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An Update on Pharmacotherapy for Leishmaniasis

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Abstract

Introduction—Leishmaniasis broadly manifests as visceral leishmaniasis (VL), cutaneous leishmaniasis (CL) and mucocutaneous leishmaniasis (MCL). The treatment of leishmaniasis is challenging and the armamentarium of drugs is small, duration of treatment is long, and most drugs are toxic.

Areas covered—A literature search on treatment of leishmaniasis was done on PubMed. Single dose of liposomal amphotericin B (L-AmB) and multidrug therapy (L-AmB + miltefosine, L-AmB + paromomycin (PM), or miltefosine + PM) are the treatment of choice for VL in the Indian subcontinent. A 17-day combination therapy of pentavalent antimonials (Sb^V) and paromomycin remains the treatment of choice for East African VL. L-AmB is the recommended regimen for VL in the Mediterranean region and South America. Treatment of CL should be decided by the severity of clinical lesions, etiological species and its potential to develop into mucosal leishmaniasis.

Expert opinion—There is an urgent need to implement a single dose L-AmB or combination therapy in the Indian subcontinent. Combination therapy with newer drugs needs to be tested in Africa. Due to the toxicity of systemic therapy, a trend towards local treatment for New World CL (NWCL) is preferred in patients without risk of mucosal disease.

Keywords

leishmaniasis; visceral leishmaniasis; kala azar; cutaneous leishmaniasis

1. Introduction

1.1 Organism

Leishmaniasis, a vector-borne neglected tropical disease, caused by an obligate intracellular protozoan of the genus *Leishmania*, order Kinetoplastida, family Trypanosomatidae. Clinical manifestations range from self healing cutaneous ulcers to severe systemic

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multiorgan disease. It broadly manifests as visceral leishmaniasis (VL; also known as kala-azar), cutaneous leishmaniasis (CL) and mucocutaneous leishmaniasis (MCL).

VL is caused by the *Leishmania donovani* complex: *L. donovani*, the causative organism of VL in the Indian subcontinent and Africa; *L. infantum* (*L. chagasi*) which causes VL in the Mediterranean basin, Central and South America. CL is caused by various *Leishmania* species. Based on its geographical distribution, CL can be divided into Old World (OWCL) which includes southern Europe, the Middle East, parts of southwest Asia, Central Asia and Africa. OWCL is caused by *L. aethiopica*, *L. donovani*, *L. infantum*, *L. major* and *L. tropica*. New World cutaneous leishmaniasis (NWCL) occurs in Mexico and Latin America and is caused by multiple species of both the *Leishmania* subgenera : *L. amazonensis*, *L. infantum*, *L. mexicana*, *L. venezuelensis* and the *Viannia* subgenera: *L. braziliensis*, *L. guyanensis*, *L. panamensis*, *L. peruviana*.

MCL is caused by New World *Leishmania* species *L. braziliensis* and *L. panamensis*^{1,2}. Recently there is a case report of MCL caused by *L. major* in Iran³. Diffuse CL a severe form of CL is caused by *L. aethiopica* in the Old World and *L. mexicana* and *L. amazonensis* in the New World.^{1,2}

The only proven vectors of human disease are sand fly of species of genus *Phlebotomus* in the Old World and *Lutzomyia* in the New World.¹ Transmission is of two types: anthroponotic where the vector transmits the disease from infected to healthy humans and zoonotic where the vector transmits the disease from an animal reservoir to humans. In South Asia and the Horn of Africa, the predominant mode of transmission of VL is anthroponotic, and humans with kala-azar or post--kala-azar dermal leishmaniasis (PKDL) provide the major reservoir for transmission.^{2,4,5} In the Mediterranean, the Middle East and Brazil, VL is zoonotic, with the domestic dog as the most important reservoir host sustaining transmission.⁵ Most CL have zoonotic transmission except those caused by *L. tropica*, which is predominantly anthroponotic.

1.2 Disease

VL is the most severe form of leishmaniasis, characterized by prolonged fever, splenomegaly, hepatomegaly, pancytopenia, progressive anemia and weight loss. If untreated, VL is uniformly fatal. After recovery, about 50% of patients in Sudan and 10% in the Indian subcontinent develop dermal leishmaniasis characterized by indurated nodules or depigmented macules called PKDL.^{1,6,7} The incidence of PKDL is increasing in Bangladesh, while it is still low in India.^{8,9} Few cases of PKDL caused by *L. infantum* have also been reported.¹⁰⁻¹²

The clinical features of CL tend to vary between and within regions, reflecting different species of parasite or the type of zoonotic cycle concerned, immunological status and also perhaps genetically determined responses of patients.¹³ OWCL is often benign and self-limiting, while New World species cause a wide spectrum of manifestation, from benign to severe disease including mucosal involvement.²

1.3 Epidemiology

Approximately 0.2 to 0.4 million VL cases and 0.7 to 1.2 million CL cases occur each year. More than 90% of global VL cases occur in just six countries: India, Bangladesh, Sudan, South Sudan, Brazil and Ethiopia. CL is more widely distributed, with about one-third of cases occurring in each of three regions, the Americas, the Mediterranean basin and western Asia from the Middle East to Central Asia. The ten countries with the highest estimated case counts, Afghanistan, Algeria, Colombia, Brazil, Iran, Syria, Ethiopia, North Sudan, Costa Rica and Peru, together account for 70 to 75% of globally estimated incidence of CL.¹⁴

HIV-VL co-infection has been reported from more than 35 countries. Initially, most of these cases were from southwestern Europe, but the number of cases is increasing in sub-Saharan Africa especially Ethiopia, Brazil and South Asia.¹⁵⁻¹⁷ Two large study from the hyperendemic region of Bihar, India showed that 1.8-4.5% of VL patients were HIV-positive.^{18, 19} The incidence of VL/HIV co infection increased from 0.32/100,000 in 2007 to 1.08/100,000 in 2010 in Northern Brazil.²⁰ While 51% of 90 confirmed VL patients in a urban referral centre in Brazil were HIV coinfectd.²¹ In Ethiopia 10.4% -40% of VL patients were co-infected with HIV in different centres.^{22, 23}

2. Review of antileishmanial agents

2.1 Pentavalent antimonials (Sb^V)

Sb^V is available as Sodium stibogluconate (SSG) and meglumine antimoniate (MA). Daily injection of 20 mg/kg body weight for 28 -- 30 days have been the standard treatment for VL in most parts of the world. But in the early 1980s reports of its ineffectiveness emerged from Bihar²⁴, and the dose of Sb^V was eventually raised to 20 mg/kg for 30-40 days²⁵. This regimen cures most patients with VL except in India, where the proportion of patients unresponsive to Sb^V has steadily increased. In hyperendemic districts of north Bihar, 50-65% patients fail treatment with Sb^V²⁶. Important reasons are rampant use of subtherapeutic doses, incomplete duration of treatment and substandard drugs²⁷. In vitro experiments have established emergence of Sb^V resistant strains of *Leishmania donovani*, as isolates from unresponsive patients require 3-5 times more Sb^V to reach similarly effectiveness against the parasite as in Sb^V responders²⁸. Anthroponotic transmission in India has been an important factor in rapid increase in the Sb^V refractoriness. Pentamidine was the first drug to be used and cured 99% of these refractory patients, but over time even with double the amount of initial doses, it cures only 69-78% patients now and its use has largely been abandoned in India²⁹. Increasing refractoriness to Sb^V in the state of Bihar (India), and to some extent in adjoining Nepal^{26, 30} led to adoption of alternative treatment strategies for these regions. However, in rest of the world, it continues to be effective.²

Its major toxicities are cardiac arrhythmias, prolonged QTc interval, ventricular premature beats, ventricular tachycardia, ventricular fibrillation and torsades de pointes. Prolongation of a QTc interval (> 0.5 s) signals the likely onset of serious and fatal cardiac arrhythmias. Arthralgia and myalgia, elevated hepatic and pancreatic enzymes are other common adverse events. Side effects specially chemical pancreatitis are more common in HIV co-infected patients. HIV-positive patients seem to have increased mortality during SSG treatment as

compared to HIV negative or miltefosine-treated HIV-positive VL patients.³¹ Not only do co-infected persons have more toxicity, a recent study from Ethiopia revealed only 43.9% of HIV-VL co-infected patients were cured with SSG.³²

Antimonials have been the mainstay in therapy of CL and is administered intralesionally (1 -- 5 mL per session every 3 -- 7 days 1 -- 5 infiltrations) as well as systemically (20 mg/kg for 20 days for CL and 28 -- 30 days for ML). In OWCL intralesional antimonials have shown > 90% cure rates for CL in Saudi Arabia, Iraq, Turkey, Sri Lanka, India³³⁻³⁷ while cure rates were lower in Iran.^{38, 39} With systemic antimonials the cure rates vary from 75–98 % for *L. major* and 41–53 % for *L. tropica*.⁴⁰⁻⁴³ It has shown 85% cure rate in *L. aethiopica*.⁴⁴ Systemic antimonials is the first line treatment of NWCL and the efficacy varies between 77 and 90% depending on the species.⁴⁵⁻⁴⁸ The proportions of treatment failure depends on the species; in a study from Peru 30.4%, 24.5%, and 8.3% patients infected with *L. (V.) braziliensis*, *L. (V.) peruviana*, and *L. (V.) guyanensis* failed therapy.⁴⁹ The rate of failure not only depends on species but also the region. While *L. guyanensis* in Peru is highly responsive to antimonials the same species has high failure rate in Brazil.^{49, 50} Similarly, cure rates of *L. Mexicana* is low in Guatemala while it is excellent in Mexico.^{43, 51, 52}

The cure rate of systemic antimonials for the treatment of New world mucocutaneous leishmaniasis (NWMCL) varies from 30-91% depending upon severity of disease.⁵³⁻⁵⁶ Increasing the duration of treatment from 28 to 40 days did not improve the outcome.⁵⁵ Although Sb^V are the first line drugs for diffuse cutaneous leishmaniasis, but treatment of this condition is difficult. Initially, the disease responds to standard treatment but relapses and becomes unresponsive to further treatment.^{1, 43}

Sb^V has also been used in combination with other agents such as pentoxifylline, an inhibitor of TNF- α , allopurinol and imiquimod, an immunomodulator. In combination with pentoxifylline (400 mg t.i.d.) in ML due to *L. braziliensis*, it significantly reduces the healing time and prevents the need for further courses of Sb^V.⁵⁷ The recent PAHO guidelines for the treatment of infectious diseases recommend antimonials plus pentoxifylline for 30 days as the first-line therapeutic option for NWML.⁵⁸ Combined therapy with MA and pentoxifylline is also more effective than MA alone in CL caused by *L. major*.⁵⁹ Combination of antimonials with allopurinol at doses of 15mg/kg/day for 3weeks in *L. tropica* proved to be more effective than monotherapy but achieved a cure rate of only 46 %.⁶⁰ In *L. major*, the combined therapy of parenteral antimonials and oral allopurinol (20 mg/kg/day) for 20 days reached higher cure rate [CR] (80.6 %).⁶¹

Combination therapy of meglumine antimoniate with 7.5% imiquimod cream administered topically every other day for 20 days and was more effective than imiquimod or meglumine alone in treatment of CL in Peru.^{62, 63} This combination has also been effective in those patients who had previously not responded to meglumine antimoniate.⁶⁴ However, there was no beneficial effect of combining a 4-week course of treatment with 5% imiquimod cream and a standard course of treatment with meglumine antimoniate in patients with CL in an endemic area of *L. tropica*.⁴¹

Combination of low doses of pentavalent antimonials and immunotherapy consisting of vaccine with dead promastigotes of *L. amazonensis* have also shown excellent results.⁶⁵

2.2 Amphotericin B

Amphotericin B deoxycholate is polyene antibiotic is most commonly used for the treatment of refractory VL in India.^{66, 67} It has excellent cure rates (~ 100%) at doses of 0.75 -- 1.0 mg/kg for 15 -- 20 intravenous infusions in this region. It is also recommended for the treatment of PKDL in the Indian subcontinent at the dose of 1 mg/kg/day, up to 60 -- 80 doses over 4 months.^{1, 68} However, this drug has many adverse effects including infusion reactions, nephrotoxicity, hypokalemia and myocarditis, and thus needs close monitoring and hospitalization for 4 -- 5 weeks which ultimately escalates the cost of therapy.

To minimize the adverse events of amphotericin B, various lipid formulations have been introduced where deoxycholate is replaced with other lipids leading to less exposure of the free drug to organs. Lipid formulations are rapidly concentrated into organs such as liver, spleen and remain there for long periods. Tolerance is greatly improved and adverse effects, including nephrotoxicity, are minimized which enables delivery of large doses of the drug over short periods of time. Globally three formulations have been extensively tested in VL: liposomal amphotericin B (AmBisome_®; Gilead Sciences; L-AmB), amphotericin B lipid complex (ABLC; Abelcet_®, Enzon pharmaceuticals) and amphotericin B cholesterol dispersion (ABCD; Amphotec_®, InterMune Corp.). L-AmB is the only approved drug by the US Food and Drug Administration. The total dose requirements of lipid formulations for treatment of VL vary by region.² In India, a total dose of 10 mg/kg results in a cure rate of > 95%.⁶⁹ While in another study at the dose of 20 mg/kg of LAmB administered over 4-10 days, 2.4% patients relapsed.¹⁸ In the Mediterranean region and South America a total dose of 18 -- 21 mg/kg, administered in various regimens has been recommended.^{2, 70-74} There is limited experience in East Africa. In 1995 an open label trial for L-AmB was conducted in Sudan for the treatment of complicated VL. The optimal regimen of L-AmB in this study was administration of 4 mg/kg on days 0, 3, 6, 8, 10 and 13.⁷⁵ In a recent study from Sudan LAmB given at a total dose of 30 mg/kg, over 10 days yielded 92% initial cure, 1% treatment failures, 5% deaths and 7% relapses at 6 months in primary VL patients. In relapsed VL cases 94% had initial cure, 4% treatment failures, 1% death and 10% relapse. 38% were lost to follow up and 6% were slow responders requiring total dose of 50mg/kg of L AmB.⁷⁶ This study reemphasizes the fact that *L. donovani* in East Africa requires higher doses of L AmB than in India.

Previously, the cost of L AmB was prohibitive. A preferential pricing agreement with WHO (agreement between Gilead and WHO of 14 March 2007) reduced the price of L-AmB for endemic regions of developing countries to \$18 per 50 mg vial.⁷⁷ Encouraged by this preferential pricing and the low dose of L AmB required to cure VL in India, a single dose of 10 mg/kg of body weight L-AmB was compared to the conventional amphotericin B deoxycholate administered in 15 infusions of 1 mg/kg, given every other day during a 29-day hospitalization. Cure rates at 6 months were similar in the two groups: 95.7% (95% confidence interval [CI]: 93.4 - 97.9) in the liposomal-therapy group and 96.3% (95% CI: 92.6 -- 99.9) in the conventional-therapy group.⁶⁹ The preferential pricing, along with a

single day of hospitalization, makes a single infusion of the liposomal preparation an excellent option for this region. This regimen was further tested in primary health centres in Bangladesh where the cure rate at 6 months was 97%.⁷⁸ Although there is high acceptability of this regimen in Bangladesh, however, strengthening of infrastructure is required for its implementation in the sub-district level as the drug requires a cold chain.⁷⁹ Encouraged by the success of the single dose L AmB therapy in the Indian subcontinent a randomized controlled trial was done to compare the efficacy and safety of single dose of L AmB 7.5 - 10mg/kg body weight, or multiple doses, 7 times 3 mg/kg on days 1-5, 14, and 21 in East Africa. However, the trial was terminated after the third interim analysis because of low efficacy of all the regimens. Definitive cure was 85%, 40% and 58% in patients treated with multiple doses, single doses of 7.5 or 10 mg/kg, respectively.⁸⁰

Low toxicity for L-AmB has also made it the best option for the treatment of HIV-VL co-infection. Most studies are from the Mediterranean region.⁸¹⁻⁸³ L-AmB infused at a dose of 4 mg/kg for 10 doses (days 1-5, 10, 17, 24, 31 and 39) up to a total dose of 40 mg/kg are recommended.¹ A recent retrospective data analysis revealed that 98.4% immunocompetent patients, 90.5% non-HIV-immunodeficient patients, and 72.0% HIV-infected patients receiving L AmB in Italy were treated successfully.⁸⁴ A study from India in HIV-VL co-infected patients treated with L-AmB (a total dose of 20 - 25 mg/kg in 4 - 15 days) combined with antiretroviral therapy provided excellent initial response; however, relapse within 2 years remained frequent.⁸⁵ L-AmB at a total dose of 30 mg/kg in six doses on alternate days was found to be less effective in Ethiopia with initial cure of 92.6% in HIV-negative patients compared with only 59.5% in HIV-positive patients ($p < 0.001$), and parasitological failures in 32.3% in HIV-positive patients.⁸⁶ Secondary prophylaxis to prevent relapses have been reported in several publications. Amphotericin B lipid complex (3 - 5 mg/kg per dose once) given every 3 weeks for 12 months as secondary prophylaxis was well tolerated; after 1 year, only 22% of patients had relapsed, in comparison with 50% of patients without secondary prophylaxis.^{1, 87} In another study L-AmB (5 mg/kg) when given every 3 weeks as secondary prophylaxis, the probability of remaining free of relapse at 6 months was 89.7% ;at 12 months, it was 79.1% and at 24 and 36 months, it was 55.9%.⁸⁸

There are few studies of L-AmB in CL where excellent efficacy has been demonstrated; however, the drawbacks are its prohibitive price and lack of large randomized controlled trial.

Experience of L-AmB for OWCL is limited. At the dose of 3 mg/kg for 5 days followed by sixth dose on day 10 it has a cure rate of 84% for CL due to *L. tropica*.⁸⁹ In another retrospective study of 20 CL patients who acquired disease in five countries and with five different strains of *Leishmania* from both Old and new world were treated with L-AmB, 84% patients experienced a cure with the initial treatment regimen. All patients who did not fully heal after an initial treatment course, were cured with additional dosing.⁸⁵ A recent study in children with *L. tropica* CL treated with L AmB showed response in 83% and was found to be safe, effective and was of shorter duration.^{90, 91} A topical L-AmB formulation has also shown similar efficacy as intralesional glucantime in the treatment of CL in Iran.⁹²

There are few trials with L AmB for NWCL caused by *L (V) braziliensis* from Bolivia with cure rate of 85 -- 100%.^{93, 94} While at a lower dose of 1.5 mg/kg/day L AmB for 5 days it was much less effective than Sb^{V.95}

L-AmB has been used more commonly for MCL with excellent results. An average total dose of 35 mg/kg of LAmB yielded 100% cure rates in 8 patients with no recurrence at 25 months of median follow-up.⁹⁶ In MCL unresponsive to antimonials, L AmB at the dose of 2-3 mg/kg/day for a minimum of 20 days cured, 5 out of 6 patients at 26-38 months of follow up.⁹⁷ A recent retrospective study in 16 patients of MCL in the cumulative dose of 30 to 35 mg/kg L AmB had healing of lesions in 88% of patients.⁹⁸ Amphotericin B colloidal dispersion (ABCD) has also shown a cure rate of 100% in 5 patients of MCL with no recurrence during the follow-up period of 7-14 months.⁹⁹ AmB has been used for small number of MCL in Bolivia and Peru alone and in combination with itraconazole and had a cure rate of 90 and 80% respectively.¹⁰⁰

2.3 Miltefosine

It is an alkyl phospholipid (hexadecylphosphocholine) and the first oral antileishmanial agent registered for use in India from March 2002 following a Phase III trial in which 50 -- 100 mg/day dose for 28 days resulted in a long-term cure rate of 94%.¹⁰¹ This was followed by a large Phase IV study in which a per-protocol cure rate of 95% were recorded, though 14.2% patients were lost to follow-up.¹⁰² The drug was chosen for the elimination program in India, Nepal and Bangladesh for its ease of use and applicability in the control program.¹⁰³ However, after a decade of use of the drug in the Indian subcontinent, the relapse rate doubled and its efficacy appears to have declined.¹⁰⁴ Another recent study from India revealed a cure rate of only 92.6% at 12 month.¹⁰⁵ While in Nepal the results were worse, with relapse rate of 10.8% at 6 and of 20.0% at 12 months.¹⁰⁶ In Bangladesh a phase 4 study showed a cure rate of only 85%.¹⁰⁷ Its efficacy was low in a study from Ethiopia where the final cure among non--HIV-infected patients 6 months after treatment in the miltefosine group was only 75.6%.³¹ There is no experience with this drug for VL caused by *L. infantum*. In the treatment of PKDL in India miltefosine was effective in doses of 50 mg thrice daily for 60 days or twice daily for 90 days.¹⁰⁸ A recent open-label, randomised multicenter trial of miltefosine, 100 mg/day for 12 weeks for patients with PKDL in India showed good cure rates with very few adverse effects.¹⁰⁹ It is recommended for the treatment of PKDL in the Indian subcontinent at the dose of 50 - 100 mg for 12 weeks.¹

Limitations of miltefosine are its relatively high cost, need for monitoring of gastrointestinal side effects and occasional hepatic toxicity and nephrotoxicity. As miltefosine is teratogenic, women of child-bearing potential have to observe contraception for the duration of treatment and for an additional three months, due to its long half life of ~ 1 week, which also makes it vulnerable to the rapid development of drug resistance.

Studies of miltefosine for OWCL are scarce mostly based on case reports.¹¹⁰⁻¹¹³ In a randomized trial in Iran of OWCL due to *L. major* oral miltefosine with cure rate of 81.3 % was shown to be as effective as intralesional antimonials (cure rate 80.6 %).¹¹⁴

Miltefosine has been used for New World CL. In a large, placebo-controlled study of miltefosine therapy (2.5 mg/kg/day orally for 28 days) against CL in Colombia where *L. panamensis* is common, the per-protocol cure rates for miltefosine were 91%, whereas in Guatemala where *L. (V.) braziliensis* and *L. mexicana mexicana* are common, the per-protocol cure rates were 53%.¹¹⁵ In children from Columbia where *L. panamensis* and *L. guyanensis* predominate miltefosine at the dose of 1.8–2.5 mg/kg/day for 28 days had a efficacy of 82.7 % and was not inferior to parenteral meglumine antimoniate (CR 69%).¹¹⁶ In a small comparative trial for CL caused by *L. braziliensis* in Bolivia, the per-protocol cure rate for miltefosine was 88% as against 94% for antimony.¹¹⁷ A study from Brazil (*L. braziliensis*) showed an efficacy of 75% in the miltefosine group as compared to 53.3% in the Sb^v group.¹¹⁸ In a phase II/III randomized clinical trial of CL due to *L. guyanensis* miltefosine cured 71.4% patients as compared to 53.6% by parental antimonials.¹¹⁹

In a non-comparative trial for ML in Bolivia, 83% of patients with mild disease and 58% of patients with extensive disease were cured which was similar to the historic antimony cure rate in neighboring Peru.¹²⁰ Increasing the duration of treatment to 6 weeks increased the cure rates from 71% to 75%.¹²¹ All these studies suggest that miltefosine could be an alternative option for the treatment of CL and ML in these region however treatment of diffuse cutaneous leishmaniasis has not been encouraging.¹²²⁻¹²⁴

2.4 Paromomycin (aminosidine)

It is an aminoglycoside-aminocyclitol antibiotic, which has been used for the treatment of VL in a parenteral formulation and CL in both topical and parenteral formulations. Phase II study for VL in India established that a intramuscular dose of 16 mg/kg/day for 21 days cured 93% patients.¹²⁵; these were followed by a Phase III trial in which a dose of 15 mg/kg paromomycin (PM) sulfate (11 mg base) for 21 days gave a cure rate of 95%, and was approved by the Indian government in August 2006 for the treatment of patients with VL.¹²⁶ The results were confirmed in a large Phase IV study in India.^{2, 127} A large Phase III study in Sudan, Ethiopia and Kenya comparing the efficacy of PM alone at the dose shown to be efficacious in India against SSG alone (20 mg/kg/day for 30 days) and against a combination treatment of SSG and PM for 17 days was conducted. The overall efficacy of PM alone was significantly lower than SSG and it had to be discontinued. Efficacy varied among centers and was significantly lower in Sudan (14.3 and 46.7%) than in Kenya (80%) and Ethiopia (75 and 96.6%).¹²⁸ In a phase II dose-finding study efficacy of paramomycin for a longer treatment duration (15 mg/kg/day for 28 days) and at the higher dose of 20 mg/kg/day for 21 days was tested in Sudan. Six months after treatment, efficacy was only 80% (95% CI: 56.3 -- 94.3%) and 81% (95% CI: 58.1 -- 94.6%) in the 20 and 15 mg/kg/day groups, respectively.¹²⁹ A multi-centre randomized-controlled trial (RCT) to compare efficacy and safety of PM (20 mg/kg/day for 21 days) and PM plus sodium stibogluconate (SSG) combination (PM, 15 mg/kg/day and SSG, 20 mg/kg/day for 17 days) with SSG (20 mg/kg/day for 30 days) for treatment of VL in East Africa was conducted. The efficacy of PM was significantly lower than SSG (84.3% versus 94.1%).¹³⁰ There is no experience with this drug for VL in *L. infantum* foci (Mediterranean, South America).

Pain at the injection site was the commonest adverse event (55%), reversible ototoxicity occurred in 2% patients, 6% patients developed reversible rise hepatic transaminases. The advantage of this agent is its extremely affordable cost, approximately US\$10 per patient.¹³¹ Need for parenteral administration may pose difficulty in its adoption in a control program of a developing country, and further being an amino glycoside, monotherapy with PM might lead to development of resistance.²

Systemic use of paromomycin for CL is rare. In NWCL, the efficacy of systemic paromomycin varies with region with low cure rates in Colombia and in Belize^{132, 133}; but at 20 mg/kg/day for 20 days, it had excellent cure rate of over 90 % in Brazil.¹³⁴ The efficacy of systemic paromomycin for MCL is low with a high rate of relapse.¹³⁵⁻¹³⁷

PM is available in various topical formulations which have shown variable results in CL. In Old world species, an ointment containing 15% PM and 12% methylbenzethonium chloride (MBCL) applied for 10 - 20 days twice daily, was significantly more effective than placebo (74.2 vs 26.6%) for *L. major* infection in Israel.¹³⁸ In a recent phase 3 trial of topical treatments for CL due to *L. major* in Tunisia in patients with one to five ulcerative lesions, healing of the index lesion occurred in 81% for 15% paromomycin plus 0.5%, gentamicin (called WR 279,396), 82% for paromomycin alone, and 58% for vehicle control suggesting that paromomycin alone or with gentamicin is efficacious for ulcerative *L. major* disease.¹³⁹

In Ecuador and Guatemala, 15% PM with 12% MBCL gave 85-86% cure rates at 12 months.^{140, 141} In Columbian patients receiving WR279,396, the cure rate did not differ from placebo, but the cure time was accelerated in the PM group (35 vs 56 days).¹⁴² In a recent Phase 2 trial of 30 patients with *L. panamensis* CL, once daily topical treatment with WR 279,396 or paromomycin alone (15% paromomycin) for 20 days had a cure rate after 6 months of 87% for WR 279,396 and 60% for paromomycin alone.¹⁴³ A combination of topical paromomycin–methylbenzethonium chloride and injectable meglumine antimoniate in a shortcourse treatment of 7 days in Colombia with a higher proportion of *L. panamensis* infections resulted in cure rates of 90 %.¹⁴⁴ While another study in Columbia with *L. panamensis* and *L. brasiliensis* this combination did not improve the cure rates.¹⁴⁵

A meta-analysis of 14 randomized controlled trials showed that in placebo-controlled trials, topical PM appeared to have therapeutic activity against the Old World and New World CL, with increased local reactions, when used with MBCL compared to when used alone. In Sb^V-controlled trials, the efficacy of topical PM was not significantly different from that of intralesional Sb^V in the Old World CL (relative risk[RR] = 0.70; 95% CI: 0.26 -- 1.89), whereas topical PM was inferior to parenteral Sb^V in treating the New World CL (RR = 0.67; CI: 0.54 -- 0.82).¹⁴⁶

2.5 Pentamidine

Pentamidine was used in early 1980s for the treatment of refractory VL in India; however, its use has been abandoned for VL due to its serious toxicities such as insulin-dependent diabetes mellitus and declining efficacy.¹⁴⁷ The main adverse reactions related to pentamidine are pain, induration and sterile abscess at the injection site, as well as nausea,

vomiting, dizziness, myalgia, headache, hypotension, syncope, transient hyperglycemia and hypoglycemia.^{1, 2}

While it is no longer used for VL, it has been used for NWCL. In *L. braziliensis* infection in Brazil, pentamidine at the dose of 4mg/kg/day on alternate days, for one week cured 71.05% patients while with *L. guyanensis* infection in Surinam cure rate was 90%.^{148, 149} However cure rates were lower for *L. guyanensis* infection in Brazil.¹⁵⁰ In another study from French Guiana, a single injection of pentamidine isethionate, at 7 mg/kg cured 78.8% as compared to 83.6% of two such injections (given 48 h apart).¹⁵¹ In Columbia CL due to *L. panamensis* 2mg pentamidine isethionate/kg, administered every other day in seven injections, was 95% curative.¹⁵²

It has also been used for the treatment of MCL in Brazil where at the dose of 4 mg/kg every 48 hours till the lesions healed it cured 90-94% of patients.¹⁵³⁻¹⁵⁵

2.6 Sitamaquine

It is another orally administrable primaquine analogue which has completed Phase II trials for VL in India and Kenya. In India, at the dose of 1.75 and 2 mg/kg/day for 28 days, the cure rates were 89 and 100%, respectively.¹⁵⁶ In Kenya, with 2, 2.5 and 3 mg/kg/day doses, the cure rates were 80, 82 and 91%, respectively.¹⁵⁷ The drug was nephrotoxic in doses of more than 2 mg/kg, and in a follow-up study in India, the drug cured 85% patients at 2 mg/kg/day for 21 days.¹⁵⁸ Its clinical development has since been abandoned due to its low efficacy.

2.7 Azoles

Azoles block ergosterol synthesis of *Leishmania* parasites. Ketoconazole, itraconazole and fluconazole have all been used for CL in several studies.

In a large placebo-controlled study, oral fluconazole 200 mg/day for six weeks was found to be more effective than placebo (59 vs 22%) in Saudi Arabia (*L. major*). Adverse effects include gastrointestinal symptoms and hepatotoxicity.¹⁵⁹ The cure rates were lower (44.4%) in *L. major*-infected travellers in another study.¹⁶⁰ However on increasing the dose of fluconazole to 400mg the cure rate increased to 81%.¹⁶¹ For NWCL due to *L. braziliensis*, fluconazole at the dose of 8 mg/kg per day, the cure rate was 100%.¹⁶²

Itraconazole, although superior to placebo in one small Indian trial (*L. tropica*)¹⁶³, was not more efficient than placebo in Iran (*L. major*).^{164, 165} At the dose of 400 mg daily over 28 days itraconazole was no better than placebo in NWCL in Colombia (CR25 %).¹⁶⁶ In MCL caused by *L. braziliensis* in Brazil, doses of 4 mg/kg/day for 6 weeks resulted in a CR of 60 %¹⁶⁷ while in Ecuador cure rates were low (23 %) even after 12 weeks therapy.¹⁶⁸

For OWCL Ketoconazole at a dose of 600 mg/day for adults and 10 mg/kg/day for children for 4-6weeks obtained 89 and 80% efficacy in Iran and Kuwait while it was ineffective in Turkey.¹⁶⁹⁻¹⁷¹ In Egypt combination of intralesional SSG and oral ketoconazole was 92.3% effective.¹⁷²

Ketoconazole at 600 mg/day for 28 days is 76 and 89% effective in *L. (V.) panamensis* and *L. mexicana* CL in Panama and Guatemala but not effective for *L. braziliensis*.^{173, 174}

2.8 Combination or multidrug therapy

The growing resistance of the parasite to antileishmanial drugs suggests that the currently used monotherapy needs to be reviewed. The rationale behind multidrug therapy are increased activity through use of compounds with synergistic or additive activity acting at different sites, shorter duration of therapy and lower dose requirement, thereby reducing chances of toxic side effects and cost, and preventing the emergence of drug resistance.² In an experimental study Seifert and Croft demonstrated activity enhancement index (AEI) of different drugs *in vivo*, where the highest potentiation of miltefosine activity was achieved with amphotericin B (AEI of up to 11.3). No significant interaction was observed when miltefosine was combined with SSG (AEI of up to 2.38). The potentiation of miltefosine *in vivo* was also achieved with the combination of miltefosine and PM (AEI of up to 7.22).¹⁷⁵

The combination of Sb^v and PM has been extensively used in Southern Sudan by Médecins Sans Frontières (MSF), initially in patients who relapsed after conventional Sb^v and since 2002 as first-line therapy for VL. A large retrospective field evaluation by MSF showed that the initial cure rates and survival of patients on 17 days combination therapy with PM plus Sb^v was 97% compared with 92.4% among patients with 30-day Sb^v monotherapy.¹⁷⁶ In a recent large multi centre trial this combination for 17 days had comparable efficacy to SSG treatment.¹³⁰ This combination is now the preferred regimen in this region.

Multidrug therapy has been studied in the India. In a randomized, non-comparative, group-sequential, triangular design study, 181 subjects were assigned to treatment with 5 mg/kg of L-AmB alone, 5 mg/kg of L-AmB followed by miltefosine for 10 days or 14 days or 3.75 mg/kg of L-AmB followed by miltefosine for 14 days. When it became apparent that all regimens were effective, 45 additional, nonrandomized patients were assigned to receive 5 mg/kg of L-AmB followed by miltefosine for seven days. Final cure rates were high (> 95%) and similar in all the groups. These results suggest that single infusion of L-AmB (in most instances, administered in an outpatient setting) followed by a brief self-administered course of miltefosine could be an excellent option against Indian kala-azar.¹⁷⁷

In a subsequent large Phase III study in the Indian subcontinent, three drug combinations (single injection of 5 mg/kg L AmB and 7-day 50 mg oral miltefosine or 10-day 11 mg/kg intramuscular PM; or 10 days each of miltefosine and PM) were tested for the treatment of VL. All the combinations showed an excellent cure rate (> 97%).¹⁷⁸

These trials established that the combination therapies are safe and effective options in the Indian subcontinent. They also require shorter duration of hospitalization which will lead to decongestion of the overcrowded treatment centers. Encouraged by this new treatment approach, an exploratory study with miltefosine alone and combinations of single dose of L-AmB (10 mg/kg) with SSG (20 mg/kg) for 10 days and L-AmB (10 mg/kg) with miltefosine for 10 days is being done in East Africa.¹⁷⁹

2.9 Local therapy

2.9.1 Thermotherapy—Laboratory studies have shown that *Leishmania* parasites do not multiply at temperatures $> 39^{\circ}\text{C}$ *in vitro*. Although heat therapy may be given in various ways, thermotherapy with radio-frequency waves has been most commonly studied both for Old and New World CL.

A randomized control trial in Afghanistan tested the efficacy of thermotherapy for CL for single lesion caused by *L. tropica*. In this study, thermotherapy using radiofrequency waves (1 treatment of >1 consecutive application at 50°C for 30 s) had a cure rate of 69.4% compared to 75.3% with intralesional and 44.8% with intramuscular SSG.¹⁸⁰ Another recent study from Afghanistan showed that single localized treatment with thermotherapy was more effective than 5 days of intralesional administration of Glucantime (82.5% vs 74%).¹⁸¹ It was also seen to have similar albeit low efficacy as SSG for skin lesions caused by *L. major* (48% vs 54%).¹⁸² In another study from Iran, thermotherapy once weekly for 4 weeks had a cure rate of 80.7 % compared to 55.3 % with intralesional antimonials.¹⁸³ In a recent study single application of thermotherapy was also found to be safe, cosmetically acceptable and effective (98%) in inducing a long-term cure of CL. due to *L. tropica* in India.¹⁸⁴

In a placebo controlled trial, thermotherapy (3 treatments of 50°C for 30 s at 7-day intervals) was as effective as antimony therapy (73%) in treating *L. braziliensis* and *L. mexicana* infection.⁵¹ For *L. mexicana*-infected patients thermotherapy (a single treatment of 50°C for 30 s) showed 90% (172 of 191 patients) cure rate at 8 weeks.¹⁸⁵ Efficacy of meglumine antimoniate was seen to be greater than that of thermotherapy (72% vs 58%) in a phase III trial from Columbia, however, side effects and longer duration of therapy are its major drawback.¹⁸⁶ In another trial from Columbia 50 mg of miltefosine three times per day for 28 days was compared with thermotherapy (Thermomed®) application of 50°C for 30 seconds over the lesion and surrounding area, showed a cure rate of 59% for both.¹⁸⁷ In Peru, a low-cost heat pack (HECT-CL) at an initial temperature of $52^{\circ}\text{C} \pm 2^{\circ}\text{C}$ for 3 minutes to each lesion, repeated daily for 7 days gave a clinical cure rate of 60%.¹⁸⁸

2.9.2 Cryotherapy—Cryotherapy with liquid nitrogen (-195°C) applied once or twice to the lesion up to its edge weekly up to 6 weeks was $> 95\%$ effective in Israel, Greece and Jordan, but less effective (77%) in Turkey.¹⁸⁹⁻¹⁹³ In a study from Ethiopia, the per protocol cure rate for cryotherapy and Pentostam was 93.3% and 89.5% for *L. aethiopica*.⁴⁴ For CL due to *L. donovani* 91.7% of patients were cured with one to seven cryosessions.¹⁹⁴

The combination of superficial cryotherapy and intralesional antimony was more effective than each technique used alone in Iran and United Arab Emirates¹⁹⁵⁻¹⁹⁷

3. Present treatment guidelines

As the efficacy and required dosage of the antileishmanial agents vary in different areas, in 2010 WHO published the treatment recommendation based on these regional differences.¹ In 2013 recommendations for the treatment of leishmaniasis in America formulated by Pan American Health Organization (PAHO) was published.⁵⁸ In 2014, 'LeishMan'

(Leishmaniasis Management), a group of experts from 13 institutions in eight European countries, published a guideline for the management of cutaneous and mucocutaneous leishmaniasis for travellers.¹⁹⁸

3.1 Visceral leishmaniasis

At present, single dose of L-AmB and combination therapy are the preferred treatment options in the Indian subcontinent. The combination of SSG with PM for 17 days is treatment of choice in East Africa and Yemen, whereas L-AmB up to a total dose of 18 -- 21 mg/kg remains the choice in Mediterranean Basin, Middle East, Central Asia. In the recent PAHO guidelines L-AmB(20mg/kg), Sb^v and conventional AmB are the recommended drugs for the treatment of VL in the New World. It also recommends L-AmB or conventional AmB if L-AmB is not available, as the drug of choice in patients with age > 50 years or <1 year, renal insufficiency, hepatic impairment, heart failure, QTc > 450 ms, concomitant use of drugs that alter the QT interval, hypersensitivity to Sb^v, HIV infection, comorbidities that compromise immunity, use of immunosuppressive medication, failure to Sb^v or other medicines used to treat VL and pregnant women.⁵⁸

3.2 Post--kala-azar dermal leishmaniasis

In India, Amphotericin B 60 -- 80 doses over 4 months or miltefosine for 12 weeks are the recommended regimens. In East Africa, PKDL is not routinely treated, as the majority of cases (85%) heal spontaneously within 1 year. Only patients with severe or disfiguring disease, those with lesions that have remained for > 6 months, those with concomitant anterior uveitis and young children with oral lesions that interfere with feeding are treated, with either SSG (20 mg/kg/day per day) for up to 2 months or a 20-day course of L-AmB at 2.5 mg/kg/day.¹

3.3 HIV-Leishmaniasis co-infection

Lipid formulations infused at a dose of 3 -- 5 mg/kg/day or intermittently for 10 doses (days 1 -- 5, 10, 17, 24, 31 and 38) up to a total dose of 40 mg/kg are recommended. Antiretroviral therapy should be initiated and secondary prophylaxis should be given till the CD4 counts are > 200/ μ L.¹ However, the recent PAHO guidelines recommends secondary prophylaxis for all patients with CD4 T-cell count < 350/mm³.⁵⁸ For HIV-CL co-infection, it is imperative to look for visceral involvement as immunosuppression due to HIV facilitates dissemination and may lead to disseminated CL and to VL.¹⁹⁸[196]

3.4 Cutaneous & Mucocutaneous leishmaniasis

In the OWCL, local wound care with careful follow-up are indicated for patients with confirmed or strongly suspected infection with *L. major*; fewer than four lesions requiring immediate treatment; lesions <5 cm in diameter; no potentially disfiguring or disabling lesion (face, joints, toes and fingers); no immunosuppression and possibility for follow-up. If at least one criterion is absent, local therapy should be given. The options for local therapy are PM ointments, intralesional Sb^v, thermotherapy and cryotherapy.¹ Systemic therapy is given for severe and complex lesions (Table 1). Old world mucosal leishmaniasis due to *L.*

infantum/donovani is very rare. It is commonly associated with immunosuppression but is more amenable to therapy with Sb^v as compared to NWMCL.¹⁹⁸

The recent PAHO guidelines recommends local treatment for NWCL in patients with single lesions up to 3cm except in head or periarticular region in patients without immunosuppression but with possibility of follow up. The recommended local therapy are thermotherapy and intralesional antimonials. Systemic therapy is indicated for severe lesions and mucosal disease. Systemic antimonials are the drug of choice for NWCL (high quality and strong recommendation). For CL caused by *L. panamensis* and *L. guyanensis*, miltefosine is recommended (high quality and strong recommendation). Pentamidine can also be given for *L. panamensis* and *L. guyanensis*. Ketoconazole is recommended for CL caused by *L. mexicana* and *L. panamensis* (low quality and weak recommendation). For MCL systemic antimonials remain the treatment of choice (low quality and strong recommendation). The other alternatives are pentavalent antimonials + pentoxifylline (low quality) or liposomal amphotericin B (low quality), or amphotericin B deoxycholate (very low quality) or pentamidine isethionate (low quality) or Miltefosine (very low quality). In special situation like pregnancy, thermotherapy is recommended and in cases requiring systemic treatment L-AmB. Antimonials, miltefosine and pentamidine are contraindicated. During lactation intralesional antimonials, amphotericin B or thermotherapy is recommended. If miltefosine, is used contraception should be ensured. Patients with kidney disease, liver disease, heart disease: local treatments or L-AmB is recommended. In patients with ECG changes. antimonial salts and pentamidine are contraindicated, miltefosine may be used. Systemic antimonials should be avoided in patients older than 50 years.⁵⁸

4. Expert opinion

In the past decade, several new drugs and regimens have been introduced for the treatment of leishmaniasis. However, shortly after introduction the dwindling efficacy of miltefosine, the drug chosen for the VL elimination program in the Indian subcontinent, is a growing concern. This anthroponotic foci already has a history of development of drug resistance due to misuse of antileishmanials. Given the risk of development of resistance to established and new medicines, the Regional Strategic Framework for Elimination of Kala-azar from the South-East Asia Region recommends that monotherapy other than L- AmB should be avoided in this region.¹⁹⁹ Single dose of L-AmB and short course combination therapy with their excellent efficacy, has been major breakthrough in the treatment of VL in this region. The recent trial from Bangladesh further corroborates the fact that single dose of L-AmB is not only efficacious, it is also feasible to give this therapy at the primary health care level. Therefore, there is an urgent need for short course, highly efficient regimens like single dose L-AmB or combination therapy to be adopted by the VL elimination program. With short course combination therapy, a directly observed treatment should be ensured, as noncompliance carries the risk of failure of two drugs as both are being used in sub-therapeutic doses. The Drugs for Neglected Diseases Initiative and WHO's Special Programme for Research and Training in Tropical Diseases are presently undertaking studies to assess the feasibility, safety, and efficacy of this single-dose regimen and combination therapy at district hospitals and primary health-care services in the endemic regions of Bihar, India.

African *L. donovani* is less susceptible to L-AmB, miltefosine and PM as compared to the Indian strains. Moreover this region, especially Ethiopia, is being plagued by the growing menace of HIV-VL co-infection. All antileishmanial therapies are less effective and more toxic in HIV-positive. With the failure of single and multiple dose of L-AmB in this region it will be interesting to see whether the combination therapy which are so successful in the Indian subcontinent are efficacious for this region. At the moment the only treatment of choice remains a 17-day combination therapy of Sb^v and PM.

In the Mediterranean region, L-AmB at a total dose of 18 -- 21 mg/kg is the only option as there are hardly any study with other drugs in this region. For the VL in the New World, L-AmB, Sb^v or conventional AmB can be used.

Patients with PKDL serves as an important reservoir of infection, and in Indian subcontinent, treatment is essential. However, the inordinately long regimens especially for patients without any physical handicap lead to frequent noncompliance. Better and shorter and acceptable options need to be developed. Most of the currently recommended regimens are unacceptable.

Recommendations for HIV-VL co-infection are still based on studies from the Mediterranean region where lipid-based amphotericin B is the treatment of choice. The PAHO also recommends L-AmB as the preferred drug for HIV-VL co infection. However, studies have shown that L-AmB as well as Sb^v has limited efficacy in Ethiopia, the new hub for HIV--VL co-infection. The need of the hour is better therapeutic options for the co infected patients. A clinical trial evaluating high dose liposomal amphotericin B or a combination with miltefosine in HIV co-infection is about to be initiated in Ethiopia. It remains to be seen whether combination therapy would decrease the relapse rate and the development of resistance in these patients.

As far as CL is concerned, there is still lack of large randomized controlled trials. Moreover, among the trials that have been conducted many have been designed and reported poorly, resulting in a lack of evidence for potentially beneficial treatments.^{195,196} A guidelines for authors conducting clinical trials aimed at the development of effective therapies in CL has been proposed, which will improve the design and reporting of RCTs.¹⁹⁷ Treatment of CL should be decided by the clinical lesions, etiological species and its ability to develop into mucosal leishmaniasis. Presence of multiple (>4), large (>4–6 cm²), lesions localized above the belt, of >4months duration, caused by *Leishmania braziliensis* or *Leishmania panamensis*, acquired in Bolivia, immunosuppression, and those treated inappropriately are at high risk of developing MCL. In the absence of these risk factors the probability of developing MCL is low.²⁰⁰ Due to the toxicity of systemic therapy a trend towards local treatment for NWCL is now being encouraged. CL still remains the neglected area of leishmaniasis, and there is an urgent need to generate evidences. Combination of Sb^v with pentoxifylline or Sb^v alone are preferred treatment for NWCL.

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Highlight

- Single dose of L-AmB and multidrug therapy (L-AmB + miltefosine, L-AmB + paromomycin (PM), or miltefosine + PM) are the preferred treatment of VL in the Indian subcontinent.
- A 17-day combination therapy of Sb^V and PM is the best option for African *L. donovani*.
- L-AmB is the drug of choice for VL in the Mediterranean region and for HIV-VL co-infection.
- L-AmB, Sb^V or conventional AmB are the drugs recommended for VL in South America.
- Treatment of CL varies with species and regions.
- In the absence of risk factors for developing MCL, local therapy can be given for NWCL.

Table 1Recommended treatment regimens for Old World CL (not ranked by preference).¹

Local therapy
<i>L. major</i>
<ul style="list-style-type: none"> • 15% PM/12% MBCL ointment b.i.d. for 20 days (^A) • Intralesional antimonials, 1 -- 5 mL per session plus cryotherapy (liquid nitrogen: --195_C), both every 3 -- 7 days (1 -- 5 sessions) (^A) • Thermotherapy, 1 -- 2 sessions with localized heat (50_C for 30 s) (^A) • Intralesional antimonials or cryotherapy independently, as above (^D)
<i>L. tropica</i>, <i>L. aethiopica</i> * and <i>L. infantum</i> *
<ul style="list-style-type: none"> • 15% PM/12% MBCL ointment, as above (^D) • Intralesional antimonials plus cryotherapy, as above (^D) • Thermotherapy, as above (^A) • Intralesional antimonials, alone, as above (^B) • Cryotherapy, alone, as above (^C)
Systemic therapy
<i>L. major</i>
<ul style="list-style-type: none"> • Fluconazole, 200 mg/day oral for 6 weeks (^A) • Sb_v, 20 mg Sb₅+ /kg/day intramuscularly or intravenously for 10 -- 20 days (^D) • Sb_v, 20 mg Sb₅+ /kg/day intramuscularly or intravenously plus pentoxifylline, 400 mg t.i.d. for 10 -- 20 days (^A)
<i>L. tropica</i> and <i>L. infantum</i> *
<ul style="list-style-type: none"> • Sb_v, 20 mg Sb₅+ /kg/day intramuscularly or intravenously for 10 -- 20 days (^D) • Sb_v, 15 -- 20 mg Sb₅+ /kg/day intramuscularly or intravenously for 15 days plus oral allopurinol 20 mg/kg for 30 days, to treat leishmaniasis recidivans caused by <i>L. tropica</i> (^C)
<i>L. aethiopica</i>
<ul style="list-style-type: none"> • Sb_v 20 mg Sb₅+ /kg/day intramuscularly or intravenously plus PM, 15 mg (11 mg base)/kg/day intramuscularly for 60 days or longer to treat diffuse CL

* Few data are available on therapy for CL caused by *L. infantum* and *L. aethiopica*.

^A Evidence obtained from at least one properly designed randomized controlled trial;

^B evidence obtained from well-designed trials without randomization;

^C opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees;

^D expert opinion without consistent or conclusive studies.