MAJOR ARTICLE

Travelers With Cutaneous Leishmaniasis Cured Without Systemic Therapy

G. Morizot,[1] E. Kendjo,[2] O. Mouri,[2] M. Thellier,[2] A. Pérignon,[3] F. Foulet,[5] F. Cordoliani,[6] E. Bourrat,[6,7] E. Laffitte,[8] I. Alcaraz,[9] N. Bodak,[10] C. Ravel,[4] M. Vray,[11] M. Grogl,[12] D. Mazier,[2] E. Caumes,[3] L. Lachaud,[4] P. A. Buffet,[1,2,13] and the Cutaneous Leishmaniasis French Study Group[a]

[1]Unité d'Immunologie Moléculaire des Parasites, Institut Pasteur de Paris, [2]Service de Parasitologie-Mycologie and [3] Service de Maladies Infectieuses et Tropicales, Hôpital Pitié-Salpêtrière, Paris, [4] French Reference Centre on Leishmaniasis, Montpellier, [5]Service de Parasitologie-Mycologie, Hôpital Henri Mondor, Créteil, [6]Service de Dermatologie, Hôpital Saint-Louis, Paris, and [7]Service de Pédiatrie générale, Hôpital Robert Debré, Paris, France; [8]Clinique de Dermatologie, Hôpitaux Universitaires de Genève, Switzerland; [9]Service de Maladies Infectieuses et Pathologie du voyageur, Hôpital Gustave Dron, Tourcoing, [10]Service de Dermatologie, Hôpital Necker, Paris, [11]Unité de Recherche et d'Expertise Épidémiologie des Maladies Émergentes, Institut Pasteur de Paris/INSERM, France; [12]Walter Reed Army Institute of Research, Silver Spring, Maryland; and [13]UMRs 945 INSERM–Paris 6 University, France

(See the Editorial Commentary by Bailey on pages 381–3.)

Background. Cutaneous leishmaniasis (CL) is a disfiguring but not life-threatening disease. Because antileishmanial drugs are potentially toxic, the World Health Organization (WHO) recommends simple wound care or local therapy as first-line treatment, followed or replaced by systemic therapy if local therapy fails or cannot be performed.

Methods. To determine the feasibility and impact of the recommended approach, we analyzed the results of a centralized referral treatment program in 135 patients with parasitologically proven CL.

Results. Infections involved 10 *Leishmania* species and were contracted in 29 different countries. Eighty-four of 135 patients (62%) were initially treated without systemic therapy. Of 109 patients with evaluable charts, 23 of 25 (92%) treated with simple wound care and 37 of 47 (79%) treated with local antileishmanial therapy were cured by days 42–60. In 37 patients with large or complex lesions, or preexisting morbidities, or who had not been cured with local therapy, the cure rate with systemic antileishmanial agents was 60%. Systemic adverse events were observed in 15 patients, all receiving systemic therapy.

Conclusions. In this population of CL patients displaying variable degrees of complexity and severity, almost two-thirds of patients could be initially managed without systemic therapy. Of these, 60 were cured before day 60. The WHO-recommended stepwise approach favoring initial local therapy therefore resulted in at least 44% of all patients being cured without exposure to the risk of systemic adverse events. Efforts are needed to further simplify local therapy of CL and to improve the management of patients with complex lesions and/or preexisting comorbidities.

Keywords. cutaneous leishmaniasis; systemic antimony; intralesional antimony; liposomal amphotericin B; miltefosine.

Typically, cutaneous leishmaniasis (CL) presents as 1 or several chronic, infiltrated lesions on exposed parts of the body [1]. CL lesions are not spontaneously painful, but they do result in marked local discomfort when ulcerated or infected with bacteria [2]. In immunocompetent subjects, wide dissemination of CL is uncommon and visceral spread causing pathology is exceptional [1]. Most if not all published reports of death in patients with CL are related to systemic therapy,

Received 8 November 2012; accepted 25 February 2013; electronically published 30 April 2013.

[a]Members of the Cutaneous Leishmaniasis French Study Group are listed in the Acknowledgments.

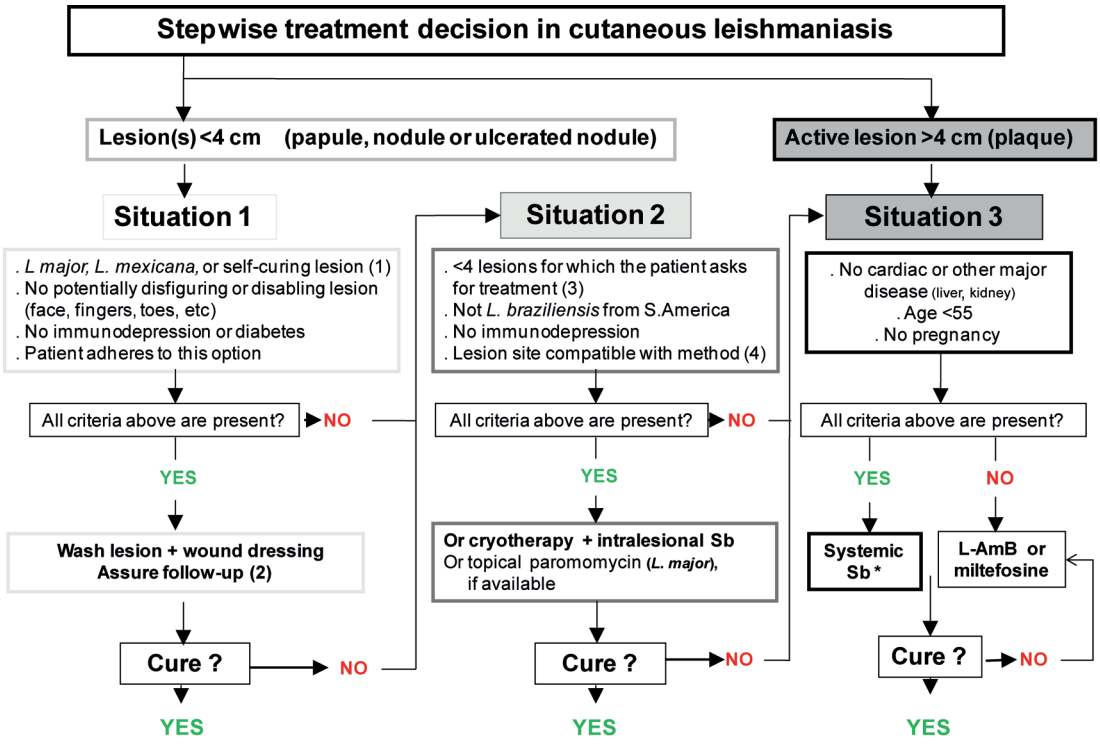
Correspondence: Pierre A. Buffet, MD, PhD, Groupe Hospitalier Pitié-Salpêtrière, 47 Boulevard de l'hôpital, 75651 Paris Cedex 13 France (pierre.buffet@psl.aphp.fr).

Clinical Infectious Diseases 2013;57(3):370–80

DOI: 10.1093/cid/cit269

sometimes with a toxic drug lot [3–6]. Systemic administration of reference agents such as pentavalent antimony, pentamidine, formulations of amphotericin B, or oral miltefosine can indeed cause systemic toxicity [3, 5, 7–13]. International and national treatment guidelines for CL thus favor options that increase the likelihood of rapid healing of CL lesions with the smallest risk of severe adverse events [14–16]. Unspecific wound care followed by patience, a cheap treatment devoid of toxicity, has been recommended [15, 16], but the proportion of patients who can actually benefit from it has not been determined and may be low. Spontaneous healing rates in patients with CL are indeed highly variable (0%–71%, [17]) and furthermore influenced by the infecting species. Simple wound care is not an optimal option in patients with disfiguring lesions [14–16]. The implementation of local antileishmanial therapy is logistically demanding and dependent on lesion topography. For example, the local therapy currently recommended in France requires the sequential application of cryotherapy and intralesional injections of antimony (Cryo + IlSb). The procedure is highly effective [18–20] but is relatively painful and difficult to apply to "complex" lesions (ie, those located on the ears, eyelids, or lips, or those close to small joints). Additionally, it can only be performed by trained physicians who have access to liquid nitrogen.

Not least, no systemic therapeutic option is effective and applicable in all forms of CL [21]. Although high-dose oral fluconazole was effective in Iran [22] and Brazil [23], observance and cost may limit its impact. Miltefosine has been equivalent [24] or superior [25] to systemic Glucantime in some settings, but its teratogenicity and long half-life are issues for wide-scale use. Considering the limitations of the different options and the variable severity of CL, recent guidelines recommend using wound care without antileishmanial therapy whenever possible, then local therapy whenever possible, and finally systemic therapy if local therapy fails or cannot be performed (Figure 1) [15, 16]. This stepwise process is intended to limit the risk of severe adverse events and reduce costs while preserving efficacy. It



(1) Self-curing lesions show flattening or reduction in the surface of the ulceration and/or induration.
(2) Washing lesion, wound dressing, and follow-up were performed in all situations.
(3) Lymphatic dissemination per se did not influence treatment decision. However, because it increased the number of lesions requiring therapy it sometimes justified the use of systemic therapy.
(4) Most lesions of limbs, trunk, cheek, upper-cheek, chin, and front were injected, including those close to large joints. Ears, fingers, toes were not injected. In children premedication facilitated the injection.
* Systemic pentamidine for *L. guyanesis/panamensis.*

Figure 1. Stepwise treatment approach in cutaneous leishmaniasis. Summary of recent French recommendations for the therapy of cutaneous leishmaniasis [27], expressed as a treatment algorithm. This algorithm was used by the French leishmaniasis reference center experts involved in the centralized referral treatment program. Abbreviations: L-AmB, liposomal amphotericin B; Sb, pentavalent antimony.

integrates many parameters, including the size, aspect, topography, and number of lesions, the suspected or proven infecting species, and the patient's age and general health status (Figure 1) [26]. These treatment guidelines are based on clinical experience and analyses of published data [16, 27] but have not been evaluated in clinical practice.

In the present report, we analyzed data collected by experts with the French leishmaniasis reference center (NRCL); these experts provide treatment advice to physicians attending patients with leishmaniasis. Data regarding 135 consecutive CL patients over 6 years were captured and used to determine the applicability of the recommended approach. Specifically, we focused on determining—in the general population of CL patients—the proportion of patients who could be treated without systemic therapy, and the proportion of positive outcome in each treatment category (ie, simple wound care, local therapy, and systemic therapy).

MATERIALS AND METHODS

Patients, Medical Care, and Data Collection

From 2006 through 2011, data were collected each time treatment advice was sought from an expert at the NRCL. Data from patients with parasitologically confirmed tegumentary leishmaniasis were collected. Diagnostic procedures were not modified by the process, expert treatment advice was part of normal medical care, and data collection was in the context of national health surveillance. Patients were informed of the process by their attending physician using a procedure common to all French National Reference Centers (http://www.parasitologie.univ-montp1.fr/conseil.htm) and gave their oral consent for data collection. Mention of this consent was written in the medical chart.

Parasitological Confirmation of Diagnosis: Species Identification

Parasitological diagnosis was performed and analyzed as previously described [17, 28] by lesion scraping, biopsy, or aspirate followed by direct examination of Giemsa-stained smears, histological analysis of Hematein-Eosin-Safran- or Giemsa-stained tissue sections, culture, or polymerase chain reaction (PCR). Whenever possible, tissue samples and aliquots of positive cultures were sent to the NRCL for confirmation and species identification using a multilocus sequence typing approach based on the analysis of 7 single-copy coding DNA sequences (C. Ravel, personal data).

Physicians

Attending physicians were general practitioners, dermatologists, infectious diseases specialists, parasitologists, or pediatricians who were aware of the expert advice available from the NRCL.

Experts, Guidelines, Formalized Process for Treatment Advice, and Outcome

Treatment advice to physicians was provided by 2 specialists (L.L, P.A.B.) with expertise in leishmaniasis therapy [17, 29, 30], who furthermore participated in the establishment of the French national guidelines. The availability of the experts was permanent via a mobile phone. Advice was generally provided within 48 hours, most often during the first interaction. Guidelines were initially based on expert reviews published in French [30, 31] or in English [14, 32, 33]. The content of the published guidelines is recapitulated as an algorithm in Figure 1; treatment decisions were made according to this algorithm. The only important modification between 2006 and 2011 was the removal of oral fluconazole as a first-line option for the treatment of *Leishmania major* CL (at end 2006), when results obtained in French travelers [17] did not confirm the previous encouraging results in *L. major* CL from Saudi Arabia [34]. In the context of the treatment advice embedded in the national surveillance program, we optimized data collection as follows. During initial interactions with attending physicians, information essential for an accurate therapeutic decision was collected on a standardized NRCL form by the experts. This included demographics, travel history, risk factors, medical history, physical examination including lesion topography, aspect, and size, and available laboratory parameters. Data from parasitological tests performed to confirm diagnoses and determine infecting *Leishmania* species were also captured. The infecting *Leishmania* species may influence treatment choice and treatment outcome; thus, the experts indicated what was the presumptive infecting species based on epidemiological and clinical data and used this information to immediately select the treatment option consistent with guidelines. Six to 8 weeks after the advice had been provided, the attending physician was contacted by one of the experts and asked to provide complementary information on species identification, treatment actually administered, disease outcome (including lesion size and lesion healing according to a harmonized criterion used in recent cohort studies and clinical trials [17, 28]), and occurrence of side effects related to any utilized drugs. The quality of data collection was checked by retrieving available written information (on medical charts or reports collected during follow-up) to compare it with all available items in the database.

Database and Data Analysis

The employed database was approved by the French national commission for information technology rights. Variables were summarized as frequencies and percentages, means and standard deviations, or medians and interquartile ranges (IQR), as appropriate, then compared using the χ^2 test when appropriate. Concordance between suspected and confirmed species was analyzed using the κ statistic. Physicians' treatment options were

compared to the expert advice using χ^2 tests or Fisher exact test when appropriate. Statistical analysis was performed using Intercooled Stata software, version 10 for Windows. All reported *P* values are 2-tailed.

RESULTS

Characteristics of Patients and Lesions

Of 168 patients for whom physicians requested expert advice from the NRCL, 135 had parasitologically confirmed tegumentary leishmaniasis. This represents 34% of the 402 patients with CL reported to the NRCL from metropolitan France during the same period. The group included 128 patients with localized CL, 5 with mucosal or mucocutaneous leishmaniasis, 1 with disseminated cutaneous leishmaniasis, and 1 with post–kala-azar dermal leishmaniasis. The demographic and clinical characteristics of patients are summarized in Supplementary Table 1. Twelve patients (9%) had underlying immunosuppression (1 with chronic lymphocytic leukemia, 6 with immunosuppressive therapy, 5 with human immunodeficiency virus [HIV] infection). The duration of disease at the time of diagnosis was ≤36 months, with the exception of 1 patient with HIV coinfection

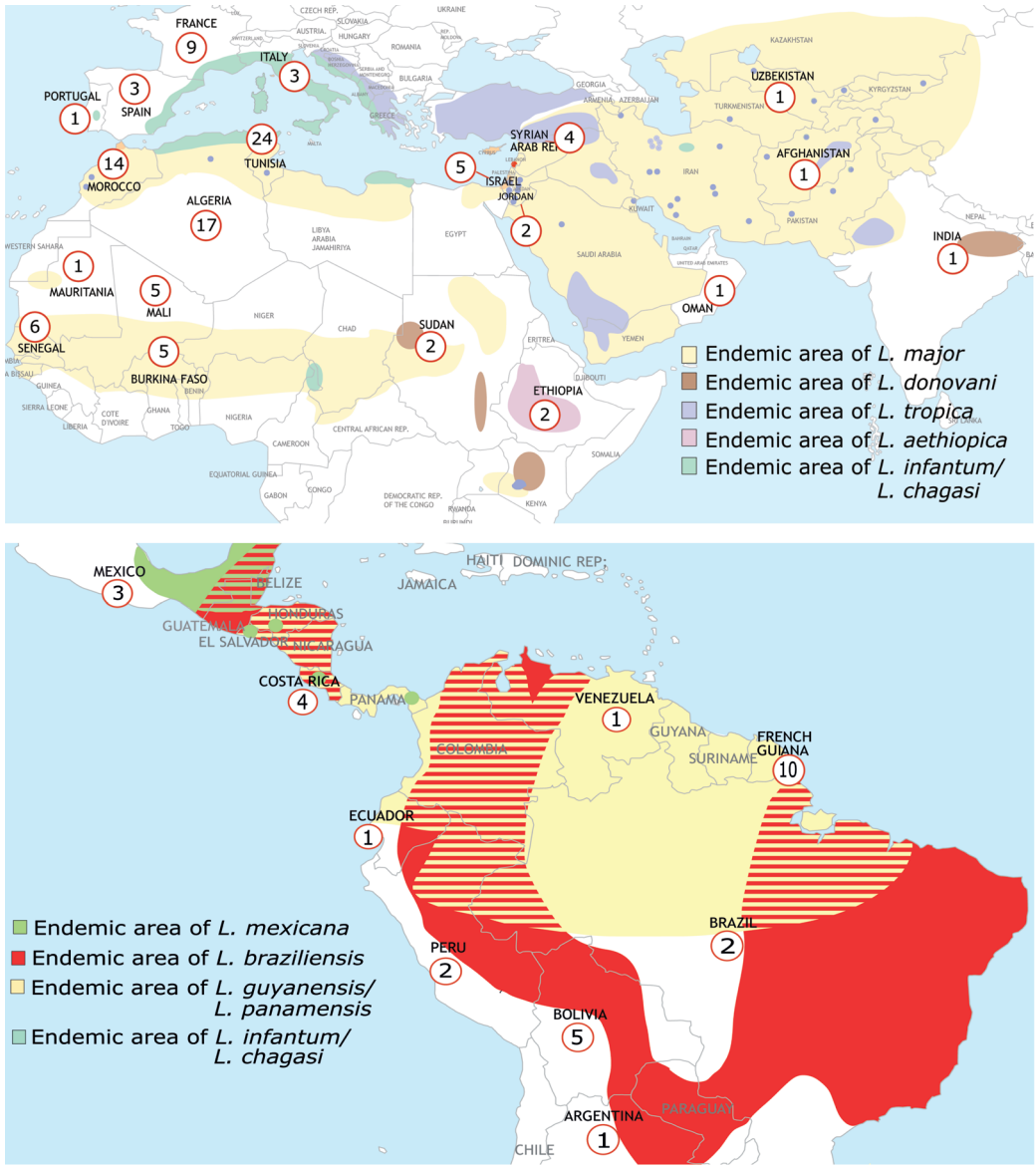


Figure 2. Total number of patients who acquired the infection in each country (in circles) and geographical distribution of the main *Leishmania* species causing cutaneous leishmaniasis in humans in the Old World (upper panel) or in the New World (lower panel; background color as adapted from [35] and [36]).

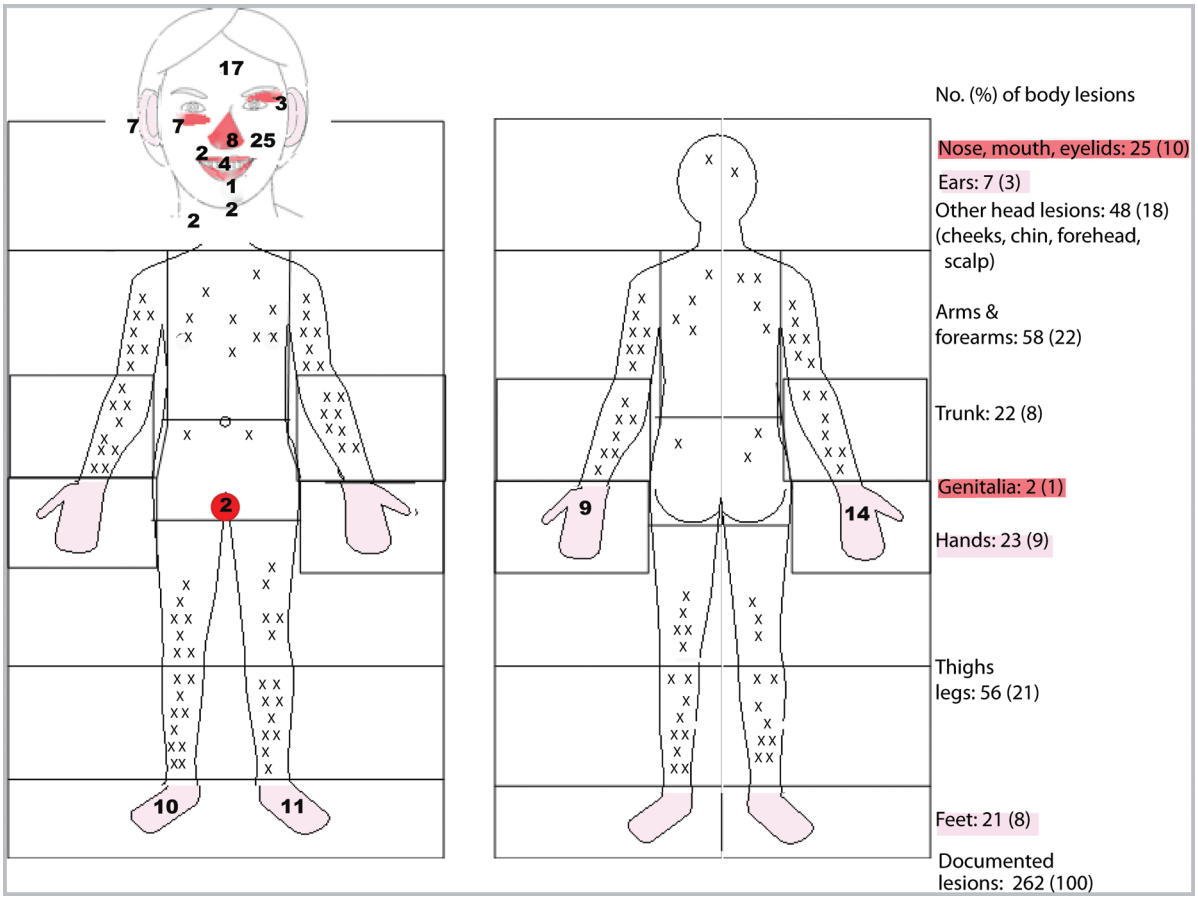


Figure 3. Number (%) of lesions per main body area for 262 documented lesions in 135 patients with cutaneous leishmaniasis. Light red areas correspond to lesion locations where performing intralesional injections is particularly painful or potentially harmful but where a topical cream can be applied; dark red areas correspond to lesion locations where neither intralesional injection nor application of a cream can be performed easily. Based on topography, 83% and 89% of lesions can be treated by local injections or application of ointments, respectively.

whose lesion had been present for 10 years. CL was contracted in 29 different countries (Figure 2). Old World tegumentary leishmaniasis occurred in 107 patients (79% of all cases), 90 of whom were travelers and 17 of whom were permanent residents in endemic areas for *L. infantum* in South Western Europe. New World tegumentary leishmaniasis (Figure 2) occurred in 28 patients (21% of all cases), 26 of whom were travelers and 2 of whom lived in endemic areas. Analysis of lesion topography (Figure 3) showed that 83% and 89% of lesions were located in body areas where local injections and application of ointments, respectively, can be performed.

Characteristics of Physicians Seeking Expert Advice

Ninety physicians asked for advice: 65 used the system once, 25 more than once (range, 2–7); 9% were general practitioners, 51% dermatologists, 19% infectious diseases specialists, 16% parasitologists, and 5% from other health provider categories.

Parasitological Confirmation and Species Determination

Parasitological diagnosis was confirmed by a single method (smear, histology, culture, or PCR) in 65 patients (48%) and by 2 or more methods in 70 (52%). The infecting species was identified in 70 of the 135 patients (52%). The infecting species predicted by the expert (based on epidemiological and clinical data) before formal parasitological identification was confirmed by PCR in patients infected in the Old World in 96% of cases with a κ of 0.93 (95% CI, 0.92–1.00), and in patients infected in the New World in 74% of cases with a κ of 0.59 (95% CI, 0.45–0.82; Supplementary Table 2).

Treatment Outcome

A detailed analysis focused on the main treatment options (Table 1) was performed on 109 medical charts that contained outcome data at least at day 42 through day 60. All patients included in this detailed analysis had been treated according to the recommended algorithm (Figure 1). The 26 patients not

Table 1. Main Characteristics and Initial Outcome of 109 Evaluable Patients

Characteristic and Outcome	Situation 1 (n = 25) Simple Wound Care	Situation 2 (n = 47) Cryotherapy Plus Intralesional Antimony	Situation 3 (n = 37) Systemic Therapy (Sb, L-AmB, Pentamidine, Miltefosine)
Patients			
Age, y, median (IQR)	30 (8–52)	44 (12–57)	51 (34–61)
Sex, M/F, No.	11/14	23/24	27/10
Diabetes, cardiac, or renal history	3 (12)	6 (13)	9 (24)
Immunocompromised patients	0 (0)	3 (6)	7 (19)
Infecting *Leishmania* species, suspected or proven			
L. major	20 (80)	28 (60)	13 (35)
L. mexicana	1 (4)	1 (2)	. . .
L. tropica	. . .	5 (11)	1 (3)
L. aethiopica	. . .	2 (4)	. . .
L. infantum/L. donovani	2 (8)	9 (19)	8 (22)
L. braziliensis	. . .	2 (4)	6 (16)
L. guyanensis/L. panamensis	2 (8)	. . .	9 (24)
Lesions			
No., median (IQR)	2 (1–4)	2 (1–4.5)	2 (1–4)
Longest diameter, mm, median (IQR)	15 (14–24)	20 (10–30)	27.5 (20–50)
Outcome			
Cure	23 (92)	37 (79)	22 (60)
Failure	2 (8)	5 (11)	13 (35)
Relapse	0 (0)	2 (4)	2 (5)
Lost to follow-up	0 (0)	3 (6)	0 (0)
Systemic adverse events	0 (0)	0 (0)	12 (32)
Local adverse events	0 (0)	3 (6)	0 (0)

Data are No. (%) unless otherwise specified.

Abbreviations: IQR, interquartile range; L-AmB, liposomal amphotericin B; Sb, pentavalent antimony.

included in this detailed analysis had been managed with options not included in the recommendations (14 patients), or had received oral fluconazole (when fluconazole was still recommended as a first-line option; 6 patients), or had been lost to follow-up (6 patients). Twenty-three (92%) of the 25 patients receiving simple wound care had positive outcomes at days 42–60. As expected from the algorithm used (Figure 1), none of these patients had underlying immunodepression and most were infected with *L. major* or *Leishmania mexicana* (84%; Table 1). The outcome of Cryo + IlSb could be analyzed in 47 patients, 37 of whom (79%) were cured at days 42–60. These patients were predominantly infected either with *L. major* or *L. mexicana* (29 patients [62%]), or with other Old World species—*Leishmania tropica*, *Leishmania aethiopica*, or *L. infantum* (16 patients [34%]; Table 1). Four of 19 patients (21%) with suspected or proven *Leishmania braziliensis* or *Leishmania panamensis/guyanensis* infection were treated and cured without systemic therapy. The outcome after systemic therapy could be analyzed in 37 patients, 22 of whom (60%) were cured by days 42–60. In this group, the infecting species was almost equally distributed between *L. major* (13 patients [35%]), other Old World species (9 patients [25%]), and New World species including *L. braziliensis* (6 patients [16%]) and *L. guyanensis/L. panamensis* (9 patients [24%]). Some patients required additional courses of treatment, but all were finally cured (excluding the 6 lost to follow-up). Of 10 evaluable immunosuppressed patients, 3 were treated locally and cured, whereas 3 of 7 patients receiving systemic treatment were cured.

Adverse Events

Of the 50 patients receiving systemic therapy, 15 (30%) experienced at least 1 systemic adverse event (AE). All systemic AEs occurred in patients receiving systemic antimony (7 of 14), systemic liposomal amphotericin B (7 of 21), or miltefosine (1 of 1; Table 2). The grading according to the National Cancer Institute Common Terminology Criteria for Adverse Events definition (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5×7.pdf) was 1 (mild) = 5 patients;

Table 2. Main Features of Reported Adverse Events in the 135 Patients Involved in the Centralized Referral Treatment Program

Age/Sex	First-Line Drug	AEs in Patients Receiving Either Systemic or Local Therapy as Initial or Second-Line Treatment	Grade[a] (CTCAE)[b]	Preexisting Morbidity	Rx Stopped	Final Outcome of AE *and CL*
51/F	L-AmB	Acute renal failure	2	Anti–TNF-α immunosuppressive therapy for ankylosing spondylitis	Daily dose reduction	No sequelae *Healing*
57/M	L-AmB	Raised serum creatinine	1	HABP	Yes	No sequelae *Healing after oral miltefosine ×15 d*
60/F	L-AmB	Raised serum creatinine	1	Diabetes, chronic active hepatitis C	Yes	No sequelae *Healing after 2 d course of L-AmB*
63/M	L-AmB	Acute renal failure	2	Hypertensive cardiopathy immunosuppressive therapy: alkylating agent for lymphoma	Yes	No sequelae *Healing*
80/M	L-AmB	Congestive cardiac failure	2	History of heart and kidney disease	Yes	No sequelae *Healing after oral miltefosine*
83/M	L-AmB	Raised serum creatinine	1	HABP	Infusions every 3 days	No sequelae *Healing after oral miltefosine*
85/M	L-AmB	Acute renal failure	2		No	No sequelae *Relapse healing after Cryo + IISb*
21/M	MA	Fever	1	None	No	No sequelae *Healing*
42/M	MA	Raised liver enzymes (AST)	2	Positive serology AgHBs	Yes	No sequelae *Healing*
45/M	MA	DRESS[c] Hypereosinophilia, fever, paresthesia, rash	2		Yes	Paresthesia for 6 mo *Healing*
50/M	MA	Dyspnea, thoracic oppression, myalgia, raised lipase, thrombocytopenia, lymphopenia	2		Yes	No sequelae *Healing*
57/M	MA	Raised serum amylase and lipase	4	Diabetes, hypertensive cardiopathy	Yes	No sequelae *Healing*
71/M	MA	Raised serum amylase and lipase	4	HABP	Yes	No sequelae *Healing*
74/M	MA	Inflammatory syndrome, macrocytic anemia, and lymphopenia	2		Yes	No sequelae *Healing*
61/M	Miltefosine	Raised liver enzymes (AST)	1	Immunosuppressive therapy: MTX and corticoids for rheumatoid polyarthritis	Yes	No sequelae *Relapse then lost to follow-up*

Table 2 continued.

Age/Sex	First-Line Drug	AEs in Patients Receiving Either Systemic or Local Therapy as Initial or Second-Line Treatment	Grade[a] (CTCAE)[b]	Preexisting Morbidity	Rx Stopped	Final Outcome of AE *and CL*
3/M	Cryo + IlSb	Self-resolving local edema	1	None	No	No sequelae *Healing*
42/F	IlSb	Blistering	1	None	Yes	No sequelae *Healing*
68/F	Cryo + IlSb	Fever + local erythema	1	None	Yes	No sequelae *Healing*

Abbreviations: AE, adverse event; AgHb, hepatitis B surface antigen; AST, aspartate aminotransferase; CL, cutaneous leishmaniasis; Cryo + IlSb, cryotherapy + intralesional antimony; HABP, high arterial blood pressure; L-AmB, liposomal amphotericin B; MA, systemic meglumine antimoniate; MTX, methotrexate; Rx: treatment; TNF, tumor necrosis factor.

[a] Acute renal failure, grade 2: creatinine 2–3 times above baseline/raised serum creatinine, grade 1: >1–1.5 times baseline; greater than upper limit of normal (ULN) –1.5 × ULN. Raised serum amylase and lipase, grade 4: >5.0 × ULN/raised liver enzymes (AST), grade 2: >3.0–5.0 × ULN.

[b] National Cancer Institute Common Terminology Criteria for Adverse Events (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5×7.pdf).

[c] Drug rash with eosinophilia and systemic symptoms. This medical history has been reported elsewhere [37].

2 (moderate) = 8 patients; 4 (life threatening) = 2 patients. In 14 patients receiving systemic antimony, the median age was 50.7 years (IQR, 44.1–55.7 years) for those experiencing a systemic AE, and 41.4 years (IQR, 34.6–47.4 years) for those without systemic AE. Only 3 (6%) AEs (all mild) were reported in the 47 patients receiving Cryo + IlSb.

DISCUSSION

Our analysis, based on a nationwide, centralized, referral treatment program, shows that a majority of travelers with CL can be treated locally rather than systemically, and that this guideline-based approach is generally associated with a positive outcome. More than half of the patients (62%) were indeed initially managed without systemic therapy, either by simple wound care (19%), by Cryo + IlSb (41%), or by topical therapy with ointments. Cure rates at days 42–60 in patients with complete charts were 92% for simple wound care and 79% for Cryo + IlSb. Relatively few patients had been infected in the New World (21%), and 56% of all patients were infected with *L. major*. Our analysis was thus partially skewed toward a simple wound care approach. Yet, the high proportion of positive outcomes in this subgroup (92%) suggests that the criteria used to recommend this option accurately predict patients who will self-cure; this furthermore included several patients who were not infected with *L. major*. When appropriately selected, and informed about the lack of risk for themselves and others, a vast majority of patients followed this approach until cure. Predictably, no AEs were reported in this group.

Conversely, AEs occurred in 15 (30%) of the 50 patients receiving systemic therapy. None of these AEs resulted in long-term sequelae but treatment was prematurely interrupted in 11 of these patients. We emphasize that these decisions to discontinue treatment were based on close monitoring of clinical and laboratory parameters. This evokes the question of what would have been the outcome if laboratory parameters had been less easily accessible, a frequent situation in several CL-endemic countries where systemic antimony, and possibly other systemic regimens, are administered with no systematic follow-up of laboratory findings. In a recent analysis of systemic antimony toxicity in 67 travelers without preexisting morbidity, close follow-up of laboratory data was key for a timely suspension of treatment in 6 patients [38]. Recent observations in Tunisia suggest that antimony-induced severe adverse events affecting the kidney or liver are not exceptional [39]. Taken together, these observations reinforce the current assertion that the benefit-risk ratio of systemic anti-leishmanial therapy for CL requires cautious evaluation in the general population of patients. In 14 patients receiving systemic antimony, the median age was 50.7 years (IQR, 44.1–55.7 years) for those experiencing a systemic AE, and 41.4 years (IQR, 34.6–47.4 years) for

those without systemic AE. The risk of mortality under systemic antimony for visceral leishmaniasis is significantly greater in patients older than 45 years [40, 41]. Although based on a limited number of patients, our observation suggests that older age may also be associated with an increased risk of antimony-induced systemic AE in patients with CL, either directly or as a surrogate for preexisting comorbidities. Whereas the population of volunteers in many clinical trials of systemic antimony has been markedly biased toward young adult males without preexisting morbidity [32, 42–45], our population encompassed a broad spectrum of clinical situations, including prior antileishmanial therapy (24%), preexisting comorbidities (16%), and immunosuppression (9%; Supplementary Table 1). Our data also suggest that in older patients with frequent comorbidities and/or large lesions (situation 3 in the algorithm), infection with all species (including *L. major*) may be difficult to cure, thus justifying a specific management and adapted research strategies. International initiatives (eg, LeishMan European network, http://www.tropnet.net/index.php?id=103) will allow for a powerful determination of factors associated with positive outcome and help further improve treatment algorithms and recommendations.

Limiting the proportion of patients receiving systemic therapy is likely a simple way of reducing therapeutic risk. AEs were infrequent in the 47 patients receiving Cryo + IlSb; those that did occur were mild. Although the proportion of patients selected for local therapy (including simple wound care) may be smaller in countries/areas where *L. major* is less prevalent, we nonetheless believe that the general stepwise approach analyzed here will be useful elsewhere. Indeed it provides a simple, harmonized strategy for general treatment decisions in CL, based on a robust equilibrium between the benefits and the risks of available options. More than two-thirds of the patients infected with *L. infantum*, *L. aethiopica*, or *L. tropica* were managed without systemic therapy, and the cure rate in this group was similar to that of the *L. major*–infected patients (83% vs 82%). Confirmation of this finding in larger cohorts of patients is needed. Although traditionally limited to systemic therapy [32], recommendations and investigations for the treatment of New World cutaneous leishmaniasis have progressively included local therapy [26, 46–48]. This decision is largely based on a detailed analysis of the relatively small risk of evolution to mucocutaneous leishmaniasis outside of Bolivia [49], and on the rise of new options to treat mucocutaneous leishmaniasis if it occurs [12, 15, 16, 50]. Four of the 19 patients (21%) with suspected or proven *L. braziliensis* or *L. panamensis/guyanensis* infection were treated and cured without systemic therapy.

Although the stepwise approach validated here optimizes the use of the existing armamentarium, the improvement of this latter remains an essential goal. Current treatment guidelines display a strong synergism with the emergence of a new formulation of topical aminoglycosides for the treatment of *L. major* CL [28, 51]. When available, this third-generation topical aminoglycoside ointment will replace simple wound care and Cryo + IlSb, thus resulting in further simplification of treatment strategies. In addition, because it is simpler to apply a cream than to perform Cryo + IlSb, the proportion of patients treated topically will surely grow compared to that of patients receiving systemic treatments. Only lesions of eyelids, lips, genitalia, and mucosae are ineligible for topical therapy, that is, 10% of lesions in our experience (Figure 3). A vast majority of patients will thus benefit from this inexpensive approach. Further evaluations of topical aminoglycoside formulations in CL due to other Old World and New World species are ongoing or planned [51].

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Acknowledgments. We thank the Cutaneous Leishmaniasis French Study Group, who provided and cared for study patients: CHU, Amiens (Y. El Samad, V Salle); Antony (N. Gounod); CHI, Aulnay Sous Bois (A. Dallot); Hôpital Saint-Jacques, Besançon (G. Belot, S. Pelletier-Cunat); CHU, Cachan (M. Belon); Caen (R. Verdon); CH, Chamberry (O. Rogeaux); Chamonix-Mont-Blanc (G. Grossetête); CHU, Clermont–Ferrand (O. Lesens); CH, Compiègne (A. Clabaut, E. Maus); Corbeil-Essonnes (L. Jouy); CH Sud Francilien, Corbeil-Essonnes (G. Gener, P. Perrin); CHU, Dijon (N. Roch); Fontenay-aux-roses (A. Herve); Hôpital Raymond Poincaré, Garches (D. Le Duc); CHU, Grenoble (E. Cuchet, D. Maubon); CH, Lagny-sur-Marne (B. Hillion); CH, Laon (E. Menot); Hôpital, Le Kremlin-Bicêtre (F. Guillemot); CH, Le Mans (N. Benetton-Benhard, P. Celerier); Hôpital Militaire, Metz (A. L. Dupuis De Fonclare); Hôpital Jacques Monod, Montivilliers (D. Carre); CHU, Montpellier (A. Bourgeois); Hôpital l'Archet, Nice (P. Marty, C. Pomares); CHU, Nîmes (L. Meunier); Pantin (H. Abergel, F. Timsit); Paris (J. C. Amoric, P. Busquet, S. Karam, Y. F. Moisson, F. Mouly, J. C. Ortoli); Centre Médical Institut Pasteur, Paris (P. H. Consigny, M. Jouan); GH Pitié-Salpêtrière, Paris (F. Caby, A. Datry, P. Hochedez, F. Rozembaum); Hôpital Bichat, Paris (C. Dumortier); Hôpital Cochin, Paris (T. Ancelle, N. Dupin, A. Paugam); Hôpital Georges Pompidou, Paris (B. Ranque); Hôpital Necker, Paris (M. E. Bougnoux, A. Canestri, M. F. Galezowsky, S. Hadj Rabia, D. Hamel, P. Schneider, M. Wolter-Desfosses); Hôpital Saint-Joseph, Paris (M. Janier); Hôpital Saint-Louis, Paris (M. Baccard, M. Bezier, M. Broissin, N. Colin De Verdiere, F. Durupt, E. Hope Rapp, C. Juillard, A. Levy, I. Moraillon, A. Petit, S. Regner); CH, Pau (D. Barthelme); Persan (J. M. Tamarin); CH René Dubos, Pontoise (E. Begon); Hôpital Maison Blanche, Reims (C. Strady); CHU, Rennes (J. P. Gangneux); CH, Roubaix (O. Carpentier); Hôpital Militaire Bégin, Saint-Mandé (F. Mechai); Hopital Civil, Strasbourg (C. Kieffer); Hôpital Beauregard, Thionville (P. Dellestable); Hôpital Paul-Brousse, Villejuif (S. Rebauder).

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Reithinger R, Dujardin JC, Louzir H, Pirmez C, Alexander B, Brooker S. Cutaneous leishmaniasis. Lancet Infect Dis **2007**; 7:581–96.
2. Van Der Vliet D, Le Guern AS, Freitag S, et al. *Pseudomonas aeruginosa* otochondritis complicating localized cutaneous leishmaniasis: prevention of mutilation by early antibiotic therapy. Am J Trop Med Hyg **2006**; 75:270–2.
3. Masmoudi A, Maalej N, Mseddi M, et al. Glucantime injection: benefit versus toxicity [in French]. Med Mal Infect **2005**; 35:42–5.
4. Ribeiro AL, Drummond JB, Volpini AC, Andrade AC, Passos VM. Electrocardiographic changes during low-dose, short-term therapy of cutaneous leishmaniasis with the pentavalent antimonial meglumine. Braz J Med Biol Res **1999**; 32:297–301.
5. Rodrigues ML, Costa RS, Souza CS, Foss NT, Roselino AM. Nephrotoxicity attributed to meglumine antimoniate (Glucantime) in the treatment of generalized cutaneous leishmaniasis. Rev Inst Med Trop Sao Paulo **1999**; 41:33–7.
6. Ezzine Sebai N, Mrabet N, Khaled A, et al. Side effects of meglumine antimoniate in cutaneous leishmaniasis: 15 cases [in French]. Tunis Med **2010**; 88:9–11.
7. Sands M, Kron MA, Brown RB. Pentamidine: a review. Rev Infect Dis **1985**; 7:625–34.
8. Castello Viguer MT, Echanove Errazti I, Ridocci Soriano F, Esteban Esteban E, Atienza Fernandez F, Cuesta Estelles G. Torsades de pointes during treatment of leishmaniasis with meglumine antimoniate [in Spanish]. Rev Esp Cardiol **1999**; 52:533–5.
9. Rodrigues AM, Hueb M, Nery AF, Fontes CJ. Possible cardioprotective effect of angiotensin-converting enzyme inhibitors during treatment of American tegumentary leishmaniasis with meglumine antimoniate. Acta Trop **2007**; 102:113–8.
10. Franke ED, Wignall FS, Cruz ME, et al. Efficacy and toxicity of sodium stibogluconate for mucosal leishmaniasis. Ann Intern Med **1990**; 113:934–40.
11. Cornely OA, Maertens J, Bresnik M, et al. Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad trial). Clin Infect Dis **2007**; 44:1289–97.
12. Soto J, Toledo J, Valda L, et al. Treatment of Bolivian mucosal leishmaniasis with miltefosine. Clin Infect Dis **2007**; 44:350–6.
13. Oliveira LF, Schubach AO, Martins MM, et al. Systematic review of the adverse effects of cutaneous leishmaniasis treatment in the New World. Acta Trop **2011**; 118:87–96.
14. Bailey MS, Green AD, Ellis CJ, et al. Clinical guidelines for the management of cutaneous leishmaniasis in British military personnel. J R Army Med Corps **2005**; 151:73–80.
15. World Health Organization. Control of the leishmaniases: report of a meeting of the WHO Expert Committee on the control of leishmaniases, Geneva, 22–26 March 2010. WHO technical report series **2011**; 949:1–185.
16. Buffet PA, Rosenthal E, Gangneux JP, et al. Therapy of leishmaniasis in France: consensus on proposed guidelines [in French]. Presse Med 2011; 40:173–84.
17. Morizot G, Delgiudice P, Caumes E, et al. Healing of Old World cutaneous leishmaniasis in travelers treated with fluconazole: drug effect or spontaneous evolution? Am J Trop Med Hyg **2007**; 76:48–52.
18. el Darouti MA, al Rubaie SM. Cutaneous leishmaniasis. Treatment with combined cryotherapy and intralesional stibogluconate injection. Int J Dermatol **1990**; 29:56–9.
19. Asilian A, Sadeghinia A, Faghihi G, Momeni A. Comparative study of the efficacy of combined cryotherapy and intralesional meglumine antimoniate (Glucantime) vs. cryotherapy and intralesional meglumine antimoniate (Glucantime) alone for the treatment of cutaneous leishmaniasis. Int J Dermatol **2004**; 43:281–3.
20. Asilian A, Sadeghinia A, Faghihi G, Momeni A, Amini Harandi A. The efficacy of treatment with intralesional meglumine antimoniate alone, compared with that of cryotherapy combined with the meglumine antimoniate or intralesional sodium stibogluconate, in the treatment of cutaneous leishmaniasis. Ann Trop Med Parasitol **2003**; 97:493–8.
21. Blum J, Desjeux P, Schwartz E, Beck B, Hatz C. Treatment of cutaneous leishmaniasis among travellers. J Antimicrob Chemother **2004**; 53: 158–66.
22. Emad M, Hayati F, Fallahzadeh MK, Namazi MR. Superior efficacy of oral fluconazole 400 mg daily versus oral fluconazole 200 mg daily in the treatment of cutaneous leishmania major infection: a randomized clinical trial. J Am Acad Dermatol **2011**; 64:606–8.
23. Sousa AQ, Frutuoso MS, Moraes EA, Pearson RD, Pompeu MM. High-dose oral fluconazole therapy effective for cutaneous leishmaniasis due to *Leishmania* (*Vianna*) *braziliensis*. Clin Infect Dis 2011; 53: 693–5.
24. Rubiano LC, Miranda MC, Muvdi Arenas S, et al. Noninferiority of miltefosine versus meglumine antimoniate for cutaneous leishmaniasis in children. J Infect Dis **2012**; 205:684–92.
25. Chrusciak-Talhari A, Dietze R, Chrusciak Talhari C, et al. Randomized controlled clinical trial to access efficacy and safety of miltefosine in the treatment of cutaneous leishmaniasis Caused by *Leishmania* (*Viannia*) *guyanensis* in Manaus, Brazil. Am J Trop Med Hyg **2011**; 84:255–60.
26. Modabber F, Buffet PA, Torreele E, Milon G, Croft SL. Consultative meeting to develop a strategy for treatment of cutaneous leishmaniasis. Institute Pasteur, Paris, 13–15 June 2006. Kinetoplastid Biol Dis **2007**; 6:3.
27. Berman J. Recent developments in leishmaniasis: epidemiology, diagnosis, and treatment. Curr Infect Dis Rep **2005**; 7:33–8.
28. Ben Salah A, Buffet PA, Morizot G, et al. WR279,396, a third generation aminoglycoside ointment for the treatment of *Leishmania major* cutaneous leishmaniasis: a phase 2, randomized, double blind, placebo controlled study. PLoS Negl Trop Dis **2009**; 3:e432.
29. Soto J, Buffet P, Grogl M, Berman J. Successful treatment of Colombian cutaneous leishmaniasis with four injections of pentamidine. Am J Trop Med Hyg **1994**; 50:107–11.
30. Buffet P, Caumes E, Gentilini M. Treatment of localized cutaneous leishmaniasis [in French]. Ann Dermatol Venereol **1994**; 121:503–11.
31. Buffet PA, Morizot G. Cutaneous leishmaniasis in France: towards the end of injectable therapy? [in French]. Bull Soc Pathol Exot **2003**; 96:383–8.
32. Herwaldt BL, Berman JD. Recommendations for treating leishmaniasis with sodium stibogluconate (Pentostam) and review of pertinent clinical studies. Am J Trop Med Hyg **1992**; 46:296–306.
33. Blum JA, Hatz CF. Treatment of cutaneous leishmaniasis in travelers 2009. J Travel Med **2009**; 16:123–31.
34. Alrajhi AA, Ibrahim EA, De Vol EB, Khairat M, Faris RM, Maguire JH. Fluconazole for the treatment of cutaneous leishmaniasis caused by *Leishmania major*. N Engl J Med **2002**; 346:891–5.
35. Magill AJ. Epidemiology of the leishmaniases. Dermatol Clin **1995**; 13:505–23.
36. Dedet JP. Leishmania et leishmanioses du continent ame'ricain. Annales de L'Institut Pasteur: Actualités **1993** 4:S3–25.
37. Jeddi F, Caumes E, Thellier M, et al. Drug hypersensitivity syndrome induced by meglumine antimoniate. Am J Trop Med Hyg **2009**; 80:939–40.
38. Wise ES, Armstrong MS, Watson J, Lockwood DN. Monitoring toxicity associated with parenteral sodium stibogluconate in the day-case management of returned travellers with New World cutaneous leishmaniasi. PLoS Negl Trop Dis **2012**; 6:e1688.
39. Mlika RB, Hamida MB, Hammami H, et al. Should we continue to indicate meglumine antimoniate as first-line treatment for cutaneous leishmaniasis in Tunisia. Dermatol Ther **2012**; 25:615–8.
40. Mueller Y, Mbulamberi DB, Odermatt P, Hoffmann A, Loutan L, Chappuis F. Risk factors for in-hospital mortality of visceral leishmaniasis patients in eastern Uganda. Trop Med Int Health **2009**; 14: 910–7.

41. Chappuis F, Alirol E, Worku DT, Mueller Y, Ritmeijer K. High mortality among older patients treated with pentavalent antimonials for visceral leishmaniasis in East Africa and rationale for switch to liposomal amphotericin B. Antimicrob Agents Chemother **2011**; 55: 455–6.
42. Khatami A, Firooz A, Gorouhi F, Dowlati Y. Treatment of acute Old World cutaneous leishmaniasis: a systematic review of the randomized controlled trials. J Am Acad Dermatol **2007**; 57:335 e1–29.
43. Tuon FF, Amato VS, Graf ME, Siqueira AM, Nicodemo AC, Amato Neto V. Treatment of New World cutaneous leishmaniasis—a systematic review with a meta-analysis. Int J Dermatol **2008**; 47:109–24.
44. Gonzalez U, Pinart M, Rengifo-Pardo M, Macaya A, Alvar J, Tweed JA. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database Syst Rev **2009**:CD004834.
45. Gonzalez U, Pinart M, Reveiz L, Alvar J. Interventions for Old World cutaneous leishmaniasis. Cochrane Database Syst Rev **2008**: CD005067.
46. Arana BA, Mendoza CE, Rizzo NR, Kroeger A. Randomized, controlled, double-blind trial of topical treatment of cutaneous leishmaniasis with paromomycin plus methylbenzethonium chloride ointment in Guatemala. Am J Trop Med Hyg **2001**; 65:466–70.
47. Lopez L, Robayo M, Vargas M, Velez ID. Thermotherapy: an alternative for the treatment of American cutaneous leishmaniasis. Trials **2012**; 13:58.
48. Soto J, Rojas E, Guzman M, et al. Intralesional antimony for single lesions of bolivian cutaneous leishmaniasis. Clin Infect Dis **2013**; 56:1255–60.
49. Blum J, Lockwood DNJ, Visser L, et al. Local or systemic treatment for New World cutaneous leishmaniasis? Re-evaluating the evidence for the risk of mucosal leishmaniasis. International Health **2012**;4:153–63.
50. Amato VS, Nicodemo AC, Amato JG, Boulos M, Neto VA. Mucocutaneous leishmaniasis associated with HIV infection treated successfully with liposomal amphotericin B (AmBisome). J Antimicrob Chemother **2000**; 46:341–2.
51. Ben Salah A, Ben Messaoud N, Guedri E, et al. Topical paromomycin with or without gentamicin for cutaneous leishmaniasis. N Engl J Med **2013**; 368:524–32.