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REVIEW

LeishMan Recommendations for Treatment of Cutaneous and Mucosal Leishmaniasis in Travelers, 2014

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See the Editorial by Glenn Wortmann, pp. 77–78 of this issue.

Background. Treatment of cutaneous leishmaniasis (CL) and mucosal leishmaniasis (ML) in travelers is still controversial. Over the last decade, national and international consortia have published recommendations for treating CL in travelers. These guidelines harmonize many issues, but there are some discrepancies.
Methods. *Leishmania* parasites causing CL can now be genotyped by polymerase chain reaction techniques for detecting *Leishmania* DNA. Therefore, treatment recommendations can now be species based rather than based on geographical exposure. To review the evidence on which the recommendations were based, "LeishMan" (**Leish**maniasis **Man**agement), a group of experts from 13 institutions in eight European countries, performed a PubMed (MEDLINE) literature search and considered unpublished evidence and the experts' own personal experiences. The Oxford evidence grading system was used to evaluate the information.
Results and Conclusion. In this article, the authors provide practical treatment recommendations for imported CL and ML in Europe, drawn up from the review by the European experts.

Treatment of cutaneous leishmaniasis (CL) and mucosal leishmaniasis (ML) in travelers is still controversial. Current treatment recommendations are based on data from endemic regions, which may not be applicable to travelers who have different exposure rates and immunity toward *Leishmania* parasites.

Leishmania parasites causing CL can now be genotyped by polymerase chain reaction (PCR) techniques for detecting *Leishmania* DNA. Therefore, species-based treatment guidelines are now possible and are increasingly replacing previous guidelines that were based on geographical exposure. Species-oriented treatment guidelines for imported CL have been drawn up by national advisory bodies (Germany, France, UK, and WHO) and by several authors.[1–9] The WHO 2010 recommendations are mainly written for endemic countries and not for travelers.[9] Important differences exist between these guidelines, often because of insufficient evidence to support the recommendations. In this article, we provide practical treatment recommendations

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for imported CL and ML in Europe, drawn up from the review by the European expert group, "LeishMan" (**Leish**maniasis **Man**agement).[10] To review the evidence on which recommendations are based, LeishMan performed a PubMed (MEDLINE) literature search using the key words "CL" and "treatment," to select for controlled clinical trials published between 1962 and 2013 and using "mucosal/mucocutaneous leishmaniasis," to select clinical trials published between 1960 and 2013. The search included articles published in English, French, German, and Spanish. In addition, LeishMan included unpublished evidence and the expert group's own personal experiences.

The Oxford evidence grading system was applied when reviewing information. The highest ranking **A** was assigned to randomized controlled trials in representative patient groups. Randomized controlled trials in less homogenous patient groups (small numbers, different species included) as well as cohort trials and case-control studies in representative patient groups were given a ranking **B**. Cohort trials or case-control studies in less homogenous patient groups, as well as case series of representative patient groups were given a ranking **C**. Case series of less homogenous patient groups and expert opinion were ranked as **D**.

General Treatment Considerations for CL and ML

Patient Evaluation Before Treatment

CL lesions range from a single limited skin lesion, that may heal spontaneously, to large and multiple locally destructive skin lesions, which may spread to or involve mucosa. So, treatment depends on the clinical aspect of the lesion and the infecting species. Mucosal spread may affect the nostrils, the nasal septum, and the oral mucosa. Referral to an Ear, Nose, and Throat specialist may be warranted.

The possibility of CL being part of visceral leishmaniasis (VL) occurs rarely but should be considered if the patient has fever and hepatosplenomegaly and laboratory markers of VL infection (pancytopenia, positive *Leishmania* antibody titers). This clinical presentation is more likely if a patient has underlying immunosuppression.

Definition of Healing and Follow-Up

Cutaneous lesions usually heal within a month after starting treatment with pentavalent antimonials, either by local infiltration [Old World cutaneous leishmaniasis (OWCL)] or given systemically [New World cutaneous leishmaniasis (NWCL)], but large ulcers may take longer. Treatment failure is present when reepithelialization is incomplete 3 months after starting therapy. A relapse is defined as the reappearance of the ulcer after complete healing, or a renewed increase in the indurated area of a nodular lesion. Parasitological confirmation is not required, except in clinically complex cases. In such cases, parasite identification (by microscopy and or culture) is preferred, as *Leishmania* DNA can be detected by PCR in lesions several years after successful treatment.[11,12] A follow-up visit at 3 and at 12 months is required to ascertain complete cure.

General Considerations: Local Versus Systemic Treatment for CL

The choice for topical or systemic treatment is determined by the following factors.

1. Risk of developing mucosal leishmaniasis

This is the main reason for recommending systemic treatment in all patients with CL from the New World (except *Leishmania mexicana* infections). Recent data suggest that the risk is higher when lesions are (i) infected with *Leishmania braziliensis* or *Leishmania panamensis*, (ii) acquired in Bolivia, (iii) multiple (>4), large (>4–6 cm^2), (iv) present for >4 months, (v) localized above the belt, (vi) associated with acquired or induced immunosuppression, and (vii) treated inappropriately.[13] Whether local treatment predisposes patients to ML (compared to systemic treatment) has never been studied systematically, but there are no reports on ML developing in NWCL patients treated with paromomycin or methylbenzethonium chloride ointment or with local infiltration with antimonials.[13]

If none of the above risk factors are present in patients with NWCL, the risk of developing ML is probably low. Local treatment is thus an option for those who can comply and for whom long-term follow-up is feasible. Experts in Latin America have recently adopted this stance and studies evaluating local therapy for NWCL are underway.

2. Failure of prior local treatment

Local treatment includes topical treatment with ointment, cryotherapy, and intralesional injection with antimonials. Failure to respond may indicate the need for systemic treatment.

3. Size, number, and localization of lesions

Lesions that are multiple and large, that affect the nose, lips, eyelids, or ears, or that are located close to small joints are, for practical reasons, less suited for local therapy.

4. Lymphatic spread

It is not clear whether local lymphadenopathy and lymphangitis is an absolute indication for systemic treatment. It may indicate extra-dermal parasite spread and thus a risk of subsequent ML. In studies with local treatment, concomitant lymphadenopathy was either an exclusion criterion[14,15] or was not reported.[16–18] It is therefore unknown whether lymphatic spread of leishmaniasis responds to local treatment.

5. Toxicity of systemic treatment

Table 1 summarizes the adverse events associated with current systemic treatment options, based on data from CL and ML studies conducted mainly in young and otherwise healthy patients. Adverse events may be more severe and frequent in patients with

Table 1 Drugs and follow-up for treatment of cutaneous leishmaniasis

Drug	Adverse effect	Management/Follow-up
Systemic pentavalent antimonials	Cardiac toxicity with reversible ECG alterations is seen in 30%–60% - Repolarization alterations affecting T wave and ST segment - Prolongation of the corrected QT interval - Fatal arrhythmias have not been documented in CL patients treated with the usual dose ≤20 mg Sb/kg[19–23] - Hypokalemia associated with risk of arrhythmias	ECG checks 1–2 every week Interruption of treatment if - Significant arrhythmias - QTc longer than 0.5 second (age-adapted limits in children) - QTc longer than 0.45 second: monitoring/dose reduction - Concave ST segment - Potassium weekly
	Hepatotoxicity seen in 50%, reversible	Transaminases weekly Treatment interruption if transaminases higher than five times the upper limit of normal value (ULN)[24]
	Hematotoxicity (anemia, leukopenia, thrombopenia)[25]	Hemoglobin, leukocytes, and platelets weekly
	Pancreatitis can occur either very early in therapy (and is then often symptomatic) or more progressively during the course of therapy. Serum levels of amylase and lipase may decline despite continued treatment with antimonials	Amylase and lipase after 48 h of treatment and then weekly Treatment interruption if serum amylase levels became >4 times the ULN or lipase levels of >15 times the ULN, regardless of symptoms. Therapy can be resumed once these values tend significantly toward normal value[26,27]
	Subjective complaints: musculoskeletal symptoms, headache, gastrointestinal complaints, pain at the injection site	
	Rare complications: glomerulonephritis, acute renal failure,[28] peripheral nephritis,[29] exfoliate dermatitis, herpes zoster,[30] hypersensitivity syndrome[31]	Weekly examination of urine, creatinine
Pentamidine	Aseptic abscess (accidental contact of pentamidine with the subcutaneous tissue)	Pentamidine has to be given by infusion or injected slowly and strictly intramuscular with a long needle (50 mm)
	Hypoglycemia, diabetes, proteinuria	Fasting glycemia and urine for proteinuria and glycosuria have to be checked before every injection and 3 weeks and 2 months after the last injection[32]
	Rhabdomyolysis[33,34]	CK in case of clinical signs of rhabdomyolysis such as myalgia or kidney failure
	Hypotension[35,36]	The blood pressure and heart rate have to be measured before and after the injection (every 15 min for 1 h)[32] less frequent when administered by slow infusion
	Subjective complaints: myalgia, nausea and gustative abnormalities, headache, pain at the injection site, abdominal pain[36]	
Miltefosine	Subjective complaints: nausea (36%), vomiting up to 40% often during the first week, motion sickness (29%), headache (27%), diarrhea (6%–16%), vomiting (32%–38%)[37,38]	
	Impaired renal function: Creatinine increased above the normal range in 32%, in 31% <1.5 times the upper limit of normal, and in 1% between 1.5 and 3 times the upper limit of normal[37]	Creatinine weekly
	Hepatotoxicity: The AST was elevated in 8% and the ALT in 10% but always less than 2.5 times the upper limit of normal value.[37]	Transaminases weekly
	Teratogenic, subtherapeutic miltefosine concentrations in the blood beyond 4 months after treatment	Avoid pregnancy until 4 months after end of treatment
	Discoloration of sperma	
Ketoconazole	Hepatotoxicity reversible, usually mild,[39] sometimes severe	Transaminases weekly Treatment interruption if transaminases higher than five times ULN
	Diminution of testosterone values (70%), but without diminution of libido or beard growth[39]	Reversible, no controls needed
	Subjective complaints: abdominal pain, headache, nausea, fever, and malaise[39]	
Fluconazole	Hepatotoxicity	Transaminases Treatment interruption if transaminases higher than five times ULN
	Allergic skin reactions	
	Hematotoxicity (anemia, leukopenia, thrombopenia)	Hemoglobin, leukocytes, and platelets
	Subjective complaints: headache, gastrointestinal complaints	
Liposomal amphothericin B	Renal toxicity Hypokalemia	Creatinine and potassium before each infusion Avoid other potential nephrotoxic drugs
	Infusion-related reactions including chest pain, flank pain, dyspnea, flushing urticaria	May be partially prevented by hydrocortisone
	Nausea, anorexia, vomiting	

ULN, upper limit of normal value.

comorbidities such as cardiac, renal or hepatic disease, diabetes mellitus, or immunosuppression. Miltefosine has a very long half-life and is still detectable in blood samples 6 months after a standard 28-day treatment.[40] Women of childbearing age should adopt contraceptive measures during treatment and for 4 months after treatment completion.[41]

Species based Treatment of CL

Treatment of L. major

a. Up to three lesions, not cosmetically disfiguring, patients not immunosuppressed, option acceptable to patient:

No antileishmanial treatment; simple wound care

b. Up to three lesions with diameters <30 mm—local treatment:

1. "Flash" cryotherapy plus local infiltration with antimonials [**A**][42–46]
2. 15% Paromomycin or 12% methylbenzethonium chloride ointment bid for 10 to 20 days [**A**][47–51]
3. Local heat therapy (50°C for 30 seconds) [**A**][52–55]

c. More than three lesions, diameter >30 mm, delicate location, and/or refractory to local treatment:

1. Miltefosine (50 mg tid × 28 days) [**B**][56–58]
2. Fluconazole (200 mg bid × 6 weeks) [**C**][59–61]
3. Liposomal amphotericin B (18 mg/kg total dose: 3 mg/kg/day, days 1 to 5 and at day 10) [**D**][62]
4. Systemic pentavalent antimonial (Sb 20 mg/kg) and pentoxifylline (3 × 400 mg/20 days) [**A**] or systemic pentavalent antimonial (Sb 20 mg/kg for 10–20 days) [**D**][55,57,63–65]

Watchful waiting is a critical requirement. Studies reported spontaneous cure rates of 53% at 8 weeks,[66] from 40% to 90% at 3 months[67] and close to 100% at 12 months.[2] However, CL acquired in Afghanistan often does not heal spontaneously and may require systemic treatment.[56]

In a large study of 634 patients with CL (*L. major* or *Leishmania tropica*), combining cryotherapy and intralesional injection with antimonials (Figures 1 and 2) had better cure rates (89%–91%) than either cryotherapy (57%–68%) or intralesional antimonials alone (44–75%).[42,45,46] Local heat therapy (50°C for 30 seconds) had a cure rate comparable to that of systemic pentavalent antimonials (Sb 20 mg/kg for 10 days) (48% vs 54%, $n = 54$).[55] Compared to intralesional antimonials the cure rates of local heat application were superior (81% vs 55%, $n = 116$)[54] (83% vs 74%, $n = 382$),[53] or similar (98% vs 94%, $n = 100$).[52] Local heat therapy is a promising method for local treatment and is a valuable option for centers with necessary equipment (ie, Thermomed Device).

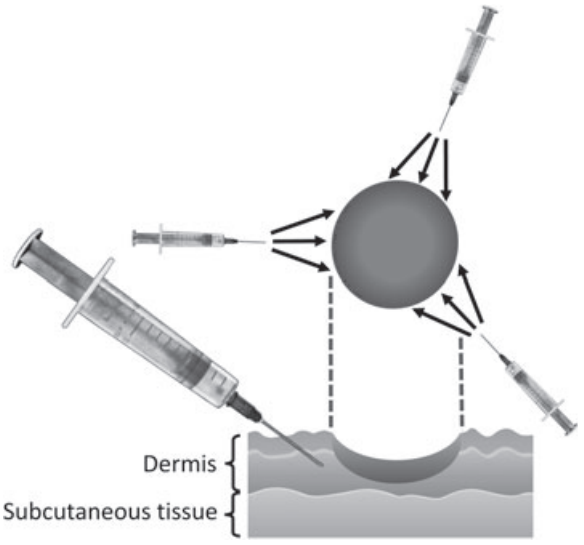

Figure 1 Procedure for intralesional treatment with pentavalent antimony.[46] Advance the needle while injecting under pressure in the dermis, covering the whole lesion including the center.

Topical application of an ointment containing 15% paromomycin and 12% methylbenzethonium chloride appears to be more effective than an ointment with 15% paromomycin plus 10% urea, but also causes more local inflammation.[68] A newly developed topical aminoglycoside formulation is more effective than a placebo among Tunisian patients and French travelers (*L. major*), with cure rates consistently above 80% at 3 months.[48,51]

Miltefosine at 150 mg daily for 28 days is a treatment option for patients who have not responded to intralesional pentavalent antimonials. In treatment studies of *L. major* CL (three studies, $n = 81$) cure rates of miltefosine had a mean of 93% (range: 87% to 100%).[56–58] This was somewhat superior to the 85% cure rates of systemic meglumine antimoniate (20 mg/kg for 14 days).[57]

In OWCL, the efficacy of systemic pentavalent antimony is poorly documented.[69] In an open, uncontrolled study (pentavalent Sb 20 mg/kg for 10 days), cure rates ranged from 52% to 87% at 3 weeks[55,57,63–65] and was 90% at 12 months.[55] Systemic Sb treatments had the same cure rate as a placebo.[70] Adding allopurinol (15–20 mg/kg/daily for 20 days) produced only marginally better cure rates than Sb alone (80% vs 74%),[64] but when used in combination with pentoxifylline three times 400 mg daily for 20 days, the cure rate improved significantly (26/32 = 81% vs 16/31 = 52%).[63]

Fluconazole (200 mg daily for 6 weeks) was a well-tolerated treatment for *L. major* leishmaniasis in Saudi Arabia, with a cure rate of 79% (63/80) versus 34% (22/65) for the placebo group at 3 months.[59] Unfortunately, this favorable result could not be reproduced elsewhere.[60] Increasing the dosage of fluconazole to 400 mg daily produced a higher cure rate (81%) than fluconazole 200 mg daily (48%) at 2 months,

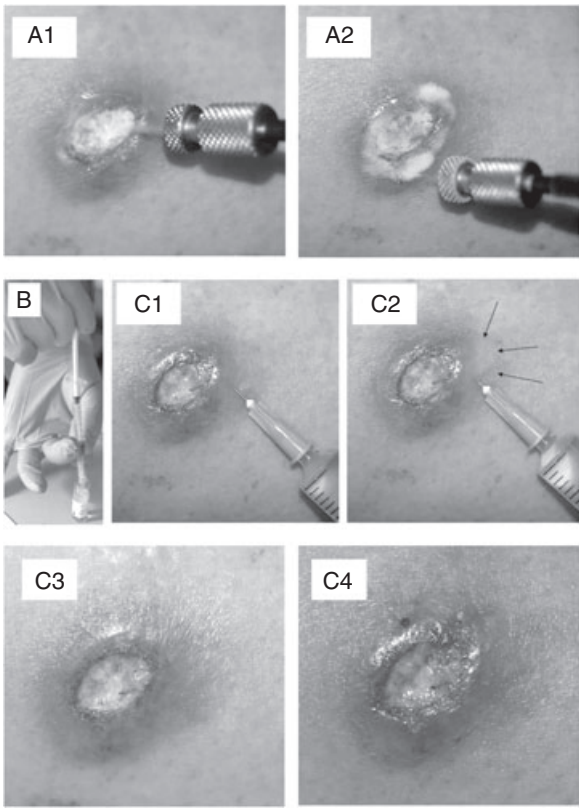

Figure 2 Procedures for superficial cryotherapy and/or intralesional injection of antimony. The lesion is first swabbed with antiseptics several minutes before starting the procedure. (A) Cryotherapy: cryotherapy with liquid nitrogen is then applied on the lesion (A1) and immediate borders (A2)—ideally with a sprayer—3- to 5-second blanching is obtained. (B and C) Intralesional injection: Antimony as formulated for parenteral administration by the manufacturer (B) is injected into the lesion (C1) and should induce blanching of the borders (C2, arrows), until the lesion is entirely swollen (before procedure C3, end of procedure C4). The procedure is usually repeated 2 to 10 times at 2 to 8 day intervals.

but with increased adverse events rate. Adverse events included raised serum creatinine or liver enzymes (4%), cheilitis (45%), and nausea (10%) leading to treatment interruption.[61]

Ketoconazole, another imidazole compound, showed an acceptable cure rate of 70% (5/8) in a small case series.[71] It was superior to intralesional antimonials in a study with *L. major* and *L. tropica* CL, with cure rates of 89% (57/64) and 72% (23/32), respectively.[72] No placebo controlled studies exist with ketoconazole.

Treatment of L. tropica, Leishmania infantum/donovani, *and* Leishmania aethiopica

a. Up to three lesions, not cosmetically disfiguring and patients not immunosuppressed, option acceptable to patient:

Simple wound care

b. Up to three lesions with diameter <30 mm—local treatment:

1. Local infiltration with antimonials with or without cryotherapy [**A**] [42,45,46]
2. 15% Paromomycin/12% methylbenzethonium chloride ointment bid for 10 to 20 days [**D**]
3. Local heat therapy (50°C for 30 seconds) [**A**][54,73]

c. More than three lesions, diameter >30 mm, delicate location, and/or refractory to local treatment:

1. Liposomal amphotericin B (18 mg/kg total dose: 3 mg/kg/day, days 1 to 5 and at day 10) [**C**][62,74]
2. Miltefosine (50 mg tid × 28 days) [**D**][75–77]
3. Pentavalent antimonials (Sb 20 mg/kg for 10–20 days) (+/− allopurinol) [**C**][73,78–80]

Treatment data are scarce for *L. tropica* and nearly non-existent for *L. infantum/donovani* or *L. aethiopica* CL lesions. Spontaneous cure for *L. tropica* CL is estimated at 1% to 10% at 3 months, 68% at 12 months, and close to 100% at 6 months to 3 years.[2,79]

As mentioned above, cryotherapy combined with intralesional antimonials (see Figures 1 and 2) produced excellent cure rates in *L. major* or *L. tropica* CL and may be successful in *L. aethiopica* and *L. infantum/donovani* CL as well.[42,45,46,81] Thermotherapy and photodynamic therapy were effective in *L. tropica and L. major* CL and is a valuable option for centers with the necessary equipment (ie, Thermomed Device).[54,55,82]

Liposomal amphotericine (AmBisome, 3 mg/kg/day for five consecutive days and at day 10, with a total dose of 18 mg/kg) had a cure rate of 84% in 13 travelers and immigrants with *L. tropica* CL.[74]

For *L. tropica*, *L. major*, and *L. infantum/donovani* CL, experience with miltefosine is limited to case reports[75–77,83,84] and small case series, with all patients cured.[58] Two patients with *L. infantum* ML were completely cured with miltefosine.[85,86] Cure rates of systemic antimonials in *L. tropica* CL ranged from 41% to 55%,[73,78–80] but were not studied for *L. infantum/donovani* CL. For *L. tropica* CL, adding allopurinol (15–20 mg/kg/day for 20 days) increased cure rates to 46%, compared with 24% in the antimony-only group.[87] According to European experts, systemic pentavalent antimonials are effective for treating complex CL lesions and are recommended in some national guidelines.[2,5,88]

There are no systematic treatment studies of *L. aethiopica*. Cryotherapy has been widely used. Liposomal Amphothericin B and miltefosine were used successfully in some cases.[89]

Treatment of L. panamensis

Although many experts consider *L. guyanensis* and *L. panamensis* as a single species complex, we analyzed them separately, since trials were performed on each species. As knowledge of the taxonomy of *Leishmania* increases,

Table 2 Drug properties

Drug	Special precautions	Administration	Dosage	Duration	Half-life	Metabolic and elimination pathways	Pregnancy category†	Renal function impairment
Systemic pentavalent antimonials	Age >60 years Cardiopathy Liver disease Renal impairment Pancreatitis	IM / IV	20 mg/kg of Sb^5 base equivalent	(10)-20 days ML: 28 days	Approximately 2 h and 33–76 h*	Renal excretion	Unknown	Dose adjustment[144]
Pentamidine	Renal impairment Liver disease Pancreatitis Diabetes	IV (IM)	4 mg/kg base	3	Approximately 9–13 h and approximately 28 days*	Small extent renal excretion (4%–17% in 24 h)	C	Not indicated due to nephrotoxicity
Miltefosine	Pregnancy	Oral	150 mg/day	28 days	7 days and 31 days*	Phospholipases	Teratogenic (contraception required until 4 months post-treatment)	No dose adjustment indicated
Ketoconazole	Liver disease	Oral	600 mg/day	28 days	2 h and 8h*	Hepatic; mainly biliary excretion	C	No dose adjustment indicated
Fluconazole		Oral	400 mg/day	6 weeks	30 h	Hepatic; mainly renal excretion	C	CrCl <50 mL/min: 50% of daily dose
Liposomal Ampho-tericin B		IV	3 mg/kg/day, days 1–5, 10; 18 mg/kg total dose		Terminal: 152 h	No extensive metabolism; very little renal and biliary excretion	B	Close monitoring of renal function, if progressive: daily dose reduction (eg, 50%)

Category A: No fetal risk, Category B: Relatively safe to use during pregnancy, Category C: fetal risk is unknown, Category D: Some evidence of fetal risk, Category X: Causes abnormalities.
*Bi-phasic elimination, typically relating to the distribution and elimination phase of the drug.
†Pregnancy categories.

there may be justification for merging recommendations in the future.

a. Single or few lesion(s), not cosmetically disfiguring, lesions with diameter <30 mm, no lymphatic spread, option acceptable to patient—local treatment considered:

1. 15% Paromomycin/12% methylbenzethonium chloride ointment [**B**][14,16]
2. Local heat therapy [**A**][90]

b. Multiple lesions or large single lesion—systemic treatment:

1. Miltefosine (50 mg tid × 28 days) [**A**][91–94]
2. Pentamidine isethionate (4 mg/kg, three infusions over 5 days) [**A**][35,95]
3. Ketoconazole (600 mg × 28 days) [**B**][39]
4. Pentavalent antimonials (Sb 20 mg/kg for 20 days) [**A**][35,90,96,97]

Data on local treatment are scarce. In a group of 52 patients infected mainly with *L. panamensis*, topical treatment with 15% paromomycin or 12% methylbenzethonium chloride ointment od or bid for 20 days produced cure rates of 90% at 3 months and of 85% after 1 year. Reinfections could not be distinguished from relapses.[16] This topical treatment (once daily for 30 days; $n = 29$; cure rate 79%) was inferior to systemic treatment with systemic pentavalent antimonials (20 mg/kg od for 10 days; $n = 36$; cure rate 92%).[14] However, because of toxicity and the lack of superiority to other drug regimens, systemic pentavalent antimonials are no longer the treatment of choice. As cure rates with thermotherapy were mediocre (14/24 = 58%) and inferior to systemic meglumine antimoniate (23/32 = 72%), thermotherapy cannot yet be proposed as a first line treatment.[90]

Cure rates with miltefosine were variable (60%–94%),[91–94] but superior to a placebo in one study (91% vs 38%).[93] Compared to pentavalent antimonials, cure rates with miltefosine treatment were similar in Colombia (18/30; 60% vs 23/32; 72%),[94] but higher in 43 patients from Brazil (92% vs 63%).[92]

Pentamidine was tested in different dosages (two to six injections of 2 to 4 mg/kg) in patients with predominantly *L. panamensis* CL. Cure rates were comparable with pentavalent antimonials (96% vs 91%) and were highest with dosages of three to five times, 4 mg/kg (96%).[35,95]

Treatment of L. guyanensis

a. Single lesion, not cosmetically disfiguring, no lymphatic spread and infection not acquired in Bolivia:

No data on local treatment: no recommendation possible

b. All other cases—systemic treatment:

1. Pentamidine isethionate (4 mg/kg: three infusions over 5 days) [**A**].[33,35,36,95,98–100]
2. Miltefosine (50 mg tid × 28 days) [**B**][101]

Pentamidine is the first line treatment for *L. guyanensis* CL in French Guyana, Surinam, and Brazil, with cure rates around 90%.[35,95,98,100,36,33] Although these studies included many patients (>2,000 patients), most are retrospective observations and different dosages were used. Cure rate was lower (77%) in a study from Surinam, possibly due to a very low follow-up rate.[102] For *L. guyanensis* acquired in North-East Brazil, the cure rate was higher with miltefosine (40/56; 71%) than with meglumine antimoniate group (16/28; 57%).[101]

Treatment of L. braziliensis, Leishmania peruviana

L. braziliensis and *L. peruviana* species are genetically very similar. Data on treatment come from studies of *L. braziliensis* CL.

a. Single or few lesion(s), not cosmetically disfiguring, lesion with diameter <30 mm, no lymphatic spread, not from Bolivia—local treatment possible:

1. Local infiltration with antimonials +/− cryotherapy [**B**][17]
2. 15% Paromomycin/12% methylbenzethonium chloride ointment [**B**][18,88]
3. Thermotherapy [**A**][90]

b. All other cases—systemic treatment:

1. Pentavalent antimonials (Sb 20 mg/kg for 20 days) [**A**][37,90,93,94,103–105]
2. Liposomal amphotericin B (18 mg/kg total dose: 3 mg/kg/day, days 1 to 5 and at day 10) [**B**][62,106]
3. Miltefosine (only Bolivia, Brazil) (50 mg tid × 28 days) [**C**][105,107]

Local treatment with intralesional antimonials was only reported in one study involving 74 patients with *L. braziliensis* CL. Cure rate without relapse or development of ML was 80%.[17] For CL due to *L. braziliensis* (75%) and *L. mexicana* (25%), topical treatment with 15% paromomycin/12% methylbenzethonium chloride ointment ($n = 35$) was more effective than placebo ($n = 33$; response rate at 12 weeks was 91% vs 39%)[18] and had a cure rate of 76% after 8 weeks ($n = 53$)[108] but was not compared to systemic treatment with pentavalent antimonials. In studies of topical treatment of NWCL, patients were followed up either until healed[108,109] or until a year after treatment.[14,16,18] Although none developed ML, the observation periods were too short and the sample size too small to assess that risk accurately. Since cure rates of thermotherapy were mediocre (31/95 = 53%) and inferior to those of systemic meglumine antimoniate (34/52 = 65%), thermotherapy cannot yet be proposed as a first line treatment.[90]

Pentavalent antimonials are the principal treatment for *L. braziliensis* CL.[19,26,110,111,112] Cure rates range from low (50%)[113,114] to excellent (96%–100%).[97,104,115] The variation may be attributed to strain and site differences.[113] In CL patients infected with *L. peruviana* ($n=46$), 76% were cured with systemic antimonials.[116,117]

Liposomal amphotericin B has been used after treatment failure in immunocompromised patients and when pentavalent antimonials are contraindicated. Case series in travelers and immigrants showed that AmBisome (3 to 5 mg/kg daily for five consecutive days and a sixth dose on day 10, cumulative doses 18–30 mg/kg) cured 29 of 34 (85%) patients with *L. braziliensis* CL in Israel[106,118] and 12 of 14 (86%) patients in Germany.[119] Using similar cumulative doses, AmBisome had a cure rate of about 84% in patients with OWCL ($n=10$) and NWCL lesions ($n=10$) alike.[62]

Treatment with miltefosine has been disappointing, with cure rates varying with the geographical origin of the infection. A small series from Guatemala had unacceptably low cure rates (33%) compared to placebo (8%).[93] However, cure rates were comparable to that of pentavalent antimonial treatment in Colombia (60% vs 65%, $n=93$)[94] and Bolivia (88% vs 94%, $n=57$),[105] and slightly better in Brazil (75% vs 53%, $n=90$).[107] Differences in drug susceptibility in some subspecies of *L. braziliensis* may account for the wide cure rate variation observed (Table 2).

Fluconazole has only been evaluated in small series of *L. braziliensis* CL patients and different dosage schemes have been used. Cure rates increased with dosage, from 75% at 5 mg/kg ($n=8$) to 93% at 6.5 mg/kg ($n=14$) and to 100% at 8 mg/kg ($n=8$), respectively. Surprisingly, no significant adverse events were reported.[120] Because of a lack of solid evidence and intolerance at higher doses (400 mg/day) reported in patients with *L. major*, experts are reluctant to recommend fluconazole for *L. braziliensis* CL at present.

Treatment of L. mexicana

a. Up to three lesions not requiring immediate therapy, not cosmetically disfiguring and option acceptable to patient:

No antileishmanial medication, simple wound care, mostly self-limiting

b. More than three lesions with diameter<30 mm—local treatment:

1. Cryotherapy/local infiltration with antimonials
2. 15% Paromomycin/12% methylbenzethonium chloride ointment[18,108]

c. More than three lesions with diameter >30 mm, delicate location and/or refractory to topical treatment—systemic treatment:

1. Ketoconazole (600 mg/day × 28 days) [**B**][104]
2. Miltefosine (50 mg tid × 28 days) [**B**][93]
3. Pentavalent antimonials (Sb 20 mg/kg for 20 days) [**D**]

Published data on systemic treatment of *L. mexicana* CL are scarce, and have involved small patient groups only. Ketoconazole produced superior cure rates at 13 weeks compared to placebo (8/9; 89% vs 9/16; 56%) and to pentavalent antimonials (8/9; 89% vs 5/7; 71%).[104] Miltefosine had only limited efficacy (9/14; 64%)[93] and fluconazole was not tested.

Treatment of Other NWCL Species: Leishmania naiffi, Leishmania lainsoni, Leishmania amazonensis, Leishmania venezuelensis

Only a few case reports provide some data regarding the treatment.

L. naiffi: In Surinam, patients with five small lesions in total were successfully treated with pentamidine[121] and three small lesions in two patients disappeared without treatment.[122] Therefore, *L. naiffi* CL calls for a "wait and see" policy when only a few non-cosmetically disfiguring lesions are present.

L. amazonensis: Genetically speaking, this subspecies is closely related to *L. mexicana*, which suggests that a similar treatment approach could be used. However, there are no data to support this.

L. venezuelensis and ***L. lainsoni***: Treatment data are not available. Cases were mostly treated as *L. braziliensis*.

Treatment of Mucocutaneous or Mucosal Leishmaniasis

Systemic treatment is mandatory in ML cases; the spread and localization makes local treatment impractical or ineffective.

Old World Mucosal Leishmaniasis

1. Miltefosine (50 mg tid × 28 days) [**D**][85,86,123]
2. Pentavalent antimonials (Sb 20 mg /kg for 20–28 days) [**D**][124,125]
3. Liposomal amphotericin B (21–40 mg/kg total dose) [**D**][123,124]

There have not been any controlled studies on treating OWML and the treatment options mentioned above were successfully used and reported in case reports.[85,123,124] There are no comparative studies between the treatment options and preference is guided by practical considerations, such as drug availability and costs.

New World Mucosal Leishmaniasis

1. Pentavalent antimonials (Sb 20 mg/kg/day for 28–30 days) [**A**].[126,127] Addition of pentoxyfilline (400 mg tid for 30 days) [**A**][128–130]
2. Liposomal amphotericin B [**C**][126,127] (30–40 mg/kg total dose)

3. Miltefosine (150 mg od × 28 days) [**B**][131,132]

Pentavalent antimonials are still the gold standard of treatment,[127,133] with an overall cure rate of 88%.[127] Increasing the dosage beyond 20 mg Sb/kg/day for 30 days did not improve the already high cure rate of 91%. However, recurrence rates were high for all dosages used (22% to 25%).[126]

Destructive mucosal lesions contain few parasites, while tumor necrosis factor (TNF) levels are high. This suggests that an unmodulated immune response with increased production of pro-inflammatory cytokines (IL 10) is responsible for the tissue damage. Pentoxyfilline downregulates TNF-α and inhibits leukocyte migration and adhesion. Combining antimonials (20 mg/kg Sb/day for 30 days) with pentoxifylline (400 mg/tid for 30 days) cured 9 of 10[130] and 2 of 2[129] patients with refractory mucosal leishmaniasis. In a small controlled randomized study, 11 of 11 ML patients treated with the above combination were cured, whereas 5 of 12 (42%) patients treated with antimonials only required a second course of antimonials. Time lapse to cure was 83 days in the pentoxyfylline or antimonials treatment group and 145 days in the "antimonials only" group. No relapses were seen in either group at the follow-up visit 2 years later. Pentoxifylline is well tolerated, with only mild adverse effects (gastrointestinal symptoms and arthralgia).[128]

Amphotericin B deoxycholate (2 to 3 mg/kg/day for 20 days) is effective in NWML.[127] Treatment of ML with liposomal amphotericin B (total dose ranging from 34 to 50 mg/kg) cured all patients in a small study in Brazil.[134] The newer formulations of amphothericin B (colloid dispersion, liposomal) had better cure rates (12/12; 100%) than amphothericin B deoxycholate (5/8; 63%), and higher rates of treatment completion (12/13; 92% vs 8/17; 53%).[126]

In NWML (mainly caused by *L. braziliensis*), miltefosine cured 83% of patients with mild disease (ie, nasal mucosa) and 58% of patients with more extensive disease (involving pharynx, larynx, and palate).[131] Prolonging treatment from 4 to 6 weeks did not substantially increase cure rates (71% to 75%).[132]

Reported Differences Between ML Due to New World and Old World Species

Five reviews involving 43 patients[85,123,125,135,136] with Mediterranean ML (*L. infantum/donovani*), mostly reported as case reports, indicate some differences between NWML and OWML:

1. The nasal cavity was affected in over 90% of NWML cases, but only in 15% of Mediterranean ML cases.
2. Patients with ML acquired in the Mediterranean region had a better prognosis than those who acquired ML in Latin America. 17 of 17 (100%) patients with OWML treated with meglumine antimoniate (Sb 20 mg /kg for 20–28 days) were healed, but one of them had a relapse a year later.
3. About half of the patients with ML due to Old Word species had some kind of immunosuppression.
4. In NWML, destructive lesions with few parasites and high levels of TNF have been reported. In Mediterranean ML, a high parasite burden was found in the lesions.[135]
5. Host factors might also play a role: more destructive NWML lesions were observed in African descendants than in Latinos. However, a paucity of parasites and a pronounced inflammatory response was observed in lesions from both racial groups.[137]

Treatment in Special Groups

Children

In general, the guidelines above also apply to children.[138] A common problem is CL caused by *L. infantum* in the face of a child. One is reluctant to do infiltrations on the faces of children younger than 7 years. Small nodular lesions may be left alone or treated with cryotherapy only and multiple or large lesions can be treated with fluconazole or with miltefosine (2.5–3 mg/kg).

Pregnancy

CL is not known to affect the fetus. As none of the systemic treatments are known to be safe during pregnancy, systemic treatment should be withheld until after delivery; topical treatment may be applied before.[139] However, whether intralesional injections of antimony or topical paromomycin are completely safe during pregnancy is not known. Simple wound care or physical methods like cryotherapy, thermotherapy, or CO_2 laser are preferred, despite the low level of evidence for efficacy. The lesions of pregnant women with *L. braziliensis* CL are larger than in non-pregnant women and have a cauliflower-like appearance rather than the typical well-demarcated ulcer with raised border.[139] In rare situations when lesion location, size, impact and persistence, despite local therapy, require systemic therapy, liposomal amphotericin B probably has the best benefit : risk ratio.

Patients Receiving Immunosuppressive Treatment or Coinfection With HIV

In most patients treated with a TNF-α antagonist, methotrexate or prednisone, the clinical presentation is similar to that of healthy persons; however, there might be some differences. The last exposure to leishmaniasis from an endemic region might date back several years, and multiple lesions, ML, disseminated CL, or the combination with VL, have been reported. The lesions usually respond well to antileishmanial treatment. If possible, immunosuppressive treatment should be discontinued until after the skin lesion has healed and then restarted under close observation.[140,141]

HIV-positive patients with CL should be carefully assessed for coexisting VL. Localized CL in HIV-infected individuals tends to be associated with minimal immunosuppression and is clinically identical to CL in HIV-negative CL patients, but has a higher rate of recurrence after treatment. However, relevant immunosuppression due to HIV facilitates dissemination and may lead to disseminated CL and to VL.[142]

Outlook

Since these treatment recommendations are based on data from patients in endemic regions, they may not apply to travelers[143] who have different exposure rates and immunity toward *Leishmania* parasites; an international survey in travelers is ongoing. Data on species, detailed molecular description, clinical presentation, morbidity, and response to treatment for CL and ML in travelers will be studied in a multicenter and multinational study so that the recommendations can be adapted accordingly.

Declaration of Interests

P. B. has accepted support for research and has served on advisory board for Sanofi-Aventis. The other authors state that they have no conflicts of interest to declare.

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