

Short Report: Can We Use a Lower Dose of Liposomal Amphotericin B for the Treatment of Mucosal American Leishmaniasis?

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Abstract. Liposomal amphotericin B has been used as an alternative treatment of mucosal leishmaniasis, but the optimal dose is not established. We retrospectively reviewed the clinical outcome of eight patients with mucosal leishmaniasis treated with liposomal amphotericin B. The mean total dose was 35 mg/kg (range 24–50 mg/kg), which resulted in the healing of all the lesions in all patients and no recurrences were observed during the follow-up period (mean 25 months; range 7–40 months).

Tegumentary American leishmaniasis is a zoonotic disease caused by protozoan parasites of the genus *Leishmania*, transmitted through the bite of various species of female phlebotomine sandflies¹; the disease is an important public health problem in Brazil and is expanding its range through the state of São Paulo. Nevertheless, in terms of research, prevention, and control initiatives, leishmaniasis is a neglected disease that draws little interest from financial donors, public health authorities, and professionals.¹ The mucosal leishmaniasis is the most severe form of the cutaneous disease, caused by progressively destructive lesions of the nasal, oral, pharyngeal, and laryngeal tissues, causing severe facial deformation and respiratory disturbances.²

Pentavalent antimonials are the current drugs of choice for the treatment of mucosal leishmaniasis (ML), although they are far from ideal because of serious adverse side effects.³ Similarly, pentamidine and amphotericin B deoxycholate are parenteral agents that can be poorly tolerated by patients and require close medical supervision to avoid well-known serious adverse events with both drugs. Liposomal amphotericin B has been used as an alternative treatment of cutaneous leishmaniasis and, in comparison to conventional amphotericin B deoxycholate, has demonstrated a similar efficacy and lower toxic effects, although the optimum dosing regimen is undefined.^{4,5}

We performed a retrospective study in eight patients to evaluate the efficacy and total dose of liposomal amphotericin B (AmBisome NeXtar, San Dimas, CA) used for the treatment and clinical cure of ML. This study had the permission and the Institutional approval provided by the Clinic of Infectious and Parasitic Diseases, Hospital das Clínicas of University of São Paulo and it was considered respectful and ethical in its treatment of human subjects.

The drug was administered in 3–5 mg/kg/day doses. The dosage was determined by the prescriber and the duration of the treatment. Doses and outcomes are presented in Table 1.

All patients received liposomal amphotericin B because there was contraindication for antimonials. The respective contraindications are described in the Table 1. Patient nos. 3, 6, 7, and 8 were from the state of Bahia, localized in the Northeast. Patient 1 was from Paraná, a state localized in the

South, and other patients (2, 4, and 5) were from the state of São Paulo. The patient 8 had human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) under antiviral therapy. The cure and failure criteria were previously described.⁶ Figure 1 describes a case showing the image of nasal septum before and after the treatment of ML.

Side effects were observed in six patients and included chills, myalgia, back pain, nausea, and headache. Reduced glomerular filtration rate and hypokalemia were observed in two patients, but both levels returned to normal 2 days after the discontinuation of the drug and its subsequent reintroduction. All of the patients were clinically cured, and no failure or recurrence of disease was observed during the follow-up period (range 7–40 months; mean 25 months). Retreatment was not required for any of the patients.

Lipid formulations of amphotericin B have been effective treatments for visceral leishmaniasis in many countries, including Brazil.^{7–9} This formulation is packaged with cholesterol and other phospholipids within a small unilamellar liposome that binds to parasite ergosterol precursors, causing disruption of the parasite membrane without substantial harm to mammalian cell membranes. Additionally, the concentration of liposomal amphotericin B is high in macrophages, which enhances drug concentration in infected tissues, particularly the liver and spleen.¹⁰ This is an important benefit of the liposomal formulation, as *Leishmania* parasites are often present in host macrophages.

Despite a small overall number of cases evaluated, the results of this study are similar to findings in previous studies.^{4,5} The current World Health Organization (WHO) Technical Report Series recommends 2–3 mg/kg daily up to a total dose of 40–60 mg/kg of liposomal amphotericin B.¹¹ We showed that a total lower dose can be used and with a shorter admission time because we used higher daily doses (3–5 mg/kg). The ideal dose of liposomal amphotericin B has not yet been established; a mean total dose of 2,500 mg or 35 mg/kg resulted in the healing of lesions in all patients independent of lesion severity, with no recurrences observed during the follow-up period. This reduced dose can be important to decrease costs. In Brazil, the price of 50 mg of the liposomal amphotericin is around US\$200 and the total treatment would be from US\$8,000 to US\$12,000. However, the cost of antimonial is US\$176.55 for the total treatment.³ Therefore, we believe that further studies are needed to confirm these findings in additional relevant populations.

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TABLE 1
Characteristics and outcomes of patients with mucosal leishmaniasis treated with liposomal amphotericin B*

Sex/age, years	Lesion site	Previous treatment	Contraindication(s)†	Total cumulative dose, mg	Weight, Kg	Dose mg/Kg	Outcome	Duration of hospital stay/follow-up
1 M/64	Nasal septum	None	AVR	2100	65	32.3	Cure	15 days/8 months
2 M/40	Nasal septum	None	AVR	2910	100	29.1	Cure	15 days/9 months
3 M/84	Nasal septum	None	AVR, CRF	2000	70	28.6	Cure	23 days/40 months
4 M/76	Nasal septum	(2 years earlier)	AVR, ARF	3000	60	50	Cure	21 days/37 months
5 M/47	Palate, larynx	(3 years earlier)	AVR, DM	3000	60	50	Cure	40 days/35 months
6 M/66	Nasal septum	(9 days earlier)	ARF	2600	68	38.2	Cure	24 days/25 months
7 M/35	Nasal septum, palate	(10 days earlier)	AVR	2250	85	26.5	Cure	21 days/40 months
8 M/52	Nasal septum, palate	(5 days earlier)	ARF	2240	93	24	Cure	14 days/7 months
Mean				25,125	75,125	34.83		21,625 days/25,125 months

*ARF = acute renal failure; AVR = altered ventricular repolarization; CRF = chronic renal failure; DM = diabetes mellitus.

†Contraindications to the use of antimonials, pentamidine, or deoxycholate amphotericin B.

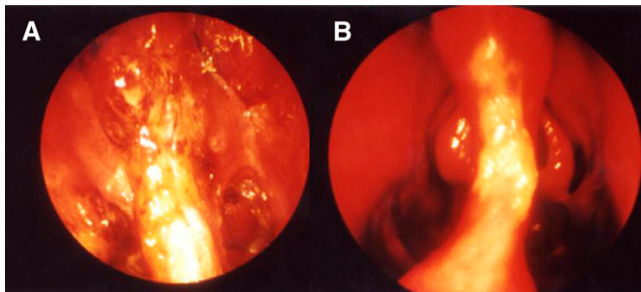


FIGURE 1. (A) Patient no. 8, nasofibrolaryngoscopy of nasal cavities showing mucosal edema and granuloma of nasal septum before treatment and (B) the healed lesion after treatment, allowing the visualization of the middle turbinate.

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