

## Treatment of Mucosal Leishmaniasis in Latin America: Systematic Review

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**Abstract.** Mucosal leishmaniasis (ML) is an important endemic disease and public-health problem in underdeveloped countries because of its significant morbidity and mortality. Increases in ecological tourism have extended this problem to developed countries. This form of leishmaniasis, caused by reactivation after primary cutaneous lesion, has a natural history of progressive destruction of the nasal septa and soft and hard palates, causing facial disfiguration and leading to respiratory disturbances. Treatment of ML, based on several therapies, depends on use of toxic compounds, and few drugs have emerged over the past 40 years. Drug resistance has increased, and the cure rate is no better than 70% in the largest studies. Despite these data, there has been no systematic review of therapies used to treat this important tropical disease. The aim of this study is to determine the best drug management for treatment of ML in Latin America based on the best studies offered by the medical literature. The MEDLINE, LILACS, EMBASE, Web of Science, and Cochrane Library databases were searched to identify articles related to ML and therapy. The studies were independently selected by 2 authors. Articles with sufficient data for cure and treatment failures, internal and external validity information, and > 4 patients in each treatment were included. Validation of this systematic review was based on guidelines to guarantee quality; 22 articles met our inclusion criteria. Stibogluconate achieved a 51% cure rate (76/150 patients), and 88% of patients treated with meglumine were cured (121 patients). Pentamidine and amphotericin were as effective as meglumine. Use of itraconazole and other therapies (pentoxifylline, allopurinol, or interferon- $\gamma$ ) was controversial, and numbers of patients in some studies were insufficient for statistical analysis. Meglumine may be the drug of choice in the treatment of ML, as it offers similar cure rates when compared with amphotericin B and pentamidine. Cost, adverse effects, local experience, and availability of drugs to treat ML are strong points to be considered before determining the best management of this disease, especially in developing countries.

### INTRODUCTION

Mucosal leishmaniasis (ML) is an important endemic disease in numerous areas of Latin America.<sup>1</sup> ML is a public-health problem and causes significant morbidity and mortality. In recent years, economic globalization and increased travel have extended its reach to people in developed countries. This infection is extremely rare in the United States and is found most often among travelers returning from endemic areas.

The incidence of leishmaniasis among travelers returning from endemic areas is 38 per 1,000 patients with cutaneous disorders. This number increases to 143 per 1,000 travelers returning from South America with cutaneous disorders.<sup>2</sup>

This form of leishmaniasis is caused by reactivation of the disease months or even years after the onset of the primary cutaneous lesion, although in some cases there is no history of a cutaneous lesion.<sup>3</sup> Nonetheless, < 5% of the patients suffering from the cutaneous form will develop mucosal metastatic disease.<sup>4</sup> The natural history of ML consists in the development of progressive destruction of the nasal septa and soft and hard palates, eventually causing severe facial disfiguration and respiratory disturbances that do not heal spontaneously.<sup>5,6</sup> There are several reports of the disease affecting the nose both exclusively and with concurrent lesions in the larynx, trachea, and palate.<sup>7</sup>

It is important to note that, even though the major responsible agents for the disease in Brazil are of the *L. braziliensis* species, other species (*L. amazonensis*, *L. guyanensis*, and *L. panamensis*) have been described.<sup>8,9</sup> These descriptions have

been more common with development of nucleic acid amplification tests.

Because of the complications of ML, its treatment should be started promptly after diagnosis, in this way preventing possible disfiguring lesions, alimentation disturbances, and fatal airway obstruction.<sup>3</sup>

Nowadays, treatment of ML is performed with old drugs, such as glucantime and pentamidine, but with considerable success. Nevertheless, new drugs have been developed, with fewer adverse effects and contraindications but without controlled randomized trials. This landscape has promoted not only a large number of case series publication but also non-evidence-based treatments. This approach popularizes treatments that can be medically useless to the public, patient communities, educational institutions, and continuing education of practicing professionals. Unfortunately, few studies have the statistical power to determine an ideal treatment in the ML, and most of these are designed to find appropriate doses (single drug trials).

The goal of this systematic review is to determine the best drug for treatment of ML.

### MATERIALS AND METHODS

**Search strategy.** A systematic search was performed on the medical literature. The databases included MEDLINE (1966 to January 2007), LILACS (1982 to January 2007), EMBASE (1966 to January 2006), and Web of Science (1965 to January 2007) as well as the Cochrane Library database (to 2006). Search terms were “leishmaniasis,” “mucosa,” “mucocutaneous,” “american tegumentar,” and “new world.” We included other search terms, too: “Leishmania,” “espundia,” “glucantime,” “meglumime,” “stibogluconate,” “paramomycin,” “pentamidine,” “pentostam,” and “allopurinol.” Bibliographies from the studies included in this article. The

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references from primary studies, narrative reviews, and systematic reviews were reviewed to search for additional primary studies that could have been missed by the electronic search.<sup>10</sup>

**Study selection and methodological quality.** The studies were initially selected by 2 authors (F.T. and A.S.) independently. Disagreements were resolved by a third author or by consensus. The selected articles had no language restriction because the studies were from Latin America; several of them were published in local journals.

We included manuscripts with ML treatment from Latin America. Other forms of leishmaniasis were excluded, including mucosal forms outside Latin America, post-kala-azar leishmaniasis cases from Africa and the Mediterranean, and cases of patients who traveled to tropical areas.

The studies were classified as comparative (drug versus another drug), dose-finding (comparisons of different dosing regimens of the same drug), or noncomparative (single-arm studies). For comparative and dose-finding studies, we assessed the adequacy of methods for further calculation and, when possible, included them in a meta-analysis. The rest of the studies were allocated sequentially, and the response to treatment was evaluated (see data extraction).

All studies should 1) provide data necessary for computation of cures and failures to treatment; 2) include information for establishing internal and external validity, such as randomized, blinded, exclusion and inclusion criteria, time of follow-up, form of disease, method of diagnosis, species of *Leishmania*, and method of species determination; 3) data of population studied, including the region of patients and the most prevalent species of *Leishmania*; and 4) > 4 patients in case series of treatments. The methodological quality of each selected paper was assessed, and validity criteria (internal and external) were examined as previously described.<sup>11</sup> Quality assessment was performed using methods adapted from guidelines on systematic reviews of treatment studies (Table 1). If no data on the above criteria (internal and external validity) were reported in the primary studies, then the value was zero. If data were present, it received 1 point. A high-quality study was arbitrarily defined as that which met at least 3 of 4 of the internal and external validity criteria; a moderate-quality study met at least 2 of 4 criteria; and a low-quality study met < 2 of 4 criteria. Each column of Table 1, after the year and country of the study, is a validity criterion.

**Data extraction.** Cases included patients with diagnostic criteria for ML, which were defined as the epidemiologic, clinical, and histopathological criteria previously described.<sup>12–16</sup> Confirmation of the diagnosis was based on the findings of stain and/or culture of lesion scrapings, aspiration samples, or biopsy specimens.<sup>14</sup> Patients with CL or visceral leishmaniasis were excluded. Severity of ML was determined by criteria also previously described.<sup>17</sup> Epidemiologic data—such as infecting species, sex, age, and locale of the study—were considered. Serology, cutaneous tests, and other methods of diagnosis were not considered as confirmed cases and were excluded from systematic review or meta-analysis.

Daily and total dose, duration, and method of administration were recorded in the database. We extracted efficacy and safety information from each study. Cure was determined as complete cicatrization of the mucosal lesion 1 year after treatment.

**Statistical analysis.** The validation of this systematic review was based on guidelines to guarantee quality as well as on good article selection and data extraction.<sup>18–20</sup> For all, we recalculated exact CIs using Epi-Info. For comparative studies,  $\chi^2$ , odds ratios, and 95% CIs were calculated using SPSS 11.5, and significance was defined as having a *P* value of < 0.05.

## RESULTS

**Description of included studies.** Our search strategy yielded a total of 1,095 studies, and 1,027 of them were excluded after initial screening. From the 68 remaining articles, 22 articles (635 patients) met inclusion criteria. The number of controlled and randomized studies was not sufficient to perform a meta-analysis (Figure 1). The country and number of patients from each manuscript are detailed in Figure 2.

**Study characteristics and quality.** Eighty-five percent of studies were classified as moderate or low quality of external and internal validity (Table 1). Only 3 studies were classified as high quality. The mean inter-rater agreement between the two reviewers for items in the quality checklist of internal and external validity was 0.93. Some data were affected by incomplete reporting from the primary studies. Descriptive data from studies are shown in Table 1, including internal and external validity. All studies were prospective, and 8 studies identified the *Leishmania* spp. by isoenzymes or monoclonal antibodies.

**Results of the variables. Therapy.** Pentavalent antimonials (PA) were the most-used drugs in this systematic review. Amphotericin B was the second most-used drug. Other drugs that we could evaluate in our study were aminosidine, itraconazole, allopurinol, immunotherapy, and combination therapy with pentoxifylline.

Fourteen studies evaluated patients with ML without previous treatment (586 patients), and 6 studies evaluated the treatment of recurrent ML (50 patients).

Unfortunately, the number of studies using combined therapy is insufficient to perform a statistical analysis.

**Pentavalent antimonials.** Eight studies evaluated the use of PA as first-line therapy of ML (271 patients): 4 of them evaluated *N*-methylglucamine or meglumine (Glucantime) (121 patients), and the other 4 evaluated stibogluconate (Pentostam) (150 patients). Only 1 study (with 35 patients) evaluated the use of PA in reduced doses (< 20 mg/kg/d). Although the results in this study were equivalent to the results with traditional doses ( $\approx$  20 mg/kg/d), the number of patients was small and included only low- to moderate-grade lesions. The therapeutic response to PA in a total of 271 patients was 67%, despite lesion severity (Table 2).

The comparison between meglumine and stibogluconate showed different cure rates (88% versus 51%; *P* < 0.05). In the meglumine group, all studies were from Brazil; and in the stibogluconate group, the studies were from Peru and Panama. The cure rate of stibogluconate was worse than the cure rates of amphotericin and pentamidine (*P* < 0.05) (Table 3).

No study used PA alone after the first failure of treatment. Three studies evaluated the use of PA associated with pentoxifylline (10 patients), allopurinol (6 patients), or interferon- $\gamma$  (9 patients), but the number of patients was small and did not allow statistical analysis with studies that used PA alone.

TABLE 1  
Internal and external validity from articles on ML

Author	Year	Country	Randomized/ blinded	Exclusion/inclusion criteria	Controlled trial/prospective	Follow-up (months)	Gold standard diagnosis	Species identification	Quality
First therapy									
Franko	1990	Peru	No	Yes	Prospective	12	Culture	<i>L. braziliensis</i>	Moderate
Franko	1994	Peru	Yes	No	Prospective	12	Culture or amastigotes on biopsy	<i>L. braziliensis</i>	High
Rodriguez	1995	Bolivia	No	Yes	Prospective	12	Culture or amastigotes on biopsy	<i>L. braziliensis</i>	High
Romero	1998	Brazil	No	No	Prospective	12	—	—	Low
Romero (A)	1996	Brazil	No	Yes	Prospective	12	Culture or amastigotes on biopsy	—	Moderate
Saenz	1991	Panama	No	Yes	Prospective	12	Culture or amastigotes on biopsy	<i>L. braziliensis</i>	Moderate
Oliveira	1995	Brazil	No	No	Prospective	12	Culture or amastigotes on biopsy	—	Moderate
Lianos-Cuentas	1997	Peru	Yes	Yes	Prospective	12	Culture or amastigotes on biopsy	—	Moderate
Oliveira-Neto	2000	Brazil	No	No	Prospective	2	Culture or amastigotes on biopsy or PCR	<i>L. braziliensis</i>	High
Passos	2001	Brazil	No	No	Prospective	12	Culture or amastigotes on biopsy or PCR	—	Moderate
Dedet	1995	Bolivia	No	No	Prospective	—	Histology/skin test/serology	—	Low
Calvopina	2004	Ecuador	No	Yes	Prospective	12	—	—	Low
Amato	2000	Brazil	No	No	Prospective	12	Culture or amastigotes on biopsy or PCR	—	Moderate
Netto	1990	Brazil	No	No	Prospective	6	Culture or amastigotes on biopsy	—	Low
Amato	1996	Brazil	No	No	Prospective	12	Histology/skin test/serology	—	Low
Amato	1998	Brazil	No	Yes	Prospective	12	Culture or amastigotes on biopsy	—	Moderate
Amato	1998	Brazil	No	Yes	Prospective	12	Culture or amastigotes on biopsy	—	Moderate
Failure to antimominal									
Romero (B)	1996	Brazil	No	Yes	Prospective	12	Culture or amastigotes on biopsy	—	Moderate
Sampaio	1997	Brazil	No	No	Prospective	24	Histology/skin test/serology	<i>L. braziliensis</i>	Moderate
Amato	2007	Brazil	No	No	Prospective	12	Histology/skin test/serology	—	Low
Lessa	2001	Brazil	No	Yes	Prospective	12	Culture or amastigotes on biopsy	<i>L. braziliensis</i>	Moderate
Badaro	2006	Brazil	No	No	Prospective	12	Culture or amastigotes on biopsy or PCR	—	Moderate
Falcoff	1994	Argentina	No	No	Prospective	12	Culture or amastigotes on biopsy or PCR	—	Moderate
Sampaio	1990	Brazil	No	No	Prospective	12	Histology/skin test/serology	<i>L. braziliensis</i>	Low
Sampaio	1990	Brazil	No	No	Prospective	12	Histology/skin test/serology	<i>L. braziliensis</i>	Moderate

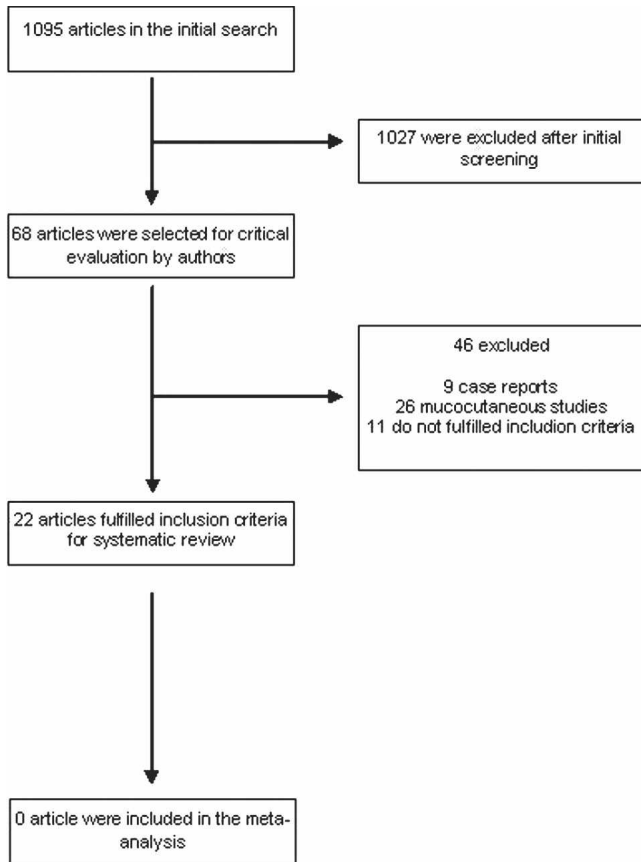


FIGURE 1. Study selection process.

**Pentamidine.** Treatment of ML with pentamidine was evaluated exclusively in treatment-naïve patients. The therapeutic approach with pentamidine showed excellent results in patients with moderate- to high-grade lesions, although both studies were published by the same group study from Brazil (total of 27 patients). When compared with stibogluconate, pentamidine was more effective ( $P < 0.05$ ); when compared with meglumine, there was no difference in the cure rate ( $P = 0.68$ ) (Table 3).

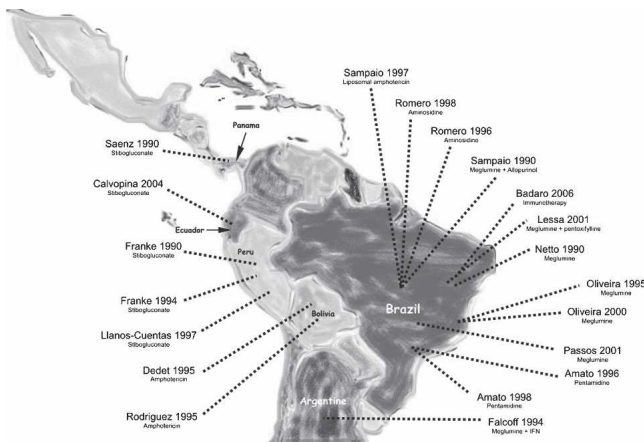


FIGURE 2. Origins of publications on treatment of ML in Latin America.

**Amphotericin.** Amphotericin achieved excellent results in the treatment of ML, as demonstrated in a Bolivian study with > 200 patients achieving a cure rate of 88%. When compared with meglumine, the same result was obtained with amphotericin B ( $P = 1$ ) (Table 3). Lipid formulations of amphotericin B showed better results than deoxycholate formulation (> 90%). Nevertheless, both studies included in this review evaluated 5 and 6 patients, with similar rates of cure (83.3% and 100%, respectively).

**Itraconazole.** Itraconazole was evaluated only in three studies, obtaining controversial results (33 patients). Two studies using itraconazole alone found cure rates of 23% in one article (13 patients) and 60% in another (10 patients). When associated with amphotericin B, there was no significant difference compared with amphotericin B alone (10 patients). After all publications were obtained and the results were compared with the group of patients that received meglumine, itraconazole obtained the worst cure rate of drugs evaluated (39%).

**Aminosidine.** This drug was evaluated in 2 publications (34 patients) from the same research group, and the result was worse than that achieved with meglumine. Although there was no significant statistical difference when compared with PA, one study found a cure rate < 50%.

**Selection bias.** The number of studies for each drug evaluated may be considered small but sufficient to determine a cure rate for the most used drugs to treat ML, such as PA and amphotericin B. Alternative therapies (immunotherapy, allopurinol, itraconazole, pentamidine, and interferon- $\gamma$ ) need studies with larger number of patients to determine more precisely the role of these therapies.

A statistical analysis to compare cure rates of standardized therapies in our review (meglumine) with other drugs was done in an attempt to obtain data on available therapies. Nevertheless, this method may be questioned as no controlled randomized studies were available for comparison.

## DISCUSSION

ML represents a health care problem in Latin America; the problem is justified by the widespread distribution of ML on the continent and the severity of its morbidity.<sup>21</sup> The term “espondia” is often used to describe metastatic mucosal leishmaniasis, compared with sponge-like lesions found in horses.<sup>22</sup> ML can develop many years after the cutaneous infection and should worry tourists who travel to endemic areas.<sup>23,24</sup> In addition, ever more troubling is the risk of reactivation of the disease in its mucosal form after episodes of immunosuppression. Cases of ML reactivation have been reported among HIV-positive patients, among kidney and heart transplant recipients, and among chronic users of corticosteroids.<sup>25–28</sup>

Meglumine or stibogluconate in treatment of ML has been considered as first-line therapy in several countries. The World Health Organization (WHO) recommends use of PA in treatment of ML.<sup>29</sup> When, in employing the standard dose of 20 mg/kg/d, the success rate at a given location surpasses 95% and there is no late recurrence of the disease, reduced dosages can be attempted. However, this is scarcely achieved. Because of the regional variability in response, lower doses of antimonials cannot be standardized, so it falls to local physicians, based on the local experience, to determine appropriate dosages.<sup>30</sup>

TABLE 2  
Different studies of ML treatment and retreatment

Author year/country	Therapy	Dose	Total patients	Cures	%	Failures	%	Severity	Subject of study	Drug origin
<b>First therapy</b>										
Franko 1990/Peru	Sibogluconate	20 mg/kg/d 28x	29	8	28%	21	72%	Not classified	Drug efficacy	
Franko 1994/Peru	Sibogluconate	20 mg/kg/d 28x	16	10	63%	6	38%	Not classified	Drug finding	Wellcome
Saenz 1991/Panama	Sibogluconate	20 mg/kg/d 40x	19	12	63%	7	37%	Not classified	Drug efficacy	Pentostam
Llanos-Cuentas 1997/Peru	Sibogluconate + allopurinol	20 mg/kg/d 28x	38	23	61%	15	39%	Moderate to severe	Drug comparison	Burroughs
Oliveira 1995/Brazil	Meglumine	20 mg/kg/d 30x	32	14	44%	18	56%	Not classified	Observational longitudinal study	
Oliveira-Neto 2000/Brazil	Meglumine	5 mg/kg/d 30x	21	21	100%	0	0%	Mild to moderate	Dose finding	
Passos 2001/Brazil	Meglumine	15 mg/kg/d 10x	10	7	70%	3	30%	Not classified	Observational longitudinal study	
Netto 1990/Brazil	Meglumine	5 mg/kg/d 45x	4	4	100%	0	0%	Not classified	Observational longitudinal study	
Dedet 1995/Bolivia	Meglumine	20 mg/kg/d 30x	18	17	94%	1	6%	Not classified	Observational longitudinal study	
Rodriguez 1995/Bolivia	Meglumine	20 mg/kg/d 30x	17	15	88%	2	12%	Not classified	Observational longitudinal study	
Romero 1998/Brazil	Meglumine	2,250 mg (total dose)	211	186	88%	25	12%	–	Observational longitudinal study	
Romero (A) 1996/Brazil	Amphotericin B	2,500 mg (total)	10	9	90%	1	10%	Moderate to severe	Drug comparison	
Calvopina 2004/Ecuador	Amphotericin B + itraconazole	Above + 400 mg 6 weeks	10	8	80%	2	20%	Moderate to severe	Drug efficacy	
Amato 2000/Brazil	Aminositidine	16 mg/kg/d 20x	21	14	67%	7	33%	Not classified	Drug efficacy	
Amato 1996/Brazil	Aminositidine	16 mg/kg/d 20x	13	4	31%	9	69%	Not classified	Drug efficacy	
Amato 1998/Brazil	Itraconazole	400 mg 12 weeks	13	3	23%	10	77%	Mild-severe	Drug efficacy	
Subtotal	Itraconazole	400 mg 6 weeks	10	6	60%	4	40%	Moderate	Drug efficacy	
	Pentamidine	2,140 mg (total dose)	10	9	90%	1	10%	Severe	Drug efficacy	
	Pentamidine	2,025–4,320 mg (total dose)	17	16	94%	1	6%	Severe	Drug finding	
	Subtotal		586	437	75%	149	25%			
<b>Second therapy after antimonial failure</b>										
Romero (B) 1996/Brazil	Aminositidine	16 mg/kg/d 20x	8	6	75%	2	25%	Not classified	Drug efficacy	
Sampaio 1997/Brazil	Liposomal amphotericin	5,100–2,000 mg (total dose)	6	5	83%	1	17%	Not classified	Dose finding	
Amato 2007/Brazil	Amphotericin B colloidal dispersion	40 mg/kg (total dose)	5	5	100%	0	0%	Moderate to severe	Dose finding	
Lessa 2001/Brazil	Meglumine + pentoxifylline	20 mg/kg 30x + 1,200 mg/d	10	9	90%	1	10%	Severe	Drug efficacy	
Badaro 2006/Brazil	Immunotherapy	*	6	6	100%	0	0%	Not classified	Therapy efficacy	
Falcoff 1994/Argentina	Meglumine + IFN	10 mg/kg 30x + 2 MIU	8	7	88%	1	13%	Not classified	Therapy efficacy	
Sampaio 1990/Brazil	Meglumine + allopurinol	20 mg/kg/d 45x	6	2	33%	4	67%	Not classified	Therapy efficacy	
Subtotal			49	40	82%	9	18%			
Total			635	477	75%	158	25%			

TABLE 3

Comparison of ML treatments: systematic comparison with meglumine

Author year/country	Therapy	Total patients	Cure	%	P value
Franke 1990/Peru	Stibogluconate	29	8	28%	
Franke 1994/Peru	Stibogluconate	16	10	63%	
Saenz 1991/Panama	Stibogluconate	19	12	63%	
Llanos-Cuentas 1997/Peru	Stibogluconate	16	9	56%	
	Stibogluconate + allopurinol	38	23	61%	
	Stibogluconate	32	14	44%	
Total		150	76	51%	$P < 0.05$
Oliveira 1995/Brazil	Meglumine	51	42	82%	
Oliveira-Neto 2000/Brazil	Meglumine	21	21	100%	
	Meglumine	10	7	70%	
	Meglumine	4	4	100%	
Passos 2001/Brazil	Meglumine	18	17	94%	
Netto 1990/Brazil	Meglumine	17	15	88%	
Total		121	106	88%	“Control”
Dedet 1995/Bolivia	Amphotericin B	211	186	88%	
Rodriguez 1995/Bolivia	Amphotericin B	10	9	90%	
	Amphotericin B + itraconazol	10	8	80%	
Total		221	195	88%	$P = 1$
Romero 1998/Brazil	Aminosidine	21	14	67%	
Romero (A) 1996/Brazil	Aminosidine	13	4	31%	
Total		34	18	53%	$P < 0.05$
Calvopina 2004/Ecuador	Itraconazole	13	3	23%	
Amato 2000/Brazil	Itraconazole	10	6	60%	
Total		23	9	39%	$P < 0.05$
Amato 1996/Brazil	Pentamidine	10	9	90%	
Amato 1998/Brazil	Pentamidine	17	16	94%	
Total		27	25	93%	$P = 0.68$

Primary resistance to PA is reported in 14% of the cases. When therapy is correctly used, treatment failure does not seem to be directly tied to the mechanism of action of the drug.<sup>31</sup> Most cases result from using subtherapeutic doses (< 10 mg/kg/d), treating for shorter periods of time than recommended, and not being able to exceed the maximum dose of 3 ampoules for patients > 68 kg.<sup>32</sup> Much has been discussed as to why responses vary so much when comparing different geographical areas. Such incongruence suggests the existence of subspecies of the parasites with various degrees of drug sensibility.<sup>33,34</sup> Although frequently noted, little is known regarding this regional variability.<sup>35</sup>

Meglumine and stibogluconate are antimonials pentavalent with similar cure rates in treatment of cutaneous leishmaniasis (CL).<sup>36</sup> The mechanism of action of both drugs is the same.<sup>37</sup> The cure rate in ML is not established, whereas data from cutaneous disease are acceptable. The comparison between meglumine and stibogluconate showed different cure rates in our systematic review. This difference was statistically

significant, and the number of patients is acceptable. The lower response of stibogluconate is significant in comparison with amphotericin B and pentamidine. Nevertheless, the cure rate of meglumine was not different from these 2 drugs. Unfortunately, some bias could have occurred in this evaluation. First, the regional response to therapy—in the meglumine group, all studies were from Brazil, whereas in the stibogluconate group, the studies were from Peru and Panama. In Brazilian studies, resistance to meglumine is low enough to decrease the current dose of 20 mg/kg/d to 5 mg/kg/d in Rio de Janeiro.<sup>38</sup>

Second, another relevant point concerns name-brand and generic formulations of stibogluconate. Even considering brand formulation, different reactions can occur during production. Stibogluconate and meglumine are prepared by reaction of pentavalent antimony with gluconic acid and *N*-methyl-D-glucamine, respectively.<sup>39</sup> Previous work on stibogluconate suggested that it was a complex mixture of components with apparent molecular masses ranging from 100 to 4,000 Da. The clinical effectiveness of stibogluconate appears to be influenced by its composition. Some lots of the drug have been associated with poor clinical outcomes and have had higher osmolalities than clinically effective lots.<sup>40</sup> These data suggest that subtle differences in the composition of stibogluconate may be important for clinical antileishmanial activity.

Amphotericin is the drug of choice in the Bolivia, and we demonstrated no difference in cure rate when compared with meglumine.<sup>41</sup> There are difficulties in using amphotericin B outside of the hospital environment, and its potential renal toxicity thwarts its use as a first-choice drug. In Bolivia, the drug is started at a lower dosage, increasing slowly up to 0.5 mg/kg/d, and the incidence of renal failure is < 10%.<sup>41</sup> Lipid-based formulations are alternatives to amphotericin B deoxycholate because of their milder side effects. Reductions of up to 50% of complications are demonstrated, especially when concerning renal function impairment. This is highly relevant, because kidney failure can be serious and impede continued treatment.<sup>42</sup> In spite of these advantages, no studies yet available compare lipid-based drugs and deoxycholate formulations. On the other hand, a more significant number of ML patients have been treated with lipid formulations of amphotericin, and very good responses have been verified with doses between 2 and 3 mg/kg/d for at least 20 days.<sup>43,44</sup> In 1 study, 5 ML patients who had absolute contraindications for use of antimonials and pentamidine were included; 100% of the cases responded with cure and low levels of toxicity.<sup>45</sup> A total dose of 40 mg/kg was needed to heal the lesions.<sup>45</sup> Sampaio and others showed similar results with liposomal amphotericin B.<sup>46</sup> Hence, meglumine still has advantages over amphotericin B.

When compared with stibogluconate as an alternative to treat ML, pentamidine is more effective, but this difference does not occur with meglumine. Initial studies suggested that they had similar responses.<sup>47</sup> In the mucosal or mucocutaneous form of leishmaniasis, maximum doses are limited by the risk of toxicity, especially to pancreatic function, which may compromise the efficacy of the treatment. Studies that administered 2–4 g of pentamidine had excellent responses, obtaining cure rates from 90% to 94% of patients with ML.<sup>48,49</sup>

Itraconazole was another drug tested as a treatment option for leishmaniasis. Initially there were only case reports, taking 10 years before *in vitro* testing began.<sup>50–54</sup> These experimental

TABLE 4  
Comparison of cost of treatment of ML

Drug	Cure rate (mean in %)	Dose	Daily cost (USD)	Proposed therapy	Total cost (USD)
Antimonial pentavalent	67%	1 ampole = 5 mg Sb <sup>5+</sup>	6.32	20 mg/kg/d 28×	176.96
Pentamidine	90%	1 ampole = 300 mg	59.19	2,140 mg	422.22
Itraconazole	39%	1 tablet = 100 mg	6.73	400 mg 6 weeks	282.86
Amphotericin B deoxicholate	88%	1 ampole = 50 mg	11.67	2,500 mg	583.50
Liposomal amphotericin B	≈ 100%	1 ampole = 50 mg	205.00	2,500 mg	12,300.00
Coloidal dispersion of amphotericin B	≈ 100%	1 ampole = 50 mg	139.00	2,200 mg	6,139.00

results were not satisfactory, but clinical tests kept on showing promising results for this drug as a last resource for relapsing cases of CL.<sup>55</sup> Association of itraconazole and amphotericin B was not superior to use of the latter alone. This is probably an effect of the good response to amphotericin B and consequent statistical difficulties in calculating significant results with small numbers of patients.<sup>56</sup> Despite the promising studies that already exist, there is not yet enough evidence to support exclusive use of itraconazole as safe. Further data are needed before it can be added to the current therapeutic arsenal.

Several drugs had been tried in patients with ML. Pyrimethamine was used in some patients in Panama with excellent results; however, Viegas and others could not duplicate them years later.<sup>57</sup>

Since 1982, *in vitro* studies demonstrate the possible benefits of allopurinol as a therapeutic option to leishmaniasis.<sup>58</sup> Allopurinol, a xanthine oxidase inhibitor, proved to be effective in treating CL in Asia. In the Americas, however, only an initial study had positive results.<sup>59</sup> Use of allopurinol has not been justified since Marsden and others published their findings in 1984.<sup>60</sup> They treated 3 patients with allopurinol 15 mg/kg/day, and no ulcer was cured. In our review, this drug was not effective.

Nifurtimox is known to reduce *Trypanosoma* parasitemia by an effect on the amastigote phase. Considering this effect, this drug was used in the treatment of ML in 1979 by Marsden and others.<sup>61,62</sup> Unfortunately, the result of this therapy was poor, with a cure in only 13% of patients. Considering these results, this drug should not be prescribed to treat ML.

Aminosidine achieved remission of mucosal lesions with the same result of PA. Nevertheless, nephrotoxicity and ototoxicity are severe adverse effects of aminosidine use.<sup>63</sup>

The cost of antimonials is similar to itraconazole, but the cure rate of this drug is unacceptable. Pentamidine shows that a complete treatment cost 3 times more than PA, but its side effects permit use of this drug as a second-line therapy. The cost of the amphotericin B deoxycholate could be justified by the high cure rate, but hospital admission and renal failure also should be considered. Unfortunately, the cost of the lipid formulation of amphotericin B is prohibitive in underdeveloped countries. The lipid formulation of amphotericin B may be used in the developed countries if we consider the once-daily therapy at an outpatient clinic, high rate of cure, and low incidence of adverse effects. The mean prices of these drugs were considered with import tax (Table 4). The number of patients that left treatment during the study was < 10% of the total number of patients included (data not shown). We did not include these patients in the study.

After this review, meglumine may be the first-line therapy in the treatment of ML, but several considerations should be evaluated before planning local therapeutic strategy. More

studies are needed before excluding stibogluconate from the arsenal of ML treatment, once several countries use this drug with success. We suggest reports of cure rates from countries that use stibogluconate as antimonials. Despite amphotericin B results, side effects of this therapy may be difficult to manage in developing countries. One possible solution for this problem is use of a lipid formulation of amphotericin B. Again, the problem of such drugs is the cost. The success rate of 88% that we found in our systematic review of meglumine calls for the attention of medical centers in developing countries to determine a good protocol of second-line drugs after relapse or failure to cicatrization of mucosal lesions. In this group, we can include amphotericin and pentamidine. If the resources of the local community are sufficient and the incidence of relapse/failure is low, then the lipid formulation may be considered. Third line therapies can include drugs with cure rate < 67% or with similar results and with tolerable adverse effects, such as aminosidine and itraconazole. Combined therapies with PA should be performed with care, and more studies are needed. Other treatments, such as immunotherapy and pentoxifylline, are not well established, and controlled trials are still needed to prove their efficacy and/or effectiveness.

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