

Clinical, epidemiological and therapeutic study of 402 patients with american cutaneous leishmaniasis attended at University Hospital of Brasilia, DF, Brazil*

*Estudo clínico, epidemiológico e terapêutico de 402 pacientes com leishmaniose tegumentar americana atendidos no Hospital Universitário de Brasília, DF, Brasil**

Roberto Querido Name¹
João Herman Duarte Sampaio⁴

Karinne Tavares Borges²
Pedro Luiz Tauil⁵

Lucas Souza Carmo Nogueira³
Raimunda Nonata R. Sampaio⁶

Abstract: BACKGROUND - American cutaneous leishmaniasis is a disease with high prevalence and incidence in Brazil. The Brazilian Central-Western Region currently holds the third largest incidence and the first growth rate of this disease in the country. OBJECTIVES - to evaluate clinical, epidemiological and treatment features of patients with American cutaneous leishmaniasis seen at the University Hospital of Brasília.

METHOD - a case series study with 402 patients was carried out, spanning the period between January 1st, 1994 and February 28th, 2003. The following variables were studied: sex, age, occupation, state of origin, clinical features, diagnostic techniques, treatment with pentavalent antimony and side effects. Follow-up was one year after the end of treatment.

RESULTS - the predominant group of patients was composed by male rural laborers who presented mainly the cutaneous form of the illness. The greatest efficacy of the antimony was observed in patients presenting the cutaneous form treated up to six months after the onset of symptoms, and in females in general (both differences were statistically significant in multivariate analysis). The early treatment of the mucocutaneous form also presented better results, although not statistically significant. Electrocardiographical alterations were more frequent in the group of patients receiving a 20mg SbV/Kg/day for a 30-day schedule than those with the same dosage for 20 days. Eosinophilia was found in 17.5%.

CONCLUSIONS - Early treatment, female gender and cutaneous form presented higher levels of cure. Electrocardiographic changes rose as time of treatment was increased. The remarkable report of eosinophilia as a side effect of N-methylglucamine deserves further investigation.

Keywords: Leishmaniasis, Mucocutaneous/diagnosis; Leishmaniasis, Mucocutaneous/epidemiology; Leishmaniasis, Mucocutaneous/therapy

Resumo: FUNDAMENTOS - A leishmaniose tegumentar americana é doença em expansão no Brasil. A região Centro-Oeste é hoje a terceira em incidência e a primeira em crescimento da doença.

OBJETIVOS - Avaliar pacientes com leishmaniose tegumentar americana atendidos no Hospital Universitário de Brasília, quanto a aspectos clínicoepidemiológicos e resposta ao tratamento com antimonial pentavalente.

MÉTODOS - Estudo do tipo série de casos de 402 pacientes, segundo sexo, idade, ocupação, procedência, formas clínicas, métodos de diagnóstico, tratamento com antimonial pentavalente e efeitos colaterais, no período de 1/1/1994 a 28/2/2003. O acompanhamento foi de um ano pós-tratamento.

RESULTADOS - Predomínio de homens, lavradores, de 20 a 39 anos, com a forma cutânea. A eficácia do antimonial foi maior em pacientes com forma cutânea tratados até seis meses depois do início dos sintomas, e em pacientes do sexo feminino (diferenças estatisticamente significativas na análise multivariada). O mesmo ocorreu para pacientes com forma mucocutânea, mas sem diferença estatística significativa. Alterações eletrocardiográficas foram mais frequentes no grupo tratado com 20mg SbV/kg/dia por 30 dias em relação ao tratado por 20 dias. Eosinofilia ocorreu em 17,5% dos casos.

CONCLUSÕES - Tratamento precoce, sexo feminino e a forma cutânea apresentaram índices mais elevados de cura. Alterações do eletrocardiograma aumentaram com o tempo de tratamento com antimoniais. A eosinofilia como efeito colateral ao uso do antimonial merece maior investigação.

Palavras-chave: Leishmaniose mucocutânea/diagnóstico; Leishmaniose mucocutânea/epidemiologia; Leishmaniose mucocutânea/terapia

Received on July 19, 2004.

Approved by the Consultative Council and accepted for publication on May 04, 2005.

* Work done at Universidade de Brasília - UnB: Dermatology Service of Hospital Universitário de Brasília - HUB; Laboratory of Dermatomyology at Universidade de Brasília (DF) - Brazil.

¹ Medical Student, Universidade de Brasília - UnB (DF).

² Medical Student, Universidade de Brasília - UnB (DF).

³ Resident Doctor at the Dermatology Service of Hospital Universitário de Brasília - HUB (DF).

⁴ Cardiologist at Hospital Universitário de Brasília - HUB (DF).

⁵ Professor of Epidemiology, Chairman of the Social Medicine Department at Universidade de Brasília - UnB Medical School(DF).

⁶ Dermatology Professor at Universidade de Brasília (UnB) Medical School, Head of Dermatology Service of Hospital Universitário de Brasília - HUB (DF).

INTRODUCTION

The World Health Organization (WHO) includes American cutaneous leishmaniasis (ACL) among the six most important infectoparasitary diseases in the world. It is a prevalent problem, particularly in Africa, Asia and Latin America, thus characteristically affecting developing countries more intensely.^{1,2} In Brazil, this illness is widely distributed, occurring in all the states.³ It exhibits high incidence, with a registered number of 36,601 cases in 2001, according to the National Health Foundation.⁴ The Central-Western region appears as third in incidence and first in the disease growth rate in this country.⁴

ACL can have two more frequent clinical forms: cutaneous (CF) and mucocutaneous (MCF).

The manifestation of human infection is much varied and not totally elucidated yet, although factors like parasite species, genetic characteristics and host immune response have recognized importance.^{5,6}

The predominant presentation pattern of the CF is characterized by exsudative and painless ulcers with elevated borders and granulomatous floors.⁷ Mucosal lesions are most frequent in the nasal mucosa, although they may grow beyond the septum and affect other regions, such as the hard and soft palate, oral mucosa and lips. There may as well be infiltrations, ulcerations and perforations in the nasal mucosa and septum and affect, in a few cases, the pharynx, the larynx and even the trachea.^{3,7}

The Montenegro intradermal reaction is even today the most widely used method for the diagnosis of ACL.^{8,9} This reaction has a high predictive value, being positive in over 90% of leishmaniasis cases.¹⁰ Other laboratory tests such as smear, culture, inoculation in hamster, histopathological examination, indirect immunofluorescence and polymerase chain reaction (PCR) are also employed in order to increase diagnostic accuracy.^{3,11} The treatment of Leishmaniasis is still unsatisfactory. It is aimed at the interruption of the parasitic evolution cycle, thus reducing disease severity and the deformity caused by it. The drugs used are pentavalent antimony, Amphotericin B (liposomal form included) and pentamidine, the first being the initial choice, and the others generally used in situations of contraindication or antimonial inefficacy.^{12,13} Treatment with antimonials can produce several side effects, such as arthralgia, myalgia, headache, gastrointestinal disorders, electrocardiographic, renal hepatic and pancreatic alterations, cutaneous rash, blood dyscrasias, herpes zoster and others.¹⁴

The aim of this work was to study clinical and epidemiological data of patients with ACL that were seen at the Brasilia University Hospital (BUH), and to assess pentavalent antimony treatment response.

METHODS

A retrospective study was carried out by analyzing standardized protocols that were attached to the records of patients suffering from CF and MCF of ACL, seen at BUH between 01/01/1994 and 02/28/2003. The protocols were filled by BUH Dermatology Service resident doctors, under the supervision of the physicians responsible for the ACL ambulatory. Variables like place of birth, place of origin, likely place of infection, gender, age, occupation, clinical form of the disease, diagnostic methods, initial results of treatment, side effects, and incidence of relapse in a one-year follow-up period were assessed.

In this study, patients diagnosed on the basis of clinical and epidemiological history and with an ACL-compatible physical examination were included. Moreover, they had to exhibit positivity in at least one laboratorial diagnostic test, i.e., either parasitologic (culture, smear or inoculation in hamster), immunological (indirect immunofluorescence and Montenegro intradermal reaction) or histopathological. Immunofluorescence was considered positive when titles were greater than or equal to 1/40. For the histopathological examination, in addition to the presence of the parasite, the forms described by Magalhães et al.¹⁵ were considered compatible with ACL.

Two antimony treatment schedules were compared: single series intravenous N-methyl-glucamine 20 mg of pentavalent antimony/kg/day, for 20 days for CF and 30 days for MCF. Sodium Stibogluconate, when used, was done so in doses, number of days and type of administration equal to those of N-methyl-glucamine. The choice between N-methyl-glucamine and Stibogluconate depended on their availability at BUH.

Clinical and laboratorial evaluation of the patients was done before, during, and after treatment. Clinical follow-up was carried out for one year after the end of treatment. Follow-up tests included blood count, uranalysis, blood biochemistry and electrocardiogram (ECG), which were done weekly during treatment. All results obtained were compared to those of control tests done immediately before the beginning of treatment.

Patients were divided into two groups: one with exclusively cutaneous lesions, the other with mucocutaneous lesions.

Cure criteria were clinical: lesion epithelialization, absence of local infiltration and erythema at the end of treatment and up to one year after it. Relapses were characterized as the reactivation of an old lesion or the appearance of a new one next to the original lesion after the clinical cure period.

All data were stored and processed in the software Epi-info 2002 (Centers for Disease Control &

Prevention (CDC) - World Health Organization, July/2002). Statistical analysis considered relative risk values (RR), with a confidence interval (CI) of 95%, and significance level of 5%. A logistic regression-type multivariate analysis was carried out in the software SAS, version 8.02.

RESULTS

Two hundred and sixty-four of the 402 patients (65.6%) were men. As to skin color, 57.2% were brown, 27.9% white and 13.2% black. Orientals e Indians corresponded to 2% of the cases.

Patients ranged from 1 to 81 years of age at the start of treatment. The most frequent age range was that between 20 and 39 years of age (41.8%), followed by 0 to 19, 26.4%; 40 to 60, 24.1%; over 61, 7.2%.

The most frequently encountered professional activity was agricultural (23.9%); 26.9% of the patients had jobs directly linked to the rural environment, e.g., they were housekeepers, ranch-hands or lumberjacks. Students made up 17.2% of the cases.

As to state of origin, 20.7% came from the state of Goiás, 18.2% from Bahia, 17.9% from Minas Gerais, 12.9 from Distrito Federal and 6.2% from Maranhão.

Two hundred and thirty-eight patients (59.2%) presented CF, whereas 164 (40.8%) presented MCF.

The most frequent type of lesion was ulcers with infiltrated borders and granulomatous floors (72.4%). An infiltrative lesion or papula was observed in 15.6% of the patients, and vegetation in 8.8%. Together, other types of lesions represented 3.2%.

With respect to the location of the cutaneous lesion, distribution was as follows: lower limbs, 56.5%; upper limbs, 28.4%; and head, 13.6%.

In MCF cases, the nasal septum was the main site of affection (86.6%). Other affected mucosal membranes were those of the oropharynx, nasopharynx, hard and soft palate and nasal mucosa.

The main symptom related to MCF was nasal obstruction (68.3%), followed by coryza (26.8%). Asymptomatics represented 14.6%.

75.6% of the patients with CF sought medical help within six months after symptoms onset. Other 23.1% did so between six months and a year, and after that, 1.3%. For MCF, 14.6% sought specialized aid for leishmaniasis treatment within six months of symptoms onset, 9.8% between six and twelve months, and 75.6% after a year.

In relation to diagnostic methods, Montenegro's intradermal reaction had a 96% positivity. As to other tests performed, positivity percentages were 67.6 for indirect immunofluorescence, 65.6% for histopathological testing (reports suggestive of ACL or with presence of the parasite), 47.6% for culture, and 47.5% for smear. Of

the performed histopathological tests, parasite visualization occurred in 20.4% of instances. Hamster inoculation was positive in 44.7% of the inoculated.

The most used drug for the treatment of ACL was pentavalent antimony: 217 patients displaying CF (91.2%) used the 20mg SbV/kg/day for 20 days schedule, 177 of which were cured and presented no relapses for up to or more than one year (81.6%); 148 patients with MCF (90.2%), used the 20mg SbV/kg/day for a 30-day schedule, 103 of those having been cured for up to or over a year. Pentavalent antimony treatment efficacy was greater in females in the CF group and in patients presenting CF whose treatment began less than six months after symptoms started. These differences were statistically significant both in the univariate and multivariate statistical analyses (Table 1). Pentavalent antimony treatment efficacy was greater in patients with a single lesion; however, this difference was not statistically significant when this group was compared to that exhibiting multiple lesions. Sodium Stibogluconate was used in 34 patients. Other drugs, such as pentamidine and afoterecin B, were employed in 10% of the cases.

The most encountered alteration in blood count was eosinophilia (17.5%). Blood biochemistry showed an increase in transaminases activity, of 9.3% in TGO and 6.8% in TGP. In urinalysis (UA), the main alteration was pyuria (12.8%).

Electrocardiographical alterations were found in 20.3% of the patients that used the 20mg SbV/kg/day for 20 days schedule and in 46.6% of those who used the 30-day schedule. Sixty-two patients (17%) had already been treated with pentavalent antimony. Of these, only 42% (26 patients) had completed treatment.

DISCUSSION

In this study, predominance of ACL incidence was observed in male agricultural workers in the economically active age range. When compared to the results obtained by Sampaio et al.¹⁰ in the 1980s, differences such as reduction of the percentage of workers (23.9%), in relation to the then reported 56%, were observed. Moreover, the percentage of patients with MCF in the present study (40.8%) was lower than what was observed in the Sampaio study (52.7%). This is likely to be due to the fact that the number of cases coming from the Federal District in this study is larger than that of the cited case study (only one case), i.e., with a larger number of patients from the Federal District presently (12.9%), an earlier diagnosis may have been possible relative to the other study, thus allowing the disease to be diagnosed in its more initial stages, hence with greater probability of identifying it in its exclusively cutaneous form.

TABLE 1: Characteristics of ACL patients seen at BUH from 01/01/1994 to 02/28/2003 treated with pentavalent antimony and efficacy obtained with treatment

	Cured	Non cured	RR	IC 95%	p	*OR Adjusted	*CI 95%	*p
Sex								
Female	105	18						
Male	175	67	1.18	1.06-1.31 (S)	< 0.01	2.32	1.07-5.00	< 0.05 (S)
Clinical Form								
Cutaneous	177	40						
Mucocutaneous	103	45	1.17	1.04-1.33 (S)	< 0.05	3.58	1.81-5.00	< 0.001 (S)
Time between symptoms onset beginning of treatment - CF								
≤ 6 months	149	19						
> 6 months	26	23	1.67	1.28-2.19 (S)	< 0.001	2.21	1.11-4.41	< 0.05 (S)
Time between symptoms onset beginning of treatment - MCF								
≤ 6 months	19	3						
> 6 months	84	42	1.30	1.05-1.59 (NS)	0.109	-	-	-
Number of cutaneous lesions - CF								
One lesion	109	27						
More than one lesion	63	18	1.03	0.89-1.19 (NS)	0.80	-	-	-
Origin								
FD	42	9						
Outside FD	238	76	1.09	0.94-1.25 (NS)	0.39	-	-	-

(S) - Statistically significant; (NS) - Non-significant

* Obtained by logistic regression

CF - Cutaneous Form; MCF - Mucocutaneous Form

FD -Federal District

Patients coming from the FD represented an expressive share in the study, considering that up to only a few years ago no ACL cases had been diagnosed in this unit of the Brazilian federation.¹⁴ It is noteworthy that in the year 2003 a surge was recorded in the town of São Sebastião,¹⁶ reinforcing the autochthony of the disease. Supporting these observations, research has revealed the presence of the disease vectors in the Federal District, although they have not been found to bear parasites.¹⁷

Even though the percentage of MCF cases is very high,^{3,14,18,19} a predominance of the CF of the disease was observed, which is certainly due to the fact that this study was carried out in a hospital and reference center. Previous studies have demonstrated that the predominant species in this case series is *Leishmania (V) braziliensis*, with the possibility of occurrence, in a smaller proportion, of *L (V) amazonensis* or even other species such as *L (V) shawi*.^{14,20}

Patients with CF sought medical help earlier than patients with MCF, probably because of aesthetic reasons. Factors that usually delay the search for a medical service are, for instance, home treatments that try to solve the problem, which occur very commonly. In patients presenting mucosal lesions, the

attribution of symptoms to causes like rhinitis, sinusitis and flu is very frequent. Only when facing persistence of the picture or worsening of lesions will the patients look for specialized help. It is likely that the greater number of relapses and treatment difficulties of MCF is in part due to the greater delay in seeking for proper assistance and in the initiation of the correct treatment, which leads us to believe that the active search for these patients would be of great importance.

Among the most used diagnostic methods, Montenegro intradermal reaction was the one with higher positivity percentages, agreeing with other reports in the literature.^{14,21} As shown in table 2, direct search for amastigotes was confirmed to be more sensitive in CF rather than in MCF, possibly because it allows for an earlier diagnosis.

The time gap between lesions and the beginning of treatment seems to interfere with the prognosis of the disease. In the present study, a statistically significant difference was found in patients with CF that began treatment earlier (Table 1).

The found laboratory alterations are compatible with the literature, with the exception of the most frequent finding here described, namely, eosinophil-

TABLE 2: Form of ACL and presence of the amastigota in the histopathological examination of patients seen at BUH, from 01/01/1994 to 02/28/2003

Type of lesion	Amastigotes		Total
	Present	Absent	
Cutaneous	94	109	203
Mucocutaneous	38	99	137
Total	132	208	340

RR = 1,67; CI 95% 1,23 - 2,27; p < 0,001 (statistically significant)

TABLE 3: Comparison of the electrocardiographical alterations between the 20-day and the 30-day 20mg SbV/kg/day therapeutical schedules in ACL patients seen at BUH from 01/01/1994 to 02/28/2003

Therapeutical schedule	Test		Total
	Altered	Non-altered	
20mg SbV/kg/day for 30 days	69	79	148
20mg SbV/kg/day for 30 days	44	173	217
Total	113	252	365

RR = 2,30; CI 95% 1,68 - 3,15; p < 0,0001 (statistically significant)

ia, more restrictly divulged.^{14,17}

Electrocardiographical alterations occurred more often in the 30-day regimen. This difference was statistically significant. (Table 3). This datum corroborates the observations that more prolonged therapeutic schedules tend to cause more side effects.⁷

CF cure rates attained with the use of pentavalent antimony were compatible to those found by other authors.^{14,22,23} In the case of MCF, these rates were smaller, thus reaffirming the greater difficulty found in the treatment of this form of the disease (Table 1). Results indicating otherwise might be derived, for instance, from methodologies different than the one employed in this study.^{19,24,25,26}

The search for treatments lasting for smaller periods of time and using smaller daily doses has attracted the interest of many researchers.^{25,26} observed cure in 100% of the 21 patients with MCF after using a 5mg SbV/kg/day regimen for 30 days. In spite of the fact that the antimony dose used in this study is four times as large as the one used by the latter author, the observed cure rates were not as high. It is possible that the differences encountered can be

explained by differences in the species or subspecies of *Leishmania* that prevail in the two places where the studies were carried out, not to mention methodological disparities. Clinical studies in Brazil have confirmed different sensitivities to pentavalent antimony among different species.^{27,28}

CONCLUSION

Epidemiologic data express a professional pattern in the disease, and it is likely that the high number of patients presenting MCF is due to the case series of a reference center that receives more complex cases.

Early search for treatment improves prognosis for CF. The difference in relation to MFC was not statistically significant. The CF exhibited higher cure rates.

Electrocardiographic alterations are directly proportional to the duration of treatment.

Females had better treatment results. Eosinophilia was the most important side effect of N-methyl-glucamine use, a finding that deserves further investigation. □

ACKNOWLEDGEMENTS

We thank Prof. Maria Teresa Leão Costa, Assistant Professor at the Statistics Department of Universidade de Brasília, for doing the logistic regression-type multivaried statistical analysis. Our

thanks to the resident doctors at the Dermatology Service of BUH, as well as to Dr. Jorgeth Carneiro de Oliveira Motta and Dr. Cármen Déa Ribeiro for their supervision.

REFERENCES

1. Gontijo B, Carvalho ML. American cutaneous leishmaniasis. *Rev Soc Bras Med Trop.* 2003;36:71-80.
2. Lucciola GV, Passos VMA, Patrus AO. Mudança no padrão epidemiológico da leishmaniose tegumentar americana. *An Bras Dermatol.* 1996;71:99-105.
3. Ministério da Saúde. Fundação Nacional de Saúde. [sitio da internet]. Manual de controle da leishmaniose tegumentar americana. Brasília/DF, 2000. Disponível em: http://www.saude.ms.gov.br/externo/downloads/Leishmaniose_Tegumentar.pdf. Acessado em: Janeiro 05, 2005.
4. Ministério da Saúde. Fundação Nacional de Saúde. [sitio da internet]. Situação da prevenção e controle das doenças transmissíveis no Brasil. Brasília/DF, setembro de 2002. Disponível em: http://www.funasa.gov.br/epi/pdfs/situacao_doencas.pdf. Acessado em: Setembro 10, 2002.
5. Barral-Netto M, Brodskyn C, Carvalho EM, Barral A. *Human_leishmaniasis@cytokines.bahia.br.* *Braz J Med Biol Res.* 1998;31:149-55.
6. Ribeiro-de-Jesus A, Almeida RP, Lessa H, Bacellar O, Carvalho EM. Cytokine profile and pathology in human leishmaniasis. *Braz J Med Biol Res.* 1998;31:143-8.
7. Grevelink SA, Lerner EA. Leishmaniasis. *J Am Acad Dermatol.* 1996;34:257-72.
8. Medeiros AC, Rodrigues SS, Roselino AM. Comparison of the specificity of PCR and the histopathological detection of leishmania for the diagnosis of American cutaneous leishmaniasis. *Braz J Med Biol Res.* 2002;35:421-4.
9. Dimier-David L, David C, Dedet J. Parasitological Diagnosis of Mucocutaneous Leishmaniasis due to *L. B. braziliensis* in Bolivia. *Rev Soc Bras Med Trop.* 1991;24:231-4.
10. Sampaio RNR, Marsden PD, Cuba-Cuba C, Furtado F, Barreto AC, Campbell G. Avaliação clínico-laboratorial de 114 casos hospitalares de leishmaniose cutâneo-mucosa. *An Bras Dermatol.* 1989;64:201-5.
11. Oliveira-Neto MP, Schubach A, Araujo ML, Pirmez C. High and low doses of antimony (SbV) in american cutaneous leishmaniasis. A five years follow-up stud of 15 patients. *Mem Inst Oswaldo Cruz.* 1996;91:207-9.
12. Croft SL, Yardley V. Chemotherapy of leishmaniasis. *Curr Pharm Des.* 2002;8:319-42.
13. Hellier I, Dereure O, Tournillac I, Pratlong F, Guillot B, Dedet JP, et al. Treatment of Old World cutaneous leishmaniasis by pentamidine isethionate. An open study of 11 patients. *Dermatology.* 2000;200:120-3.
14. Nogueira LSC, Sampaio RNR. Estudo hospitalar da leishmaniose tegumentar americana (LTA): epidemiologia e tratamento. *An Bras Dermatol.* 2001;76:51-62.
15. Magalhães AA, Moraes MAP, Raick AN, Llanos-Cuentas A, Costa JML, Cuba CC, et al. Histopatologia da leishmaniose tegumentar por *Leishmania braziliensis braziliensis*: padrões histopatológicos e estudo evolutivo das lesões. *Rev Inst Med Trop S Paulo.* 1986;28:253-62.
16. Porto C. Autoctonia da leishmaniose tegumentar americana no Distrito Federal: estudo em seres humanos e cães na cidade de São Sebastião [tese]. Brasília: Faculdade de Medicina da Universidade de Brasília; 2004.
17. Silva TAV, John, FP, Sampaio RNR, Rodrigues R. Autoctonia da leishmaniose tegumentar americana no Distrito Federal, Brasil: estudo de vetores. *Anais do 9º Congresso de iniciação científica da Universidade de Brasília; 2003 Ago 20-22; Brasília, Brasil.* Brasília: Editora Universidade de Brasília.
18. Rojas CA. An ecosystem approach to human health and the prevention of cutaneous leishmaniasis in Tumaco, Colombia. *Cad Saude Publica.* 2001;17: S193-200.
19. Wanke CF, Birkenhauer MC, Macieira JMP, Silva FC, Perez M. Leishmaniose tegumentar: estudo retrospectivo de 65 casos. *An Bras Dermatol.* 1991;66:49-54.
20. Paula CD, Sampaio JH, Cardoso DR, Sampaio RN. A comparative study between the efficacy of pentamidine isothionate given in three doses for one week and N-methyl-glucamine in a dose of 20mgSbV/day for 20 days to treat cutaneous leishmaniasis. *Rev Soc Bras Med Trop.* 2003;36:365-71.
21. Cuba-Cuba C, Marsden PD, Barreto C, Rocha R, Sampaio RNR, Patzlaff L. Diagnostico parasitologico e imunologico de leishmaniasis tegumentaria americana. *Bol of Sanit Panam.* 1980;89:195-206.
22. Azeredo-Coutinho RB, Mendonca SC. An intermittent schedule is better than continuous regimen of antimonial therapy for cutaneous leishmaniasis in the municipality of Rio de Janeiro, Brazil. *Rev Soc Bras Med Trop.* 2002; 35:477-81.
23. Martinez S, Gonzalez M, Vernaza M. Treatment of cutaneous leishmaniasis with alopurinol and citobogluconate. *Clin Infec Dis.* 1997;24:165-9.
24. Falqueto A, Sessa PA, Veronesi. *Tratado de infectologia.* São Paulo: Editora Atheneu; 1997. p. 1221-33.
25. Oliveira-Neto MP, Mattos M, Pirmez C, Fernandes O, Goncalves-Costa SC, Souza CF, Grimaldi G Jr. Mucosal leishmaniasis ("espundia") responsive to low dose of N-methyl glucamine (Glucantime) in Rio de Janeiro, Brazil. *Rev Inst Med Trop São Paulo.* 2000; 42:321-5.
26. Oliveira-Neto MP, Schubach A, Mattos M, da Costa SC, Pirmez C. Intralesional therapy of American cutaneous leishmaniasis with pentavalent antimony in Rio de Janeiro, Brazil - an area of *Leishmania (V) braziliensis* transmission. *Int J Dermatol.* 1997;36:463-8.
27. Romero GA, Guerra MV, Paes MG, Macedo VO. Comparison of cutaneous leishmaniasis due to *Leishmania (Viannia) braziliensis* and *L. (V) guyanensis* in Brazil: therapeutic response to meglumine antimoniate. *Am J Trop Med Hyg.* 2001;65:456-65.
28. Romero GA, Vinitius De Farias Guerra M, Gomes Paes M, de Oliveira Macedo V. Comparison of cutaneous leishmaniasis due to *Leishmania (Viannia) braziliensis* and *L. (V) guyanensis* in Brazil: clinical findings and diagnostic approach. *Clin Infect Dis.* 2001;32:1304-12.

MAILING ADDRESS:

Profa. Raimunda Nonata Ribeiro Sampaio
SHIS QI 25 conj. 02 casa 1
Brasília DF 71660-220
Tel.: (61) 367-1331 / Fax: (61) 367-3825
E-mail: rnrsampao@hotmail.com