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. The large number of travellers from industrialized countries visiting 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 braziliensis*, but is also described in *Leishmania panamensis*.10,11 *Leishmania
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. A study in Colombia (with L. panamensis, L. brasilensis and L. mexicana) found that a short-course, low-dose regimen of pentamidine 10 mg/kg/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. Further controlled studies with various species are needed before miltefosine can be proposed as a routine treatment of cutaneous leishmaniasis.

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. 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 34 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. 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 lower toxicities than the free drug have been developed, and have proved to be
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Table 2. Drugs and follow-up for treatment of cutaneous leishmaniasis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse effect</th>
<th>Management/follow-up</th>
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<tbody>
<tr>
<td>Pentavalent antimonials</td>
<td>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; hepatotoxicity seen in 50%; reversible</td>
<td>ECG checks 1–2 every week; interruption of treatment if: (a) significant arrhythmias; (b) QTc longer than 0.5 s; (c) concave ST segment</td>
</tr>
<tr>
<td>Pentamidine</td>
<td>aseptic abscess (accidental contact of pentamidine with the subcutaneous tissue); diabetes, hypoglycaemia, proteinuria</td>
<td>pentamidine has to be injected slowly and strictly intramuscular with a long needle (50 mm); 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; blood pressure and heart rate have to be measured before and after the injection (every 15 min for 1 h)</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>hepatotoxicity reversible, usually mild</td>
<td>transaminases weekly; treatment interruption if transaminases &gt;5× ULN reversible, no controls needed</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>hepatotoxicity; allergic skin reactions; haematotoxicity (anaemia, leucopenia, thrombopenia); subjective complaints: headache, gastrointestinal complaints</td>
<td>transaminases; treatment interruption if transaminases &gt;5× ULN</td>
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</table>

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. 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%).

Other drugs. Other drugs, such as rifampicin, dapsone and oral zinc sulphate, 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 cautery, excision, cryotherapy and the application of local heat. Cryotherapy
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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.41,42 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
two sessions of cryotherapy in Egypt (30/30 patients with clinical
and parasitological cure within 4–5 weeks).43 Jordan (effective and
significant clinical response in 214/215 patients within an undeter-
minded 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 accom-
panied 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 applica-
tions 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 amino-
sidine) has been used systemically against both visceral and cutan-
eous 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 Leish-
maniasis, however, experts are hesitant to treat cutaneous lesions top-
tically because of the risk of mucosal disease, although this ointment
was reported to have much better cure rates than placebo in two stud-
ies.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.

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 treat-
ments, it should be reviewed in 1 month, when a decision about
reverting to systemic treatment should be made.49 Intrallesional infil-
tration 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 paromo-
mycin 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. brasiiliensis* 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 ≤ 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. brasiiliensis* was
much lower (7/23 versus 24/25).53

Considering the virtually non-existent risk of mucosal leishmaniasis
with *L. mexicana* infection, 15% paromomycin/12% methylbenzen-
thonium ointment is recommended as the first-line treatment. Where
it is not available, infiltration with glucantime may be an easily acces-
sible 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. 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). (ii) Pentavalent antimonials. The response to antimonials is dose dependent: patients treated with 10–13 mg/kg/day had cure rates of only 68–72%, whereas patients treated with 20 mg/kg/day for 20 days had a 96–100% cure rate.5

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, and equal to a 20 day regimen, 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.5,6

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).5,6 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.5,6

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. braziliensis_ (50.8%; _P_ = 0.003).5,25 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%. 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.5,15,16,22,58 The cure rates found in various studies range from low (50%–72%) to excellent (96–100%).5,22,53 Different study sites and strains as well as different patient selection may contribute to these varying findings.5,7

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%, 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 cannot 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.2,22,58 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.2,22,58

**(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).5,21 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).5,6 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 Iran65 and Tunisiad64 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...
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.40,41 Pentavalent antimonials were efficient in six patients with a dose of 20 mg Sb/kg/day over 10–20 days,5 and are an alternative in cases of treatment failure.

An ointment containing 15% paromomycin and 12% methylbenzethonium chloride, intraleisional 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.

### Table 3. Treatment by species

<table>
<thead>
<tr>
<th>Species</th>
<th>Drug</th>
<th>Dosage</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>L. mexicana</em></td>
<td>local: ointment: 15% paromomycin plus 12% methylbenzethonium chloride</td>
<td>twice daily for 20 days</td>
<td>B47,52</td>
</tr>
<tr>
<td></td>
<td>ketoconazole</td>
<td>600 mg daily for 28 days</td>
<td>B53</td>
</tr>
<tr>
<td><em>L. panamensis</em></td>
<td>ketoconazole</td>
<td>600 mg daily for 28 days</td>
<td>A54</td>
</tr>
<tr>
<td></td>
<td>pentavalent antimonials</td>
<td>20 mg Sb/kg/day for 20 days</td>
<td>A1,2</td>
</tr>
<tr>
<td></td>
<td>pentavalent antimonials and in addition allopurinol</td>
<td>20 mg Sb/kg/day given in four doses for 15 days</td>
<td>A36,37</td>
</tr>
<tr>
<td><em>L. guyanensis</em></td>
<td>pentamidine isethionate</td>
<td>four injections of 3 mg/kg/day every other day</td>
<td>C6,25</td>
</tr>
<tr>
<td><em>L. brasiliensis</em></td>
<td>pentavalent antimonials</td>
<td>20 mg Sb/kg/day for 20 days</td>
<td>A22,53,58</td>
</tr>
<tr>
<td><em>L. major</em></td>
<td>15% paromomycin/12% methylbenzethonium chloride ointment</td>
<td>twice daily for 10–20 days</td>
<td>A61,62</td>
</tr>
<tr>
<td></td>
<td>localized heat or cryotherapy</td>
<td>two sessions with localized heat (55°C for 5 min)</td>
<td>C45</td>
</tr>
<tr>
<td></td>
<td>local infiltration with antimonials</td>
<td>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</td>
<td>A65–67</td>
</tr>
<tr>
<td></td>
<td>fluconazole</td>
<td>200 mg daily for 6 weeks</td>
<td>A30</td>
</tr>
<tr>
<td><em>L. tropica/L. infantum</em></td>
<td>local infiltration with antimonials</td>
<td>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</td>
<td>D</td>
</tr>
<tr>
<td></td>
<td>15% paromomycin/12% methylbenzethonium chloride ointment</td>
<td>twice daily for 10–20 days</td>
<td>D</td>
</tr>
<tr>
<td></td>
<td>cryotherapy or localized heat</td>
<td>two to three sessions of topical application of liquid nitrogen; two sessions with localized heat (55°C for 5 min)</td>
<td>C31,41, D</td>
</tr>
<tr>
<td></td>
<td>pentavalent antimonials</td>
<td>20 mg Sb/kg/day for 10–20 days</td>
<td>D</td>
</tr>
<tr>
<td></td>
<td>fluconazole</td>
<td>200 mg daily for 6 weeks</td>
<td>D</td>
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</tbody>
</table>

*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.*
According to estimates made by the WHO, 90% of L. tropica lesions in Pakistan could be healed by intralesional pentavalent antimonials. This treatment gave cure rates of 72–99% in Saudi Arabia, where L. tropica and L. major are endemic (see above). However, recent experience in Israel, using PCR for species-specific diagnosis, 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. In India, a 10 week course of ketoconazole 400 mg/day was ineffective in patients with L. tropica lesions.

Anecdotal reports have shown a therapeutic response of L. infantum lesions to intralesionally injected N-methylglucamine. 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 flucytosine 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.

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.

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. 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.

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