MAJOR ARTICLE

# Clinical and Parasite Species Risk Factors for Pentavalent Antimonial Treatment Failure in Cutaneous Leishmaniasis in Peru

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***Background.*** Treatment for cutaneous leishmaniasis (CL) with standard pentavalent antimonial therapy is hampered by cumbersome administration, toxicity, and potential failure. Knowledge of factors influencing treatment outcome is essential for successful management.

***Methods.*** A case-control study of incident cases was performed with patients experiencing their first CL episode. The standard treatment for CL for these patients was 20 mg/kg/day of sodium stibogluconate for 20 days. Clinical and epidemiological data were recorded, and parasite isolates were species typed. Patients were followed up for 6 months to assess treatment outcome. Clinical cure was defined as complete wound closure and re-epithelization without inflammation or infiltration; new lesions, wound reopening, or signs of activity were classified as treatment failure. Descriptive, bivariate, and logistic regression analyses were performed.

***Results.*** One hundred twenty-seven patients were recruited; 63 (49.6%) were infected with *Leishmania (Viannia) peruviana,* 29 (22.8%) were infected with *Leishmania (Viannia) braziliensis,* 27 (21.3%) were infected with *Leishmania (Viannia) guyanensis,* and 8 (6.3%) were infected with other species. Only patients infected with the 3 most common species were selected for risk-factor analysis ($n = 119$). Final failure rate at 6 months was 24.4% (95% confidence interval [CI], 16.5%–32.1%), with 96% of failures occurring within the first 3 months of follow-up assessment. Risk factors for treatment failure identified in the final multivariate model were age (per year, odds ratio [OR], 0.95; 95% CI, 0.92–0.99; $P = .017$), stay of <72 months in area of disease acquisition (OR, 30.45; 95% CI, 2.38–389.25; $P = .009$), duration of disease <5 weeks (OR, 4.39; 95% CI, 1.12–17.23; $P = .034$), additional lesion (per lesion, OR, 2.06; 95% CI, 1.3–3.28; $P = .002$), infection with *L. (V.) peruviana* (OR, 9.85; 95% CI, 1.01–95.65; $P = .049$), and infection with *L. (V.) braziliensis* (OR, 22.36; 95% CI, 1.89–263.96; $P = .014$).

***Conclusions.*** The identification of parasite species and clinical risk factors for antimonial treatment failure should lead to an improved management of CL in patients in Peru.

Cutaneous leishmaniasis (CL) is a vector-borne disease caused by *Leishmania* species and poses increasing health problems worldwide [1]. Outbreaks and increments in its incidence have been associated with urbanization, travel, climatic change, and social conflict in several regions of the world [2–10]. For the past 25 years, prevalence and incidence in the Americas have been on the rise [11–13].

CL is a major health problem in Peru, with ~6500 cases per year [14]. Seventy percent of the country has endemic disease, which results in high morbidity, lifelong scarring, and cumbersome treatment to many already–resource-deprived communities. *Leishmania (Viannia) peruviana, Leishmania (Viannia) guyanensis,* and *Leishmania (Viannia) braziliensis* cause the majority of cases [15]. This last species (i.e., *L. [V.] brazil-*

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*iensis*) is the principal etiological agent of mucosal leishmaniasis, a chronic infiltrative disease of delayed onset that affects the upper airways and, through factors yet unknown, appears in 2%–3% of CL cases [6, 16–18].

Pentavalent antimonials are still considered, after nearly 50 years of use, first-line treatment for CL (either meglumine antimoniate or sodium stibogluconate [SSG]). Administration is parenteral, for 20–30 days, with frequent adverse effects [19]. Several studies of antimonial therapy performed in Latin America show marked differences in cure rates, varying from 26.3% to 100%, even within the same country [20–26]. Determinants for this wide range can be due to host factors, parasite characteristics, variable drug quality, concentration, or even study design. Few studies have been conducted on the influence of clinical, epidemiological, and host factors (i.e., immune response and genetic background) on treatment outcome [27–29]. Similarly, the effect of parasite species has been investigated in a limited fashion [27, 30]. The in vitro models currently used for measuring susceptibility to antimonials in parasite isolates show wide variation and have no apparent relation to actual clinical outcome after therapy [31, 32].

To investigate these issues, the Leishnatdrug-R consortium was formed. Data dealing with the isolated effect of parasite species and CL clinical outcome were published elsewhere [33]. In the present study, we increase our scope and aim to determine which clinical and epidemiological factors, after adjustment by parasite species, play a role in treatment outcome for CL. Using standard therapy and close patient follow-up, we intend to build a risk-factor model that will serve as a useful set of indicators for predicting antimonial treatment failure.

## MATERIALS AND METHODS

***Study population.*** We performed a prospective case-control study of incident cases. The study took place between November 2001 and December 2004 at the Leishmaniasis Clinic located in the Instituto de Medicina Tropical "Alexander von Humboldt," Universidad Peruana Cayetano Heredia, in Lima, Peru. The clinic serves patients from nearly all areas of endemicity in the country. Subjects from both sexes and all ages with a first episode of parasitologically confirmed CL were recruited. Those who completed treatment with SSG and had *Leishmania* species typed were included in the final patient group. Patients with mucosal involvement, who were pregnant or breast-feeding, or who had major diseases were excluded. The study protocol and informed consent were approved by the Research Ethics Committees of Universidad Peruana Cayetano Heredia (Lima, Peru) and Institute of Tropical Medicine (Antwerp, Belgium). Informed consent was obtained from all participating subjects or their legal guardians.

***Procedures.*** A clinical examination and epidemiological questionnaire were completed at the time of recruitment. Information included age, sex, main activity, region of disease acquisition, duration of stay in an area of endemicity, and duration of disease. Main activity was classified as low or high risk of exposure to insect bites; high-risk activities included agriculture, mining, and logging. Region of disease acquisition was the geographic location where infection was acquired; endemic areas were grouped in 4 regions: 1 highland and 3 jungle regions (northern, central, and southern). Duration of stay was defined as the period of time spent in the region where infection occurred, measured in months. Duration of disease was recorded as the time elapsed from when the patient first noticed a lesion until therapy started, measured in weeks. Lesion description included number, diameter, type, location, and lymph node involvement. Diameter was taken as the longest distance between the edges of the biggest lesion, measured in centimeters. Types considered were ulcers, nonulcers (i.e., nodules and plaques), and mixed forms.

Patients underwent leishmanin skin testing, prepared with protein lysate from *L. (V.) guyanensis* LP52 strains (30 $\mu$g/mL). A wheal >5 mm was considered positive, 48 h after inoculation of 0.1 mL of lysate. Parasitological confirmation was done by Giemsa-stained direct smear, culture of a lesion aspirate specimen, or PCR. Culture samples were inoculated into Tobie blood agar medium [34]. Qualitative PCR was done by minicircle kinetoplast DNA assay [35, 36]. For species identification, multilocus PCR restriction-fragment–length polymorphism was performed, as described in a previous publication from this study group [33].

Subjects received treatment on site, with standard supervised daily administration of SSG following World Health Organization guidelines (20 mg $Sb^{5+}$/kg/day for 20 days by intravenous or intramuscular injection). Drugs were provided by 2 sources: Albert-David, India (lot 3P12001), and Viteco, Colombia (lots 10700, 10800, 20600, 20700, and 30600). Quality control for $Sb^{5+}$ concentration in all batches was performed by the International Dispensary Association (Amsterdam, The Netherlands). Lesion progression was monitored during treatment. Follow-up visits were scheduled for 1, 2, 3, 6, and 12 months after treatment ended. At each visit, patients were classified clinically for 2 possible outcomes: (1) cure, defined as complete wound healing, with epithelization and absence of any sign of activity or inflammation; and (2) failure, increased inflammation around the initial lesion, with or without epithelization, clinical regression of a healed lesion, or presence of new lesion(s) or a satellite lesion around the initial one.

Lesions in the process of closure were considered to be pending until they reached 1 of the 2 final outcomes. The treatment was considered to be a failure if lesions remained at 6-month follow up. Once treatment failure was determined, follow-up assessment stopped, and second-line treatment was administered. Cured patients were still observed until 12 months to

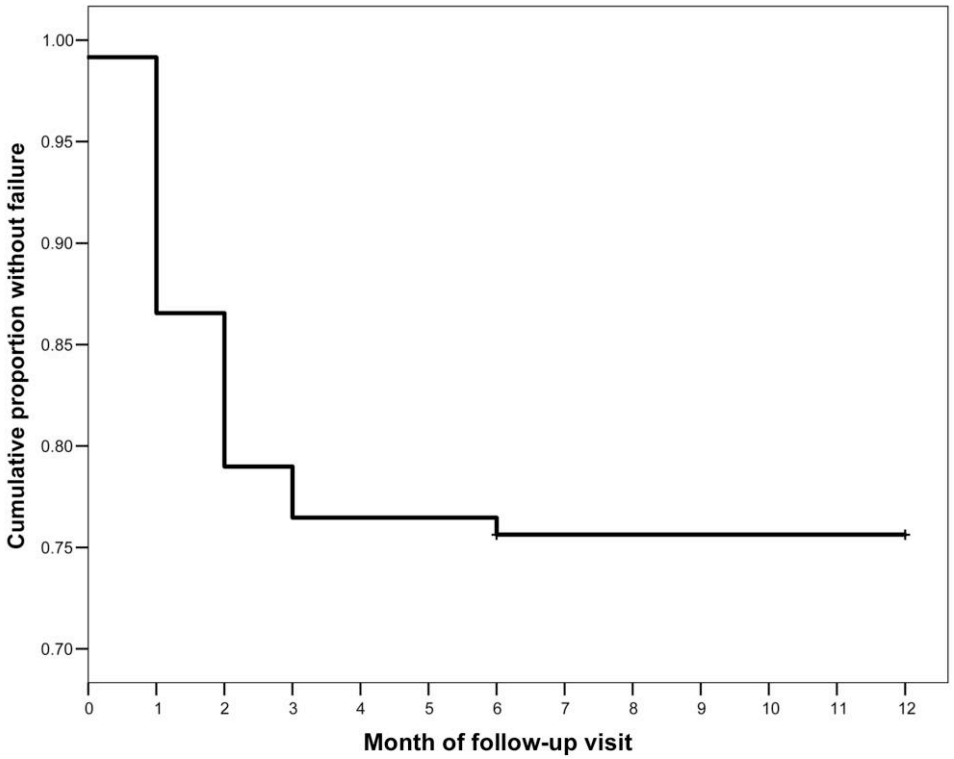


**Figure 1.** Kaplan-Meyer survival curve showing clinical failures detected during follow-up visits in Peruvian patients with cutaneous leishmaniasis ($n = 119$).

detect possible relapses, defined as reappearance of active infection after cure was achieved. In the case of multiple lesions, clinical outcome was defined by the status of the least well-healed lesion.

***Statistical analysis.*** Statistical analysis was performed using EpiInfo, version 3.3.2 (Centers for Disease Control and Prevention), and NCSS Statistical Software, version 2006 (Number Cruncher Statistical Systems). Frequencies and proportions were used to describe categorical variables. Means, medians, and SDs were obtained for numeric variables. Distributions of continuous variables were further analyzed; those without normal distribution were stratified using quartiles. Kaplan-Meier survival curves were obtained to assess failure rates over time; pending and cure cases were grouped together. Variables were grouped according to clinical outcome at the sixth month, considered the final end point, because no more pending cases remained. Pearson's $\chi^2$ test was used for categorical variable comparison, and Mann-Whitney $U$ and Kruskal-Wallis tests were used for nonnormal numeric variables. ORs were calculated for variables with significance levels $\leq .10$, by simple logistic regression. These risk factors were then introduced in order of significance into a multivariate model and were tested by means of multiple logistic regression and receiver-operating-characteristic (ROC) curves. Possible interactions between variables were analyzed. Confounders and risk factors that lost significance were excluded from the final model. Significance was set at $P < .05$.

## RESULTS

***Species typing.*** A total of 127 patients met the selection criteria. The 3 most common species identified were *L. (V.) peruviana, L. (V.) braziliensis,* and *L. (V.) guyanensis,* with 63 samples (49.6%), 29 samples (22.8%), and 27 samples (21.3%), respectively. The remaining isolates were typed as *L. (V.) lainsoni* ($n = 6$), *L. (L.) mexicana* ($n = 1$), and a *L. (V.) peruviana/braziliensis* hybrid ($n = 1$). *L. (V.) peruviana* was the most common species in the Andean highlands (88.5%). The jungle regions showed a diverse distribution: *L. (V.) guyanensis* was more common in the central jungle (57.1%), whereas *L. (V.) braziliensis* predominated in the southern jungle (64.7%). There was significant association ($P < .001$, by $\chi^2$ test) between species and geographical region.

***Outcome end points.*** Patients with the 3 most common species were selected for outcome comparison ($n = 119$). Each had at least 1 follow-up visit during the first 3 months and 1 visit after 6 months. A total of 29 patients (24.4%; 95% CI, 16.5%–32.1%) had treatment failure at some point in the follow-up period. The survival curve (figure 1) shows that the majority of treatment failures occurred within the first 3

months after therapy finished: at 1 month, 54% of failures had already occurred; at 2 months, 81% had occurred; and at 3 months, 94.6% of failures had occurred.

Failure rates at 6 months were 7.4% (95% CI, 2.3%–23.5%) for *L. (V.) guyanensis,* 28.6% (95% CI, 18.9%–40.7%) for *L. (V.) peruviana,* and 31.0% (95% CI, 17.3%–49.4%) for *L. (V.) braziliensis* (figure 2). Pair-by-pair comparisons were performed; *L. (V.) guyanensis* was associated with a significantly lower clinical failure than was *L. (V.) peruviana* ($P = .037$) or *L. (V.) braziliensis* ($P = .026$). The difference in clinical outcome between *L. (V.) peruviana* and *L. (V.) braziliensis* was not significant.

***Description of patient characteristics by treatment outcome.*** Demographic, epidemiological, and clinical characteristics, categorized by the 2 clinical outcomes, are shown and statistically compared in table 1. Patients whose treatment failed were significantly younger than cured patients (16.0 vs. 31.2 years) and were more likely to have stayed <72 months (75th percentile) in the disease-transmission area. High-risk activities were more common among cured patients, although the difference was not significant. Sex and region of disease acquisition were not found to be associated with clinical outcome. Infection treated early (<5 weeks after onset; 25th percentile) and multiple lesions were significantly more common in patients whose treatment failed. There was a trend toward smaller lesion diameter and absence of enlarged lymph nodes in patients with clinical failures. Lesion location showed no statistical difference, with similar distributions between groups.

Detection rates were 88.2% for direct smear and 81.5% for culture. There was no statistical difference between cure and failure groups in either test ($P = .349$ and $P = .367$, respectively).

***Bivariate and multivariate risk-factor analysis.*** Risk factors for treatment failure in the final multivariate model were age, duration of stay in the region where disease was acquired, duration of disease, number of lesions, and parasite species (table 2).

Four variables with significance in the bivariate analysis were excluded from the multivariate model because of interactions. High-exposure occupations depended strongly on age ($P <$ .001, by Student *t* test), because children (from infants to school students) were classified as part of the low-risk activity group. Species type influenced lesion presentation; nonulcerative or mixed lesions occurred more frequently with *L. (V.) peruviana* infection ($P = .067$, by $\chi^2$ test). The presence of enlarged lymph nodes was found to depend on lesion diameter ($P = .013$, by Mann-Whitney *U* test), and this parameter, in turn, was influenced by 2 other factors: duration of disease ($P = .073$, by

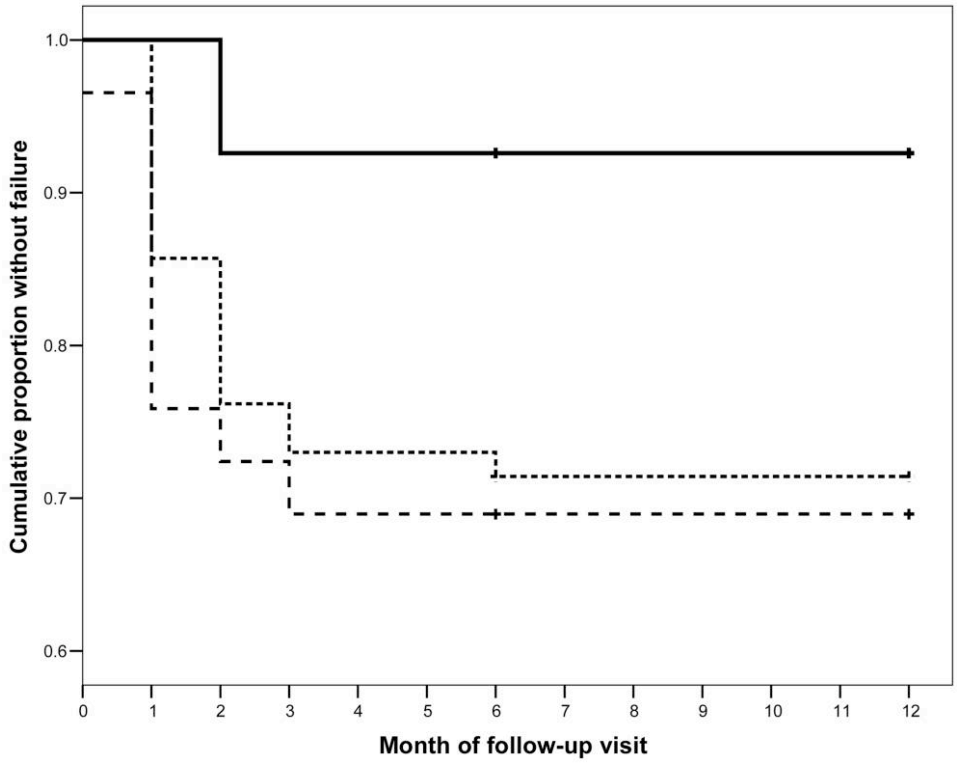


**Figure 2.** Kaplan-Meyer survival curve showing clinical failures detected during follow-up visits, stratified by the 3 main species analyzed ($n =$ 119). *Solid line, Leishmania (Viannia) guyanensis; dotted line, Leishmania (Viannia) peruviana; dashed line, Leishmania (Viannia) braziliensis.*

**Table 1. Demographic, epidemiological, and clinical characteristics of cutaneous leishmaniasis–affected patients and cure and failure outcome after antimonial treatment.**

| Factor | Treatment outcome at 6 months | | $P$[a] |
|---|---|---|---|
| | Failure ($n$ = 29) | Cure ($n$ = 90) | |
| Age, years | | | |
| Mean ± SD | 16.04 ± 13.6 | 31.17 ± 20.5 | |
| Median (IQR) | 12 (7–21) | 25.5 (22–33) | .001[b] |
| Sex | | | |
| Male | 17 (58.6) | 56 (62.2) | .729 |
| Female | 12 (41.4) | 34 (37.8) | |
| Main activity | | | |
| High risk | 9 (31.0) | 44 (48.9) | .092 |
| Low risk | 20 (69.0) | 46 (51.1) | |
| Region of acquisition | | | |
| Western Andes | 14 (48.3) | 45 (50.0) | .464 |
| North Jungle | 3 (10.3) | 10 (11.1) | |
| Central Jungle | 6 (20.7) | 26 (28.9) | |
| South Jungle | 6 (20.7) | 9 (10.0) | |
| Duration of stay in area of endemicity, months | | | |
| Mean ± SD | 18.22 ± 32.6 | 113.24 ± 215.4 | |
| Median (IQR) | 3 (1–5) | 6 (3–12) | .081[b] |
| 0–72 | 28 (96.6) | 31 (69.3) | .003 |
| >72 | 1 (3.4) | 27 (30.7) | |
| Duration of disease, weeks | | | |
| Mean ± SD | 11.87 ± 8.7 | 14.80 ± 11.4 | |
| Median (IQR) | 11 (6.6–13.1) | 12.4 (8.9–13.7) | .169[b] |
| 0–5 | 8 (27.6) | 9 (10.0) | .019 |
| >5 | 21 (72.4) | 81 (90.0) | |
| Lesions, no. | | | |
| Mean ± SD | 2.44 ± 1.7 | 1.73 ± 1.2 | |
| Median (IQR) | 2 (1–3) | 1 (1–2) | .018[b] |
| Lesion diameter, cm | | | |
| Mean ± SD | 1.80 ± 1.2 | 2.48 ± 1.7 | |
| Median (IQR) | 1.4 (1–2.3) | 2 (1.9–2.5) | .075[b] |
| Lesion type | | | |
| Ulcer | 19 (65.5) | 70 (77.8) | .170 |
| Nonulcer | 1 (3.4) | 6 (6.7) | |
| Mixed | 9 (31.0) | 14 (15.6) | |
| Lesion location | | | |
| Face | 8 (27.6) | 23 (25.6) | .892 |
| Upper extremities | 6 (20.7) | 24 (26.7) | |
| Lower extremities | 7 (24.1) | 24 (26.7) | |
| Trunk | 1 (3.4) | 4 (4.4) | |
| Multiple | 7 (24.1) | 15 (16.7) | |
| Regional lymph nodes | | | |
| Yes | 4 (13.8) | 26 (28.9) | .103 |
| No | 25 (86.2) | 64 (71.1) | |
| Leishmanin skin test, result | | | |
| Positive | 22 (91.7) | 79 (92.9) | .833 |
| Negative | 2 (8.3) | 6 (7.1) | |

**NOTE.** Data are no. (%) of case patients, unless otherwise indicated. Pearson's $\chi^2$ test was performed on all discrete variables. IQR, interquartile range.

[a] $\alpha < .05$.

[b] Determined by Mann-Whitney $U$ test.

**Table 2. Bivariate and multivariate analysis of risk factors for treatment failure in patients with cutaneous leishmaniasis.**

| | Bivariate analysis | | Multivariate analysis[a] | |
|---|---|---|---|---|
| Factor | OR (95% CI) | $P$[b] | OR (95% CI) | $P$[b] |
| Age (in years), per each additional year | 0.95 (0.92–0.98) | .001 | 0.95 (0.92–00.99) | .017 |
| High-risk main activity | 0.47 (0.19–1.14) | .096 | … | |
| Duration of stay, ⩽72 months | 12.39 (1.60–96.1) | .016 | 30.45 (2.38–389.25) | .009 |
| Duration of disease, ⩽5 weeks | 3.43 (1.18–9.96) | .024 | 4.39 (1.12–17.23) | .034 |
| No. of lesions, per each additional lesion | 1.42 (1.06–1.89) | .017 | 2.06 (1.30–3.28) | .002 |
| Lesion diameter, per each additional cm, cm | 0.69 (0.48–1.00) | .052 | … | |
| Lesion type | | | | |
| Ulcer | 1.00 | | … | |
| Nonulcer | 0.61 (0.07–5.41) | .661 | … | |
| Affected lymph node | 0.39 (0.12–1.24) | .112 | … | |
| Species | | | | |
| *Leishmania (Viannia) guyanensis* | 1.00 | | … | |
| *Leishmania (Viannia) peruviana* | 5.00 (1.07–23.3) | .040 | 9.85 (1.01–95.65) | .049 |
| *Leishmania (Viannia) braziliensis* | 5.63 (1.09–28.99) | .039 | 22.36 (1.89–263.96) | .014 |

**NOTE.** Eligible factors for entrance into the logistic regression model had $P < .10$.

[a] The final model included 117 patients. Adjustment score, 31; likelihood ratio, 42.97; $P < .001$.

[b] $\alpha < .05$.

Mann-Whitney $U$ test) and species type, because larger lesions were more common with *L. (V.) guyanensis* infection ($P = .058$, by Kruskal-Wallis test).

## DISCUSSION

This study found an overall treatment-failure rate of 24.4% for CL-affected patients after a first course of SSG treatment, consistent with past findings in Peru [37, 38]. Only treatment-naive, first-infection patients were included in the study, to control for biases and confounders related to clinical and outcome differences after treatment failure. The majority of treatment failures occurred within the first 3 months after treatment finished (figure 1), as described elsewhere [27]. It can be safely assumed that, by the third month, the full effect of therapy would have already been observed. Cures occurring after this period are more likely to be related to spontaneous cure than to a delayed effect of therapy [39].

Among the risk factors found, young age was the most solid predictor of treatment failure. Previous studies also report this finding, even linking failure to pediatric population [27–29]. Although there is not yet a clear explanation, possible differences in child immune response, drug pharmacokinetics, and exposure to antigens may affect outcome. Impaired cellular and acquired immunity due to immune-system immaturity may determine poor parasite clearance and prolonged infection. Differences such as cytokine profile, Th1/Th2 T cell polarity, and macrophage function between children and adults have been documented in tuberculosis and other parasitic infections [40–42]. Different pharmacokinetics may also explain poor treatment response, suggesting the need for dose adjustment, because children achieve lower peak concentrations and have higher clearance [28, 43]. It has also been suggested that poor response in children could be related to short exposure to parasite antigens and sand fly saliva [44]. In this study, most of the age effect was found to be independent of duration of stay, suggesting a direct role. Regardless of the explanation, it is clear that children are at greater risk of treatment failure and warrant close supervision during therapy.

Duration of stay was a second important factor influencing outcome. Evidence shows that protective immunity increases with permanence. Long-time dwellers are chronically exposed to vector saliva and subclinical parasite inoculations, which may influence immune system preparedness for a full-scale infection [44]. Visitors lacking this long-term exposure find themselves acutely exposed, with an immune system prone to fail in mounting an adequate response [9]. Furthermore, healthy individuals with positive skin test results or past infections are less susceptible to secondary infection [37]. The present study found that it takes 6 years in an area of endemicity to achieve protection. In practice, this slow process will benefit only long-term residents. An indirect measure of exposure to sand fly bites is the frequency of outdoor activities, yet evidence for its role is contradictory [45–47]. In this case, high-exposure activities were not a significant factor influencing treatment outcome.

Another important determinant for treatment failure was disease duration. In contrast to many infectious diseases, early treatment in CL apparently is not beneficial. Prompt diagnosis

and management within 5 weeks of infection significantly increased failure rate, to 47%. A previous study reported a similar failure rate of 46% in patients with <20 days of disease [48]. Intervention before reaching an effective acquired immunity is the likely explanation of this phenomenon. The initial response to infection was shown to be nonspecific and not fully directed toward parasite elimination [48]. A 2-phase mouse model of infection has been reported. The initial phase, which lasted 4–5 weeks, favored parasite amplification in the dermis without lesion formation. In the second phase, lesions appeared concurrently with inflammatory cell infiltration and IFN-$\gamma$ increase, giving way to parasite clearance [49]. Human tissue with early disease (<8 weeks) had high IL-10 and low IFN-$\gamma$ concentrations. As lesions progressed, the IFN-$\gamma$ level increased, whereas the IL-10 level decreased [50]. It is possible that regulatory T cells play a major role in this process, because they suppress T cell effector response through IL-10 [51]. They block parasite eradication from the tissue to ensure protective immunity to reinfection [52–55]. In summary, evidence suggests that treatment during the early phase of illness may be unsuccessful because of inadequate effector response. Additional studies are needed to determine whether delaying therapy is a warranted measure for early CL.

Failure rate increases with each additional lesion, as seen in other studies [27, 29, 37]. An increased number of lesions may imply greater parasite load, which impairs clearance. An alternative explanation is that each lesion corresponds to different sand fly bites, which leads to the coexistence of several parasite clones with dissimilar susceptibility profiles. Although bivariate analysis showed an increased risk with small lesions (<5 mm), this association lost significance in the multivariate model, because of interaction with duration of disease. The lack of response in small and mixed lesions is probably due to their early nature, as previously discussed.

Several studies have shown the influence of parasite species on clinical outcome after antimonial treatment. *L. (V.) braziliensis* had lower failure rates than did *L. (V.) guyanensis* and *L. mexicana* in Brazil and Guatemala, respectively [27, 30]. In contrast, the present study found that treatment of *L. (V.) guyanensis* had a lower failure rate than for either *L. (V.) braziliensis* or *L. (V.) peruviana*. Apart from study-design differences, it is possible to explain the disparities by considering the existence of genetic variations within individual species. A considerable intraspecific polymorphism has been documented for *L. (V.) braziliensis* and *L. (V.) guyanensis* [56–58]. In addition, 2 distinct genotypes of *L. (V.) guyanensis* have been linked to different clinical presentations and ecological regions [59]. The same phenomenon may exist in Peru and Brazil.

Natural tolerance of the parasite to antimonials could influence treatment outcome. In vitro studies have shown varying intrinsic susceptibility among species [32]. Nevertheless, a recent study did not find any correlation between treatment outcome and natural tolerance to antimonials in *L. (V.) braziliensis* and *L. (V.) guyanensis* strains [31]. This discrepancy may reflect the inadequacy of the in vitro amastigote-macrophage model to assess chemotherapy outcome in the patient. It is possible that each species produces a particular immune response that, combined with the host's genetic background, could ultimately influence clinical outcome [60, 61].

Exact species identification is still an elaborate process and is not performed routinely. Data from past Peruvian surveys could provide a practical solution by linking the region of disease acquisition to a predominant parasite species [15, 33]. Nevertheless, this approach may not be sufficient when current changes in worldwide transmission cycles are considered [62]. Particular efforts should be undertaken to increase accessibility and to simplify molecular assays for species identification. Several approaches are promising: (1) loop-mediated isothermal amplification, which needs a simple water bath; and (2) PCR-oligochromatography, which allows visualization after 5 min on a dipstick, via hybridization with a gold-conjugated probe [63, 64].

In conclusion, young patients with short stays in areas of endemicity, <5 weeks of disease, multiple lesions, and *L. (V.) braziliensis* infection are at the highest risk of experiencing failure of SSG therapy. This risk-factor model can be explained by 4 key determinants: (1) incipient immune response (young age and early disease), (2) short exposure to parasites and vector bites (duration of stay), (3) higher parasite load (number of lesions), and (4) the inherent characteristics of the individual *Leishmania* species.

Precise knowledge of the clinical and epidemiological behavior, treatment evolution, and healing process in leishmaniasis is of utmost importance for improving public health policies. A risk-factor approach, including predominant pathogen species, is essential for optimal clinical management of CL and would make the burden of disease more bearable; ultimately, development of more efficacious, safe, and practical drugs for the treatment of CL is urgently needed.

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