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Review

Local or systemic treatment for New World cutaneous leishmaniasis? Re-evaluating the evidence for the risk of mucosal leishmaniasis

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ABSTRACT

This review addresses the question of whether the risk of developing mucosal leishmaniasis (ML) warrants systemic treatment in all patients with New World cutaneous leishmaniasis (CL) or whether local treatment might be an acceptable alternative. The risk of patients with New World CL developing ML after the initial infection has been the main argument for systemic treatment. However, this statement needs re-evaluation and consideration of all the available data. The putative benefit of preventing ML should outweigh the toxicity of systemic antileishmanial therapy. To assess the need for and risk of systemic treatment the following factors were reviewed: the incidence and prevalence of ML in endemic populations and in travellers; the severity of mucosal lesions; the efficacy of current options to treat ML; the toxicity and, to a lesser extent, the costs of systemic treatment; the risk of developing ML after local treatment; and the strengths and limitations of current estimates of the risk of developing ML in different situations. Local treatment might be considered as a valuable treatment option for travellers suffering from New World CL, provided that there are no risk factors for developing ML such as multiple lesions, big lesions (>4 cm^2), localisation of the lesion on the head or neck, immunosuppression or acquisition of infection in the high Andean countries, notably Bolivia.

1. Introduction

National consortia (France, Germany, UK, WHO) and individual groups of authors have published guidelines and recommendations for the treatment of cutaneous leishmaniasis (CL) and mucosal leishmaniasis (ML) in

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travellers in the past decade.[1–8] Most of the guidelines had species-oriented treatment. The most important controversy is whether to use local or systemic treatment for CL in travellers, especially for CL caused by New World *Leishmania* species. Local procedures such as intralesional antimony[9] alone or combined with cryotherapy,[10–12] thermotherapy,[13,14] and application of a paromomycin-based antileishmanial ointment,[15–20] have been tested with good results in immunocompetent patients. New formulations[21] are being developed. The potential benefits of local treatment in terms of reduced systemic toxicity and cost have been discussed,[22] but whether local treatment is associated with a higher risk of developing ML needs careful analysis.

In existing guidelines and recommendations, several factors were used to decide whether local or systemic treatment should be used, namely the size and number of lesions, the localisation of lesions ('delicate' localisation in eyelids, lips, nose, ears or joints), lymphatic spread, the existence of comorbidities (cardiac, hepatic or renal disease, diabetes mellitus, malignancy, pre-existing or drug-induced immunosuppression) or specific conditions (pregnant women, children, elderly patients), the previous administration of antileishmanial therapy, and the infecting *Leishmania* species itself that strongly influences the risk of developing ML.

This review looks at the evidence on whether the risk of developing ML warrants systemic treatment in all travellers with New World CL or whether local treatment could be used in some patients. Systemic treatment is recommended for CL caused by all species of the New World except for *L. mexicana*, whereas local treatment is recommended for treating CL caused by all species of the Old World. The risk of patients with New World CL developing ML even many years after the initial episode has been the main argument against local treatment. However, this statement needs re-evaluation and has been questioned by expert panels[23] as well as by the WHO technical report on control of the leishmaniases.[22] The putative benefit of preventing ML should indeed outweigh the risk of toxicity of systemic therapy.

The exact risk in an individual traveller with CL of developing ML cannot be precisely estimated. Only complex prospective studies with long-term follow-up comparing systemic and local treatment in CL patients can estimate the exact risk. As such studies are not available, the following factors were reviewed to assess the need for and risk of systemic treatment in travellers: the incidence and prevalence of ML in endemic populations and in travellers; the severity of mucosal lesions; the efficacy of current options to treat ML; the toxicity of systemic treatment of CL and ML; the risk of developing ML after local treatment; and the strengths and limitations of current estimates of the risk of developing ML in different situations.

We performed a Pubmed (MEDLINE) literature search using the keywords 'mucosal leishmaniasis' (published between 1960 and 2011, no exclusion criteria) and 'cutaneous leishmaniasis and treatment' (controlled clinical trials, published between 1962 and 2011) and included the languages English, French, German and Spanish.

2. Estimating the risk of mucosal leishmaniasis in patients with cutaneous leishmaniasis and in populations living in endemic areas

The published rates of ML in subjects living in CL foci or in patients with CL are summarised in Tables 1 and 2, respectively. These rates vary according to species and country, but are also influenced by the study design. Whereas the percentage of ML in epidemiological surveys is quite low, the ML/CL ratio can be as high as 30% in patients at tertiary medical centres. The quality of the published data is suboptimal.

The ML/CL ratio depends on the geographical area.[7] In Brazil, it ranges from 0.4% in the south[24] to 1.4% in the central region[25] and to 2.7% in the northeast.[26] In Andean countries, ML reaches mean rates of 7.1%.[27] ML/CL ratios are highest in Bolivia (16–37%),[28,29] medium in Ecuador (7.7%),[30] low in Colombia (2.3%) and lowest in Venezuela (0.4%).[27]

2.1. *Leishmania braziliensis*

The lifetime risk of late mucosal disease in patients with cutaneous *L. braziliensis* infections is 2–10% among untreated cases.[26,31] Using retrospective estimates on an actively surveyed population of 3020 patients with CL in Peru, the lifetime risk estimate of developing ML was 12.8%.[27] Among 140 CL (*L. braziliensis*) patients treated in a 4-year period in Sao Miguel, Brazil, five (3.6%) developed ML, but the treatment completion rates were not reported.[32] In *L. braziliensis* transmission regions (in Brazil) around 3% of CL patients developed ML, but full treatment data was not provided.[33] The time interval between having a cutaneous lesion and the development of ML is usually a few years, but may extend to 50 years.[34]

2.2. *Leishmania panamensis*

ML was observed in 4.2% of patients with CL due to *L. panamensis* in Panama.[35] A study on *L. panamensis* in Colombia showed that ML was detected in 12% of the population with CL. However this study had a large case definition for ML including erythema, infiltration of the anterior nasal mucosa (77%) and perforation of the nasal septum (23%).[36] In a prospective clinical trial performed in Colombia, which has both *L. braziliensis* (16%) and *L. panamensis* (84%) infections, CL patients were treated with antimonials (66 patients), allopurinol (55 patients) or placebo (46 patients). In three patients ML occurred during the 1-year follow-up period (2 in the allopurinol group, 1 in the placebo group)[37] giving a rate of 3% in evaluable patients. Whether patients with ML were infected with *L. panamensis* or *L. braziliensis* was not determined. At least seven clinical trials were performed in areas mainly endemic for *L. panamensis* (Colombia, Ecuador, Panama)[38–42] or *L. braziliensis* and *L. mexicana* (Guatemala)[13,43] and collectively included 136 patients who were either untreated or received a placebo. None of these patients was reported to have ML during the 6-month to 1-year follow-up period. These data from prospective clinical trials show that ML is infrequent

Table 1
Proportion of mucosal leishmaniasis (ML) versus cutaneous leishmaniasis (CL) in different cohorts/groups (endemic region)

	Study design	% of ML/CL
L. braziliensis, Brazil[77]	All CL/ML patients registered in Brazil during 2002–2009 (n=206 906)	4.6–10.7
North		6.1–10.8
Central West		5.3–13.2
Northeast		2.6–5.8
Southeast		4.1–16.1
South		4.2–18.1
L. braziliensis, Brazil[26]	Prospective study in 2494 surveyed persons for 6 years	2.7
L. braziliensis, Brazil[32]	140 CL patients treated in a 4-year period; 5 (3.6%) developed ML	3.3
L. braziliensis, Brazil[24]	Epidemiological survey; 123 CL patients	0.8
L. braziliensis, Brazil[25]	Epidemiological survey; 72 CL patients	1.4
L. braziliensis, Brazil, Bahia[78]	Prospective clinical study	2.7
L. braziliensis, Brazil, Rio de Janeiro[79]	Clinical description of 71 CL patients	0
L. braziliensis, Brazil, Rio de Janeiro[66]	Clinical description of 753 CL and ML patients	12.7
L. braziliensis, Brazil[64]	Case comparison study; 2675 CL and 145 ML patients	5.1
L. braziliensis, Brazil[32]	Survey of 140 CL patients	3.6
L. braziliensis (mainly), *L. amazonensis*, Brazil[29]	Retrospective analysis; 2788 CL and 552 ML patients	16.5
L. braziliensis (mainly), *L. mexicana*, Belize[80]	ML extremely rare, mostly in immunocompromised patients	Close to 0
L. braziliensis, Colombia[81]	Restrospective analysis of 91 patients	11
L. panamensis, Colombia[81]	Restrospective analysis of 397 patients	4.8
L. panamensis, Panama[35]	Prospective study of 361 patients	4.2
L. panamensis, Colombia[36]	Prospective survey of 1380 people	12
L. panamensis/braziliensis, Colombia[36]	National case notification 2006–2011; 58 004 CL and 781 ML patients	1.35
Colombia[27]	Ratio CL/ML 1:44	2.3
L. braziliensis/amazonensis/panamensis, Ecuador[30]	Review of published cases; 240 CL and 18 ML patients	6.9
L. braziliensis/amazonensis, Bolivia[82]	Active case detection for ML; 446 CL and 34 ML patients	7
L. braziliensis/amazonensis, Bolivia[28]	National case notification 2006	Ratio LCL/ML: 6:1
L. braziliensis/amazonensis, Bolivia[28]	Notification Universidad Mayor de San Simón in Cochabamba (2002–2005); 828 CL and 225 ML patients	37
L. braziliensis/amazonensis, Bolivia[29]	Instituto Boliviano de Biologia de Altura, La Paz, which has received ML patients; 848 CL and 407 ML patients	32
L. braziliensis/amazonensis, Bolivia[29]	Several non-governmental organisations, rural campaigns, passive and active case detection; 1338 CL and 145 ML patients	10
L. braziliensis/amazonensis, Bolivia[29]	Centro National de Enfermedades Tropicales of Santa Cruz passive and active case detection; 143 CL and 72 ML patients	33
L. braziliensis/amazonensis, Bolivia[29]	Review of publications, passive and active case detection; 623 CL and 115 ML patients	18
L. braziliensis/amazonensis, Bolivia[83]	Campaign with active and passive case detection; 2959 CL and 326 ML patients	10
Argentina[84]	Clinical description of 39 CL/ML patients	2.6
Venezuela[27]	Ratio CL/ML 1:264	0.4
L. braziliensis, Peru[27]	Retrospective estimates of actively surveyed population (n=3020)	12.8
L. guyanensis, Peru[45]	Case description	
L. amazonensis, Peru[45]	Case description	
L. amazonensis, Brazil[44]	Description of 5 patients with ML	

during the first 6–12 months of observation of untreated CL patients. The advantage of the prospective, close observation is confounded by the low number of patients and a follow-up period which is much shorter than the decades-long period during which ML can occur after CL.

2.3. Other species

Leishmania amazonensis infections have various clinical presentations, including CL, ML and visceral leishmaniasis (VL).[44–46] ML due to *L. guyanensis* has been reported from Peru[45] and Colombia.[47] New data from the Brazilian Amazon show that ML caused by *L. guyanensis* is more frequent than previously believed, yet the prevalence remains generally low.[48] Improved species determination will probably show how often ML occurs in infections due to species other than *L. braziliensis* and *L. panamensis*.

3. Frequency of cutaneous and mucosal leishmaniasis in travellers

The prevalence of CL and ML is difficult to estimate, because the disease is not notified to health authorities in most northern countries. CL is often misdiagnosed and may heal spontaneously. Thus the numerator, the number of infected travellers, is underreported and the denominator, the number of travellers going to infected areas, is unknown.[4]

No study has prospectively evaluated the risk of travellers with CL developing ML later. The proportion of CL and ML in imported leishmaniasis is summarised in Table 3. In a French cohort of 105 patients with CL or ML, the ML/CL ratio was 3/102 (2.9%). One ML patient was infected with *L. infantum* and the other two with *L. braziliensis*. Taking only patients with CL from the New World (25 patients) as the denominator, the ratios were 8% (P. Buffet, personal data). The ML/CL ratio was 1/48 for *L. braziliensis* infection among 140 German travellers with CL (G. Harms, personal

Table 2
Mucosal leishmaniasis (ML) occurrence in patients with cutaneous leishmaniasis (CL), interval and risk factors for developing ML

	Study design Description of patients	Time of observation	ML occurring in CL	Interval CL–ML	Risk factors
L. panamensis Colombia[36]	Prospective survey of 1380 people: 12% ML 77% mild symptoms (erythema, ulcers or erosion on single mucosa) 23% moderate symptoms (perforated nasal septa)	19 months		Erythema 7.1 years Nasal ulcer 8.7 years Erosion 10 years Perforation 21.4 years (mean)	Male: OR 2.2 (95% CI 1.4–3.4) Location on the head: OR 2.0 (95% CI 1.3–3.0) Montenegro skin test size: OR 2.4 (95% CI 1.4–3.9) No association with age Size of the lesion not studied
L. braziliensis Brazil[64]	Case comparison study 2675 CL patients 145 ML patients (5.1%)				Male: OR 1.6 (95% CI 1.1–2.3) Age >22 years: OR 1.7 (95% CI 1.2–2.4) Severe malnutrition: OR 3.4 (95% CI 1.5–7.7) Duration CL >4 months: OR 4.1 (95% CI 2.9–5.8) >1 lesion: OR 1.2 (95% CI 0.8–1.8) >1 location: OR 1.7 (95% 95% 1.0–3.2) Localisation of lesion: no difference Size of lesion not studied
L. braziliensis Brazil[65]	Longitudinal study 239 patients: 182 CL, 57 ML	6–79 months			Multiple vs single lesion: RR 2.23 Above vs below belt: RR 2.86 Extension: >16 vs <4 cm^2: RR 5.06 4–15.9 vs <4 cm^2: RR 3.2
Species unknown *L. braziliensis* *L. amazonensis* Bolivia[82]	Active case detection for MCL 446 CL patients; 34 ML (7%)				Migrant vs natives: RR 2.31 (95% CI 1.15–5.05) Duration CL >6 months: RR 0.44 (95% CI 0.19–0.98) Not significant factors: Gender, number of lesions, correct treatment of lesions
L. braziliensis Brazil[26]	Prospective study in 2494 surveyed persons Median lesion size: 33 mm (range 5–>100) CL: below belt: 73%; head 5% CL: age <20 years: 32%		2.7%	6 years (median) (range 4–16 years)	Multiple lesions (2–8): 8/8 Inadequate treatment: 10/10 Median lesion size: 58 mm (range 33–>100) Localisation: leg 6/8; head 2/8 Age <20 years: 7/8
L. braziliensis Brazil[63]	Description of 16 ML among 170 CL patients in a specialised clinic No systemic data on CL	4 years	9%	58% <1 year 42% >1 year	Male 69% Multiple lesions 50% No/insufficient treatment 66% Correct glucantime 25% Correct pentamidine 9% No data on size and localisation of primary CL
L. braziliensis Brazil[68]	62 CL patients	4 years	3.2%		All patients treated with antimony
L. guyanensis *L. braziliensis* Brazilian Amazon[85]	Hospital-based description *L. guyanensis* 16 ML *L. braziliensis* 30 ML			14.9 years: *L. guyanensis* 16.9 years: *L. braziliensis*	Irregular treatment 63% Irregular treatment 83%
L. braziliensis[66]	Hospital-based description 658 CL, 26 MCL, 69 ML patients	11 years			61/68 (88%) ML without treatment of CL 3/658 (0.4%) treated CL developed ML No data on previous CL

MCL: mucocutaneous leishmaniasis; RR: relative risk.

Table 3
Imported cutaneous leishmaniasis (CL) and mucosal leishmaniasis (ML)

Country	Study design	Description	% ML
Netherlands[86]	Imported leishmaniasis 1996–2007	422 CL, 5 ML NW and OW, travellers and immigrants	1
USA[87]	All cases of CL and ML 1973–1991	23 OWCL 19 NWCL, 2 NWML: 1 immigrant, 1 expatriate	10
USA[88]	US travellers 1985–1990	59 NWCL	0
France[89]	Imported leishmaniasis 1992–2000	15 OWCL, 24 NWCL	0
Switzerland[90]	Imported leishmaniasis 1979–1983	18 OWCL, 5 NWCL	0
UK[91]	British troops from Belize 1978–1990	187 NWCL 78 *L. braziliensis*, 29 *L. mexicana*	0
UK, Netherlands[80,92]	British and Dutch troops from Belize 1998-2009	142 NWCL	0
Germany[93]	Imported leishmaniasis 2001–2002	21 OWCL, 14 NWCL (11 tourists, 3 working stay) 1 NWML (working stay in Peru; treated 3 years before for CL)	7
Netherlands[94]	Imported leishmaniasis	17 OW 61 NW	0
Germany[95]	Imported leishmaniasis 2001–2004	14 OWCL, 12 NWCL; 21 travellers, 5 immigrants/expatriates 3 NWML (1 HIV infection)	25
UK[52]	Imported leishmaniasis 1995–2003	79 NWCL 6 NWML	7.6
Spain[60]	Imported leishmaniasis 1995–2008	9 NWCL 3 NWML: 2 immigrants, 1 traveller	25
Australia[96]	Imported leishmaniasis 2005–2007	7 NWCL	0
Israel[97]	Experience with NWCL in Israeli travellers	12 NMCL	0

NW: New World; OW: Old World.

data). In the UK, in a cohort of 224 patients with CL or ML, 12 patients (5%) had ML (11 New World ML). Interestingly, five of these ML patients were infected in Bolivia (D.N.J. Lockwood, personal data). These data show that the overall ML/CL ratio at specialised settings in Europe is about 3% (range 0–25%). When only ML due to *L. braziliensis* and in travellers from the New World is analysed, the ML/CL ratio ranges from 1.2% to 8%. However, all these data have to be interpreted with caution. The number of imported cases is often low and not only travellers, but also immigrants and expatriates residing in the endemic region for many years are included. Previous treatment of CL is mostly not reported. A selection bias due to referral of patients with ML to specialised clinics may increase the ML/CL ratio. Variations may also be influenced by travel destination. Infections acquired in Central America appear to have a lower risk of ML than infections acquired in the Andean countries, notably in Bolivia (Tables 1 and 2). We found no major differences in the risk of developing ML when comparing data from endemic countries and data obtained in travellers, but the methodologies were different and the quality of data was variable.

4. Severity of mucosal lesions in endemic regions and in travellers

In endemic populations, the clinical picture of ML has changed and is no longer the one of mutilating conditions as previously seen, partly because of improved diagnosis and treatment.[48–51] Almost all ML lesions in travellers (except for immunocompromised patients) are not mutilating[34,52,53] and limited to the nose, and respond well to treatment.[54–57] Early diagnosis and treatment is a key issue here.

5. Success rate of treatment of mucosal leishmaniasis

The mean cure rate in local populations using pentavalent antimonials was 88%.[56,57] Most treatment failures are associated with subtherapeutic doses (<10 mg/kg/day), treatment periods shorter than recommended (<28 days), and the dose limitation to two ampoules containing 405 mg antimony for patients weighing more than 60 kg.[56,57] In ML due to *L. braziliensis*, treatment with meglumine antimoniate (n=73) and pentamidine (n=22) had a 9% failure rate and recurrence rates of 22% and 25%, respectively. In a small study, a prolongation of treatment duration with meglumine antimoniate from 28 days (n=16) to 40 days (n=19) did not improve the cure rate, which was 63% for both groups.[58] The presence of hypertension and HIV infection was associated with treatment failure, although no mechanism was proposed for hypertension.[51] In New World ML (mainly *L. braziliensis*) the cure rate of miltefosine was 83% in patients with mild disease (i.e. confined to nasal mucosa) and 58% in patients with more extensive disease (involving pharynx, larynx and palate).[55]

Five patients with ML and with absolute contraindications to antimonials and pentamidine were cured by treatment with amphotericin B in the colloidal dispersion formulation (doses of 2–3 mg/kg/day, cumulative dose of 40 mg/kg).[51,56,57,59] In travellers, uncomplicated ML usually responds well to treatment,[34,52,53] but repeated treatments with different drugs may be needed

in immunocompromised patients.[60] However, two of 11 ML patients in the UK needed two or three courses of treatment (D.N.J. Lockwood, personal data).

6. Toxicity and costs of systemic and local treatment of cutaneous and mucosal leishmaniasis

The risks of developing ML have to be balanced against the toxicity and, to a lesser extent, the costs of the drugs and the monitoring for complications. The adverse effects of the drugs and the estimated costs are summarised in Table 4.

The toxicity of local treatment such as ointment preparations containing paromomycin 15% and methylbenzethonium chloride 12%, cryotherapy or thermotherapy, or local infiltration of lesions with pentavalent antimony is limited to local adverse events such as inflammation, pain, burning sensation, pruritus or blistering and bacterial superinfection.

7. Pros and cons for the use of local therapy for New World cutaneous leishmaniasis

Data from endemic countries indicate that topical treatment may be used to treat New World CL.[9,20,61,62] Topical treatment with paromomycin ointment was more effective than placebo,[19] but inferior (in terms of healing of the cutaneous lesion) to systemic treatment with pentavalent antimony for CL due to *L. braziliensis* and *L. panamensis*.[16,20,61] In most studies with topical treatment of New World CL, the observation period was either until healing[16,62] or 1 year.[18–20] In this observation period none of the patients developed ML. However, the observation period is too short for determining the long-term risk of development of ML. These studies were also performed in areas where there was at least a moderate risk of developing ML.

8. Risk factors for developing mucosal leishmaniasis in cutaneous leishmaniasis patients

The risk factors for developing ML in patients with CL are summarised in Table 2.

8.1. Lesion type

Multiple CL lesions, and large lesions (>4 cm^2) were associated with a risk of developing ML in most studies.[26,63,64] Localisation on the head/neck[26,36] or above the belt[65] was a risk factor in some, but not all studies.[64,65]

8.2. Influence of cutaneous leishmaniasis therapy

The term 'insufficient treatment' in retrospective studies is poorly defined (unspecified drug name or doses). Contrasting observations have been published on the potential preventive effect of systemic treatment on the risk of developing ML. During an observation period of up to 11 years, only 3/658 (0.4%) of correctly treated patients with *L. braziliensis* CL developed ML.[66] In the same region, in 61/68 (88%) of ML patients no previous treatment of CL was reported.[66] Low systemic doses (5 mg of antimony/kg over 30 days) and intralesional infiltrations of pentavalent antimonials were 84% and 80% effective in treating *L. braziliensis* CL in Brazil and were not associated with ML developing during 5–10 years of follow-up.[9,67] The authors note that this *Leishmania* strain might be very sensitive to antimonials.[67] In contrast, 3.2% of CL patients (*L. braziliensis*) appropriately treated with antimony developed ML during a follow-up of 4 years.[68] In addition, ML due to *L. braziliensis* was described in three CL patients previously correctly treated with antimony and in one patient treated with pentamidine.[63]

8.3. Clinical lymph node involvement and parasite dissemination

The impact of enlarged local lymph nodes and lymphangitis in CL patients as a predictive risk marker for the development of ML is a matter of controversy. In theory, the presence of enlarged lymph nodes may indicate extradermal parasite spread and could therefore be a risk factor for subsequent ML. Lymphatic spread was observed early in the evolution of the disease and *Leishmania* DNA was detected by PCR in the lymph node aspirates of 63% (48/76) of patients with *L. braziliensis* CL. None of the patients had clinically evident ML or VL.[69]

In 21/26 patients (81%) with CL due to *L. panamensis*, *L. guyanensis or L. braziliensis*, *Leishmania* DNA was detectable by PCR in clinically unaffected mucosa.[70] *Leishmania* DNA could also be detected by PCR in the blood not only in patients with ML (35%), but also in patients with active CL (25%), cured individuals (27%) and even asymptomatic individuals with a positive Montenegro skin test (37%). The persistence of the parasite in the host might enhance a protective immune response. The mechanism that triggers the development of symptomatic ML remains unknown.[71] In patients with immunosuppression after organ transplantation ML manifestations have been observed with an interval of many years and even decades.[72] This illustrates that *Leishmania* may persist 'dormant' and clinically unapparent for many years and are able to cause clinical disease including ML once the infected patient sustains immunosuppression.[72]

8.4. Comorbidities

Arterial hypertension was found as a comorbidity in 43% of ML patients,[51] but was not studied as a risk factor for developing ML in CL patients. There are many case reports on ML developing in patients with immunosuppression, but this aspect has not been assessed systematically.

8.5. Human genetic factors

There is probably a minor genetic component in susceptibility to ML. HLA-DR2 and HLA-DQw3 have been associated with development of ML.[73] Also familial clustering has been reported.[74]

Table 4
Adverse events and costs of systemic antileishmanial treatment

Drug	Costs[a]	Adverse effect
Pentavalent antimonials	500 Euros 21 injections	Cardiac toxicity with reversible ECG alterations is seen in 30–60%[99–102] - repolarisation alterations affecting T wave and ST segment - prolongation of the corrected QT interval (16%)[98] - fatal arrhythmias have not been documented with the usual dose ≤20 mg Sb/kg[99–102] - Hypokalaemia associated with risk of arrhythmias Hepatotoxicity 43%, reversible[98] Haematotoxicity: anaemia, leucopenia (7%), thrombopenia (8%)[98,103] Hyperamylasaemia 60%[98] Subjective complaints: musculoskeletal symptoms (50%), headache (24%), gastrointestinal complaints (17%), pain at the injection site (64%)[98] Rare complications: glomerulonephritis, acute renal failure,[104] peripheral nephritis,[105] exfoliate dermatitis, herpes zoster,[106] hypersensitivity syndrome[107–109]
Pentamidine	250 Euros 4 infusions	Aseptic abscess (rare accidental contact of pentamidine with the subcutaneous tissue) in most studies not observed, no abscess in 1500 patients[41,107–112] Diabetes: not observed in low dosages but not enough prospective data to be sure[41,107–112] Hypoglycaemia: case reports, in most studies not observed or moderate[41,107–112] Proteinuria, rare, in most studies not observed[41,107–112] Rhabdomyolysis without kidney involvement[108,113] not described in most studies[41,107–112] Hypotension rare, in most studies not observed[41,107–112] Subjective complaints: myalgia (1–22%), nausea (2–6%) and gustative abnormalities (1–16%), headache (0–19%), pain at the injection side (3–19%), gastrointestinal complaints (9%)[41,107,108,112,114]
Miltefosine	3500–5000 Euros	Subjective complaints: nausea (36–76%), vomiting (28–56%), motion sickness (29%), abdominal pain (9%), headache (27–28%), diarrhoea (6–16%), diminution of ejaculate volume[48,115–121] 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[121] Hepatotoxicity: the AST was elevated in 5–8% and the ALT in 10% but always less than 2.5 times the upper limit of normal[116,121] Teratogenic, subtherapeutic miltefosine concentrations in the blood beyond 5 months after treatment
Ketoconazole	300 Euros	Hepatotoxicity reversible, usually mild,[38,43] sometimes severe (<1/10 000) Diminution of testosterone values (70%), but without diminution of libido or beard growth[38] Subjective complaints: abdominal pain (5%), headache (5%), nausea (5%), fever and malaise, allergic rash (0–3%)[38,43]
Fluconazole	300 Euros	Hepatotoxicity, mild (3%), discontinuation in <1%[122–125] Allergic skin reactions Haematotoxicity very rare (anaemia, leucopenia, thrombopenia)[122–125] Nephrotoxicity: discontinuation <1%[122–125] Subjective complaints: headache, gastrointestinal complaints (6%)[122–125]
Liposomal amphotericin B	3500–5000 Euros	Renal toxicity: 45% had renal toxicity, mostly reversible[126] Hypokalaemia Infusion related reactions: chest pain, dyspnoea, flank pain, flushing or urticaria 25%[126] Nausea, anorexia, vomiting

[a] The prices of some drugs are fluctuating, depend on the body weight of the patient and differ between countries. The costs of consultation, hospitalisation and laboratory tests and ECG have to be added to the cost of the drugs.

8.6. Immunological factors

Both CL and ML lesions are characterised by a type 1 immune response (IFN-γ and TNF-α production) and strong inflammatory response in the lesions with few parasites. However, no specific immunological factors have been identified with the development of ML in CL patients.

8.7. Leishmania antibody

Leishmania antibodies may be positive in patients with CL, but were not evaluated as a risk factor for developing ML.[7,75]

9. Limitations

The species-specific approach requires a consistent determination of the species. However, determination of the species was performed in different laboratories with different methods and discrepancies between the laboratories cannot be ruled out. Most studies were not performed in travellers, but rather in patients from endemic regions. Most of these data stem from retrospective studies with different study designs and of varied quality.

10. Discussion and recommendation

The long-lived recommendation that all patients with New World CL should be treated with systemic

antileishmanial agents was justified by the observation that 'insufficient treatments including lack of treatment' were associated with a greater risk for developing ML. In addition, ML in endemic countries is potentially a severe, mutilating disease and difficult to treat. Because there are new treatment options and new data on species-oriented treatment this recommendation needs re-evaluation. This review evaluates the risk of ML for travellers who usually seek medical help early in their disease and have access to sophisticated diagnostic and treatment facilities.

Data published in endemic countries show that the risk in Brazil is lower than 3% whereas in other Latin American countries, ML/CL ratios vary from over 30% in Bolivia to less than 1% in Venezuela, and are even lower in Central America. The overall ML/CL ratio in travellers at specialised settings in Europe is usually lower than 7%, but also depends on the country where the infection was acquired, Bolivia being again associated with a higher risk of evolution to ML.

However, there are additional risk factors for developing ML: infection with *L. braziliensis or L. panamensis* species; the acquisition of the lesion in Bolivia; the number and size of the lesion (>4–6 cm^2); long-lasting lesions (>4 months); the localisation of the lesion (above the belt; head); and concomitant disease such as immunosuppression. Except for the influence of the infecting species, the evidence for these risk factors comes from poor data sets and these risk factors could not be confirmed in all studies.

We found no evidence showing that lymphatic spread or detection of *Leishmania* DNA in the blood or the nasal mucosa are associated with a greater risk of developing ML in patients subsequently treated systemically. In studies with local treatment, concomitant lymphadenopathy was either an exclusion criterion[20,42] or was not reported.[9,18,19] The presence of concomitant lymphadenopathy has not been evaluated as a risk factor for developing ML in CL patients. Thus, it is not known whether metastatic *Leishmania* parasites in lymph nodes can be controlled by local treatment. We would therefore advise not to administer local treatment in CL patients with clinically suspected lymphatic spread.

Since hypertension, another observed risk factor, is often associated with older age and other diseases, the treatment approach in such patients is more complex and is beyond the scope of this manuscript. Other risk factors such as human genetic or immunological factors are of scientific interest, but of limited importance in daily practice.

Inappropriate systemic treatment of CL was mentioned as a risk factor for ML in several studies. Patients developing ML often have poor access to centres with good diagnostic and treatment facilities.[31,48,76] However, the assumption that systemic treatment of CL with appropriate dose and duration of treatment can prevent ML has not been proven. The development of ML has also been reported in adequately treated patients. Thus even an appropriate treatment cannot fully prevent ML. There have been no published reports of ML development in New World CL patients treated with paramomycin/methylbenzethonium chloride ointment or with local infiltration of the lesions with antimonials. However, the observation periods were too short to evaluate the risk of developing ML. In addition, local treatment was used in areas where patients with CL were at moderate risk of ML and 'treatment failures' would have been left unpublished.

When none of the above risk factors are present, the risk of developing ML is probably low. There are no data comparing the risk of ML in patients successfully treated with local treatment to the ones treated with systemic treatment. On the other hand, systemic 'appropriate treatment' with antimonials, miltefosine, pentamidine or liposomal amphotericin B is often expensive, costing several hundreds to thousands of Euros per patient and might be associated with severe adverse events. Patients are often not able to work during treatment, even if the treatment is given on an outpatient basis.

Mutilating forms of ML are decreasing in endemic countries and are only rarely reported in compliant travellers without risk factors. New treatment options such as liposomal amphotericin B, miltefosine and pentavalent antimonials in combination with pentoxifylline have improved the prognosis of ML.

One of the problems of synthesising the evidence on the risk of developing ML is that the guideline for travellers has to be developed from the risks reported in patients living in endemic countries. These patients are different to travellers in many ways. The low number of tourists with CL, a relevant selection bias (reports from specialised clinics) the retrospective character of the studies and the multitude of factors influencing the risk of developing ML (including the species) does not allow final conclusions. The paucity of data on this important complication of CL also highlights the need for globally funded studies on the risks of ML. These studies would need to be multicentre and collect data on species type, clinical features of disease and, especially, treatment outcomes.

11. Conclusion

In conclusion, local treatment can be considered as an option for travellers with New World CL under the following conditions:

- exclusion of mucosal involvement by ENT examination
- exclusion of multiple lesions
- lesion <4 cm^2
- exclusion of localisation on head or neck
- no evidence of immunosuppression
- infection acquired outside Bolivia
- no clinical evidence of lymphatic spread
- patient will be compliant with treatment and long-term follow-up is feasible.

All patients need to be informed about the risk and the symptoms of ML development. If ML is detected at an early stage systemic treatment has a good prognosis.

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