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REVIEW ARTICLE

Therapeutic Options for Old World Cutaneous Leishmaniasis and New World Cutaneous and Mucocutaneous Leishmaniasis

Begoña Monge-Maillo · Rogelio López-Vélez

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Abstract Estimated worldwide incidence of tegumentary leishmaniasis (cutaneous leishmaniasis [CL] and mucocutaneous leishmaniasis [MCL]) is over 1.5 million cases per year in 82 countries, with 90 % of cases occurring in Afghanistan, Brazil, Iran, Peru, Saudi Arabia and Syria. Current treatments of CL are poorly justified and have sub-optimal effectiveness. Treatment can be based on topical or systemic regimens. These different options must be based on *Leishmania* species, geographic regions, and clinical presentations. In certain cases of Old World CL (OWCL), lesions can spontaneously heal without any need for therapeutic intervention. Local therapies (thermotherapy, cryotherapy, paromomycin ointment, local infiltration with antimonials) are good options with less systemic toxicity, reserving systemic treatments (azole drugs, miltefosine, antimonials, amphotericin B formulations) mainly for complex cases. The majority of New World CL (NWCL) types require systemic treatment (mainly with pentavalent antimonials), either to speed the healing or to prevent dissemination to oral-nasal mucosa as MCL (NWMCL). These types of lesions are potentially serious and always require systemic-based regimens, mainly antimonials and pentamidine; however, the associated immunotherapy is promising. This paper is an exhaustive review of the published literature on the treatment of OWCL, NWCL and NWMCL, and provides treatment recommendations stratified according to their level of evidence regarding the species of *Leishmania* implicated and the geographical location of the infection.

B. Monge-Maillo · R. López-Vélez (✉)
Tropical Medicine and Clinical Parasitology, Infectious Diseases Department, Ramón y Cajal Hospital, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Carretera de Colmenar Km 9,1, 28034 Madrid, Spain
e-mail: rogelio.lopezvelez@salud.madrid.org

1 Introduction

Leishmaniases are diseases caused by protozoa of the genus *Leishmania*, which are prevalent in tropical and subtropical areas with visceral and tegumentary forms. Worldwide estimated incidence of tegumentary leishmaniasis (cutaneous leishmaniasis [CL] and mucocutaneous leishmaniasis [MCL]) is over 1.5 million cases per year in 82 countries, with 90 % of cases occurring in Afghanistan, Brazil, Iran, Peru, Saudi Arabia and Syria [1].

Old World CL (OWCL) is mainly caused by five species of *Leishmania*: *L. aethiopica*, *L. donovani*, *L. infantum*, *L. major* and *L. tropica*. Leishmaniasis recidivans, also known as lupoid or tuberculoid leishmaniasis, is produced by *L. tropica*. Diffuse CL is caused by *L. aethiopica*. Lesions of the bucal mucosa or larynx can be caused by *L. infantum*, *L. major* and *L. tropica.* New World CL (NWCL) is caused by multiple species of both the *Leishmania subgenera* [*L.*(*Leishmania*): *L. amazonensis*, *L. infantum*, *L. mexicana*, *L. venezuelensis*] and the *Viannia subgenera* [*L.*(*Viannia*): *L. braziliensis*, *L. guyanensis*, *L. panamensis*, *L. peruviana*] and, exceptionally, *L. shawi*, *L. naïffi*, *L. lainsoni* and *L. lindenbergi.*

Current treatments of CL are poorly justified and have sub-optimal effectiveness. Treatment can be based on topical or systemic regimens. These different options must be based on *Leishmania* species, geographic regions and clinical presentations. The therapeutic options for OWCL are conditioned by the possibly spontaneous healing of the lesions caused by certain *Leishmania* species within a couple of months, without any need for therapeutic

intervention. *L. major* can heal spontaneously in 40–70 % of cases at 3 months and close to 100 % at 12 months. Spontaneous cure rates (CRs) for *L. tropica* are 1 % at 3 months, 68 % at 12 months and usually close to 100 % in 3 years [2–4]. No data are available for *L. infantum*. However, there are no definitive data about whether the residual scarring is smaller in treated patients than in those who are not treated. In certain cases, when there are few (fewer than four) lesions, the lesions are small (<4–5 cm), lesions are not localized on joints or esthetically compromised areas (eyelashes, lips), and there are no signs of lymphangitic dissemination or immunosuppression, local therapies (thermotherapy, cryotherapy, paromomycin ointment, local infiltration with antimonials) are good options that offer less systemic toxicity and the possibility for ambulatory treatment. Hence, systemic treatment (azole drugs, miltefosine, antimonials, amphotericin B formulations) for OWCL is thus reserved for complex cases.

Lesions of NWCL caused by *L. mexicana* may resolve spontaneously within 3–4 months; meanwhile, those caused by *L. braziliensis, L. panamensis, L. guyanensis* and *L. peruviana* may take more than 6 months [5, 6]. Moreover, NWCL lesions can secondarily disseminate to adjacent skin or mucosa, causing an MCL (NWMCL). Spread to the mucosa takes place in 2–30 % of untreated cutaneous cases (low risk with *L. amazonensis* and with *L. guyanensis*, 10 % with *L. panamensis* and up to 30 % with *L. braziliensis*). The development of mucosal affectation depends on various factors, such as the quantity (more than four lesions), the size (>4 cm) and the location (more on the upper part of the body) of lesions, as well as the duration of the lesions (>4 months), the nutritional and immune status of the patient, the virulence of the strain, and a suboptimal and insufficient treatment. The highest-risk geographical areas for NWMCL are the Andean and the Amazonian regions [7]. The common practice for NWCL is to treat the majority of CL types with systemic treatment, mainly pentavalent antimonials administered intravenously or intramuscularly. However, this measure may not guarantee total prevention of later MCL, which has been found in <5 % of cases [8]. Moreover, a high rate of adverse effects, the length of treatment and relapses in up to 25 % of cases highlight the limitations of such therapy. Evidence of other treatments varies among the different *Leishmania* species. Published data referring to *L. braziliensis*, *L. mexicana* or *L. panamensis* is quite profuse; meanwhile, for others such as *L. amazonensis*, *L. lainsoni*, *L. naïffi*, *L. peruviana* or *L. venezuelensis*, data are very scarce [8]. Treatment is always required for NWMCL as these types of lesions are potentially serious, and recurrence and relapse are frequent. The treatment is based upon antimonials and pentamidine; however, randomized clinical trials are scarce and the associated immunotherapy is promising [9].

The objectives of this article are to exhaustively review the literature on OWCL, NWCL and NWMCL treatment; to analyse the methodology and results of the reviewed studies; to give treatment recommendations based on the leishmaniasis presentation form, country of origin and *Leishmania* species; and, finally, to stratify the strength of the recommendations based on the Infectious Diseases Society of America (IDSA) grade classification.

2 Methods

At the Tropical Medicine Unit of Ramón y Cajal Hospital in Madrid, Spain, the medical literature was searched, using databases such as MEDLINE, EMBASE, Web of Science and the Cochrane Library database. No limits were placed with respect to the date of publication. No language restrictions were imposed. The chosen search terms were 'old world cutaneous leishmaniasis' OR 'cutaneous leishmaniasis' OR 'leishmaniasis recidivans' OR 'diffuse cutaneous leishmaniasis' OR 'new world cutaneous leishmaniasis' OR 'mucocutaneous leishmaniasis' OR 'cutaneous leishmaniasis' OR 'new world diffuse cutaneous leishmaniasis' OR 'new world leishmaniasis' and 'treatment' OR 'local treatment' OR 'thermotherapy' OR 'cryotherapy' OR 'nitric oxide' OR 'topical paromomycin' OR 'intralesional or local pentavalent antimonials' OR 'systemic treatment' OR 'azole drugs' OR 'miltefosine' OR 'pentavalent antimonials' OR 'pentamidine' OR 'amphotericin B'. Other search terms were '*L. aethiopica*', '*L. donovani*', '*L. infantum*', '*L. major*' and '*L. tropica*' OR '*L.(V.) braziliensis*' OR '*L.(V.)guyanensis*', '*L.(V.)panamensis*', '*L.(V.) peruviana*', '*L.mexicana*', '*L. amazonensis*', '*L. venezuelensis*'.

Bibliographical references from the included studies were also reviewed. The reference sections of primary studies, narrative reviews and systematic reviews were examined to search for additional primary studies that might have been missed during the electronic search.

Initially, only clinical trials were selected in order to obtain data with the highest-grade evidence. In the absence of good-quality evidence studies, a second review was conducted in order to obtain CR information. Later searches included original articles where data on results and treatment regimens were shown, such as large case series and multicentre studies, and also case reports when relevant results were reported.

Data collected and analysed for each of the selected articles were the methodology, treatment regimens (doses and duration), CRs (always using the last CR reported after the longest period of follow-up; when not specified, the intention-to-treat CR is given; when data of per-protocol CR is known, this is also reported), the country in which

the study was performed and the *Leishmania* species isolated. These data were summarized in tables for each of the leishmaniasis forms of presentation studied.

Based on the methodology and the results of the studies, treatment recommendations were outlined for each leishmaniasis presentation form, country of origin and *Leishmania* species. The strength of such recommendations was stratified based on the IDSA grade classification (Table 1) [10, 11]. In this system, letters A–E signify the strength of the recommendation for or against a therapeutic measure and the roman numerals I–III indicate the quality of evidence supporting the recommendation [10, 11]. The strength of the recommendation was given based on several factors, such as the number of studies performed, the methodology of the studies, the number of patients included, if the specific *Leishmania* sp. was isolated or the time of follow-up.

3 Treatment for Cutaneous Leishmaniasis: Physical Therapies

Table 2.

3.1 Physical Therapies for Old World Cutaneous Leishmaniasis (OWCL)

3.1.1 Thermotherapy

The mechanism of action of thermotherapy is based on the ability to directly destroy the parasite through the application of heat. Several randomized clinical trials have compared thermotherapy with other therapeutic alternatives. One of them demonstrated that it achieved the same efficacy (CR 54.3 %) as intralesional antimonials (CR 59.8 %) in Afghanistan (*L. tropica*) [12]. Later, other studies undertaken in Iran proved the superiority of thermotherapy with radiofrequency (CR 80.7 %) compared with intralesional antimonials (CR 55.3 %) [13]. A third study comparing thermotherapy with intravenous antimonials in Iran and Kuwait (*L. major*) obtained similar CRs but with much fewer side effects than parenteral antimonials (CR thermotherapy 48 %; CR intravenous antimonials 54 %) [14].

Table 1 Infectious Diseases Society of America (IDSA) grade classification

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from one or more randomized clinical trial
II	Evidence from one or more well designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees

3.1.2 CO_2 Laser

The CO_2 laser is capable of thermolysis on damaged tissues, and causes hardly any damage to the surrounding healthy tissue [15]. Recently, a randomized clinical trial was conducted in Iran in which thermotherapy using a CO_2 laser was compared with combined therapy with cryotherapy plus intralesional antimonials. The results of the trial demonstrated that one single session of thermotherapy with a CO_2 laser was more effective (CR 93.7 %) than the combined therapy (CR 78 %) [16].

3.1.3 Photodynamic Therapy

Light-mediated cytolysis of *Leishmania* parasites is a new technique in the treatment of CL. A randomized controlled trial performed in Iran showed evidence that photodynamic therapy can be used safely as a rapid and highly effective alternative treatment choice for OWCL (CR 93.5 %) [17].

3.1.4 Cryotherapy

Cryosurgery is not a new mode of treatment. Using a CO_2 cryomachine, a CR of 100 % in 30 patients in Saudi Arabia with *L. major* CL was obtained [18]. Later, liquid nitrogen was demonstrated to have the same qualities, reaching an efficiency rate of over 95 % in Jordan, Israel and Greece [19–22] and of 78 % in Turkey [23].

Several clinical trials have highlighted the superiority of the combination of cryotherapy and intralesional pentavalent antimonials with CRs from 89.5 to 100 %, compared with using any of the two therapies on their own for *L. major* and *L. tropica* CL in the United Arab Emirates and in Iran [24–27]. However, the combination of nitric oxide (NO) in the form of an ointment at 3 % with cryotherapy did not prove more effective than cryotherapy on its own in a randomized trial in Iran with CRs of 83.3 and 74.1 %, respectively [28].

A clinical trial performed in Iran in a pediatric population demonstrated that cryotherapy (CR 52.5 %) was more

Table 2 Physical therapy for cutaneous leishmaniasis

References	Country; *Leishmania* spp.	Type of study	Regimen administered	CR
OWCL				
Thermotherapy				
Reithinger et al. [12]	Afghanistan *L. tropica*	Randomized controlled trial	Group 1 ($N = 148$): intralesional SSG, 5 injections of 2–5 ml every 5–7 days for a total of up to 29 days Group 2 ($N = 117$): parenteral SSG 20 mg Sb^{v+}/kg/day for 21 days Group 3 ($N = 138$): localized ThermoMed^{TM} device heat treatment applied at 50 °C for 30 s in one session	CR at 100 days follow-up: 71.9, 59.8, 54.3 %, respectively
Sadeghian et al. [13]	Iran *Leishmania* sp. not isolated (most probably *L. major* or *L. tropica)*	Randomized controlled trial	Group 1 ($N = 57$): thermotherapy by radiofrequency at 50 °C for 30 s once weekly for 4 weeks Group 2 ($N = 60$): intralesional MA once weekly for 4 weeks	CR at 6-month follow-up: 80.7, 55.3 %, respectively
Aronson et al. [14]	US military infected in Iraq or Kuwait *L. major*	Randomized controlled trial	Group 1 ($N = 28$): parenteral SSG 20 mg Sb^{v+}/kg/day for 10 doses Group 2 ($N = 28$): localized ThermoMed^{TM} device heat treatment applied at 50 °C for 30 s in one session	CR at 2-month follow-up: 54, 48 %, respectively
CO_2 laser				
Shamsi Meymandi et al. [16]	Iran *Leishmania* sp. not isolated (most probably *L. major* or *L. tropica*)	Prospective, randomized, open-label trial	Group 1 ($N = 96$): one session of CO_2 laser therapy Group 2 ($N = 95$): combined cryotherapy biweekly with intralesional MA weekly until the earlier of complete cure or up to 12 weeks	CR at 16-week follow-up: 93.7, 78 %, respectively
PDT				
Asilian and Davami [17]	Iran *Leishmania* sp. not isolated (most probably *L. major* or *L. tropica*)	Placebo-controlled randomized trial	Group 1 ($N = 20$): weekly topical PDT for 4 weeks Group 2 ($N = 20$): 15 % paromomycin sulphate plus 12 % methylbenzothoium chloride applied topically bid for 28 days Group 3 ($N = 20$): soft white paraffin-based ointment only with no active ingredient	CR at 2-month follow-up: 93.5, 41.2 and 13.3 %, respectively
Cryotherapy				
el Darouti and al Rubaie [27]	United Arab Emirates *Leishmania* sp. not isolated (most probably *L. major*)	Non-randomized comparative study	Group 1 ($N = 15$): cryotherapy for 10 s repeated 3 times once every 2 weeks + intralesional SSG 2–5 ml according to the sizes of the lesion (first injection administered immediately after first session of cryotherapy and repeated every other day until 10 sessions) Group 2 ($N = 14$): cryotherapy Group 3 ($N = 15$): intralesional SSG	CR at 6-week follow-up: 100, 68, 44 %, respectively
Osama al-Majali et al. [21]	Jordan *Leishmania* sp. not isolated (most probably *L. major*)	Non-randomized trial	Group 1 ($N = 193$): cryotherapy twice in each session for 15–20 s and a thaw of 1 min, repeated for up to 3 sessions, with an interval of 3 weeks Group 2 ($N = 148$): parenteral SSG 10 mg Sb^{v+}/kg/day for 2 weeks Group 3 ($N = 27$): sulfamethoxazole 400 mg and trimethoprim 80 mg for 2 weeks	CR in group 1: 215 were followed-up and all cured except for 1. There are no data for the other groups
Gurei et al. [23]	Turkey *Leishmania* sp. not isolated (most probably *L. tropica*)	Non-randomized comparative trial	Group 1 ($N = 42$): cryotherapy using liquid nitrogen twice for 2 months Group 2 ($N = 55$): intralesional SSG	CR at 3-month follow-up: 78, 92 %, respectively

Table 2 continued

References	Country; *Leishmania* spp.	Type of study	Regimen administered	CR
Asilian et al. [25]	Iran *Leishmania* sp. not isolated (most probably *L. major* or *L. tropica*)	Non-randomized comparative trial	Group 1 ($N = 40$): cryotherapy to complete healing or maximum 9 weeks + intralesional MA fortnightly for 6 weeks or complete healing Group 2 ($N = 40$): cryotherapy to complete healing or maximum 6 weeks + intralesional MA fortnightly for 6 weeks or complete healing Group 3 ($N = 100$): intralesional MA for 6 weeks or complete healing	CR at 6-month follow-up: 89.5, 92.3, 50 %, respectively
Asilian et al. [26]	Iran *Leishmania* sp. not isolated (most probably *L. major* or *L. tropica*)	Randomized clinical trial	Group 1 ($N = 100$): cryotherapy + intralesional MA fortnightly Group 2 ($N = 200$): cryotherapy fortnightly Group 3 ($N = 100$): intralesional MA fortnightly	Cure rate at 6-month follow-up: 90.9, 57.1, 55.6 %, respectively
Salmanpour et al. [24]	Iran *Leishmania* sp. not isolated (most probably *L. major* or *L. tropica*)	Randomized clinical trial	Group 1 ($N = 20$): intralesional MA 0.2–0.5 ml per lesion per week Group 2 ($N = 20$): cryotherapy with liquid nitrogen with a cotton applicator over 10–30 s with a thawing interval of 20 s Group 3 ($N = 20$): combination of cryotherapy and intralesional MA All modalities were performed weekly for a total of 6–8 times for each case	CR at the end of treatment: 75, 67.8, 89 %, respectively
Layegh et al. [29]	Iran *Leishmania* sp. not isolated (most probably *L. major* or *L. tropica*)	Randomized clinical trial	Group 1 ($N = 39$): MA 0.5–2 ml injected into each lesion until lesion is completely blanched Group 2 ($N = 40$): liquid nitrogen was applied twice to the lesion in each session and repeated weekly up to 6 weeks	CR after 6-month follow-up: IT 25 and 52.5 %, respectively. PP 27 and 58.3 %, respectively
Ranawaka et al. [30]	Sri Lanka *L. donovani*	Cross-sectional, open-label clinical trial	($N = 65$): Liquid nitrogen cryotherapy applied using cotton swabs, repeated until entire lesion included. Number of applications varied from 1 to 6 or more depending on lesion size. After each session, all patients prescribed topical and/or oral antibiotics. Cryosessions performed for 15–20 s, weekly for 1–3 weeks, fortnightly for 4–5 weeks, then monthly until cure	CR after 6-month follow-up: 91.7 %
Jowkar et al. [28]	Iran *L. major* ($n = 33$) and *L. tropica* ($n = 4$)	Double-blind, randomized, placebo-controlled clinical trial	Group 1 ($N = 36$): for 12 weeks simultaneous cryotherapy once a week and two creams; one containing 3 % salicylic acid aqueous cream (emulsifying ointment 30 g phenoxyethanol 1 g), the other 3 % sodium nitrite in aqueous cream Group 2 ($N = 27$): for 12 weeks simultaneous cryotherapy once a week and a cream containing 3 % salicylic acid in aqueous cream and aqueous cream alone	CR at the end of treatment: 83.3 and 74.1 %, respectively
NWCL				
Thermotherapy				
Navin et al. [32]	Guatemala *L. mexicana* (13), *L. braziliensis* (40), unknown (13)	Placebo-controlled, randomized clinical trial	Group 1 ($N = 22$): MA 15 mg Sb^{v+}/kg/day IM for 15 days Group 2 ($N = 22$): local heat 50 °C for 30 s, 3 treatments at 7-day intervals Group 3 ($N = 22$): placebo	CR at 13 weeks after beginning treatment: 73, 73, 27 %, respectively

Table 2 continued

References	Country; *Leishmania* spp.	Type of study	Regimen administered	CR
Vega et al. [34]	Colombia *Leishmania* sp. not isolated (most probably *L. guyanensis* or *L. panamensis*)	Open-label observational study	Group 1 ($N = 47$): thermotherapy 50 °C one or more consecutive for 30 s Group 2 ($N = 68$): MA 20 mg Sb^{v+}/kg/day IM for 20 days	CR at 100 days follow-up: 38.3, 41.7 %, respectively
López et al. [33]	Colombia *L. panamensis* (56), *L. braziliensis* (111)	Open-label, randomized phase III, clinical trial	Group 1 ($N = 149$): thermotherapy 50 °C in a single session Group 2 ($N = 143$): MA 20 mg Sb^{v+}/kg/day IM for 20 days	CR at 6-month follow-up: IT: 58, 72 %, respectively. PP: 64, 85 %, respectively
Topical NO				
López-Jaramillo et al. [36]	Colombia *L. panamensis*	Controlled, randomized, blinded, clinical trial	Group 1 ($N = 90$): MA IM 20 mg/kg/day for 20 days Group 2 ($N = 88$): topical nanofibre NOP (3.5 μmol NO/cm^2/day for 12 h for 20 days, NOP)	CR at 3-month follow-up: 94.8, 37.1 %, respectively

bid twice daily, *CR* cure rate, *IM* intramuscular, *MA* meglumine antimoniate, *NO* nitric oxide, *NOP* nitric oxide-releasing patch, *NWCL* new world cutaneous leishmaniasis, *OWCL* old world cutaneous leishmaniasis, *PDT* photodynamic therapy, *SSG* sodium stibogluconate, *IT* per intention-to-treat analysis, *PP* per protocol analysis

effective than intralesional antimonials (CR 25 %). The simplicity of its technique, the low cost and few side effects could make cryotherapy a good therapeutic option in children [29].

Recently, another clinical trial has highlighted the high efficiency (CR 91.7 %) of cryotherapy with liquid nitrogen in OWCL by *L. donovani* [30].

Recommendations

	Grade
Thermotherapy regimens	
Thermotherapy by radiofrequency or by ThermoMed™ (local) applied at 50 °C for 30 s once weekly for 4 weeks	AI: OWCL in Afghanistan, Iraq, Iran, Kuwait caused by *L. major* or *L. tropica* CI: OWCL in Afghanistan caused by *L. tropica*, in Iraq and Kuwait caused by *L. major*
CO_2 laser regimens	
Thermotherapy by CO_2 laser (local) single session	AI: OWCL in Iran caused by *L. major* or *L. tropica*
Photodynamic regimens	
Photodynamic therapy (local) applied once weekly for 4 weeks	AI: OWCL in Iran caused by *L. major* or *L. tropica*
Cryotherapy regimens	
(Regimen 1) Cryotherapy with liquid nitrogen (frozen for 10–30 s and thaw) applied locally 2–3 times in each session, repeated every 1–4 weeks to complete healing (usually 2–4 sessions, but some require additional sessions)	AI: OWCL in Iran caused by *L. major* or *L. tropica* (Regimen 2) BI: OWCL in Iran caused by *L. major* or *L. tropica* (Regimen 1) BII: OWCL in United Arab Emirates, Jordan, caused by *L. major*, Turkey caused by *L. tropica* (Regimen 1) BIII: OWCL in Greece, Israel, Jordan caused by *L. major* (Regimen 1)
(Regimen 2) Cryotherapy as above + sodium stibogluconate or meglumine antimoniate (intralesional) 2–5 ml according to the size of the lesion, 2–3 times a week until healing (usually ten sessions, but some require additional sessions)	

3.2 Physical Therapies for New World Cutaneous Leishmaniasis (NWCL)

3.2.1 Thermotherapy

The direct application of heat can accelerate the cure of the lesions [31]. The first data about its efficacy were obtained in Guatemala with *L. mexicana* and *L. braziliensis*, reaching a response rate similar to those of antimonials of higher than 70 % [32]. However, in two studies undertaken in Colombia, the response rate only reached about 40–60 %

[33, 34], but without the adverse reactions or the cost of antimonials, which positions thermotherapy as a first-line treatment in this country.

3.2.2 Topical Nitric Oxide

The first studies were performed with an ointment of *S*-nitroso-*N*-acetyl penicillamine (SNAP), a compound that generates NO. The results were promising when it was applied for 10 days in Ecuador on infections by *L. braziliensis* [35]. However, a recent study in lesions caused by *L. panamensis*, where NO was administered with transdermal patches of continuous delivery of NO (produced by the technique of electrospinning capable of releasing topical levels of NO of 3–5 μmol) for 12 h a day and for 20 days in Colombia proved ineffective, with CRs of 37.1 % [36].

Recommendations	
	Grade
Thermotherapy regimens	
Thermotherapy by ThermoMed™ device (local) applied at 50 °C for 30 s in one to three sessions	BI: NWCL in Guatemala caused by *L. mexicana* or *L. braziliensis* BI (alternative): NWCL in Colombia caused by *L. panamensis* or *L. braziliensis* or *L. guyanensis*
Topical NO Regimens	
Transdermal patches of continuous delivery of NO for 12 h a day for 20 days	DI: NWCL in Colombia caused by *L. panamensis*

4 Treatment for Cutaneous Leishmaniasis: Drug Therapy

Table 3.

4.1 Topical Drug Therapy

4.1.1 Topical Drug Therapies for OWCL

4.1.1.1 Topical Paromomycin Several clinical trials undertaken since the 1990s have already described the possible efficacy of topical paromomycin for the treatment of OWCL [37]. Administered as an ointment (15 % paromomycin sulphate ointment in 12 % methylbenzethonium chloride) in Iran for *L. major* twice a day for 20 days, it achieved an efficacy of up to 77 % compared with 27 % for placebo [38].

Later, the randomized clinical trials for *L. major* infection that were developed in Iran with topical paromomycin (15 % paromomycin sulphate ointment in 10 % urea) administered for 14 days demonstrated a significant improvement on finalizing the treatment when compared with a placebo group. But after 105 days of follow-up, the CR was the same as that of the placebo group (CR 68 %) [2]. In another randomized clinical trial in Tunisia for *L. major* infection, patients were treated with topical paromomycin (15 % paromomycin sulphate ointment in 10 % urea) for 14 days. This treatment was of no greater efficacy after 105 days of follow-up (CR 66.7 vs 92.3 %) than placebo [4].

These results encouraged questions over whether the difference between the response rates was related to the duration of the treatment. For this reason, a trial was developed in Iran for *L. major* and *L. tropica* infections in which 4 weeks of therapy was compared with 2 weeks of therapy. The initial CRs were significantly higher in the 4-week group. After 105 days of follow-up, the results were still better for the prolonged therapy, albeit differences were no longer as significant (CR 57 vs. 43 %) [39]. This suggests that the differences found in the CR were probably not due to the duration of the treatment and, in fact, in a recent Iranian clinical trial with topical paromomycin applied for 30 days, the CRs were no higher than those for placebo after 60 days' follow-up (CR 67 and 69 %, respectively) [40]. These differences are likely to be due to the components of the ointment; for the treatment of OWCL by *L. major*, the combination of 15 % paromomycin sulphate plus 12 % methylbenzethonium chloride ointment was more effective than 15 % paromomycin sulphate ointment plus 10 % urea.

Different studies have aimed to investigate whether or not topical paromomycin is superior to other local therapies. In Iran, two different studies compared intralesional administration of antimonials and topical administration of paromomycin (15 % paromomycin sulphate ointment in 10 % urea) for infections by *L. major* and *L. tropica.* In the first study, both treatments achieved low response rates, even though intralesional antimonials were higher (16.6 vs. 41.7 %) [41]. In the second study, the response rate was higher in both cases and without any significant differences between the two local therapies (67 % intralesional antimonials vs. 69 % paromomycin) [42].

More recently, in a study in Tunisia, the efficacy of a new combination of ointment (WR279,396) composed of paromomycin at 15 % plus gentamycin at 0.5 % applied twice daily for 20 days for *L. major* infections when compared with placebo obtained response rates of 94 and 71 %, respectively [43].

Table 3 Drug therapy for cutaneous leishmaniasis

Reference	Country; *Leishmania* spp.	Type of study	Regimen administered	CR
Topical drugs				
OWCL				
Topical paromomycin				
el-Safi et al. [37]	Sudan *L. major*	Double-blind, clinical trial	Group 1 ($N = 20$): topical paromomycin (15 % paromomycin sulphate, 25 % white soft paraffin, 25 % water, 35 % wool fat) bid for 10 days Group 2 ($N = 20$): placebo	CR at 20 days after treatment: 75, 53 %, respectively but not significant (patients in group 1 showed better healing of lesions)
el-On et al. [38]	Israel *L. major*	Randomized, double-blind, controlled study	Group 1 ($N = 30$): topical paromomycin[a] bid for 20 days Group 2 ($N = 32$): topical paromomycin[a] bid for 10 days Group 3 ($N = 11$): topical paromomycin[a] bid for 20 days Group 4 ($N = 9$): topical paromomycin[a] bid for 10 days Group 5 ($N = 15$): Placebo	CR: 74.2 % in treated groups, 26.6 % in placebo
Asilian et al. [2]	Iran *Leishmania* sp. not isolated (most probably *L. major* or *L. tropica*)	Randomized, double-blind, placebo-controlled clinical trial	Group 1 ($N = 126$): topical paromomycin[b] bid for 14 days Group 2 ($N = 125$): placebo	CR at 105-day follow-up: 68, 68 %, respectively
Ben Salah et al. [4]	Tunisia *Leishmania* sp. not isolated (most probably *L. major*)	Randomized, double-blind, placebo-controlled study	Group 1 ($N = 57$): topical paromomycin[b] bid for 14 days Group 2 ($N = 58$): placebo	CR at 105-days follow-up: 66.7, 92.3 %, respectively
Ozgoztasi and Baydar [72]	Turkey *Leishmania* sp. not isolated (most probably *L. tropica*)	Open-label, randomized, clinical trial	Group 1 ($N = 40$): topical paromomycin[a] bid for 15 days Group 2 ($N = 32$): ketoconazole 400 mg oral/day (200 mg oral/day for patients <12 years old) for 30 days	CR at 4 weeks of treatment: 37.5, 0 %, respectively
Faghihi and Tavakoli-kia [41]	Iran *Leishmania* sp. not isolated (most probably *L. major* or *L. tropica*)	Randomized clinical trial	Group 1 ($N = 48$): topical paromomycin[b] bid for 45 days Group 2 ($N = 48$): intralesional MA weekly	CR at the end of treatment: 16.6, 41.7 %, respectively
Asilian et al. [39]	Iran *Leishmania* sp. not isolated (most probably *L. major* or *L. tropica*)	Randomized, double-blind clinical trial	Group 1 ($N = 117$): topical paromomycin[b] bid for 4 weeks Group 2 ($N = 116$): topical paromomycin[b] bid for 2 weeks + 2 more weeks of placebo	CR at 105 days: 57, 43 %, respectively
Shazad et al. [42]	Iran *L. major*	Randomized, open-label, comparative clinical trial	Group 1 ($N = 30$): intralesional MA (1 ml) every day for 20 days Group 2 ($N = 30$): topical paromomycin[b] bid for 29 days	CR 1 week after treatment: 67, 69 %, respectively
Iraji and Sadeghinia [40]	Iran *Leishmania* sp. not isolated (most probably *L. major* or *L. tropica*)	Randomized, double-blind, placebo-controlled clinical trial	Group 1 ($N = 30$): topical paromomycin[b] bid for 30 days Group 2 ($N = 35$): placebo	CR at 60-day follow-up: 17, 20 %, respectively

Table 3 continued

Reference	Country; *Leishmania* spp.	Type of study	Regimen administered	CR
Ben Salah et al. [43]	Northern Africa *L. major*	Randomized, double-blind controlled trial	Group 1 ($N = 50$): topical paromomycin[c] bid for 20 days Group 2 ($N = 42$): topical placebo	CR at 180-day follow-up: 94, 71 %, respectively
Ben Salah et al. [180]	Tunisia *L. major*	Randomized, vehicle-controlled, phase III trial	Group 1 ($N = 125$): topical paromomycin[c] od for 20 days Group ($N = 125$): topical paromomycin od for 20 days Group 3 ($N = 125$): vehicle control	CR at 6-month follow-up: 81, 82, 58 %, respectively
Intralesional antimonials				
Sharquie et al. [46]	Iraq *Leishmania* sp. not isolated (most probably *L. major* or *L. tropica*)	Case-controlled study	Group 1 ($N = 60$): intralesional SSG at 8-day intervals Group 2 ($N = 30$): no treatment	CR at 42-day follow-up: 94.6 % (80 % one, 15.4 % two, 4.6 % six injections), 0 %, respectively
Harms et al. [50]	Syria *L. tropica*	Randomised trial	Group 1 ($N = 20$): intralesional MA once weekly for 5 consecutive weeks Group 2 ($N = 20$): recombinant interferon 1 ml (25 μg/ml) once weekly for 5 consecutive weeks	CR at 10 week follow-up: 76, 3 %, respectively
Tallab et al. [45]	Saudi Arabia *Leishmania* sp. not isolated (most probably *L. major*)	Non-randomized, prospective comparative study	For all groups intralesional SSG until complete blanching (maximun dose per visit not > 20 mg) Sb^{v+}/kg) Group 1 ($N = 21$): daily for total of 3 injections Group 2 ($N = 39$): on alternate days for a total of 3 injections Group 3 ($N = 69$): weekly for total of 3 injections	CR at 3 weeks after the end of treatment: 67, 97 and 91 %, respectively
Alkhawajah et al. [44]	Saudi Arabia *Leishmania* sp. not isolated (most probably *L. major*)	Randomized clinical trial	Group 1 ($N = 40$): parenteral MA 15 mg Sb^{v+}/kg/day (maximum 850 mg Sb^{v+}/kg) daily 6 days a week until 12 injections Group 2 ($N = 40$): intralesional MA 0.2–0.8 ml/lesion/day on alternate days over 30-day period	CR at day 30 of end of treatment: 84, 88 %, respectively
Chahed et al. [49]	Tunisia *L. major*	Randomised, placebo-controlled trial	Group 1 ($N = 52$): intralesional MA twice a week over 2 weeks Group 2 ($N = 57$): local treatment (eosin 5 %, alcohol 95 %)	CR 105 days after treatment: 93, 91 %, respectively
Faghihi and Tavakoli-kia [41]	Iran *Leishmania* sp. not isolated (most probably *L. major* or *L. tropica*)	Randomized clinical trial	Group 1 ($N = 48$): topical paromomycin[b] bid for 3 months until complete recovery (mean 45 days) Group 2 ($N = 48$): intralesional MA (0.2–0.8 ml) for 3 months until complete recovery	CR after 1-year follow-up: 16.6, 41.7 %, respectively
Asilian et al. [25]	Iran *Leishmania* sp. not isolated (most probably *L. major* or *L. tropica*)	Non-randomized clinical trial	Group 1 ($N = 100$): intralesional MA (0.5–2 ml) Group 2 ($N = 40$): cryotherapy + intralesional MA (0.5–2 ml) Group 3 ($N = 40$): cryotherapy + intralesional SSG (0.5–2 ml). Treatments administered fortnightly for 4 weeks	CR at 6-month follow-up: 50, 89.5, 92.3 %, respectively
Munir et al. [53]	Pakistan *L. tropica*	Randomized clinical trial	Group 1 ($N = 20$): parenteral MA 20 mg Sb^{v+}/kg/day (max 850 mg) for 21 days Group 2 ($N = 20$): intralesional MA (0.5 ml) + parenteral MA IV or IM as above for 21 days Group 3 ($N = 20$): no treatment	CR at 3-month follow-up: 55, 75, 10 %, respectively

Table 3 continued

Reference	Country; *Leishmania* spp.	Type of study	Regimen administered	CR
Ranawaka and Weerakoon [51]	Sri Lanka *L. donovani*	Randomized, double-blind, comparative, clinical trial	Group 1 ($N = 87$): intralesional SSG 0.2–4 ml per lesion Group 2 ($N = 67$): intralesional 7 % hypertonic sodium chloride 0.2–4 ml per lesion In both groups, first 3 injections were administrated weekly, 4th and 5th fortnightly, then monthly until cure	CR at 18-month follow-up: 100 % with 1–6 injections, 92.2 % with 1–10 injections
El-Sayed and Anwar [54]	Yemen *Leishmania* sp. not isolated (most probably *L. major* or *L. tropica*)	Randomized clinical trial	Group 1 ($N = 10$): intralesional SSG, doses varied 0.3–3 ml and injections given on days 1, 3 and 5 in one session Group 2 ($N = 10$): 20 mg/kg/day of SSG, part of it was administered intralesionally on days 1, 3 and 5 as in group 1. The remaining dose was given IM simultaneously on the same days Group 3 ($N = 10$): intralesional SSG as in group 1 + ketoconazole (200 mg tid) for 4 weeks	CR at 6-month follow-up: 58.3, 93.3 and 92.3 %, respectively
Topical imidazoles				
Larbi et al. [59]	Saudi Arabia *Leishmania* sp. not isolated (most probably *L. major*)	Randomized, double-blind trial	Group 1 ($N = 31$): 1 % clotrimazole cream applied to lesion bid for 30 days Group 2 ($N = 23$): 2 % miconazole cream applied to lesion bid for 30 days	CR at 6-week follow-up: 15.7, 0 %, respectively
NWCL				
Intralesional antimonials				
Soto et al. [68]	Bolivia *L. braziliensis*	Randomized clinical trial	Group 1 ($N = 30$): MA 650 µl intralesional days 1, 3, 5 Group 2 ($N = 20$): liquid nitrogen for 5–20 s days 1, 14 Group 3 ($N = 30$): placebo cream for 20 days	CR at 6-month follow-up: 70, 20 and 17 %, respectively
Topical paromomycin				
Krause and Kroeger [61]	Ecuador *L. panamensis*	Non-randomized trial	Group 1 ($N = 37$): topical paromomycin[a] bid for 10 days Group 2 ($N = 15$): topical paromomycin[a] od for 20 days Group 3 ($N = 23$): no treatment	CR at 12-month follow-up: 85, 85, 9 %, respectively
Soto et al. [66]	Colombia *L. panamensis* (26), *L. braziliensis* (4) .	Open-label, phase II clinical trial	Group 1 ($N = 20$): topical paromomycin[a] bid for 10 days + MA 20 mg IM Sb^{v+}/kg/day IV or IM for 7 days Group 2 ($N = 19$): topical paromomycin[a] bid for 10 days + MA 20 mg IM Sb^{v+}/kg/day IV or IM for 3 days	CR at 12-month follow-up: 90, 42 %, respectively
Neva et al. [64].	Honduras *L. mexicana* (18), *L. chagasi* (8)	Double-blind, randomized, placebo-controlled trial	Group 1 ($N = 36$): topical 15 % paromomycin and 10 % paraffin ointment Group 2 ($N = 52$): placebo	CR at 4.5-month follow-up: only 2 patients of each group

Table 3 continued

Reference	Country; *Leishmania* spp.	Type of study	Regimen administered	CR
Soto et al. [65]	Colombia *L. panamensis* (49), *L. braziliensis* (20)	Randomized clinical trial	Group 1 ($N = 59$): topical paromomycin[a] bid plus MA 20 mg Sb^{v+}/kg/day IM for 7 days Group 2 ($N = 30$): topical placebo plus MA 20 mg Sb^{v+}/kg/day IM for 7 days Group 3 ($N = 30$): topical paromomycin[a] bid + MA 20 mg Sb^{v+}/kg/day IM for 3 days Group 4 ($N = 31$): MA 20 mg Sb^{v+}/kg/day IM for 20 days	CR at 9- to 12-month follow-up: 58, 53, 20, 84 %, respectively
Arana et al. [62]	Guatemala *Leishmania* sp. not identified, (most probably *L. braziliensis* and *L. mexicana*)	Randomized, controlled, double-blind trial	Group 1 ($N = 35$): topical paromomycin[a] bid for 20 days Group 2 ($N = 33$): placebo	CR at 12-month follow-up: 85.7, 39.4 %, respectively
Armijos et al. [63]	Ecuador *Leishmania* sp. not isolated (most probably *L. guyanensis*, *L. braziliensis* and *L. panamensis*)	Randomized controlled trial	Group 1 ($N = 14$): topical paromomycin[a] bid for 30 days Group 2 ($N = 40$): topical paromomycin[b] bid for 30 days Group 3 ($N = 40$): MA 20 mg Sb^{v+}/kg/day IM for 10 days	CR at 3-month follow-up: 79.3, 70, 91.7 %, respectively
Oral drugs				
OWCL				
Azoles				
Dogra et al. [74]	India *Leishmania* sp. not isolated (most probably *L. tropica*)	Randomized clinical trial	Group 1 ($N = 15$): oral itraconazole 4 mg/kg/day for 6 weeks Group 2 ($N = 5$): placebo	CR at 3-month follow-up: 66.7, 0 %, respectively
Alsaleh et al. [73]	Kuwait *Leishmania* sp. not isolated (most probably *L. major*)	Non-randomized trial	Group 1 ($N = 18$): oral ketoconazole 600 mg/day for 6 weeks Group 2 ($N = 15$): oral ketoconazole 800 mg/day for 6 weeks	CR at 6-week follow-up: 80, 81.8 %, respectively
Momeni et al. [75]	Iran *Leishmania* sp. not isolated (most probably *L. major* or *L. tropica*)	Randomised, double-blind trial	Group 1 ($N = 65$): oral itraconazole 7 mg/kg/day for 3 weeks Group 2 ($N = 66$): placebo	CR at 1-month follow-up: 95, 44.3 %, respectively
Ozgoztasi and Baydar [72]	Turkey *L. tropica*	Open-label, randomized, clinical trial	Group 1 ($N = 40$): topical paromomycin[a] bid for 15 days Group 2 ($N = 32$): oral ketoconazole 400 mg/day for 30 days	CR at 4 weeks post treatment: 37.5, 0 % (21.9 % had incomplete healing), respectively
Salmanpour et al. [71]	Iran *Leishmania* sp. not isolated (most probably *L. major* or *L. tropica*)	Randomized clinical trial	Group 1 ($N = 64$): oral ketoconazole 600 mg/day for adults and 10 mg/kg/day for children for 30 days Group 2 ($N = 32$): intralesional MA biweekly up to 6 injections	CR at 6 weeks post treatment: 89, 72 %, respectively
Alrajhi et al. [69]	Saudi Arabia *L. major*	Randomized, double-blind, placebo-controlled trial	Group 1 ($N = 106$): PO fluconazole 200 mg/day for 6 weeks Group 2 ($N = 103$): placebo	CR at 3-month follow-up: 79, 34 %, respectively

Table 3 continued

Reference	Country; *Leishmania* spp.	Type of study	Regimen administered	CR
Nassiri-Kashani et al. [76]	Iran *Leishmania* sp. not isolated (most probably *L. major* or *L. tropica*)	Randomized, double-blind trial	Group 1 ($N = 100$): PO itraconazole 200 mg/day for 8 weeks Group 2 ($N = 100$): placebo	CR at the end of treatment: 59, 53 %, respectively
Emad et al. [70]	Iran *Leishmania* sp. not isolated (most probably *L. major*)	Randomized clinical trial	Group 1 ($N = 60$): fluconazole PO 200 mg/day for 6 weeks Group 2 ($N = 60$): fluconazole PO 400 mg/day for 6 weeks	CR at the end of the treatment: 48.3, 81 %, respectively
Miltefosine				
Mohebali et al. [80]	Iran *L. major*	Randomized, open-label trial	Group 1 ($N = 32$): PO miltefosine 2.5 mg/kg/day for 28 days Group 2 ($N = 31$): parenteral MA 20 mg Sb^{v+}/kg/day for 14 days	CR at 6-month follow-up: IT 81.3, 80.6 %; PP 92.9, 83.3 %, respectively
NWCL				
Azoles				
Navin et al. [84]	Guatemala *L. mexicana* (34), *L. braziliensis* (64), unknown (21)	Randomized clinical trial	Group 1 ($N = 40$): SSG 20 mg Sb^{v+}/kg/day IV for 20 days Group 2 ($N = 38$): ketoconazole 600 mg/day PO for 28 days Group 3 ($N = 40$): placebo	CR at 52-week follow-up: for *L. braziliensis*: 96, 30 and 7 %, respectively; for *L. mexicana*: 57, 89, 38 %, respectively
Saenz et al. [83]	Panama *L. panamensis* (30), *L. mexicana* (1)	Randomized controlled trial	Group 1 ($N = 19$): SSG 20 mg Sb^{v+}/kg/day IM for 20 days Group 2 ($N = 21$): Ketoconazole 600 mg/day PO for 28 days Group 3 ($N = 11$): placebo	CR at 12 months: 68, 76, 0 %, respectively
Soto-Mancipe et al. [85]	Colombia *Leishmania* sp. not isolated (most probably *L. panamensis*, *L. braziliensis*, and *L. mexicana*)	Randomized clinical trial	Group 1 ($N = 23$): MA 20 mg Sb^{v+}/kg/day IM for 20 days Group 2 ($N = 27$): pentamidine 2 mg/kg/eod IM for total 7 injections Group 3 ($N = 20$): itraconazole 200 mg PO bid for 28 days Group 4 ($N = 22$): no treatment	CR at 6- to 12-month follow-up: 91, 96, 25, 36 %, respectively
Miltefosine regimens				
Soto et al. [87]	Colombia *L. panamensis* (10), *L. amazonensis* (5), unknown (57)	Randomized controlled trial	Group 1 ($N = 16$): miltefosine 50 mg/day PO for 20 days Group 2 ($N = 19$): miltefosine 50 mg/day PO on days 1–7, then 100 mg/day on days 8–20 Group 3 ($N = 17$): miltefosine 100 mg/day PO on days 1–7, then 150 mg PO on days 8–20 Group 4 ($N = 20$): miltefosine 150 mg/day PO for 28 days	CR at 6-month follow-up: IT 56, 63, 82, 80 %; PP 64, 67, 100, 89 %, respectively
Soto et al. [86]	Colombia *L. panamensis* (7) Guatemala *L.braziliensis* (29), *L.mexicana* (17)	Randomized, placebo-controlled, double-blind, multicentre trial	Colombia: Group 1 ($N = 49$): miltefosine 2.5 mg/kg/day PO for 28 days. Group 2 ($N = 24$): placebo Guatemala: Group 1 ($N = 40$): miltefosine 2.5 mg/kg/day PO for 28 days. Group 2 ($N = 20$): placebo	CR at 6-month follow-up: Colombia IT 82, 32 %; PP 91, 38 %, respectively. Guatemala IT 50, 20 %; PP 53, 21 %, respectively

Table 3 continued

Reference	Country; *Leishmania* spp.	Type of study	Regimen administered	CR
Soto et al. [89]	Bolivia *Leishmania* sp. not isolated (probably *L. braziliensis*)	Randomized clinical trial	Group 1 ($N = 44$): miltefosine 2.5 mg/kg/day PO for 28 days Group 2 ($N = 18$): SSG 20 mg Sb^{v+}/kg/day IM for 20 days	CR at 6-month follow-up: IT 81.8, 88.8 %; PP 88, 94 %, respectively
Velez et al. [88]	Colombia *L. panamensis* (62), *L. braziliensis* (103), unknown (123)	Randomized, open-label, phase III clinical trial	Group 1 ($N = 145$): miltefosine 150 mg/day PO for 28 days Group 2 ($N = 143$): MA 20 mg Sb^{v+}/kg/day IM for 20 days	CR at 6-month follow-up: IT 58.6, 72 %; PP 69.8, 85.1 %, respectively
Machado et al. [90]	Brazil *L. braziliensis*	Randomized controlled trial	Group 1 ($N = 60$): miltefosine 2.5 mg/kg/day PO (max 150 mg/day) PO for 28 days Group 2 ($N = 30$): MA 20 mg Sb^{v+}/kg/day IV (max 1,215 mg Sb^{+v}/day) for 20 days	CR at 6-month follow-up: 75, 53 %, respectively
Chrusciak-Talhari et al. [91]	Brazil *L. guyanensis*	Randomized, phase II/III clinical trial	Group 1 ($N = 60$): miltefosine 2.5 mg/kg/day PO for 28 days Group 2 ($N = 30$): MA 15–20 mg Sb^{v+}/kg/day IV for 20 days	CR at 6-month follow-up: 71.4, 53.6 %, respectively. There were no differences in CRs between age groups
Rubiano et al. [94]	Colombia Parasites isolated in 60/116: *L. panamensis* (71.6 %); *L. guyanensis* (26.6 %)	Randomized, non-inferiority, masked evaluation trial in pediatric population	Group 1 ($N = 58$): MA 20 mg Sb^{v+}/kg/day IM for 20 days Group 2 ($N = 58$): miltefosine 1.5–2–5 mg/kg/day PO for 28 days	CR at 26-week follow-up: IT 69, 82.7 %; PP 71.4, 87.3 %, respectively
Azithromycin and allopurinol				
Krolewiecki et al. [95]	Argentina *L. braziliensis*	Randomized, open-label trial	Group 1 ($N = 23$): MA 10 mg Sb^{V+}/kg/day IM for 28 days Group 2 ($N = 22$): azithromycin 500 mg/12 h PO on first day, followed by 500 mg every 24 h for 27 days	CR at 12-month follow-up: IT 82.6, 45.5 %; PP 71.4, 87.3 %, respectively
Guderian et al. [100]	Ecuador *L. panamensis* (12), *L. guyanensis* (5), *L. braziliensis* (3), *L. mexicana* (3), rest unknown	Randomized controlled trial	Group 1 ($N = 28$): SSG 20 mg Sb^{V+}/kg/day IM for 20 days Group 2 ($N = 21$): allopurinol 1,500 mg PO od + probenecid 500 mg PO od for 28 days Group 3 ($N = 12$): untreated controls	CR at 12-month follow-up: 96, 42.8, 75 %, respectively
Velez et al. [98]	Colombia *L. panamensis* and *L. braziliensis*	Randomized controlled trial	Group 1 ($N = 55$): allopurinol 20 mg/kg/day PO for 28 days Group 2 ($N = 46$): placebo Group 3 ($N = 56$): MA 20 mg Sb^{v+}/kg/day IM for 20 days	CR at 12-month follow-up: 29.1, 34.7, 93 %, respectively
Parenteral drugs				
OWCL				
Pentavalent antimonials				
Belazzoug and Neal [107]	Algeria *L. major*	Randomized trial	Group 1 ($N = 97$): parenteral MA 17 mg Sb^{v+}/kg/day IM for 15 days Group 2 ($N = 108$): placebo	CR at 1-month follow-up: 48, 55 %, respectively

Table 3 continued

Reference	Country; *Leishmania* spp.	Type of study	Regimen administered	CR
Zerehsaz et al. [106]	Iran *Leishmania* sp. not isolated (most probably *L. major* or *L. tropica*)	Double-blind, randomized clinical trial	Group 1 ($N = 85$): topical placebo applied to lesions for 5 consecutive days + parenteral MA 15–20 mg Sb^{v+}/kg/day for 20 days Group 2 ($N = 86$): topical herbal extract Z-HE[d] applied to lesions for 5 consecutive days + placebo injection for 20 consecutive days	CR at 6 weeks post treatment: 27.1, 74.4 %, respectively
Momeni et al. [110]	Iran *L. major*	Randomized controlled trial	Group 1 ($N = 36$): MA 30 mg/kg/day for 20 days Group 2 ($N = 36$): allopurinol 20 mg/kg/day + MA 30 mg/kg/day for 20 days	CR at 1-month follow-up: 74.2, 80.6 %, respectively
Esfandiarpour and Alavi [109]	Iran *L. tropica*	Randomized clinical trial	Group 1 ($N = 50$): oral allopurinol 15 mg/kg/day for 3 weeks Group 2 ($N = 50$): parenteral MA 30 mg/kg/day for 2 weeks Group 3 ($N = 50$): combination of both	CR at end of treatment: 18, 24, 46 %, respectively
Firooz et al. [105]	Iran *Leishmania* sp. not isolated (most probably *L. major* or *L. tropica*)	Randomized, blinded, prospective trial	Group 1 ($N = 59$): parenteral MA 20 mg Sb^{v+}/kg/day for 14 days + topical 5 % imiquimod cream 3 times weekly for 28 days Group 2 ($N = 60$): parenteral MA 20 mg Sb^{v+}/kg/day for 14 days + topical placebo cream	CR at 20-week follow-up: 50.8, 53.3 %, respectively
Sadeghian and Nilforoushzadeh [111]	Iran *L. major*	Double-blind, randomized, controlled clinical trial	Group 1 ($N = 32$): parenteral SSG 20 mg Sb^{v+}/kg/day + oral pentoxifyline 400 mg tid for 20 days Group 2 ($N = 31$): parenteral SSG 20 mg Sb^{v+}/kg/day + oral placebo (three tablets daily) for 20 days	CR at 3-month follow-up: 81.3, 51.6 %, respectively
Layegh et al. [108]	Iran *Leishmania* sp. not isolated (most probably *L. tropica*)	Non-randomized clinical trial	MA 20 mg/kg/day IM for 20 days Group 1 ($N = 56$): children Group 2 ($N = 56$): adults	CR at 45-day follow-up: IT 32.1, 55.4 %, respectively. PP 35.3, 63.3 %, respectively
NWCL				
Pentavalent antimonial regimens				
Ballou et al. [126]	American soldiers returning from Panama *L. panamensis* (22), *L. chagasi* (1)	Double-blind, randomized, controlled trial	Group 1 ($N = 21$): SSG 10 mg Sb^{v+}/kg/day IV for 20 days Group 2 ($N = 19$): SSG 20 mg Sb^{v+}/kg/day IV for 20 days	CR at 9-week follow-up: 76.2, 100 %, respectively
Navin et al. [32]	Guatemala *L. braziliensis* (40), *L. mexicana* (13), unknown (13)	Placebo-controlled, randomized clinical trial	Group 1 ($N = 22$): MA 15 mg Sb^{v+}/kg/day IM for 15 days Group 2 ($N = 22$): local heat 50 °C for 30 s, 3 treatments at 7-day intervals Group 3 ($N = 22$): placebo	CR at 13-week follow-up: 73, 73, 27 %, respectively
Saenz et al. [83].	Panama *L. panamensis*	Randomized controlled trial	Group 1 ($N = 19$): SSG 20 mg Sb^{v+}/kg/day IM for 20 days Group 2 ($N = 21$): ketoconazole 600 mg/day PO for 28 days Group 3 ($N = 11$): placebo	CR at 1-month follow-up: 68, 76, 0 %, respectively

Table 3 continued

Reference	Country; *Leishmania* spp.	Type of study	Regimen administered	CR
Guderian et al. [100]	Ecuador *L. panamensis* (12), *L. guyanensis* (5), *L. braziliensis* (3), *L. mexicana* (3), rest unknown	Randomized, placebo-controlled trial	Group 1 ($N = 28$): SSG 20 mg Sb^{v+}/kg/day (with no upper limit) IM for 20 days Group 2 ($N = 21$): allopurinol 500 mg/day PO + probenecid 500 mg/day PO for 28 days Group 3 ($N = 12$): untreated control	CR at 12-month follow-up: 96, 42.8, 75 %, respectively
Navin et al. [84]	Guatemala *L. braziliensis*, *L. mexicana*	Placebo-controlled, randomized clinical trial	Group 1 ($N = 40$): SSG 20 mg Sb^{v+}/kg/day IV for 20 days Group 2 ($N = 38$): ketoconazole 600 mg/day PO for 28 days Group 3 ($N = 40$): placebo	CR at 52-week follow-up: *L. braziliensis* 96, 30, 7 %, respectively. *L. mexicana* 57, 89, 38 %, respectively
Arana et al. [127]	Guatemala *L. braziliensis*	Randomized controlled trial	Group 1 ($N = 21$): MA 20 mg/kg/day IV for 20 days Group 2 ($N = 20$): MA 20 mg Sb^{v+}/kg/day IV for 10 days Group 3 ($N = 22$): MA 20 mg Sb^{v+}/kg/day IV for 10 days + alternate-day injections of interferon-gamma	CR at 12-month follow-up: IT 90, 90, 100 %, respectively
Romero et al. [125]	Brazil *L. braziliensis* (61), *L. guyanensis* (57)	Quasi-experimental study	Group 1 ($N = 61$): *L. braziliensis* treated with MA 20 mg Sb^{v+}/kg/day IM for 20 days Group 2 ($N = 57$): *L. guyanensis* treated as group 1	CR at 6-month follow-up: 49.2, 73.7 %, respectively
Wortmann et al. [128]	US military personnel at Panama *L. panamensis* (18), *L. braziliensis* (2), *L. guyanensis* (1), *L. naïffi* (1), *L. major* (6), *L. tropica* (1)	Randomized, double-blind study	Group 1 ($N = 19$): SSG 20 mg Sb^{v+}/kg/day IV for 10 days Group 2 ($N = 19$): SSG 20 mg Sb^{v+}/kg/day IV for 20 days	CR at the end of 20 days treatment: 95 % for both groups
Soto et al. [119]	Bolivia, Colombia *L. panamensis* in Colombia, *Leishmania* sp. not identified in Bolivia (most probably *L. braziliensis*)	Randomized, double-blind study	Group 1 ($N = 50$): SSG 20 mg Sb^{v+}/kg/day IM for 20 days Group 2 ($N = 16$): MA 20 mg Sb^{v+}/kg/day IM for 20 days Group 3 ($N = 48$): generic SSG 20 mg Sb^{v+}/kg/day IM for 20 days	CR at 6-month follow-up: 83, 86, 91 %, respectively
Andersen et al. [121]	Peru *L. braziliensis* (70)	Open-label randomized trial	Group 1 ($N = 40$): pentamidine isethionate 2 mg/kg eod for 7 IV injections Group 2 ($N = 40$): MA 20 mg Sb^{v+}/kg/day IV for 20 days	CR at 6-month follow-up: 35, 78 %, respectively
Miranda-Verastegui et al. [130]	Peru *Leishmania* sp. not isolated (most probably *L. peruviana and L. braziliensis*)	Randomized, double-blind clinical trial	Group 1 ($N = 20$): MA 20 mg Sb^{v+}/kg/day IM or IV for 20 days + imiquimod 5 % cream applied 125–250 mg to each lesion eod for 20 days Group 2 ($N = 20$): MA 20 mg Sb^{v+}/kg/day IM or IV for 20 days + placebo cream applied 125–250 mg to each lesion eod for 20 days	CR at 12-month follow-up: 72, 75 %, respectively

Table 3 continued

Reference	Country; *Leishmania* spp.	Type of study	Regimen administered	CR
Machado-Pinto et al. [131]	Brazil *Leishmania* sp. not isolated (most probably *L. braziliensis*)	Double-blind, placebo-controlled trial	Group 1 ($N = 47$): daily SC injection of 0.5 ml of vaccine + MA 8.5 mg Sb^{v+}/kg/day IM for 10 days Group 2 ($N = 49$): daily SC injection of 0.5 ml of placebo + MA 8.5 mg Sb^{v+}/kg/day IM for 10 days Patients were re-evaluated every 20 days. If not cured, a new cycle started after 10 days of rest, maximum 4 cycles	CR at 12-month follow-up: 100, 8.2 %, respectively
LAB				
Solomon et al. [136]	Bolivia *L. braziliensis*	Prospective, observational comparative study	Group 1 ($N = 34$): LAB 3 mg/kg IV for 5 consecutive days, sixth dose on day 10 Group 2 ($N = 34$): SSG 20 mg Sb^{v+}/kg/day IV for 20 days	CR at 3-month follow-up: 85 and 70 %, respectively
Motta and Sampaio [137]	Brazil *L. braziliensis* (16), *L. amazonensis* (3), *L. shawi* (1)	Open-label, controlled clinical trial	Group 1 ($N = 16$): LAB 1.5 mg/kg/day IV for 5 days Group 2 ($N = 19$): MA 20 mg Sb^{v+}/kg/day IV for 20 days	CR at 12-month follow-up: 81 and 100 %, respectively
Pentamidine				
de Paula et al. [140]	Brazil *L. braziliensis* (11), *L. amazonensis* (5), *L. shawi* (1), *L. guyanensis* (2)	Prospective, non-randomized, controlled trial	Group 1 ($N = 38$): pentamidine isethionate 4 mg/kg/day IM eod for total 3 injections Group 2 ($N = 41$): MA 20 mg/kg/day IV for 20 days	CR at 90 days after finishing treatment: 71, 73 %, respectively
Soto et al. [66]	Colombia *Leishmania* sp. not isolated (most probably *L. panamensis* and *L. braziliensis*, *L. mexicana*)	Non-randomized, open-label, comparative study	Group 1 ($N = 38$): pentamidine isethionate 2 mg/kg/day IM eod for total 4 injections Group 2 ($N = 56$): pentamidine isethionate 3 mg/kg/day IM eod for total 4 injections	CR at 9- to 12-month follow-up: 84, 96 %, respectively
Soto-Mancipe et al. [85]	Colombia *Leishmania* sp. not isolated (most probably *L. panamensis*, *L. braziliensis*)	Randomized clinical trial	Group 1 ($N = 23$): MA 20 mg Sb^{v+}/kg/day IM for 20 days Group 2 ($N = 27$): pentamidine isethionate 2 mg/kg/day IM eod for a total of 7 injections Group 3 ($N = 20$): itraconazole 200 mg/12 h PO for 28 days Group 4 ($N = 22$): no treatment	CR at 6- to 12-month follow-up: 91, 96, 25, 36 %, respectively
Andersen et al. [121]	Peru *L. braziliensis* (70)	Open-label randomized trial	Group 1 ($N = 40$): pentamidine isethionate 2 mg/kg/day IV eod for a total of 7 injections Group 2 ($N = 40$): MA 20 mg Sb^{v+}/kg/day IV for 20 days	CR at 6-month follow-up: 35, 78 %, respectively
Neves et al. [142]	Brazil *L. guyanensis*	Randomized clinical trial	Group 1 ($N = 74$): MA 15 mg Sb^{v+}/kg/day IV for 20 days Group 2 ($N = 74$): pentamidine isethionate 4 mg/kg IM every 72 h (maximum 300 mg/dose)	CR after 6-month follow-up: 55.5 and 58.1 %, respectively

Table 3 continued

Reference	Country; *Leishmania* spp.	Type of study	Regimen administered	CR
Paromomycin				
Soto et al. [144]	Colombia *L. panamensis* (30)	Randomized clinical trial	Group 1 ($N = 30$): paromomycin 12 mg base/kg/day IM for 7 days Group 2 ($N = 30$): paromomycin 12 mg base/kg/day IM for 14 days Group 3 ($N = 30$): paromomycin 18 mg base/kg/day IM for 14 days	CR at end of treatment: 10, 45, 50 %, respectively
Hepburn et al. [145]	British soldiers in Belize *L. mexicana* (6), *L. braziliensis* (16), unknown (12)	Randomized, open-label study	Group 1 ($N = 17$): paromomycin 14 mg/kg/day IV for 20 days Group 2 ($N = 17$): SSG 20 mg Sb^{v+}/kg/day IV for 20 days	CR at 6-month follow-up: 59, 88 %, respectively
Correia et al. [146]	Brazil *L. braziliensis*	Randomized clinical trial	Group 1 ($N = 15$): pentamidine isethionate 4 mg/kg IM every 2 days for 8 injections Group 2 ($N = 15$): paromomycin 20 mg/kg/day IM for 20 days Group 3 ($N = 16$): MA 10 mg Sb^{v+}/kg/day IM for 20 days	CR at 12-month follow-up: 86.6, 93.3, 81.2 %, respectively

bid twice daily, *CR* cure rate, *eod* every other day, *IM* intramuscular, *IT* per intention-to-treat analysis, *IV* intravenous, *LAB* liposomal amphotericin B, *MA* meglumine antimoniate, *NWCL* new world cutaneous leishmaniasis, *od* once daily, *OWCL* old world cutaneous leishmaniasis, *PO* per oral, *PP* per protocol analysis, *SC* subcutaneous, *SSG* sodium stibogluconate, *tid* three times daily

[a] Topical 15 % paromomycin sulphate ointment in 12 % methylbenzethonium chloride

[b] Topical 15 % paromomycin sulphate ointment in 10 % urea

[c] Topical 15 % paromomycin sulphate and 0.5 % gentamicin sulphate ointment in a hydrophilic base

[d] Topical Herbal Extract: Mixture of Althaea rosa, Althaea officinalis and members of the families Leguminosae, Faliaceae, Malvaceae and Lythraceae (named Z-HE)

4.1.1.2 Intralesional Pentavalent Antimonials The efficacy of intralesional pentavalent antimonials has been observed mainly for *L. major* and *L. tropica* infections in Asia and the Mediterranean, with CRs of over 90 % [41, 44–48]. In a Tunisian clinical trial for *L. major* infection, intralesional antimonials obtained a CR of 93 %, but this did not appear to be higher than that of the placebo after 105 days of follow-up [49].

Another randomized clinical trial undertaken in Syria for *L. tropica* infections administered intralesional antimonials once weekly for 5 consecutive weeks. The results, when compared with recombinant interferon-γ, showed a significantly higher response with antimonials (CR 76 vs. 3 %) [50].

A randomized clinical trial in Iran, probably for infections by *L. major* and *L. tropica*, compared the efficacy of weekly intralesional antimonials up to a maximum of 12 injections versus topical paromomycin administered as an ointment twice daily until the resolution of the lesions, taking on average 45 days. Despite the response rate not being very high, the antimonials proved to be more effective (CR 41.7 %) than paromomycin (CR 16.6 %) [41].

In Saudi Arabia, a randomized clinical trial compared parenteral therapy with antimonials (15 mg Sb^{v+}/kg/day, up to a maximum 850 mg Sb^{v+}/kg, daily on 6 days a week until 12 injections) with intralesional therapy with antimonials (0.2–0.8 ml/lesion/day on alternate days over a 30-day period). The response rates were found to be similar for systemic therapy (CR 84 %) and local therapy (CR 88 %) [44].

Another non-randomized clinical trial was performed in Saudi Arabia that compared different administration doses for intralesional antimonials. Hence, intralesional antimonials until complete blanching were compared at three different doses: daily, on alternate days and weekly. The administration on alternate days (CR 97 %) or in weekly doses (CR 91 %) proved to be more effective than daily administration (CR 67 %) [45].

A randomized double-blind clinical trial carried out in Sri Lanka (*L. donovani*) reached a CR of 100 % when injecting intralesional antimonials after an average of one to six sessions. These results were compared with those of administration of intralesional 7 % hypertonic sodium chloride, without finding any statistically relevant differences between CRs. However, lesions that received antimonials healed faster [51].

In India, a prospective comparative study was done (*L. tropica*) in which the administration of two different doses of five to seven injections of intralesional antimonials given according to the size of the lesion (total amount 0.5–5 ml per lesion per injection) were compared. In one group, the injections were administered weekly for 5–7 weeks, and in the other group, the patients received two weekly injections for 3–4 weeks. The CRs of both, long (CR 92 %) and short (CR 96 %), did not show any significant differences, even though the CR was faster for the short-term treatment [52].

On the other hand, there are various studies about the benefits of the combination of intralesional antimonials with other therapeutic options. A study undertaken in Iran (probably *L. major* or *L. tropica*) showed that the efficacy of the combination of intralesional antimonials with cryotherapy was higher than its administration as monotherapy (CR 92.3 vs. 50 %) [25]. In Pakistan (*L. tropica*) the combination of intralesional and parenteral pentavalent antimonials proved to be more effective than the intralesional antimonials on their own (CR 75 vs. 55 %) [53]. Similarly, in the Yemen (probably *L. major* or *L. tropica*) a randomized trial found that the CRs achieved with combined therapies based on the combination of intralesional pentavalent antimonials either with intramuscular antimonials (CR 93.3 %) or with oral ketoconazole (CR 92.3 %) were higher than intralesional antimonials on their own (CR 58.3 %) [54]. However, in an uncontrolled prospective comparative study in military troops in Afghanistan (*L. major*), the combination of intralesional pentavalent antimonials and cryotherapy was not superior to monotherapy with intralesional antimonials [55].

In terms of side effects, local itching, erythema, pain during administration (which occasionally requires local anaesthesia), as well as hyperpigmentation of the lesion, which tends to resolve spontaneously after a couple of months, stand out [44, 56]. In other cases, the intralesional injections can cause complications when a bacterial overinfection occurs, especially when the lesions are located on the face or on extremities [57].

4.1.1.3 Topical Imidazole Drugs Formulated as an ointment, topical applications of 1 month of clotrimazole and miconazole have been used in Saudi Arabia. With clotrimazole, a CR of 16 % was reached, while none of the cases treated with miconazole were definitely cured [58].

The only double-blind randomized clinical trial was carried out in Saudi Arabia (*L. major*), where the efficacy of 1 % clotrimazole ointment was compared with that of 2 % miconazole ointment, both applied for 30 days: 67 % were cured completely or healed predominantly in the clotrimazole group, but only 35 % of the patients in the miconazole group responded clinically [59].

Topical ketoconazole was also tested in Afghanistan, but it did not significantly change the course of the lesions [60].

Recommendations

	Grade
Paromomycin regimens	
(Regimen 1) 15 % paromomycin sulphate in 12 % methylbenzethonium chloride ointment (topical) twice a day for 20 days	AI: OWCL in Israel caused by *L. major* (Regimen 1) and in Tunisia caused by *L. major* (Regimen 2)
(Regimen 2) 15 % Paromomycin sulphate and 0.5 % gentamicin sulphate in a hydrophilic base ointment (topical) twice a day for 20 days	DI: OWCL in Turkey caused by *L. tropica* (Regimen 1) or in Iran, Sudan, Tunisia caused by *L. major* or *L. tropica* (Regimen 3)
(Regimen 3) 15 % paromomycin sulphate in 10 % urea ointment (topical) twice daily for 4 weeks	
Intralesional antimonial regimens	
Sodium stibogluconate or meglumine antimoniate (intralesional) 0.5–3 ml repeatedly administered (1–3 times a week) for 4–5 consecutive weeks	AI: OWCL in Saudi Arabia caused by *L. major* and in Sri Lanka caused by *L. donovani* BII: OWCL in Syria, Iraq and Iran caused by *L. major* or *L. tropica* and in the Mediterranean basin caused by *L. infantum* CIII: OWCL in other geographical areas (no data for *L. aethiopica*)
Topic imidazole regimens	
Regimen 1: 2 % miconazole cream applied on the lesion twice a day for 30 days	DI: OWCL in Saudi Arabia caused by *L. major* (Regimen 1 and 2)
Regimen 2: 1 % clotrimazole cream applied on the lesion twice a day for 30 days	

4.1.2 Topical Drug Therapies for NWCL

4.1.2.1 Topical Paromomycin Paromomycin at 15 % plus methylbenzethonium chloride 12 % ointment twice daily for 20 days was 70–90 % effective against NWCL caused by *L. mexicana*, *L. panamensis* and *L. braziliensis* in Ecuador and Guatemala [61, 62]. Another study also developed in Ecuador showed no significant differences between the efficacy of the topical paromomycin (CR 79.3 %) treatment and the parenteral pentavalent antimonials (CR 91.7 %), even though the time until cure was longer with paromomycin [63]. However, it turned out to be ineffective in the treatment of NWCL by *L. mexicana* and *L. chagasi* in Honduras (CR 5.5 %) [64].

On several occasions, the possibility of combining topical paromomycin with a short-course treatment of pentavalent antimonials has been considered, in order to increase its efficacy and decrease secondary effects. The results obtained are disparate. In a randomized trial performed in Colombia with *L. panamensis* and *L. braziliensis* infections, topical paromomycin-methylbenzethonium chloride and injectable meglumine antimoniate in a short-course treatment regimen of 3–7 days did not exceed the 58 % CR and was less effective than antimonials on their own in a conventional treatment of 20 days [65]. However, in another study, also undertaken in Colombia but with a higher proportion of *L. panamensis* infections, the combination of topical paromomycin–methylbenzethonium chloride and injectable meglumine antimoniate in a short-course treatment of 7 days reached a CR of 90 % [66]. This leads us to consider that short-course combined therapy could be less effective for *L. braziliensis* infections.

Recommendations

Topical paromomycin regimens	Grade
15 % paromomycin sulphate in 12 % methylbenzethonium chloride ointment (topical) twice a day for 20–30 days	BI: NWCL in Ecuador and in Guatemala caused by *L. panamensis* or *L. braziliensis* or *L. mexicana*
15 % paromomycin sulphate in 12 % methylbenzethonium chloride ointment (topical) twice a day for 10 days + meglumine antimoniate 20 mg Sb^{v+}/kg/day intravenously or intramuscularly for 7 days	BII: NWCL in Colombia caused by *L. panamensis*

4.1.2.2 Intralesional Pentavalent Antimonials The experience with intralesional pentavalent antimonials is virtually nil. In a Brazilian study developed in 74 patients with NWCL by *L. braziliensis*, meglumine an-

timoniate was injected intralesionally in the four cardinal points of the lesion, until achieving complete blanching, every 3–7 days and for a total of one to five sessions with a CR of 80 % after 10 years of follow-up [67] Grade: BIII. Recently, a randomized clinical trial was performed for NWCL caused by *L. braziliensis* in Bolivia; three doses of meglumine antimoniate were injected intralesionally with 70 % CR at 6 months follow-up [68] Grade: CI.

4.2 Oral Drug Therapy

4.2.1 Oral Drug Therapy for OWCL

4.2.1.1 Azole Drugs The important heterogeneity between the studies performed about the doses used and the species of *Leishmania* treated limits the possibility of giving general recommendations.

In the case of fluconazole, its efficacy (CR 79 %) and tolerance compared with placebo was demonstrated in a clinical trial in which a dose of 200 mg/day was administered for 6 weeks in Saudi Arabia (*L. major*) [69]. A recent clinical trial conducted in Iran (*L. major*) obtained a higher response rate when the dose of fluconazole was increased from 200 to 400 mg per day for 6 weeks (CR 81 %) [70].

Ketoconazole at a dose of 600 mg/day for adults and 10 mg/kg/day for children for 30 days obtained significantly higher CRs (89 %) than intralesional antimonials in a randomized trial in Iran (*L. major* and *L. tropica*) [71]. However, the dose of 400 mg/day for 30 days proved ineffective in Turkey (CR 0, and 21.9 % had incomplete healing) [72]. These poor results were possibly due to the high proportion of infection by *L. tropica*. Another trial developed in Kuwait with the aim of determining the most effective doses of ketoconazole compared doses of 600 mg/day (CR 80 %) and 800 mg/day (CR 81.8 %) for 6 weeks without any evidence of a difference between regimens [73].

Several randomized clinical trials have compared itraconazole with placebo. Mild results were obtained in India (*L. tropica*), where a dose of 4 mg/kg/day for 6 weeks elicited CRs of 66.7 % [74], and good results were obtained in Iran (*L. major*), where a dose of 7 mg/kg/day for 3 weeks elicited CRs of 95 % [75]. Nonetheless, itraconazole at a dose of 200 mg/day for 8 weeks in Iran (*L. major*) presented lower CRs of 59 % [76].

One case described a cure of OWCL by *L. infantum* treated with oral posaconazole [77].

4.2.1.2 Miltefosine There is scarce experience in the use of miltefosine for treating OWCL. It has been mainly used against *L. major* infections, for which response rates vary between 87 and 100 % [78, 79]. The only clinical trial performed for OWCL studied *L. major* infections in Iran and concluded that oral miltefosine (CR 81.3 %) is as effective as the intralesional antimonials (CR 80.6 %) [80]. The applicability of miltefosine for OWLC due to *L. tropica* or *L. infantum* infections is only based on a few case reports [81, 82].

Recommendations

	Grade
Azole regimens	
(Regimen 1) Fluconazole (oral) 400 mg/day for 6 weeks (Regimen 2) Ketoconazole (oral) 600 mg/day for 6 weeks (Regimen 3) Itraconazole (oral) 400 mg/day for 3–6 weeks	AI: OWCL in Saudi Arabia and Iran caused by *L. major* (Regimen 1), Iran and Kuwait caused by *L. major* (Regimen 2) and in Iran caused by *L. major* (Regimen 3) BI: OWCL in India caused by *L. tropica* (Regimen 3) CI: OWCL in Turkey caused by *L. tropica* (Regimen 2)
Miltefosine regimens	
Miltefosine (oral) 2.5 mg/kg/day (150 mg for an adult) for 28 days	BI: OWCL in Iran caused by *L. major* CIII: OWCL in other geographical areas caused by *L. major* or *L. tropica* or *L. infantum*

4.2.2 Oral Drug Therapy for NWCL

4.2.2.1 Azole Drugs There is evidence that ketoconazole at a dose of 600 mg daily taken orally over 28 days obtained a response rate of between 76 and 90 % in NWCL in Guatemala and Panama for infections by *L. mexicana*, *L. panamensis*, but not by *L. braziliensis* [83, 84]. Itraconazole at doses of 400 mg daily over 28 days did not show any benefits in a randomized trial for the treatment of undifferentiated NWCL in Colombia (CR 25 %) [85].

4.2.2.2 Miltefosine Miltefosine has been used in the treatment of several NWCL species with variable effi-

cacy. First results were obtained in Colombia, where the most frequent species is *L. panamensis* and where CRs with miltefosine were >80 % [86, 87]. However, a later clinical trial also performed in Colombia found a CR lower than 70 %, probably due to the high proportion of *L. braziliensis* cases [88]. Moreover, in NWCL in Guatemala for infections by *L. braziliensis* and *L. mexicana*, the CR with miltefosine at 6-month follow-up was <50 % [86]. Another study, performed in Bolivia in an area with a predominance of *L. braziliensis*, compared oral miltefosine with parenteral pentavalent antimonials, did not find differences between them, and reported a CR >80 % among those treated with miltefosine [89]. In Brazil, the response rate for *L. braziliensis* was 75 % [90], and slightly lower (CR 71.4 %) for *L. guyanensis* [91]. A recent study performed in Germany with imported leishmaniasis found in travelers, collected data from eight patients with cutaneous lesions caused by *L. braziliensis* after travelling to Bolivia, Costa Rica, Peru, Ecuador or Brazil and reported a 63 % overall CR [92]. The varying and lower rate of efficacy observed in the clinical trials probably reflects the lower intrinsic sensitivity of *L. braziliensis* strains to miltefosine. It has been postulated that this is due to a reduced capacity of *L. braziliensis* to internalize miltefosine from the extracellular medium [93].

Recently, the first clinical trial evaluating the effect of oral miltefosine for children aged 2–12 years with NWCL, in an area in Colombia where *L. panamensis* and *L. guyanensis* infections predominate, was performed. It showed that miltefosine 1.8–2.5 mg/kg/day for 28 days, with a CR of 82.7 %, was not inferior to parenteral meglumine antimoniate 20 mg Sb^{v+}/kg/day intramuscularly for 20 days, with a CR of 69 %, and had lower toxicity [94].

4.2.2.3 Other Oral Treatments Azithromycin initially demonstrated, in vitro and in animal models, its capacity against *L. major* [95]. Later, several non-randomized trials obtained good results in patients with cutaneous and mucocutaneous lesions [95–97]. However, the only randomized clinical trial showed that a dose of 500 mg per day for 28 days had very little efficacy (CR 45.5 %) in the treatment of NWCL by *L. braziliensis* in Argentina [98].

Several studies have evaluated the efficacy of allopurinol for the treatment of NWCL. Despite some hopeful results [99], the clinical trials showed no efficacy as monotherapy in Colombia in infections by *L. panamensis* or *L. braziliensis* (CR 29.1 %) [98], or when combined with probenecid in Ecuador (CR 42.8 %) [100].

Recommendations

Grade	
Azole regimens	
Ketoconazole (oral) 600 mg/day for 4 weeks	BI: NWCL in Guatemala caused by *L. mexicana* and in Panama caused by *L. panamensis*
Itraconazole (oral) 400 mg/day for 4 weeks	DI: NWCL in Colombia
Miltefosine regimens	
Miltefosine (oral) 2–2.5 mg/kg/day for 20–28 days: 50 mg/day for 28 days in ≥12 years old with weight <25 kg; 100 mg/day for 28 days in ≥12 years with body weight ≥25 kg; 150 mg/day for 28 days in ≥12 years with body weight >50 kg	BI: NWCL in Colombia caused by *L. panamensis* and in Brazil caused by *L. guyanensis* or *L. braziliensis*. Recommendation for *L. braziliensis* and other spp. may vary depending on the area
Azithromycin and allopurinol regimens	
Azithromycin (oral) 500 mg/day for 28 days	DI: NWCL in Argentina caused by *L. braziliensis*
Allopurinol (oral) 20 mg/kg/day for 28 days	DI: NWCL in Colombia or Ecuador caused mainly by *L. panamensis* or *L. braziliensis*

4.3 Parenteral Therapy

4.3.1 Parenteral Therapy for OWCL

4.3.1.1 Pentavalent Antimonials Pentavalent antimonials at a doses of 20 mg Sb^{v+}/kg/day (intramuscular or intravenous) for 20–30 days without an upper limit [101] have proven effective in Eastern Africa, the Middle East and the Mediterranean countries [102, 103], but with different response rates between species, with CRs of 75–98 % for *L. major* and 41–53 % for *L. tropica* [12, 103–106].

There are few studies in children. One was conducted in Algeria and demonstrated superiority over placebo when administrated for 15 days (55 vs. 48 %) [107]. Another study conducted in Iran showed a lower efficacy (74.2 vs. 80.6 %) in treating acute (<3 months) lesions in children (≤15 years old) versus adults [108].

Several studies have been conducted in Iran examining the combination of drugs at the habitual doses of parenteral antimonials, with the intention of increasing their efficacy, and have obtained disparate results. The combination of oral allopurinol at doses of 15–20 mg/kg/day for 20 days (*L. tropica*) proved to be more effective than monotherapy but only achieved a CR of 46 % [109]. However, in another study, the combined therapy

of parenteral antimonials (30 mg Sb^{v+}/kg/day) and oral allopurinol (20 mg/kg/day) for 20 days reached higher CRs (80.6 %) [110]. A clinical trial (*L. major*) found a CR of 81.3 % when using the combination of parenteral antimonials (20 mg Sb^{v+}/kg/day) and oral pentoxifylline (400 mg three times daily) for 20 days, superior to the 51.6 % CR obtained by antimonials as monotherapy [111]. The combination of topical 5 % imiquimod cream three times per week with parenteral pentavalent antimonials for 14 days does not seem to result in additional benefits (CR 50.8 %) [105].

Recommendations

Pentavalent antimonials regimens	Grade
(Regimen 1) Sodium stibogluconate or meglumine antimoniate (intramuscular or intravenous) 20 mg Sb^{v+}/kg/day for 20–30 days	BI: (Regimen 2 and Regimen 3) OWCL in Iran caused by *L. major*
(Regimen 2) Sodium stibogluconate or meglumine antimoniate (intramuscular or intravenous) 20 mg Sb^{v+}/kg/day for 20 days ± allopurinol (oral) 20 mg/kg/day for 20 days	BIII: (Regimen 1) OWCL in Iran and Afghanistan caused by *L. major*
(Regimen 3) Sodium stibogluconate (intramuscular or intravenous) 20 mg Sb^{v+}/kg/day for 20 days as above + pentoxifylline (oral) 400 mg/8 h for 20 days	CIII: (Regimen 1): OWCL in Kenya and Sudan caused by *L. tropica*

4.3.1.2 Liposomal Amphotericin B (LAB) Experience with using liposomal amphotericin B (LAB) for the treatment of OWCL is very scarce. The majority of cases that required systemic parenteral treatment received pentavalent antimonials. However, their toxicity encourages the increasing choice of LAB by more and more professionals, especially in those situations where pentavalent antimonials have failed [112–117].

A study conducted in the USA collected therapeutic response of LAB treatment for OWCL at doses of 3 mg/kg/day up to ten doses, given within a 21-day period, in ten travelers (five from Iraq and five from Afghanistan) with isolated species of *L. major* (three cases) and *L. tropica* (two cases). The general response rate when finishing the treatment was 84 %. However, all the failed attempts responded in a second cycle [118].

4.3.2 Parenteral Therapy for NWCL

4.3.2.1 Pentavalent Antimonials Currently, the first-choice treatment for NWCL in many countries continues to be pentavalent antimonials at a dose of 20 mg Sb^{v+}/kg/day, without a maximum dose of 850 mg/day and for at least 20 days. With these doses, the CRs vary between 77 and 90 % depending on the species [100, 119–121], with the exception of *L. guyanensis* infection in French Guinea where pentamidine is the first-choice treatment [122]. Despite this, other cases of NWCL by *L. guyanensis* in Peru had a response rate to pentavalent antimonials of >90 % [123, 124] or of 73.3 % [125]. Similarly, *L. mexicana* responds poorly in Guatemala (CR 57 %) [32], but very well in Mexico (CR 100 %) [124].

Due to the potential toxicity of the systemic antimonials, several trials were designed to find the lowest effective doses. Intravenous sodium stibogluconate 20 mg/kg/day was compared with intravenous doses of 10 mg/kg/day to treat cases of NWCL caused by *L. braziliensis* or *L. panamensis* in Panama, and showed that CRs were significantly lower with the lower doses (CR 76.2 vs. 100 %) [126]. Later, in another study also conducted in Panama with infections by *L. panamensis* and to a lesser extent by *L. mexicana*, it was found that, with doses of antimonials less than 13 mg/kg/day for 20 days, the CR was only 68 % [82]. Along the same lines, a randomized clinical trial was performed in Guatemala with *L. braziliensis* and *L. mexicana* infections; meglumine antimoniate was used at doses of 15 mg/kg/day for 15 days, and the CR reached 64 % [62]. However, in later studies conducted in Guatemala and Panama, where the duration of treatment was cut to fewer days, it was proven that favorable results could also be obtained by administering 20 mg/kg/day for fewer than 20 days, (CR 90 % and 95 %, respectively) [127, 128].

The Pan-American Health Organization (PAHO) guide for the treatment of infectious diseases recommends sodium stibogluconate 20 mg Sb^{v+}/kg/day intramuscularly or intravenously for 20 days as first-line treatment for all *Leishmania* spp. [129].

Combination therapy has been used in some studies. Topical administration of the immunomodulator imiquimod every other day for 20 days as adjunct therapy to pentavalent antimonials has been tested in Peru (CR 72 %). Although no significant difference among CRs was observed, imiquimod accelerated cure in comparison with antimonials alone in patients with relapsing lesions [130].

The use of immunotherapy based on the administration of a vaccine containing dead promastigotes of *L. amazonensis* associated with low doses of pentavalent antimonials was tested in Brazil in a randomized double-blind study.

Not only did it prove to be highly effective (CR 100 %), but the lesions were also cured faster than with the conventional doses of antimonials [131]. Injected autoclaved *L. mexicana* and *L. amazonensis* promastigotes together with Bacillus Calmette Guerin tuberculosis vaccine (BCG) have been tested in combination with systemic antimonials in Venezuela, with high success (CR 95.7 %) [132].

4.3.2.2 Amphotericin B and LAB Amphotericin B deoxycholate (AB) at 0.7/mg/kg/day for 25–30 doses has been used for the treatment of NWCL by *L. braziliensis*. With LAB, there is more experience with the treatment of mucocutaneous types than there is for the cutaneous form in Peru, Bolivia and Brazil caused by *L. braziliensis*, *L. guyanensis* and *L. panamensis*. The doses administered vary and usually consist of 3 mg/kg/day up to 10–15 doses (20–45 mg/kg total doses) [118, 133–135]. Not many controlled clinical trials are able to give a clear response for LAB in NWCL. In one, undertaken in Bolivia for *L. braziliensis* infection, LAB proved to be more effective (CR 85 %), better tolerated and more cost effective than antimonials [136]. Another clinical trial in Brazil, mainly for infections by *L. braziliensis*, found that low doses of LAB achieved a high CR (81 %), although lower than that obtained by pentavalent antimonials (CR 100 %) but with fewer side effects [137].

4.3.2.3 Pentamidine Isethionate Several studies have compared the efficacy of pentamidine isethionate with pentavalent antimonials when treating NWCL. The results have been disparate according to different geographical locations and species involved. Administered at intravenous or intramuscular doses of 3–4 mg/kg/day every other day for 4–10 injections, it is the drug of choice in French Guyana, where over 90 % of infections are due to *L. guyanensis* [138, 139]. Similarly, in Brazil with primarily *L. braziliensis*, and in Surinam with *L. guyanensis*, CRs of 73–100 % have been obtained [140, 141]. Nonetheless, recent clinical trials have demonstrated a low response in those cases acquired in Brazil and caused by *L. guyanensis* (CR 58.1 %), but with no significant differences in the CR in response to antimonials [142]. In Colombia, where the majority of infections are caused by *L. panamensis*, CRs of up to 95 % have been reached in patients treated with four injections of 3 mg/kg/day every other day and with a toxicity comparable to that of antimonials [85, 143]. The results obtained in Peru with *L. braziliensis* were less favorable; the efficacy of pentamidine was 35 % compared with 78 % with antimonials [121].

4.3.2.4 Paromomycin Data regarding the response to paromomycin are fundamentally limited to topical treatment, due to the lack of knowledge about their efficacy when administered parentally. Once again, the results of the different studies are disparate and the size of the groups under study rather small. Intramuscular paromomycin administered at a dose of 12–18 mg/kg/day for 14 days obtained CRs as low as 50–60 % in Colombia and in Belize [144, 145]; however, CRs in Brazil reached over 90 % [146]. It is likely that these differences are due to a heterogeneous response in different species. In any case, it is necessary to conduct more studies to be able to determine with any precision the efficacy of paromomycin and to evaluate it for use as an alternative treatment to pentavalent antimonials.

Recommendations

	Grade
Pentavalent antimonial regimens	
(Regimen 1) Sodium stibogluconate or meglumine antimoniate (intramuscular or intravenous) 20 mg Sb^{v+}/kg/day (without upper limit of 850 mg/day) for 20 days	AI: (Regimen 1) NWCL in Panama, Colombia and Ecuador caused by *L. panamensis* and in Guatemala *L. braziliensis* BI: (Regimen 1) NWCL in Peru caused by *L. braziliensis*
(Regimen 2) Sodium stibogluconate or meglumine antimoniate (intramuscular or intravenous) 20 mg Sb^{v+}/kg/day (without upper limit of 850 mg/day) for 10 days	BI: (Regimen 2) NWCL in Panama caused by *L. panamensis* and in Guatemala caused by *L. braziliensis* BII: (Regimen 1) NWCL in Brazil caused by *L. guyanensis*
LAB regimens	
Intravenous LAB 1.5–3 mg/kg/day up to 7.5–18 mg/kg total dose	BII: NWCL in Bolivia and Brazil caused by *L. braziliensis*
Pentamidine regimens	
Intravenous or intramuscular pentamidine isethionate 3–4 mg/kg/day every other day, for a total of 4–10 injections	BI: NWCL in Colombia caused by *L. panamensis* BII: NWCL in Brazil caused by *L. braziliensis* BIII: NWCL in French Guyana and Surinam caused by *L. guyanensis* DI: NWCL in Peru caused by *L. braziliensis*
Paromomycin regimens	
Intramuscular paromomycin sulphate 20 mg (15 mg base)/kg/day for 20 days	BI: NWCL in Brazil caused by *L. braziliensis* DI: NWCL in Belize and Colombia caused by *L. panamensis* or *L. braziliensis*

5 Treatment of New World Mucocutaneous Leishmaniasis

Table 4.

Table 4 Drug therapy for new world mucocutaneous leishmaniasis

Reference	Country; *Leishmania* spp.	Type of study	Regimen administered	CR
Oral drugs				
Miltefosine				
Soto et al. [150]	Colombia *L. braziliensis* (7)	Non-randomized trial	Group 1 ($N = 72$): miltefosine 2.5–3.3 mg/kg/day PO for 28 days Group 2 ($N = 14$): AB 1 mg/kg IV eod for 45 injections. Because of the lack of clinical response, 3 patients received 15 additional injections	CR at 12-month follow-up: 71, 50 %, respectively
Parenteral drugs				
Paromomycin				
Llanos-Cuentas et al. [157]	Peru *Leishmania* sp. not isolated (probably due to *L. braziliensis*)	Randomized clinical trial	Group 1 ($N = 21$): paromomycin 14 mg/kg/day IM for 21 days Group 2 ($N = 17$): MA 20 mg Sb^{v+}/kg/day IV for 28 days	CR at 12-month follow-up: 0, 47.1 %, respectively
Pentavalent antimonials				
Franke et al. [158]	Peru *L. braziliensis* (22)	Open-label study	($N = 29$): SSG 20 mg Sb^{v+}/kg/day IV for 28 days	CR at 12-month follow-up: 28.6 %
Franke et al. [162]	Peru *L. braziliensis*	Randomized controlled trial	Group 1 ($N = 16$): SSG 20 mg Sb^{v+}/kg/day IV for 28 days Group 2 ($N = 19$): SSG 20 mg Sb^{v+}/kg/day IV for 40 days	CR at 12-month follow-up: 63 % for both groups
Llanos-Cuentas et al. [163]	Peru *L. braziliensis*	Randomized, open-label trial	Group 1 ($N = 41$): SSG 20 mg Sb^{v+}/kg/day IV for 28 days Group 2 ($N = 40$): SSG 20 mg Sb^{v+}/kg/day IV for 28 days + allopurinol 20 mg/kg/day PO divided in four doses for 28 days	CR at 12-month follow-up: severe leishmaniasis 20, 0 %. Moderate leishmaniasis 75, 63.6 %, respectively
Oliveira-Neto et al. [159]	Brazil *Leishmania* sp. not isolated (probably *L. braziliensis*)	Randomized, non-comparative, open-label study in mild to moderate cases	Group 1 ($N = 21$): MA 5 mg/kg/day IM for 30 days Group 2 ($N = 10$): MA 5 mg/kg/day IM for 45 days Group 3 ($N = 4$): MA 15 mg/kg/day IM for 10 days	CR at the end of treatment: 100, 70, 100 %, respectively
Lessa et al. [168]	Brazil *L. braziliensis* (5)	Open-label study	10 patients with refractory mucosal leishmaniasis received pentoxifyline 400 mg tid PO + MA 20 mg Sb^{v+}/kg/day IV for 30 days	CR at 12-month follow-up: 90 %
Machado et al. [169]	Brazil *Leishmania* sp. not isolated (probably due to *L. braziliensis*)	Double-blind, randomized controlled trial	Group 1 ($N = 11$): MA 20 mg Sb^{v+}/kg/day IV + pentoxifyline 400 mg/8 h PO for 30 days Group 2 ($N = 12$): MA 20 mg Sb^{v+}/kg/day IV + placebo PO for 30 days	CR 100 % in both groups. Group 1: needed only one course of MA. Group 2: 41.6 % of patients needed a second course of MA. Lesions in group 1 healed in 83 ± 36 days, in Group 2 in 145 ± 99 days
Amphotericin B				
Rodriguez et al. [149]	Bolivia *Leishmania* sp. not isolated (probably due to *L. braziliensis*)	Randomized clinical trial	Group 1 ($N = 10$): AB 50 mg in 500 ml 5 % dextrose IV over 8 hr, every 2 days until lesions healed Group 2 ($N = 10$): AB 50 mg in 500 ml 5 % dextrose IV over 8 h, every 2 days until lesions healed + itraconazol 200 mg/day PO for 41 days. 10 days preceding AB, then simultaneously with AB up to 15th infusion	CR at 9-month follow-up: 90 and 80 %, respectively

AB amphotericin B deoxycholate, *contr* controlled, *CR* cure rate, *eod* every other day, *IM* intramuscular, *IV* intravenous, *MA* meglumine antimoniate, *PO* per oral, *SSG* sodium stibogluconate

5.1 Oral Treatment

5.1.1 Azole Drugs

The experience in NWMCL with azoles is fundamentally limited to itraconazole. Two studies evaluated its efficacy as monotherapy, with disparate results. In infections mainly caused by *L. braziliensis* in Brazil, doses of 4 mg/kg/day for 6 weeks resulted in a CR of 60 % [147]. However, in Ecuador and also predominantly in lesions caused by *L. braziliensis*, doses of 400 mg/day for 12 weeks only resulted in a CR of 23 % [148]. In a randomized clinical trial conducted in Bolivia and Peru, the combination of itraconazole with amphotericin B did not result in any additional benefit (CR 80 %) [149]. Grade: CIII.

5.1.2 Miltefosine

The results of several studies carried out using miltefosine in Colombia and Guatemala demonstrated an important variability in the CR depending on the geographical area and the *Leishmania* species isolated [86]. Good results observed in Colombia suggest that miltefosine may also be a good option for NWMCL. Similarly, a non-randomized clinical trial carried out in Bolivia, using miltefosine at doses of 2.5–3.3 mg/kg/day for 28 days, reached a CR of 83 % for moderate NWMCL and 58 % for severe cases, versus 50 % among those treated with AB [150]. Subsequently, the same patients were re-evaluated 24 months after the beginning of the trial. It was observed that only 2 of 41 patients relapsed. Prolonging treatment from 4 to 6 weeks was also evaluated and was seen to increase the CR to 75 % [151].

5.2 Parenteral Treatment

5.2.1 Pentamidine

Two studies published by the same research group from Brazil, in patients with moderate-to-severe NWMCL in whom pentamidine was used as first-line treatment, obtained good CRs (90 and 94 %, respectively) [152, 153]. In a more recent study, again from Brazil, in which 140 mainly slight NWMCL cases were analyzed, pentamidine obtained the same CR as antimonials [154]. The PAHO guide for the treatment of infectious recommends pentamidine as a second-line therapeutic option. Grade: BII [129].

5.2.2 Paromomycin

There are two published case series from Brazil in which patients with NWMCL were treated with paromomycin sulfate at doses of 16 mg/kg/day for 20 days and obtained a CR of between 48 and 67 % [155, 156]. A randomized clinical trial performed in Peru found that paromomycin at doses of 14 mg/kg/day over 21 days was ineffective for the treatment of NWMCL (CR 0 %) [157].

5.2.3 Pentavalent Antimonials

Studies evaluating the efficacy of pentavalent antimonials in NWMCL are scarce, and the majority is based on a small sample group. CRs vary from 30 to 90 % [158–161]. A meta-analysis that includes the different studies published regarding the use of pentavalent antimonials in NWMCL until 2007 determined a global CR of around 67 %, which appears to be conditional on the species implicated, the geographical location and the severity of the lesions [162–164]. The standard doses are 20 mg Sb^{v+}/kg/day for 28–30 days.

Because of the therapeutic failure rate of antimonials (up to 42 %) [158] and the frequent relapses (up to 20 %) [161], in many cases it is necessary to repeat the cycles of antimonials, despite their potential toxicity. Therefore, attempts have been made to find other drugs that, when combined with antimonials, improve the response rate. Tumor necrosis factor (TNF)-α appears to play an important role in the inflammatory response of the host and therefore in their healing [165, 166]. Pentoxifylline has demonstrated the ability to inhibit gene transcription of TNF-α, thus decreasing leukocyte adhesion and migration [167]. In a preliminary study, pentoxifylline was combined with antimonials in patients for whom antimonials had previously failed, obtaining a response in nine of the ten patients treated within 1 year [168]. These results gave rise to the development of a randomized clinical trial that compared combination therapy of pentoxifylline and antimonials versus antimonials alone. Both groups had the same CR (100 %); however, cure was accelerated, and the relapse rate reduced, in patients receiving pentavalent antimonials combined with pentoxifylline when compared with patients receiving antimonials alone [169]. In fact, the PAHO guide for the treatment of infectious diseases recommend antimonials plus pentoxifylline for 30 days as the first-line therapeutic option for NWML [129].

Recommendations	
	Grade
Miltefosine regimens	
Miltefosine (oral) 2.5–3.3 mg/kg/day for 28 days	BII: moderate NWMCL in Bolivia caused by *L. braziliensis*
Paromomycin regimens	
Paromomycin (intramuscular) 15 mg (11 mg base)/kg/day for 21 days	DI: NWMCL in Peru most probably caused by *L. braziliensis*
Pentavalent antimonials regimens	
Sodium stibogluconate or meglumine antimoniate (intramuscular or intravenous) 20 mg Sb^{v+}/kg/day (without upper limit of 850 mg/day) for 28–30 days	BII: NWMCL in Brazil and Peru caused by *L. braziliensis* BI: NWMCL in Brazil caused by *L. braziliensis*
Meglumine antimoniate (intramuscular or intravenous) 20 mg Sb^{v+}/kg/day (without upper limit of 850 mg/day) for 30 days + pentoxifylline (oral) 400 mg 3 times a day for 30 days	

5.2.4 Amphotericin B and LAB

Amphotericin B at a total dose of 2.25 g proved effective (CR 88 %) in Bolivia in 211 patients with NWMCL by *L. braziliensis* [149]. In a small randomized study conducted in Bolivia and Peru, doses of 50 mg every 2 days until lesions healed was very effective (CR 90 %), and the addition of oral itraconazole for 41 days did not improve the CR (80 %) [149]. Grade: BII.

Results with LAB were better than with AB, even in those cases in which therapy with antimonials had previously failed. Three published case series conducted in Brazil included a total of 15 patients with NWMCL caused by *L. braziliensis* who received LAB 2–3 mg/kg/day until a total dose of 40–50 mg/kg and achieved response rates of between 83.3 and 100 % [154, 170, 171]. Recently, a short series of cases from Brazil was published where patients received an average total dose of 35 mg/kg of LAB, yielding a CR of 100 % and no recurrence at 25 months of median follow-up. Given the results, the authors raised the possibility that lower doses of LAB than those routinely recommended could be sufficient, thus reducing the toxicity and cost of treatment [172]. Grade BIII.

6 Treatment of New World Diffuse Cutaneous Leishmaniasis (NWDCL)

Diffuse CL is a rare variety of NWCL that is caused by a cellular immunodeficiency of the host facing the parasite. Amastigotes progressively disseminate into the macrophages that are all over the skin, creating nodules or cutaneous plates. Cases have been recorded in the USA, Mexico, Dominican Republic, Honduras, Venezuela, Colombia, French Guinea, Brazil, Peru, Paraguay and Bolivia. The most frequent species involved is *L. amazonensis*, although cases of *L. mexicana* [173] and *L. panamensis* [174] have been described.

The therapeutic response to NW diffuse CL (NWDCL) is usually very poor. Pentavalent antimonials are the first-line drugs and are usually effective in the initial stages; however, in more advanced stages, recurrence is the usual outcome [175, 176]. Other drugs such as miltefosine have been tested with disparate results and in discouraging terms [177–179]. AB was tested with favorable results but lesions recurred a few months later [175]. There are no data regarding lipid formulations of AB.

7 Conclusions

Despite the lack of evidence, until the 1990s, parenteral pentavalent antimonials were the chosen drugs for the treatment of OWCL. However, things have changed recently. The fact that a high percentage of OWCL cases cure spontaneously, together with the good results obtained from different studies published about local therapies (thermotherapy, paromomycin ointment, intralesional antimonials), mean the latter are currently considered first-line treatments in most cases. Moreover, the combinations of local therapies and parenteral pentavalent antimonials have an additional therapeutic effect. The different oral therapies (azole drugs, miltefosine) decrease the costs derived from hospitalization. Little is known about the efficacy of LAB, as the current knowledge is limited to case series fundamentally based on patients in whom other treatments had previously failed.

For NWCL, local treatment can be considered in specific situations. However, the established treatment is the systemic one, although its efficacy depends on the species of *Leishmania* involved and the geographical area. Pentavalent antimonials are the most used but cause side effects, and a prolonged duration of the treatment is needed. For *L. amazonensis* and *L. peruviana*, pentavalent antimonials seem to be the best treatment option. In the case of *L.*

mexicana, oral treatment with ketoconazole or miltefosine is recommended. In the case of *L. guyanensis* and *L. panamensis*, pentamidine and miltefosine have been proposed as alternative treatments. In the case of *L. braziliensis*, AB and LAB are good alternatives. Recurrence in any case seems to respond best to LAB.

For NWMCL, it seems that systemic treatment is always the best option. The recommended drugs are pentavalent antimonials (for 30 days and best associated with pentoxifylline), AB or LAB. Many more randomized clinical trials identifying the species of *Leishmania* involved, and conducted in different geographical areas, are required in order to establish the first-line drugs and treatment of recurrences.

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