Journal of Antimicrobial Chemotherapy (2004) **53**, 158–166
DOI: 10.1093/jac/dkh058
Advance Access publication 16 January 2004

JAC

Treatment of cutaneous leishmaniasis among travellers

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Leishmaniasis is endemic in 88 countries on five continents. There are 1–1.5 million cases of cutaneous leishmaniasis reported yearly worldwide. There has been a sharp increase in recorded cases over the last 10 years. Based on geographical distribution, cutaneous leishmaniasis is divided into Old World and New World leishmaniasis. In the past, species could be inferred from geographical setting or determined by performing culture and isoenzyme analysis. The recently developed and now widely available PCR technology allows a rapid diagnosis with determination of most species, and thus enables a species-orientated treatment. While the Old World species mostly cause benign and often self-limiting cutaneous disease, the American species cause a broad spectrum of conditions from benign to severe manifestations, including mucosal involvement. The response to treatment varies according to the species. Therefore, a species-specific approach is proposed. Drugs for systemic and topical treatment are presented and discussed with regard to their application, use and adverse effects. Indications for local or systemic treatment are proposed. Drugs under investigation are also mentioned. An overview of published treatment options and a treatment recommendation is given for each of the most important species. The level of evidence of the studies leading to these recommendations is given.

Keywords: cutaneous leishmaniasis, travel, systemic treatment, local treatment

Introduction

The large number of travellers from industrialized countries visiting and increasingly enjoying outdoor activities in endemic areas are at considerable risk of contracting cutaneous leishmaniasis. Most physicians in industrialized countries have little experience with cutaneous leishmaniasis in returning travellers. This often leads to delayed diagnosis and inappropriate management. This review aims to provide recommendations for the rational and effective treatment of patients presenting with cutaneous leishmaniasis of various origins. Evidence-based data on travellers are limited to a few studies, anecdotal reports and investigations among military personnel deployed in endemic areas.[1–3] It is therefore crucial to consider the published experience among patients from endemic areas, even if the immunological background will be different in an important part of the respective study populations.[4–6] Consequently, established treatment schedules can be applied to all patients.

Leishmaniasis is endemic in 88 countries on five continents. There are 1–1.5 million cases of cutaneous leishmaniasis reported yearly among the local populations. The number of reported cases has increased sharply over the last 10 years.[7] The parasite is transmitted by the bite of various types of phlebotomine sandflies.

Based on its geographical distribution, cutaneous leishmaniasis can be divided into Old World (including southern Europe, the Middle East, parts of south-west Asia and Africa) and New World (from southern USA through Latin America to the highlands of Argentina) leishmaniasis. Cutaneous leishmaniasis is caused by various *Leishmania* species. While Old World species mostly cause benign and often self-limiting cutaneous disease, New World species cause a broad spectrum of conditions from benign to severe manifestations, including mucosal involvement. The clinical spectrum of the disease and its response to treatment vary according to the species. Therefore, a species-specific approach should be considered.[8] The traditional method is to perform an isoenzyme analysis on *Leishmania* culture to determine the species. Species can often be inferred from geographical setting, thus adding to the accuracy of the diagnosis. In addition, the recently developed PCR technology allows a rapid species-specific diagnosis for most species.[9] The introduction of this novel diagnostic species differentiation using PCR methodology further contributes to the possibility of a targeted, species-orientated treatment.

Treatment options: local versus systemic treatment

The proposed choice of local or systemic treatment of cutaneous leishmaniasis (Table 1) is guided by the risk of developing mucosal disease.

Mucosal leishmaniasis is mainly attributed to *Leishmania brasiliensis*, but is also described in *Leishmania panamensis*,[10,11] *Leishmania*

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Table 1. Proposed indications for local and systemic treatment

Proposed indications for local treatment
lack of risk of developing mucosal lesions
Old World cutaneous leishmaniasis
L. mexicana cutaneous leishmaniasis
small, single lesion
absence of lymph node metastasis
Proposed indications for systemic treatment
presence of mucosal lesion or lymph node metastasis
New World cutaneous leishmaniasis except *L. mexicana* lesions
lesions unresponsive to local treatment

guyanensis[12] and *Leishmania amazonensis.*[13] Mucosal lesions were found in Colombia among 19/397 (5%) patients with *L. panamensis* and among 10/91 (11%) patients with *L. brasiliensis* infection.[14] The risk of late mucosal disease in cases due to *L. brasiliensis* has been reported to be 2–10% among untreated cases.[15,16] However, the development of mucosal disease is subject to variation according to place. Because published data do not allow the establishment of the relative risk of mucosal disease for every species, systemic treatment is proposed for all New World species, except for *Leishmania mexicana* infection, where the risk of developing mucosal leishmaniasis is almost zero.[17] There is evidence that early systemic treatment may prevent mucosal lesions, which are seen more frequently in patients with incomplete or missing antimony treatment.[15,16,18]

Although mucosal lesions have been reported in *Leishmania donovani*[19] infections in Sudan, it is generally accepted to approach Old World cutaneous leishmaniasis with local treatment.

Local treatment is applied in patients with a small, single lesion. Based on expert opinion, systemic treatment is used in patients with multiple lesions or large lesions (>5 cm). Systemic treatment is also recommended in patients with metastatic spread and in cutaneous lesions unresponsive to local treatment. Local treatment may be considered in patients for whom systemic treatment is contraindicated, such as those who are pregnant or have cardiac problems.[20]

1. Systemic treatment (Table 2)

Pentavalent antimonials

The pentavalent antimonials meglumine antimonate (85 mg Sb/mL) for intramuscular administration and sodium stibogluconate (100 mg Sb/mL) for intravenous and intramuscular administration have been used for decades for the treatment of New World cutaneous leishmaniasis, and are the gold standard for other new investigational drugs. The biochemical basis for their effectiveness is unknown, but may involve inhibition of ATP synthesis. The drugs exist only in parenteral forms. The dosage is usually given in Sb equivalents (mg/kg/day). The pentavalent antimonials are far from being ideal drugs because of their difficult administration and toxicity.[3,21,22]

Treatment schedules and dosages have been debated and changed several times. In the 1980s, the dosage was increased from 10 to 20 mg/kg/day, with an upper limit of 850 mg/day (equivalent to two ampoules of meglumine antimonate). The upper limit of 850 mg Sb/day was abandoned in the early 1990s,[22] since studies indicated a reduced efficacy of lower doses and no higher toxicity was found with the higher doses of the drug.[1] However, the question of the optimal dose has not yet been finally answered. The results of trials in Brazil with lower doses have been published.[23,24] A possible disadvantage of low dosages and/or a short course of treatment is that they could contribute to the appearance of resistance.

Pentamidine

Pentamidine, an aromatic diamidine, is toxic for a number of protozoa and fungi including *Leishmania*, *Pneumocystis carinii* and African trypanosomes. The mechanism of action has not been established.

Pentamidine is used as an alternative to the pentavalent antimonials, and is the first line treatment for cutaneous leishmaniasis in French Guyana, where *L. guyanensis* is responsible for >90% of the cases.[6,25] A study in Colombia (with *L. panamensis*, *L. brasiliensis* and *L. mexicana*) found that a short-course, low-dose regimen of pentamidine isethionate had a similar cure rate (96%) to that of meglumine antimonate (91%), with a similar rate of side effects.[26,27]

The short-course, low-dosage regimen of pentamidine in otherwise healthy patients with cutaneous leishmaniasis was better tolerated than the higher dosages applied for *Pneumocystis* treatment in HIV-positive patients: all adverse effects were reversible and no cases of new diabetes mellitus were found among >2200 patients observed with the low-dose regimen.[6,25,26] However, the higher dosages needed for the treatment of mucosal leishmaniasis (>2000 mg) may cause diabetes mellitus.[28] Blood sugar and glycaemia need to be checked before every injection, because reversible glucosuria and hyperglycaemia have been described after just one dose of pentamidine 200 mg.[29]

Imidazoles/triazoles

The imidazoles and the structurally related triazoles were introduced as antifungal drugs, but also have an antileishmanial activity. They have the advantage of oral administration and few adverse effects, but are only effective against some species (see species-specific treatment below).

Itraconazole has also been used, but data are scarce and controversial.

Fluconazole was studied in a randomized, double-blind, placebo-controlled trial in Iran.[30] It was well tolerated and showed promising results in *Leishmania major* leishmaniasis (see below). Data on other species of leishmaniasis are lacking.

Drugs under investigation

Miltefosine. Miltefosine, a phosphocholine analogue, showed high *in vitro* activity against leishmania. The results of an uncontrolled trial in Colombia (Phase I/II) are promising. Using doses of 133–150 mg/day for 3–4 weeks, the per protocol cure rate (no parasites after therapy, complete re-epithelialization after 3 months) was 94%. However, a longer follow-up is needed to evaluate the relapse rate. The most common side effects were motion sickness, gastrointestinal complaints, headache and raised liver enzymes.[31] Further controlled studies with various species are needed before miltefosine can be proposed as a routine treatment of cutaneous leishmaniasis.

Amphotericin B/liposomal amphotericin B. The antifungal agent amphotericin B desoxycholate is active against *Leishmania* species, but has the disadvantage of a high incidence of adverse reactions (i.e. hyperpyrexia, severe malaise, hypotension, thrombophlebitis, azotaemia, renal tubular damage, hypokalaemia, anaemia and hepatitis).

Several amphotericin B lipid formulations with much lowertoxicities than the free drug have been developed, and have proved to be

Table 2. Drugs and follow-up for treatment of cutaneous leishmaniasis

Drug	Adverse effect	Management/follow-up
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 with the usual dose of ≤20 mg Sb/kg[22,76,77]	ECG checks 1–2 every week; interruption of treatment if: (a) significant arrhythmias; (b) QTc longer than 0.5 s (QTc longer than 0.45 s: monitoring/dose reduction); (c) concave ST segment
	hepatotoxicity seen in 50%; reversible	transaminases weekly; treatment interruption if transaminases >5× the upper limit of normal value (ULN)[78]
	haematotoxicity (anaemia, leucopenia, thrombopenia)[79]	haemoglobin, leucocytes and platelets weekly
	hyperamylasaemia tended to occur very early in therapy and to decline despite continued treatment with antimonials	amylase daily during the first week, then twice weekly; treatment interruption if serum amylase levels became >4× the ULN or lipase levels >15× the ULN, regardless of symptoms; therapy can be resumed, once these values tend significantly towards normal[3,80]
	subjective complaints: musculoskeletal symptoms, headache, gastrointestinal complaints, pain at the injection site	
	rare complications: glomerulonephritis, acute renal failure,[81] peripheral nephritis,[82] exfoliate dermatitis, herpes zoster[83]	weekly examination of urine, creatinine
Pentamidine	aseptic abscess (accidental contact of pentamidine with the subcutaneous tissue)	pentamidine has to be injected slowly and strictly intramuscular with a long needle (50 mm)
	diabetes, hypoglycaemia, proteinuria	fasting glycaemia and urine for proteinuria and gylcosuria have to be checked before every injection and 3 weeks and 2 months after the last injection[84]
	hypotension[6,26]	blood pressure and heart rate have to be measured before and after the injection (every 15 min for 1 h)[84]
	subjective complaints: myalgia, nausea and gustative abnormalities, headache, pain at the injection side, abdominal pain[6]	
Ketoconazole	hepatotoxicity reversible, usually mild[54]	transaminases weekly; treatment interruption if transaminases >5× ULN
	diminution of testosterone values (70%), but without diminution of libido or beard growth[54]	reversible, no controls needed
	subjective complaints: abdominal pain, headache, nausea, fever and malaise[54]	
Fluconazole	hepatotoxicity	transaminases; treatment interruption if transaminases >5× ULN
	allergic skin reactions	
	haematotoxicity (anaemia, leucopenia, thrombopenia)	haemoglobin, leucocytes and platelets
	subjective complaints: headache, gastrointestinal complaints	

useful in the treatment of visceral leishmaniasis. Based on currently available data, liposomal amphotericin B has been insufficiently studied with regard to formulation and dosage to assess its efficacy in cutaneous leishmaniasis.

Allopurinol. Allopurinol, an analogue of hypoxanthine, is generally not effective in the absence of pentavalent antimony.[32–35] However, a combination of allopurinol (20 mg/kg/day for 15 days) and stibogluconate (20 mg/kg/day for 15 days) was more effective in *L. panamensis* (cure rate 71–74%) than stibogluconate alone at the same dose (cure rate 36–39%).[36,37]

Drugs influencing the immune system. Immunomodulators represent an interesting possibility for improving the cure rates of pentavalent antimonials, but the lack of solid data does not allow respective recommendations at present.

Other drugs. Other drugs, such as rifampicin,[38] dapsone[39] and oral zinc sulphate,[40] have been tested for leishmaniasis treatment. Some are promising, but the results require confirmation before they can be recommended for treatment.

2. Local treatment

Physical methods

Cutaneous leishmaniasis has been treated in patients of all ages with a wide range of physical methods, including cauterization, surgical excision, cryotherapy and the application of local heat. Cryotherapy is performed by repeated topical applications of liquid nitrogen with a cotton-tipped applicator or a cotton swab with moderate pressure to the lesion, up to 2 mm outside the lesion margin. The freezing time per application is 15–20 s. The procedure is repeated two or three times at short intervals, resulting in a total time of 30–120 s. Adequate application is reflected in the whitening of the skin at 2–3 mm outside the margins of the lesion.[41–44] The usual post-freeze pattern is some oedema and blistering of the lesion itself for 2–3 days, followed by crusting and formation of an eschar.[41,42]

Uncontrolled studies in Old World leishmaniasis, which did not mention the species, gave cures rates of close to 100% after one to three sessions of cryotherapy in Egypt (30/30 patients with clinical and parasitological cure within 4–5 weeks),[41] Jordan (effective and significant clinical response in 214/215 patients within an undetermined time)[43] and Israel (complete clinical healing in 40 lesions in 14 patients within 3–8 weeks).[42]

However, in a comparative, non-randomized study from Turkey, the cure rates (complete healing and disappearance of all clinical features) after one or two sessions of cryotherapy were 77% (46/60) after 1 month and 73% (44/60) after 3 months, compared with 85% after 1 and 3 months following intralesional sodium stibogluconate.[44]

In an uncontrolled study in Iraq, two sessions with local heat (55°C over 5 min) provided by an infrared lamp and focused on the lesion gave a cure of 177/178 lesions (no species determination performed).[45]

However, practical experience with local heat from an infrared lamp shows that healing of the lesion was almost invariably accompanied by a heat-induced skin bulla.

Ointment containing 15% paromomycin

Topical formulations offer significant advantages over systemic therapy, such as ease of administration, fewer adverse effects and cost effectiveness. However, percutaneous absorption is hampered by the intact skin, mainly in the stratum corneum. Topical applications may be applied to open lesions that have lost their stratum corneum barrier property, but are less successful in lesions where absorption is hindered by epithelial thickening.

Paromomycin, an aminoglycoside antibiotic (identical to aminosidine) has been used systemically against both visceral and cutaneous leishmaniasis. As an ointment for topical use, it has been tested in different formulations, either with methylbenzethonium in white soft paraffin, or with urea and white soft paraffin.

The combination of paromomycin with methylbenzethonium appears to be more effective than the combination with urea, but it causes more local inflammatory reactions.[46] With New World leishmaniasis, however, experts are hesitant to treat cutaneous lesions topically because of the risk of mucosal disease, although this ointment was reported to have much better cure rates than placebo in two studies.[47,48]

Local infiltration with pentavalent antimony

Local infiltration of lesions with pentavalent antimony produces the maximum concentration in the lesions and has few systemic side effects, but does not reach metastatic infections. The basic aim is to fill the infected part of the dermis with pentavalent antimony. This means carefully infiltrating the area around the lesion, including the base of the lesion. A fine gauge (25G) needle is used to inject the drug under pressure as the needle advances. Injection into the dermis is difficult, as the tissue space is small. The drug must not be injected into the subcutaneous tissue, where it is rapidly absorbed and does not reach the site of infection.

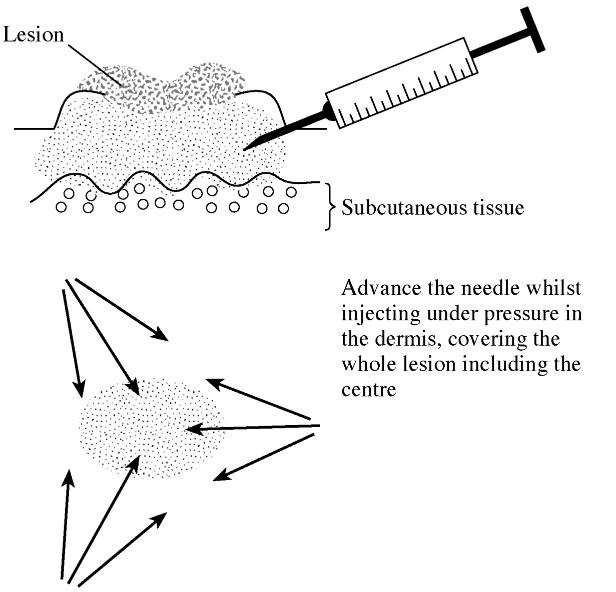

Figure 1. Procedure for intralesional treatment with pentavalent antimony (from reference 25). Reproduced with permission from WHO.

The infiltration is performed in a V-shaped pattern, advancing the needle into the base of the lesion (see Figure 1). The solution is injected under the edges of the lesion and the entire lesion until the surface has blanched. Treatment should be given every 5–7 days, a total of two to five times. If the lesion is not healing after five treatments, it should be reviewed in 1 month, when a decision about reverting to systemic treatment should be made.[49] Intralesional infiltration is painful and requires some experience to perform.[50]

Species-specific therapy (Table 3)

(A) New World leishmaniasis

L. mexicana: local treatment. Strains of *L. mexicana* isolated from Belizean patients were found to be highly susceptible to paromomycin sulphate both *in vitro* and in animal studies.[51] An ointment with 15% paromomycin/12% methylbenzethonium chloride applied twice daily over 20 days was used in Guatemala and in Belize, where *L. brasiliensis* and *L. mexicana* are endemic. In Guatemala, the final clinical response rate at the 12 months follow-up examination was higher in the treatment group (31/35, 88.6%) than in the placebo group (13/33, 39.4%) ($P \leq 0.001$).[47] In Belize, the cure rate of 53 patients was 74%.[52]

L. mexicana: systemic treatment. Ketoconazole (600 mg daily for 28 days) was compared with sodium stibogluconate in patients with cutaneous leishmaniasis in Guatemala. The outcome was related to the species. Whereas ketoconazole had a higher cure rate for *L. mexicana* (8/9 versus 4/7), the response rate in *L. brasiliensis* was much lower (7/23 versus 24/25).[53]

Considering the virtually non-existant risk of mucosal leishmaniasis with *L. mexicana* infection, 15% paromomycin/12% methylbenzethonium ointment is recommended as the first-line treatment. Where it is not available, infiltration with glucantime may be an easily accessible option, although no firm data have been published. Systemic treatment with ketoconazole is another documented option. The choice depends on the clinical aspect of the lesion (see above).

L. panamensis: local treatment. The 1 year cure rate with a 15% paromomycin/12% methylbenzethonium chloride ointment was 85% in 52 Ecuadorian patients, compared with 9% in a non-randomized untreated control group.[48] Nevertheless, experts are reluctant to apply local treatment because of the risk of mucosal leishmaniasis.

L. panamensis: systemic treatment. (i) Ketoconazole. In a randomized clinical trial, ketoconazole (600 mg daily for 28 days) had a similar efficacy (16/21, 76%) to sodium stibogluconate (20 mg/kg/day with upper limit of 850 mg, resulting in 13 mg/kg/day) (13/19, 68%), but a much better efficacy than placebo (0/11).[54] (ii) Pentavalent antimonials. The response to antimonials is dose dependent: patients treated with 10–13 mg/kg/day[1,54] had cure rates of only 68–72%, whereas patients treated with 20 mg/kg/day for 20 days had a 96–100% cure rate.[1]

The optimal duration of treatment with the dose of 20 mg/kg/day is still debated. Whereas some authors regard a 10 day course of treatment to be sufficient,[2] and equal to a 20 day regimen,[5] other studies indicate a clear positive correlation between treatment duration and efficacy: in one study the cure rates were 20% for 3 days, 53% for 7 days and 84% for 20 days treatment duration.[55]

In Guatemala, a surprisingly insufficient response (36–39%) to a 15 day course of pentavalent antimonials could be improved to 71–74% by the addition of allopurinol (20 mg/kg/day/15 days, given in four divided doses).[36,37] This combination was not compared with the usual 20 day course of stibogluconate. However, the addition of allopurinol to stibogluconate provided no clinical benefit in patients with mucosal leishmaniasis.[56]

Considering the oral application and the lower rate of side effects with ketoconazole, it can be recommended as the first choice for uncomplicated lesions (i.e. not multiple, not long-lasting lesions, with no sign of mucosal involvement), especially when a close clinical follow-up and patient compliance are guaranteed. Pentavalent antimonials are used if the response to ketoconazole is not satisfactory. Either a 20 day course or the combination with allopurinol is recommended.

L. guyanensis. There are only a few, non-randomized trials concerning the optimal treatment of *L. guyanensis*. The cure rate (6 months) of antimonials (20 mg Sb/kg/day for 20 days) was significantly lower in patients infected with *L. guyanensis* (26.3%) than in patients infected with *L. brasiliensis* (50.8%; $P = 0.003$).[57] In French Guyana, where *L. guyanensis* is responsible for >90% of cutaneous leishmaniasis, a short-course regimen of pentamidine is the first-line treatment. The cure rates are dose dependent (600 mg, 73%; 900 mg, 90%; 8 mg/kg/day, 90%). A total dose of 1200 mg was proposed.[25] Two injections with 4 mg/kg/day had a cure rate of 89%. Patients with satellite papules or more than three lesions were at a relatively high risk of not being cured. A second treatment with the same dosage had a cure rate of 80%.[6] These doses were in the same range as the dosages proposed by Soto in Columbia (i.e. pentamidine isethionate given in four injections of each 3 mg/kg/day every other day).[26,27]

Considering the poor response to pentavalent antimonials and the good experience in French Guyana, pentamidine is recommended as the first choice, in a dosage of four injections containing 3 mg/kg/day every other day. Local treatment is not recommended due to a lack of sound data.

L. brasiliensis. Because of the high risk of late mucosal disease in infections with *L. brasiliensis,* systemic treatment with pentavalent antimonials (Sb 20 mg/kg/day for 20 days) is the gold standard.[3,15,16,22,58] The cure rates found in various studies range from low (50%)[57,59] to excellent (96–100%).[2,21,53] Different study sites and strains as well as different patient selection may contribute to these varying findings.[57]

Studies with lower doses gave controversial results. In Guatemala, a shorter course with only 15 mg/kg/day over 14 days gave a final cure rate of 64%,[60] whereas studies from the state of Rio de Janeiro (Brazil) indicated that lower dosages gave similar results to higher doses. Oliveira-Neto *et al.*[24] compared a low-dose regimen (Sb 5 mg/kg/day for 30 days) with the conventional dosage of Sb 20 mg/kg/day. The cure rates were similar in the two groups (10/12 versus 9/11) after 30 days, with a lower toxicity in the lower dosage group.[24] Oliveira-Neto *et al.*[23] treated 156 patients with the lower dose; 84% were cured and did not develop mucosal disease or relapse during an observation period of 5–10 years. However, the authors concluded that although this low-dose regimen is adequate for this particular endemic region, it should not be applied without confirmation in other endemic settings.

The diversity of *L. brasiliensis* susceptibility to pentavalent antimonials means that the chance of a favourable treatment response can not be evaluated in the individual traveller. Therefore, the current recommendation to give pentavalent antimonials at the dosage of 20 mg/kg/day for 20 days is maintained.[22,58] Poor clinical response in some studies raises the question of antimonial resistance; however, there is no published evidence to date to confirm true resistance in cutaneous leishmaniasis.

Other species. Data on the treatment of other species of New World cutaneous leishmaniasis like *L. amazonensis*, *Leishmania venezuelensis* or *Leishmania peruviana* are scarce. Therefore, the current recommendation of pentavalent antimonials at the dosage of 20 mg/kg/day for 20 days is still valid.[22,50,58]

(B) Old World leishmaniasis

L. major. The risk of metastatic lesions, including mucosal leishmaniasis, is almost zero, except for *L. donovani* in Sudan, and local treatment is often used.

An ointment containing 15% paromomycin and 12% methylbenzethonium chloride (applied twice daily for 10 days) was more effective than placebo in *L. major* cutaneous leishmaniasis (cure 29/39 versus 4/15).[61] The parasitological cure rate for the same ointment was 72% (48/67) after 10 days. After an additional 20 days, the rate was 87% (58/67).[62] Apart from local inflammation and pain, the ointment was well tolerated. The use of 15% paromomycin/12% urea ointment in two randomized, placebo-controlled studies on *L. major* in Iran[63] and Tunisia[64] could not demonstrate any clinical benefit, even though there was a significant parasitological response at day 15 in the Iran study.

Local infiltration with antimonials (sodium stibogluconate 100 mg/mL 0.3–3 mL/lesion or meglumine antimonate 0.2–0.8 mL/lesion) was studied in Saudi Arabia in regions where *L. major* and *Leishmania tropica* are endemic, and where lesions of acute leishmaniasis often heal spontaneously within 7–12 months. Two to 15 infiltrations (from all sides, until the lesion has blanched) were needed to achieve cure rates of 72–99%.[65–67]

In a randomized, double-blind, placebo-controlled trial in Iran, fluconazole 200 mg daily for 6 weeks showed promising results. Healing of lesions was complete for 63/80 (79%) at the 3 months follow-up in the fluconazole group, but only in 22/65 (34%) in the

Table 3. Treatment by species

Species	Drug	Dosage	Level of evidence[a]
L. mexicana	local: ointment: 15% paromomycin plus 12% methylbenzethonium chloride	twice daily for 20 days	B[47,52]
	ketoconazole	600 mg daily for 28 days	B[53]
L. panamensis	ketoconazole	600 mg daily for 28 days	A[54]
	pentavalent antimonials	20 mg Sb/kg/day for 20 days	A[1,2]
	pentavalent antimonials and in addition allopurinol	20 mg Sb/kg/day for 15 days 20 mg/kg/day given in four doses for 15 days	A[36,37]
L. guyanensis	pentamidine isethionate	four injections of 3 mg/kg/day every other day	C[6,25]
L. brasiliensis	pentavalent antimonials	20 mg Sb/kg/day for 20 days	A[22,53,58]
L. major	15% paromomycin/12% methylbenzethonium chloride ointment	twice daily for 10–20 days	A[61,62]
	localized heat or cryotherapy	two sessions with localized heat (55°C for 5 min)	C[45]
		two to three sessions of topical application of liquid nitrogen	C[41–43]
	local infiltration with antimonials	sodium stibogluconate, meglumine antimonate complete blanching of lesion has to be achieved upper limit 5 mL per infiltration and 20 mg Sb/kg once or twice weekly one to five infiltrations	A[65–67]
	fluconazole	200 mg daily for 6 weeks	A[30]
L. tropica/*L. infantum*	local infiltration with antimonials	sodium stibogluconate, meglumine antimonate complete blanching of lesion has to be achieved upper limit 5 mL per infiltration and 20 mg Sb/kg once to twice weekly one to five infiltrations	D
	15% paromomycin/12% methylbenzethonium chloride ointment	twice daily for 10–20 days	D
	cryotherapy or localized heat	two to three sessions of topical application of liquid nitrogen; two sessions with localized heat (55°C for 5 min)	C[41–43], D
	pentavalent antimonials	20 mg Sb/kg/day for 10–20 days	D
	fluconazole	200 mg daily for 6 weeks	D

[a]Level of evidence: recommendation grade. (A) Randomized, controlled trial in representative collective. (B) Randomized, controlled trial in partially representative (small patient number, different species included) collective. Cohort trial or case control study in representative collective. (C) Cohort trial or case–control study in partially representative collective, series of cases in representative collective. (D) Series of cases in partially representative (small patient number, different species included) collective, informal expert opinion, other information.

placebo group.[30] Ketoconazole is less well studied, but appeared to be effective in *L. major* in Israel. The cure rate was 70% after 200–400 mg daily for 4–6 weeks.[68,69] Pentavalent antimonials were efficient in six patients with a dose of 20 mg/kg/day over 10–20 days,[2] and are an alternative in cases of treatment failure.

An ointment containing 15% paromomycin and 12% methylbenzethonium chloride, intralesional pentavalent antimonials and thermotherapy (see above) are possible first choices in this usually self-limiting disease, although these different treatment options have rarely been tested against one another. The choice between them depends on the experience of the treating physician and the availability of the method. If systemic treatment is indicated, fluconazole or ketoconazole is recommended.

L. tropica/Leishmania infantum. There are no randomized, double-blind, placebo-controlled clinical studies for treatment of these species.

According to estimates made by the WHO, 90% of *L. tropica* lesions in Pakistan could be healed by intralesional pentavalent antimonials.[49] This treatment gave cure rates of 72–99% in Saudi Arabia, where *L. tropica* and *L. major* are endemic (see above).[65–67]

However, recent experience in Israel, using PCR for species-specific diagnosis,[70] showed recurrent failure of local paromomycin and intralesional sodium stibogluconate treatment against *L. tropica*, and a good response to 10 days of systemic sodium stibogluconate treatment (E. Schwartz, unpublished results). In studies using ketoconazole, *L. tropica* appeared to be less responsive than *L. major*.[68] In India, a 10 week course of ketoconazole 400 mg/day was ineffective in patients with *L. tropica* lesions.[71,72]

Anecdotal reports have shown a therapeutic response of *L. infantum* lesions to intralesionally injected *N*-methylglucamine.[73]

Thermotherapy, intralesional pentavalent antimonials and ointments are possible first choices in this usually self-limiting disease. Again, the choice depends on the experience of the treating physician and the availability of the method.

The role of fluconazole in the treatment of *L. infantum* and *L. tropica* has not yet been established.

Clinical experience has shown that pentavalent antimonials are effective in severe infections with big or multiple lesions on the face or over the joints.[2]

Management issues: clinical follow-up and treatment failure

Cutaneous leishmaniasis lesions may demonstrate only a partial clinical response after 3–4 weeks, and may not completely heal until several weeks after completion of treatment. Therefore, patients should be re-evaluated 4–6 weeks after the completion of treatment.

In patients with New World cutaneous leishmaniasis, management is more complicated, since in most cases systemic treatment is warranted. The treatment of choice is pentavalent antimonials, which require meticulous follow-up because of the potential for adverse events (see Table 2). Thus, in many centres these patients are treated in hospital, although some authors have had good experience with ambulatory care.[21]

The most common and worrisome laboratory abnormalities are elevated liver enzymes and asymptomatic hyperamylasaemia. We usually continue treatment if liver enzymes are below five times the normal range and amylase less than five times the normal range (Table 2). Interestingly, by decreasing the dose or interrupting treatment for several days, the abnormal values go back towards normal, and after reinstitution of the drug, the abnormal laboratory findings may not recur.[74]

Relapse may occur several months after complete cure. It is important to distinguish between clinical and parasitological healing. Despite clinical healing of a lesion, PCR can remain positive several years later.[75]

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