult to obtain except through compounding pharmacies. The Walter-Reed formulation (WR 279,396) 15 % paromomycin-5 % gentamicin is not yet commercially available.

4. *Thermotherapy*

Leishmania amastigotes are temperature sensitive and can be targeted with localized heat generated by high-energy radiofrequency waves [22]. Radiofrequency heat therapy (RFHT) is an easily administered, single-visit treatment with minimal side effects [34]. ThermoMed Model 1.8 (Thermosurgery Technologies, Inc., Phoenix, AZ) is the only FDA-cleared current field radiofrequency generator and is not widely available [11, 12].

RFHT is effective for OWCL lesions less than 3–5 cm, with cure rates similar to both intralesional and systemic antimonials [3••, 12, 22, 34, 35, 85]. Pooled efficacy for *L. major* based on 1 RCT and 2 observational studies was 82 % (95 % CI 73–89 %) [4••]. In patients with *L. tropica*, single RFHT treatment cured 94 % at 12 weeks and 98 % at 6 months, with no relapses observed up to 1 year [34]. There was no significant difference compared with patients receiving intralesional antimony [34]. Two randomized studies of *L. tropica* in Afghanistan also found cure rates similar to intralesional antimony, with 54 % complete re-epithelialization at 100 days [35] and 83 % at 6 months [36]. A few studies noted shorter time-to-cure and superior cosmetic result using thermotherapy, but these results have not been consistently reproduced [34, 35, 39].

Thermotherapy is a possible first-line option for *L. mexicana*, with 90–95 % cure at 8–20 weeks in a prospective observational study of 201 patients [38]. Interestingly, all 23 patients with cartilage involvement of the ear (Chiclero’s ulcer) experienced complete resolution, though this area is normally difficult to treat [38, 86]. For *L. Viannia* spp. infections, thermotherapy is superior to placebo, but inferior to intralesional and systemic antimonials [16•, 39]. In two related Colombian RCTs, 6-month curative efficacy for *L. (V.) panamensis* and *L. (V.) braziliensis* in thermotherapy-treated patients was inferior to IM meglumine antimoniate (58 vs. 72 %) [87],

but similar to miltefosine (58 vs. 59 %) [37•]. Thermotherapy performed poorly in Guatemalan patients with confirmed *L. (V.) braziliensis*, curing only 9 of 14 (64 %) patients compared with 11 of 14 (79 %) treated with meglumine antimoniate and 0 of 11 in the placebo group [39].

5. *Adjunctive therapies*

Imiquimod is an immunomodulator involved in the T_H1 immune response, acting as an agonist for toll-like receptor 7 on macrophages and dendritic cells [88]. Some experts use topical imiquimod as adjunctive treatment for CL to both accelerate healing and reduce residual scarring, particularly in children and with facial lesions. Two small RCTs in *L. (V.) braziliensis* and *L. (V.) peruviana*-endemic areas revealed faster time-to-healing and improved cosmetic result using topical imiquimod in combination with systemic pentavalent antimony, compared with antimony monotherapy [88, 89]. More patients receiving imiquimod experienced local erythema, but no other major side effects occurred [88]. In meta-analysis, adjunctive topical imiquimod resulted in improved 3-month cure rates, but did not affect long-term cure at 6 and 12 months (134 participants; ITT; RR: 1.45; 95 % CI: 1.12–1.88; I₂ 0 %) [16•, 90].

Systemic Therapy

Systemic treatment is indicated for immunosuppressed patients, extensive or large numbers of lesions, mucosal involvement, local treatment failure, and lesions in sensitive locations. Older literature recommends systemic therapy for all *L. Viannia* complex NWCL, particularly *L. (V.) braziliensis*. This is no longer an absolute rule. Systemic treatments have significant associated toxicities, pose a risk to patients with comorbid illness, and are complex to administer, with intensive monitoring requirements. In choosing therapy, clinicians must weigh risk of future MCL, for which actual evidence of risk mitigation by systemic treatment does not exist, against the potential for treatment-related adverse events. Table 2 describes current indications for parenteral treatment based on expert opinion. Although systemic therapy may decrease risk of future complications, MCL can still occur despite full courses of parenteral therapy [17••, 91].

1. *Pentavalent antimony (SbV)*

Pentavalent antimonials are no longer drugs of choice for NWCL in North American travellers due to toxicity, complexity of administration, and availability of other effective treatments [92, 93]. Sodium stibogluconate is administered at a dose of 20 mg/kg IV daily for 20 days and can only be obtained in North America through a

CDC Investigational New Drug application. Due to lack of FDA approval, US health insurance plans may not reimburse costs associated with intravenous treatment, and home antibiotic infusion programs are ill-equipped to handle administration and required monitoring [9•]. Mild to moderate adverse effects occur in most patients, including fatigue, arthralgia, gastrointestinal complaints, transaminitis, elevated lipase with symptoms of pancreatitis, mild thrombocytopenia, and ECG abnormalities [11, 94, 95]. Up to 25–65 % of patients require treatment interruptions [11, 95]. Although most patients resume therapy within days, severe adverse events including more severe cytopenias, symptomatic arrhythmias, major cardiac repolarization abnormalities, acute tubular necrosis, and fulminant hepatitis can occur, primarily in patients over age 55 or with underlying co-morbidities [46]. SbV is contraindicated with any major cardiac, renal, or hepatic disease and should be used with extreme caution in older patients.

Pentavalent antimonials typically cure 70–96 % of NWCL depending on geographic location, strain, and severity [22, 39, 40, 54]. For *L. (V.) braziliensis* and *L. (V.) peruviana*, antimonials are highly effective, although foci of possible antimonial resistance are emerging in South America [16•, 96, 97]. Pentavalent antimony is not recommended for CL due to *L. (V.) guyanensis* due to low cure rates [96]. Although effective for *L. (V.) panamensis* and *L. mexicana*, other less toxic treatments have equal or better efficacy [3••, 43, 67].

Parenteral antimonials are not first-line drugs for OWCL, given poorly documented efficacy and other better tolerated treatments [22]. In published RCTs, parenteral antimonials were equivalent or inferior to those administered intraliesionally [22]. One small study suggests improved efficacy with adjunctive pentoxifylline (81.3 % $n=26/32$ vs. 50 % $n=16/32$) [49]. Despite poor evidence, experts endorse systemic antimonials in some national guidelines and continue to use them for complex, treatment refractory OWCL [47, 98].

2. Miltefosine

Miltefosine is an oral alkylphosphocholine analog emerging as an effective alternative to parenteral antimony. In March 2014, miltefosine became the first FDA-approved drug for treatment of cutaneous and mucocutaneous leishmaniasis [5]. The recommended treatment course is 2.5 mg/kg/day for 28 days (maximum dose 150 mg/day). Current approval is limited to *L. (V.) braziliensis*, *L. (V.) panamensis*, and *L. (V.) guyanensis* infection in patients over age 12, and mucocutaneous leishmaniasis due to *L. (V.) braziliensis* [5].

Pooled results of 4 RCTs demonstrated similar efficacy of miltefosine and systemic antimonials for

NWCL, with no significant difference in cure at 6 months (584 participants; RR 1.12; 95 % CI 0.85 to 1.47) [16•, 40, 44, 45, 51••]. Species-specific efficacy varies. Cure rates for *L. (V.) panamensis* range from 60 to 94 % in Colombia [37•, 40, 51••, 52, 53]. In children with *L. (V.) panamensis*, miltefosine treatment failure rates were only 8.3 %, compared with 36 % in the group receiving meglumine antimoniate [51••]. For *L. (V.) guyanensis* in Brazil, miltefosine was superior to antimonials, with 6-month cure rates of 71.4 % ($n=40/56$) compared with 53.6 % ($n=15/28$) ($p<0.05$) [44]. For *L. (V.) braziliensis*, meta-analysis revealed an overall trend towards superiority of miltefosine compared with pentavalent antimony (ITT; RR 1.41; 95 % CI 0.98 to 2.03) [16•]. However, cure rates among RCTs were heterogeneous. Miltefosine cured 88 % of *L. (V.) braziliensis* in Bolivia [54], 73 % in Brazil [45], 49 % in Colombia [40], and only 33 % in Guatemala [52]. *L. mexicana* responds poorly to miltefosine in vitro, with only 60 % efficacy in one human trial [52, 99].

Miltefosine is a successful salvage therapy for patients with refractory OWCL, but randomized controlled trial data is lacking. Miltefosine cured 88 % ($n=30/34$) of Dutch soldiers with aggressive *L. major* infection acquired in Afghanistan that did not respond to intraliesional antimony [55]. In a small open-label Iranian RCT, miltefosine cured 26 of 32 patients (81.3 %) at 3 months, compared with 25 of 31 (80.6 %) of those treated with IM meglumine antimoniate [48].

Mild adverse effects are common and usually do not require treatment interruption. Gastrointestinal complaints including vomiting (40 %) and diarrhea (20 %) occur mainly in the first week [56]. Teratogenicity is a major consideration for reproductive-aged women. Contraception should be used during therapy and for 4–5 months after treatment completion due to miltefosine's long half-life [5, 100].

Liposomal amphotericin B (L-AMB)

Expert guidelines rank liposomal amphotericin B as a first-line option based on high cure rates in observational studies and successful treatment of severe refractory disease, including in immunocompromised patients [3••, 6••, 57•]. L-AMB is FDA-approved only for visceral leishmaniasis, but is used off label for cutaneous disease in US and Canadian centers. The most common regimen is a short intravenous course of 3–5 mg/kg daily administered on days 1–5, with a sixth dose on day 10. Transient infusion reactions requiring premedication occur in up to 25 %, and reversible grade 2 nephrotoxicity affects 5–6 % of patients [57•]. Risk of nephrotoxicity is reduced by intravenous pre-hydration.

Published data on L-AMB in travellers is sparse, but observational studies document high cure rates of 80–90 %. In 19 US soldiers infected with multiple New and Old World species, including 2 with mucosal involvement and 3 failing systemic antimonials, L-AMB cured 84 % after initial treatment and all after a second course [58]. L-AMB cured 85 % ($n=30/34$) of Israeli travellers with *L. (V.) braziliensis*, which was similar to a parenteral antimony comparison group (70 %, $n=24/34$, $p>0.05$) [57•]. Single-course L-AMB cured 11 of 13 (85 %) German travellers with *L. (V.) braziliensis* [56]. *L. tropica* fully responded to L-AMB in 84 % of Israeli patients, most with prior topical treatment failure [59]. L-AMB has not been evaluated extensively in endemic settings.

3. Oral azoles (fluconazole, ketoconazole)

Fluconazole is a potential outpatient systemic treatment option, with apparent dose-dependent efficacy. Randomized controlled trial data exists only for *L. major*. Fluconazole cured 81 % of Iranian patients treated with 400 mg daily for 6 weeks, compared with 48 % in those receiving 200 mg daily [60]. Low-dose 200 mg fluconazole is not consistently effective. One Saudi Arabian RCT noted 3-month cure rates of 79 % compared with 34 % in the placebo group [61]. However, 6 weeks of fluconazole cured only 44 % of French travellers infected with *L. major*, which is similar to placebo rates in other studies [62].

One prospective observational study evaluated cure rates for cutaneous *L. (V.) braziliensis* with escalating doses of fluconazole, administered for 4–12 weeks [63]. Fluconazole cured all patients ($n=8$) treated with 8 mg/kg/day, compared with 93 % ($n=14$) dosed at 6.5 mg/kg/day and 75 % ($n=8$) at 5 mg/kg/day [63]. Ketoconazole was ineffective in Guatemalan *L. (V.) braziliensis*, but cured 89 % of patients with *L. mexicana* and was superior to both placebo and pentavalent antimony in this subgroup [101]. Some centers have entirely eliminated fluconazole from treatment recommendations due to therapeutic failures [6••].

4. Pentamidine

Rarely used in travellers, pentamidine is a first-line option for *L. (V.) panamensis* and *L. (V.) guyanensis* in areas of South America. Cure rates for *L. (V.) panamensis* are consistently greater than 90 % in older observational studies in endemic populations [41•, 64]. Treatment response for *L. (V.) guyanensis* appears similar to *L. (V.) panamensis* and comparable to antimonials [16•, 64, 65]. Emerging drug resistance is a concern, with lower cure rates approaching 60 % observed in more recent studies [43, 66]. Efficacy in *L. (V.) braziliensis* is poor and inferior to systemic antimony [16•, 67]. Pentamidine cured only 35 % of patients with *L. (V.) braziliensis* in Peru, compared with 78 % of those treated with parenteral sodium stibogluconate ($p<0.001$) [67].

Conclusion

Returned travellers with cutaneous leishmaniasis encounter significant barriers to treatment. First-line anti-leishmanial drugs are difficult to access in non-endemic settings, such that availability often determines treatment selection. Clinicians are faced with limited data to direct management. The existing literature is plagued by heterogeneous methodology with non-uniform clinical endpoints, inconsistent treatment regimens, small sample sizes, high loss to follow-up, and often absence of a control group [3••, 16•, 22]. High-quality randomized controlled trials are urgently needed in both endemic populations and travellers, as fundamental questions remain unanswered. Does species-oriented treatment improve outcome? What is the true risk of mucocutaneous leishmaniasis in travellers, and are risk factors similar to endemic populations? How do local treatments compare with systemic therapy in patients with New World CL? How should we treat high-risk groups including children, immunocompromised hosts, and patients with co-morbid illness? Facilitating rapid access to *Leishmania* molecular diagnostics and anti-leishmanial drugs, expanding treatment options, including investment in ethnopharmaceutical and novel therapeutic approaches, and rigorously evaluating existing therapies are priorities in the next decade, and will require ongoing international collaboration.

Compliance with Ethics Guidelines

Conflict of Interest Andrea Boggild and Adrienne Showler have no disclosures relevant to this work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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