Guideline for the treatment of leishmaniasis in the Americas

PAHO
Pan American Health Organization
World Health Organization
REGIONAL OFFICE FOR THE Americas

Lutzomyia spp.
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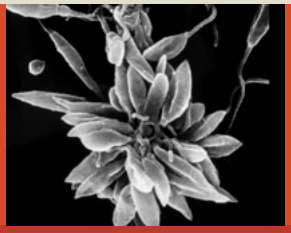

Image of a *Leishmania* spp. culture in a scanning electronic microscope
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Guideline for the Treatment of Leishmaniasis in the Americas. Second Edition

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CDE/VT/2022

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Acknowledgments

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Acronyms and abbreviations

AECID	Spanish Agency for International Development Cooperation (acronym in Spanish)
AS	aminosidine sulfate
CT	clinical trial
CDE-VT	Communicable Diseases and Environmental Determinants of Health – Neglected, Tropical and Vector-Borne Diseases
CI	confidence interval
CL	cutaneous leishmaniasis
DNDi	Drugs for Neglected Diseases Initiative
DOI	declaration of interest
EIH-KT	Evidence and Intelligence for Action in Health - Knowledge Translation
GDG	guideline development group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIV	human immunodeficiency virus
IM	intramuscular
IV	intravenous
L. (L.)	*Leishmania* subgenus *Leishmania*
L. (V.)	*Leishmania* subgenus *Viannia*
LAB	liposomal amphotericin B
MA	meglumine antimoniate

MD	mean difference
ML	mucosal leishmaniasis
NTD	Neglected Tropical Diseases
ORS	oral rehydration solution
PA	pentavalent antimoniate
PAHO	Pan American Health Organization
PICO	Population, Intervention, Comparison, Outcome
RCT	randomized controlled trial
RR	risk ratio
SAS	saline solution
Sb^{+5}	pentavalent antimony
SE	side effects
SR	systematic reviews
SS	sodium stibogluconate
VL	visceral leishmaniasis
WHO	World Health Organization

Executive summary

The leishmaniases remain neglected infectious diseases of great importance, as they mainly affect the poorest people with less access to health services. In the Americas, the leishmaniases are a public health problem due to their magnitude, wide geographical distribution, and morbidity and mortality. The Pan American Health Organization (PAHO) continues to support endemic countries in strengthening actions to achieve the goals of eliminating leishmaniasis as a public health problem, in accordance with the mandate given by the PAHO Disease Elimination Initiative, in line with the World Health Organization (WHO) Road Map for Neglected Tropical Diseases 2021–2030. In the Region in the Americas, leishmaniasis encompasses diseases caused by several species of *Leishmania*, which influence the clinical manifestations, severity of the disease, accuracy of diagnosis, and response to treatment.

Cutaneous leishmaniasis is endemic in 18 countries, with on average approximately 54,000 cases per year. It is the most frequent form in the Region, and about 90% of cases present as localized, single, or multiple lesions, being associated with 15 species of *Leishmania* as causal agents. Other clinical cutaneous forms, such as disseminated (mainly caused by *L. (V.) braziliensis*) and diffuse cutaneous (mainly produced by *L. (L.) amazonensis* and *L. (L.) mexicana*), are more difficult to treat and present frequent relapses. Visceral leishmaniasis (caused by *L. infantum*) is the most severe form, as it can cause death in up to 90% of untreated people. It is endemic in 13 countries in the Americas, with an average of around 3,500 cases per year, although 96% of cases are reported in Brazil.

In this regard, PAHO presents the Guideline for the Treatment of Leishmaniasis in the Americas, which is the result of joint work with experts in the field from the Region. This publication presents the update of the therapeutic recommendations, detailing the schemes and criteria for indication of treatment for cutaneous, mucosal, and visceral leishmaniasis in the regional context, in accordance with the standards for the development of WHO guidelines. Thus, some of the recommendations presented here may differ from the specific recommendations from other continents in view of the distinct epidemiological and biological aspects, such as the different circulating species of *Leishmania*, transmission cycles, and therapeutic responses.

Methods

The Guideline was prepared in accordance with the latest WHO Handbook for Guideline Development. The WHO guideline development process includes planning, conducting a scope and needs assessment, creating an internal WHO steering group and an external guideline development group, formulating key questions in the Population, Intervention, Comparison, Outcome (PICO) format, derived from systematic reviews, formulating recommendations using the Gradings of Recommendation Assessment, Development and Evaluation (GRADE) classification method, drafting the guideline, and planning its dissemination and implementation. This methodology ensures transparency of the link between the evidence base and the recommendations.

The development process included the participation of the following groups that helped guide and contributed greatly to the overall process: the PAHO Guidelines Steering Group, the methodological group, the Guideline Development Group (GDG), and the expert reviewers. The roles and functions are described in the 2014 WHO Handbook for Guideline Development. All participants in this guideline's development completed the WHO declaration of interest, and these were evaluated by the coordination group.

The recommendations were formulated by the GDG members after considering the balance between the certainty of the evidence from systematic reviews, the risk–benefit, the values and preferences, the implications of resources, the feasibility of the application of the intervention, the impact on equity, and the acceptability for stakeholders. The following are the questions and recommendations.

Recommendations

Recommendations for the treatment of leishmaniasis in the Americas, based on the available evidence, are described below by clinical form of the disease.

The treatment scheme, administration route, and details of indications are found in the Implementation, Adaptation, Dissemination, and Pharmacological Interventions section.

Question 1

Cutaneous leishmaniasis

What is the efficacy and safety of the different systemic and local treatments for the management of patients diagnosed with cutaneous leishmaniasis in the Americas?

RECOMMENDATIONS

Cutaneous leishmaniasis in adult patients

The application of intralesional pentavalent antimonials is recommended in patients with localized cutaneous leishmaniasis caused by *L. braziliensis* and *L. amazonensis*.

Strong recommendation, low certainty evidence

The use of miltefosine is recommended in adult patients diagnosed with cutaneous leishmaniasis caused by *L. panamensis, L. mexicana*, *L. guyanensis*, and *L. braziliensis*.

Strong recommendation, low certainty evidence

The administration of pentamidine isethionate is suggested in patients diagnosed with cutaneous leishmaniasis caused by *L. guyanensis.*

Conditional recommendation, low certainty evidence

The application of thermotherapy is suggested in patients with localized cutaneous leishmaniasis caused by *L. braziliensis*, *L. panamensis*, and *L. mexicana*.

Conditional recommendation, very low certainty evidence

The use of paromomycin is suggested in patients with cutaneous leishmaniasis caused by *L. panamensis, L. braziliensis*, and *L. mexicana*.

Conditional recommendation, very low certainty evidence

The use of pentavalent antimonials is suggested in adult patients diagnosed with cutaneous leishmaniasis caused by *L. braziliensis*, *L. panamensis*, *L. amazonensis*, *L. peruviana*, and *L. mexicana*.

Conditional recommendation, moderate to low certainty evidence

RECOMMENDATIONS

Cutaneous leishmaniasis in pediatric patients

The use of miltefosine is recommended in pediatric patients diagnosed with cutaneous leishmaniasis caused by *L. panamensis*, *L. guyanensis*, and *L. braziliensis*.

Strong recommendation, low certainty evidence

The use of paromomycin is suggested in pediatric patients with cutaneous leishmaniasis caused by *L. panamensis*, *L. braziliensis*, and *L. mexicana*.

Conditional recommendation, low certainty evidence

The use of pentavalent antimonials is suggested to treat pediatric patients diagnosed with cutaneous leishmaniasis when no other alternative is available.

Conditional recommendation, low certainty evidence

Note: The treatment scheme, administration route, and indications are found in the Implementation, Adaptation, Dissemination, and Pharmacological Interventions section (Tables 2, 3, 5, and 8)

BEST PRACTICE STATEMENTS

Treatment of any species of *Leishmania* in pediatric and adult patients with cutaneous leishmaniasis

Decision-making about the therapeutic strategy to be used in patients diagnosed with leishmaniasis should be shared with patients based on a clear explanation of the risks and benefits of the available alternatives.

It is not imperative to identify the species to initiate treatment, but if the most prevalent species in the region is known, treatment should be initiated according to the clinical condition, availability of the medication, and considering the risk–benefit balance.

Patients diagnosed with leishmaniasis should be guided about the hygienic care of skin or mucosal lesions; recognition of clinical manifestations, presence of concomitant infections, signs of non-response to treatment, and occurrence of toxicity caused by drugs.

BEST PRACTICE STATEMENTS

Treatment of any species of *Leishmania* in pediatric and adult patients with cutaneous leishmaniasis

To treat the following special cases of patients with cutaneous leishmaniasis, it is suggested:

- **Pregnant women:** Thermotherapy and cases requiring systemic treatment should be referred to the reference center. The suggested indicated medication is liposomal amphotericin B or other formulations of amphotericin B. The use of pentavalent antimonials, miltefosine, and pentamidine is contraindicated.
- **Breastfeeding women:** Intralesional antimonials, or thermotherapy, or amphotericin B, guaranteeing contraception.
- **Patients with alterations in the electrocardiogram:** Local treatment with thermotherapy or systemic with miltefosine or liposomal amphotericin B. The use of systemic pentavalent antimonials and pentamidine isethionate is contraindicated.
- **Patients with kidney disease, liver disease, heart disease:** Local treatments or the use of liposomal amphotericin B. Caution and frequent monitoring is suggested for the use of intralesional treatment with pentavalent antimonial in patients with heart disease.
- **Comorbidity with tuberculosis:** Take special care in monitoring adverse events, especially when deciding to use the two treatments concomitantly (tuberculosis and leishmaniasis).
- **Patients with HIV and other causes of immunosuppression:** Liposomal amphotericin B or amphotericin B deoxycholate and perform treatment in reference center.
- **Patients over 50 years of age:** Perform a careful clinical evaluation of each case considering the comorbidities and the possibility of therapeutic toxicities. The use of pentavalent antimonials should be avoided in patients over 50 years of age.
- **Patients with therapeutic failure:** Administer any of the recommended treatments other than the one initially used.
- **Patients with disseminated cutaneous leishmaniasis:** Use of liposomal amphotericin B, miltefosine, or pentavalent antimonials and perform treatment in reference center.
- **Patients with diffuse cutaneous leishmaniasis:** It is suggested to use pentavalent antimonials, pentamidine isethionate, or miltefosine and perform treatment in reference center.
- **Patients with atypical cutaneous leishmaniasis caused by *L. infantum*:** The use of intralesional or systemic pentavalent antimonials is suggested.

Note: The treatment scheme, administration route, and indications are found in the Implementation, Adaptation, Dissemination, and Pharmacological Interventions section (Tables 4 and 8).

Question 2

Mucosal or mucocutaneous leishmaniasis

What is the efficacy and safety of the different pharmacological treatments for the management of patients diagnosed with mucosal leishmaniasis in the Americas?

RECOMMENDATION

The use of pentavalent antimonials with or without oral pentoxifylline is recommended to treat patients with mucosal or mucocutaneous leishmaniasis.

Strong recommendation, low and very low certainty evidence

Note: The treatment scheme, administration route, and indications are found in the Implementation, Adaptation, Dissemination, and Pharmacological Interventions section (Tables 6 and 8).

BEST PRACTICE STATEMENTS

Decision-making about the therapeutic strategy to be used in patients diagnosed with mucosal or mucocutaneous leishmaniasis should be shared with the patients based on the clear explanation of the risks and benefits of the available alternatives.

The clinical course of mucosal or mucocutaneous leishmaniasis is complex and requires care and follow-up during and after treatment. Health personnel should monitor the treatment of patients and side effects.

BEST PRACTICE STATEMENTS

To treat the following special cases of patients with mucosal or mucocutaneous leishmaniasis, it is suggested:

- **Pregnant women:** Refer to the reference center. The medication suggested is liposomal amphotericin B or other formulations of amphotericin B. The use of pentavalent antimonials, miltefosine, and pentamidine is contraindicated.
- **Breastfeeding women**: Use of liposomal amphotericin B and pentavalent antimonials, ensuring contraception.
- **Patients with electrocardiogram alteration:** Administer treatments with miltefosine or amphotericin B. The use of pentavalent antimonials and pentamidine isethionate is contraindicated.
- **Patients with kidney disease, liver disease, heart disease:** The use of liposomal amphotericin B is suggested.
- **Comorbidity with tuberculosis:** It is suggested to take special care in monitoring adverse events, especially when deciding to use the two treatments concomitantly (tuberculosis and leishmaniasis).
- **Patients with HIV and other causes of immunosuppression:** The use of liposomal amphotericin B or other formulations of amphotericin B are suggested.
- **Patients over 50 years old:** Perform a careful clinical evaluation of each case. The use of pentavalent antimonials should be avoided in patients over 50 years old.
- **Patients with therapeutic failure:** Administer any of the recommended treatments other than the one initially used, by assessing the risk–benefit on an individualized basis.

Note: The treatment scheme, administration route, and indications are found in the Implementation, Adaptation, Dissemination, and Pharmacological Interventions section (Tables 7 and 8).

Question 3

Visceral leishmaniasis in non-immunocompromised patients

What is the efficacy and safety of the different pharmacological treatments for the management of non-immunocompromised patients diagnosed with visceral leishmaniasis in the Americas?

RECOMMENDATIONS
The use of liposomal amphotericin B is recommended in pediatric and adult non-immunocompromised patients to treat visceral leishmaniasis. **Strong recommendation, low certainty evidence**
The administration of pentavalent antimonials or other formulations of amphotericin B is suggested in pediatric and adult non-immunocompromised patients to treat visceral leishmaniasis. **Conditional recommendation, low certainty evidence**
We recommend against the use of miltefosine in pediatric and adult patients to treat visceral leishmaniasis. **Strong recommendation against, very low certainty evidence**

Note: The treatment scheme, administration route, and indications are found in the Implementation, Adaptation, Dissemination, and Pharmacological Interventions section (Table 9).

BEST PRACTICE STATEMENTS

For the treatment of visceral leishmaniasis (VL), the selection of the drug should consider the toxicity profile and the risk of death associated with the disease.

Given the impossibility of using liposomal amphotericin B for the situations described below, the therapeutic alternative is the use of other lipid formulations of amphotericin B.

- Age over 50 and under 1 year old
- Kidney failure
- Liver failure
- Heart failure
- Corrected QT interval greater than 450 ms
- Concomitant use of drugs that alter the QT interval
- Hypersensitivity to pentavalent antimonials or other medication used for the treatment of VL
- Therapeutic failure to pentavalent antimonials or other drugs used for the treatment of VL
- Pregnant and breastfeeding women.

Note: If the use of liposomal or lipid amphotericin B formulations is not possible, administer amphotericin B deoxycholate, with strict monitoring of toxicity.

Note: When using liposomal amphotericin B, and other formulations, it is important to carry out strict monitoring of renal functions of non-immunocompromised VL patients.

The clinical course of patients with visceral leishmaniasis is complex and requires supportive measures and experience in managing complications and toxicity caused by treatment. Therefore, it is suggested that the treatment be carried out in hospital, allowing the appropriate interventions to improve the prognosis and avoid lethality due to the disease.

Note: The treatment scheme, administration route, and indications are found in the Implementation, Adaptation, Dissemination,and Pharmacological Interventions section (Table 9).

Question 4

Visceral leishmaniasis in immunocompromised patients

What is the efficacy and safety of the different pharmacological treatments for the management of immunocompromised patients diagnosed with visceral leishmaniasis in the Americas?

RECOMMENDATIONS

The use of liposomal amphotericin B is recommended for the treatment of immunocompromised patients with visceral leishmaniasis.

Strong recommendation, very low certainty evidence

We recommend against the use of pentavalent antimonials for the treatment of immunocompromised patients with visceral leishmaniasis.

Strong recommendation against, very low certainty evidence

The use of amphotericin B lipid complex/deoxycholate is recommended when liposomal amphotericin B is not available for the treatment of immunocompromised patients with visceral leishmaniasis.

Strong recommendation, very low certainty evidence

Note: The treatment scheme, administration route, and indications are found in the Implementation, Adaptation, Dissemination, and Pharmacological Interventions section (Table 10).

BEST PRACTICE STATEMENT

The clinical course of patients with visceral leishmaniasis in immunocompromised patients is complex and requires supportive measures and experience in managing complications and toxicity caused by treatment. Therefore, it is suggested that the treatment be carried out in hospital, allowing the appropriate interventions to improve the prognosis and avoid lethality due to the disease.

Note: When using liposomal amphotericin B and other formulations, it is important to carry out strict monitoring of renal function of immunocompromised VL patients.

Question 5

Secondary prophylaxis for visceral leishmaniasis in immunocompromised patients

What is the efficacy and safety of secondary prophylaxis for the management of immunocompromised patients diagnosed with visceral leishmaniasis in the Americas?

RECOMMENDATION

The administration of liposomal amphotericin B is recommended for secondary prophylaxis in patients with HIV–visceral leishmaniasis coinfection after the first episode of visceral leishmaniasis, in all patients with a CD4 T-cell count less than 350 per mm^3.

Strong recommendation, very low certainty evidence

Note: The treatment scheme, administration route, and indications are found in the Implementation, Adaptation, Dissemination, and Pharmacological Interventions section (Table 11).

BEST PRACTICE STATEMENTS

For patients who are transplanted or have other immune-debilitating conditions not related to HIV, the indication of secondary prophylaxis after treatment of the first episode of visceral leishmaniasis should be evaluated on a case-by-case basis, based on the intensity of immunosuppression, and preferably in reference services. When secondary prophylaxis is not indicated, frequent clinical follow-up is recommended.

The clinical course of patients with visceral leishmaniasis in immunocompromised patients is complex and requires supportive measures and experience in managing complications and toxicity caused by treatment. Therefore, it is suggested that the treatment be carried out in hospital, allowing the appropriate interventions to improve the prognosis and avoid lethality due to the disease.

Note: When using liposomal amphotericin B, and other formulations, it is important to carry out strict monitoring of renal function of immunocompromised VL patients.

Introduction

The leishmaniases remain neglected infectious diseases of great importance, as they mainly affect the poorest people with less access to health services. In the Americas, the leishmaniases are a public health problem due to their magnitude, wide geographical distribution, and morbidity and mortality *(1–3)*.

The Pan American Health Organization (PAHO) continues to support endemic countries in strengthening actions to achieve the goals of eliminating leishmaniasis as a public health problem, in accordance with the mandate given by the PAHO Disease Elimination Initiative *(4)*, in line with the World Health Organization's Road Map for Neglected Tropical Diseases 2021–2030 *(5)*. Hence, actions such as access to early diagnosis, adequate treatment of cases, and reduction of contact between people and vectors have been promoted to reduce morbidity and mortality from leishmaniasis.

In the Region in the Americas, leishmaniasis encompasses diseases caused by several species of *Leishmania*, which influence the clinical manifestations, severity of the disease, accuracy of diagnosis *(6–8)*, and response to treatment *(3, 9–11)*.

Cutaneous leishmaniasis is endemic in 18 countries, with an average of approximately 54,000 cases per year. It is the most frequent form in the Region, and about 90% of cases present as localized, single, or multiple lesions, being associated with 15 species of *Leishmania* as causal agents. Other clinical cutaneous forms, such as disseminated (mainly caused by *L. (V.) braziliensis*) and diffuse cutaneous (mainly produced by *L. (L.) amazonensis* and *L. (L.) mexicana*), are more difficult to treat and present frequent relapses *(12)*. The average case distribution is concentrated in the Andean Area with 43% of the cases, in Brazil with 37%, in Central America with 18%, with the rest in the Southern Cone, Non-Latin Caribbean, and Mexico. Of the endemic countries, about 76% of the cases occur in Brazil, Colombia, Nicaragua, and Peru *(13)*. The mucosal form, most frequently caused by *L. (V.) braziliensis*, *L. (V.) panamensis*, and *L. (V.) guyanensis*, represents approximately 4% of cases of cutaneous leishmaniasis in the Americas and is a serious clinical form for causing significant mutilations and disabilities if not diagnosed and treated early *(12)*.

Visceral leishmaniasis (caused by *L. infantum*) is the most severe form, as it can cause death in up to 90% of untreated people. It is endemic in 13 countries in the Americas, with on average around 3,500 cases per year, although 96% of cases are reported in Brazil. The proportion of HIV–visceral leishmaniasis coinfection cases has been increasing over the years, reaching 11% in 2019, the highest percentage since 2012. The average case fatality rate from the disease is 7%, although 8% was registered in 2018, the highest rate since 2012 *(12–14)*.

The choice of treatment for leishmaniasis depends on many factors, such as clinical form, efficacy, therapeutic scheme, toxicity, cost, and patient acceptability *(9, 15)*. Responses to leishmaniasis treatments have been heterogeneous, depending on the species of the parasite, geographical location, the immunogenetic profile of the affected individual, and the general relationship of the parasite with its vectors, reservoirs, and hosts *(9, 12, 15)*.

Antimonials, amphotericin B, pentamidine isethionate, and miltefosine constitute the therapeutic arsenal available for systemic treatment of leishmaniasis. Pentavalent antimonials are the oldest drugs available and are still considered first-line treatments against most forms of leishmaniasis, although most of the evidence recommending their use is weak *(15, 16)*. New evidence has emerged demonstrating the benefits of using treatments previously considered as alternatives as a first choice for some clinical forms and species, such as liposomal amphotericin B for patients with visceral leishmaniasis and miltefosine for some species of cutaneous leishmaniasis, as well as local treatments for localized cutaneous leishmaniasis *(11, 15, 16)*.

In 2013, PAHO, with the support of the Spanish Agency for International Development Cooperation (AECID, Spanish acronym), developed recommendations for the treatment of leishmaniasis in the Americas using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, considering the evidence published in the Region, but also the regional clinical–epidemiological specificities, recognition of prevalent species, in addition to the characteristics of local health systems. In recent years new evidence has emerged; therefore, the updating of therapeutic recommendations has been prioritized given the burden of the disease in the Region in terms of incidence, quality of life, access, and costs *(15)*.

In this regard, PAHO presents the Guideline for the Treatment of Leishmaniasis in the Americas, which is the result of joint work with experts in the field from the Region. This publication presents the update of the therapeutic recommendations, detailing the schemes and criteria for indication of treatment for cutaneous, mucosal, and visceral leishmaniasis in the regional context, in accordance with the standards for the development of WHO guidelines *(17)*. Thus, some of the recommendations presented here may differ from the specific recommendations from other continents, in view of the distinct epidemiological and biological aspects, such as the different circulating species of *Leishmania*, transmission cycles, and therapeutic responses *(3)*.

Objectives and target audience

This guideline was developed with the objective of providing recommendations for the proper management of patients diagnosed with leishmaniasis and reducing clinical complications and deaths caused by drug toxicity, as well as the lethality of visceral leishmaniasis in the Americas.

Specific objectives

- To present recommendations for the treatment of leishmaniasis by parasite species according to the available evidence.
- To provide recommendations for the management and secondary prophylaxis of immunocompromised patients diagnosed with visceral leishmaniasis in the Americas.

These goals are aligned with PAHO's Plan of Action for the Elimination of Neglected Infectious Diseases and Post-Elimination Actions 2016–2022 *(16)*, the PAHO Disease Elimination Initiative: A Policy for an Integrated Sustainable Approach to Communicable Diseases in the Americas *(18, 19)*, and the new WHO Road Map for Neglected Tropical Diseases 2021–2030 *(5)*, which support and contribute to achieving universal health coverage by 2030 and Goal 3.3 of the Sustainable Development Goals.

The recommendations are addressed to all health sector officials responsible for the care of patients diagnosed with leishmaniasis: general practitioners, internists, dermatologists, infectious disease specialists, nurses, and other health professionals involved in the care of patients. These recommendations are addressed to the managers and technicians of the ministries of health, responsible for the formulation of the national program's guidelines or the leishmaniasis surveillance services of the American countries, as well as to those responsible for the planning and procurement of the necessary supplies to guarantee the timely and adequate access of patients to treatment.

Scope

This guideline provides recommendations for the pharmacological management of patients diagnosed with leishmaniasis in the Americas, the management and secondary prophylaxis in patients with visceral leishmaniasis and HIV, as well as immunocompromised patients with other diseases that cause immunosuppression, favoring the technical and scientific interrelationship between the countries of the Region.

This guideline does not address diagnosis or follow-up of the patients.

Methods

Methods

Clinical group and methodological consultants

The development process included the participation of several groups that helped guide and contributed greatly to the overall process. These are the PAHO Guidelines Steering Group, the methodological group, the Guideline Development Group (GDG), the expert reviewers, and the WHO Guidelines Review Committee. To constitute the GDG a large group of experts was convened, with sufficient experience in the central objective of the guideline. The GDG was attended by experts in internal medicine, infectious diseases, and dermatology. Professionals with experience in public health and clinical epidemiology were also participants in this process. The GDG was accompanied by the steering group. The full development group can be found in Annex 1.

Declaration of interest

At the time of setting up the GDG, each of the convened experts completed, in advance and in writing, the declaration of interest for a period of not less than one year. The clinical and methodological leader in charge of each one of the teams did the reading and recording of any interests—personal economic, not personal, non-economic personal, or personal economic of a family member—in the form available for this purpose. For the analysis of the declaration of interest, an independent committee was appointed to examine and resolve any potential conflicts that may arise during the development of this guide *(17)*. The analysis of the declaration of interest is provided in Annex 2.

Definition of scope and objectives

The scope and objectives of this guideline update were previously defined with the WHO committee and reviewed by the GDG. In order to ensure that the recommendations made were applicable to the regional clinical setting, while supporting all health professionals in order to provide quality and efficient medical care, the different types of leishmaniasis and associated *Leishmania* species were considered.

Editorial declaration of independence

The funding entity of the guideline has accompanied the project since the approval of the work plan for the elaboration of this guideline, thus guaranteeing the applicability of its content to the context in the Americas.

Peer review

The guideline was reviewed by thematic and methodological experts and their comments were evaluated and adjusted considering the relevance to the guideline.

Formulation of clinical questions

Based on a prioritization process, the clinical questions of the previous version of the guideline *(15)* were reviewed, identifying the controversies, knowledge gaps, unjustified variability in patient management, the existence of different therapeutic options, the availability of new evidence, the costs related to health care, and quality problems in practice, which served as an input for the updating of the generic questions of the guideline that were subsequently structured in PICO format (Population, Intervention, Comparison and Outcomes) following the guidelines of the methodological handbook and always bearing in mind the scope and objective outlined for the guideline. Finally, to answer each question, the appropriate type of study was selected and once the final list of questions was defined according to each of its components, the document with the questions was agreed between the managing body and the GDG *(17)*.

The target audience is patients of any age diagnosed with cutaneous, mucosal, visceral, dermal post-kala-azar and para-kala-azar leishmaniasis in the Americas. Women of childbearing age, pregnant women, breastfeeding women, and immunocompromised persons were included.

The questions were socialized with the stakeholders in order to obtain their contributions to the process *(15, 17)* as well as to include the perspective of the patients. Once this step was

completed, the final list of questions that configures the general structure of this Guideline was generated.

The Guideline was prepared in accordance with the latest WHO Handbook for Guideline Development *(17).* The WHO guideline development process includes planning, conducting a scope and needs assessment, creating an internal WHO steering group and an external guideline development group, formulating key questions in the PICO format, derived from systematic reviews, formulating recommendations using the Grading of Recommendation Assessment, Development and Evaluation (GRADE) classification method, drafting the guideline, and planning its dissemination and implementation. This methodology ensures transparency of the link between the evidence base and the recommendations.

Priority was given to those outcomes of efficacy, safety, quality of life, and all that is important for patients. Each outcome identified was classified as unimportant, important non-critical, or critical for patients, using a nine-unit scale proposed by the GRADE group. The thematic experts anonymously qualified the list of outcomes. At the end of this exercise, the scores obtained for each result were examined, their median was estimated, and the relevance of each outcome was established. Only those outcomes listed as critical were preserved.

Guideline questions

The following table lists the PICO questions addressed by the Guideline.

Question 1

What is the efficacy and safety of the different systemic and local treatments for the management of patients diagnosed with cutaneous leishmaniasis in the Americas?

Population	Intervention	Comparison	Critical outcomes
Children and adults diagnosed with cutaneous leishmaniasis (localized, disseminated, or diffuse) in the Americas. Analysis considerations by subgroup according to the life cycle: • Early childhood (under 1 year, 1–5 years) • Childhood (6–11 years) • Adolescence (12–14 years) • Youth (15–26 years) • Adulthood (27–50 years) • Senior (51 years and older) Special groups: • Women of childbearing age • Pregnancy • Immunocompromised • Breastfeeding women	1. Systemic treatments as monotherapy: • Liposomal amphotericin B • Amphotericin B lipid complex • Amphotericin B deoxycholate • Miltefosine • Pentamidine • Imidazoles • Macrolides • Allopurinol • Other therapies 2. Local treatments as monotherapy: • Pentavalent antimonial (local injection) • Pentamidine (local injection) • Amphotericin infiltration • Paromomycin (cream) • Thermotherapy • Cryotherapy 3. Combination therapy (including local and systemic)	Pentavalent antimonials Other interventions Placebo	General complete cure (all leishmaniasis included) Complete cure by *Leishmania* species General therapeutic failure (all leishmaniasis included) Therapeutic failure by *Leishmania* species Adverse events (mild, moderate, and serious) Quality of life

Question 2

What is the efficacy and safety of the different pharmacological treatments for the management of patients diagnosed with mucosal leishmaniasis in the Americas?

Population	Intervention	Comparison	Critical outcomes
Children and adults diagnosed with mucosal leishmaniasis in the Americas. Analysis considerations by subgroup according to life cycle: • Early childhood (under 1 year, 1–5 years) • Childhood (6–11 years) • Adolescence (12–14 years) • Youth (15–26 years) • Adulthood (27–50 years) • Senior (51 years and older) Special groups: • Women of childbearing age • Pregnancy • Immunocompromised • Breastfeeding women	As monotherapy or combination therapy: • Liposomal amphotericin B • Amphotericin B lipid complex • Amphotericin B deoxycholate • Miltefosine • Pentamidine • Imidazoles • Macrolides • Allopurinol	Pentavalent antimonials Other interventions Placebo	General complete cure (all leishmaniasis included) Complete cure by *Leishmania* species General therapeutic failure (all leishmaniasis included) Therapeutic failure by *Leishmania* species Adverse events (mild, moderate, and serious) Quality of life

Question 3

What is the efficacy and safety of the different pharmacological treatments for the management of non-immunocompromised patients diagnosed with visceral leishmaniasis in the Americas?

Population	Intervention	Comparison	Critical outcomes
Non-immunocompromised children and adults diagnosed with visceral leishmaniasis. Analysis considerations by subgroup according to life cycle: • Early childhood (under 1 year, 1–5 years) • Childhood (6–11 years) • Adolescence (12–14 years) • Youth (15–26 years) • Adulthood (27–50 years) • Senior (51 years and older) Special groups: • Women of childbearing age • Pregnancy • Immunocompromised • Breastfeeding women	• Liposomal amphotericin B • Amphotericin B lipid complex • Amphotericin B deoxycholate • Pentamidine • Paromomycin • Miltefosine • Imidazoles • Macrolides • Allopurinol • Combinations	Pentavalent antimonials	General complete cure (all leishmaniasis included) General therapeutic failure (all leishmaniasis included) Adverse events (mild, moderate, and serious) Quality of life Adherence to treatment

Question 4

What is the efficacy and safety of the different pharmacological treatments for the management of immunocompromised patients diagnosed with visceral leishmaniasis in the Americas?

Population	Intervention	Comparison	Critical outcomes
Immunocompromised children and adults (HIV coinfection, transplanted, or other debilitating conditions of the immune system) diagnosed with visceral leishmaniasis. Analysis considerations by subgroup according to life cycle: • Early childhood (under 1 year, 1–5 years) • Childhood (6–11 years) • Adolescence (12–14 years) • Youth (15–26 years) • Adulthood (27–50 years) • Senior (51 years and older) Special groups: • Women of childbearing age • Pregnancy • Immunocompromised • Breastfeeding women	• High doses of amphotericin B • Miltefosine • Paromomycin • Pentamidine • Combinations	Pentavalent antimonials Low doses of amphotericin B Other interventions	General complete cure (all leishmaniasis included) General therapeutic failure (all leishmaniasis included) Adverse events (mild, moderate, and serious) Quality of life Adherence to treatment

Question 5

What is the efficacy and safety of secondary prophylaxis for the management of immunocompromised patients diagnosed with visceral leishmaniasis in the Americas?

Population	Intervention	Comparison	Critical outcomes
Immunocompromised children and adults (HIV coinfection, transplanted, or other debilitating immune system conditions) diagnosed with visceral leishmaniasis. Analysis considerations by subgroup according to life cycle: • Early childhood (under 1 year, 1–5 years) • Childhood (6–11 years) • Adolescence (12–14 years) • Youth (15–26 years) • Adulthood (27–50 years) • Senior (51 years and older) Special groups: • Women of childbearing age • Pregnancy • Immunocompromised • Breastfeeding women	• Pentamidine • Amphotericin B	No treatment	Relapse-free survival at 12 months Relapse rate at 6 months of treatment Adverse events Mortality Adherence to treatment

Question 6

What is the efficacy and safety of the different pharmacological treatments for the management of patients diagnosed with post-kala-azar and para-kala-azar dermal leishmaniasis in the Americas?

Population	Intervention	Comparison	Critical outcomes
Children and adults diagnosed with post-kala-azar and para-kala-azar dermal leishmaniasis in the Americas.	• Paromomycin (in any presentation) • Liposomal amphotericin B • Amphotericin B lipid complex • Amphotericin B deoxycholate • Miltefosine • Any other therapy identified	Pentavalent antimonials	General complete cure (all leishmaniasis included) General therapeutic failure (all leishmaniasis included) Adverse events (mild, moderate, and serious) Quality of life Adherence to treatment

Search for evidence

A systematic and rigorous process was initiated, which sought and recovered the best available evidence for each of the clinical questions of the Guideline, following the instructions proposed by the WHO Handbook *(17)*. To do this, we identified the search terms in free and controlled language that reflected the most key components of each PICO question. Then, implementing the use of Boolean operators, proximity connectors, wildcards, and highly sensitive filters, the strategy for the research was designed, which was validated in appearance by the group of clinical experts and is presented in Annex 3, to finally be executed in the following databases:

- Ovid MEDLINE(R)
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
- Ovid MEDLINE(R) Daily Update
- Embase
- Cochrane.

The search was not restricted by date or type of language and was implemented within the different databases and was carried out until February 2021. The search also covered gray literature such as technical papers from relevant institutions and Google Scholar. References were also obtained by "snowball" of the retrieved and included references and, finally, through contact with clinical experts; all this with the aim of collecting relevant unpublished literature.

From the list of references retrieved, in the first instance we prioritized the inclusion of systematic reviews with or without meta-analysis that answered the questions asked and, if necessary, proceeded to search and recover those primary randomized controlled trials (RCT) relevant to the guideline. The list of references compiled by the information research was refined using the Mendeley software, which eliminated duplicate references; thus, the final list of references was reviewed by a clinical expert and a methodological advisor, with the aim of identifying those relevant studies in the light of the inclusion and exclusion criteria (characteristics of the target population and type of study). The discrepancies were resolved by consensus and in some instances, through consultation with a third reviewer.

To provide transparency and with the aim of granting traceability to the literature selection process, a flowchart was constructed for each question, in which the number of references identified by type of source, the number of references excluded (accompanied by the respective reason), the number of references sieved in full text, and, finally, the number of articles selected for evaluation and synthesis were recorded. The PRISMA algorithm of each question can be consulted in Annex 4 of this document along with a list of excluded studies. The AMSTAR-2 tool was used as a critical assessment tool for the included systematic reviews; this instrument reports and considers the different systematic reviews as high, medium, low, and critically low certainty, according to the result issued by the evaluation of 16 aspects. When it came to primary studies, controlled clinical trials were evaluated using the risk of bias instrument suggested by the Cochrane Group, called "Risk of Bias Tool 2.0"; and non-randomized studies were evaluated with ROBINS, which classed the study as high, unclear, and low risk of bias.

Synthesis of evidence

Methodology for the development of the meta-analyses included in the Guideline

When systematic reviews (SR) were not identified or when it was necessary to make comparisons that were not found in the identified SR, we searched for clinical trials. The risk of bias was independently assessed for each study included using the Cochrane risk of bias tool. Disagreements were resolved through discussion. Information was collected in the data extraction forms. The information was entered in the Review Manager 5 program in a paired manner to verify the certainty of the information. The detailed methodology can be found in Annex 5 *(17)*.

Creation of GRADE evidence profiles

The GRADE evidence profiles were created for each treatment comparison and population of interest using the GRADEpro program, establishing the confidence in the effect, according to the overall certainty of the evidence. The GRADE system establishes four levels of evidence.

Certainty of evidence	Interpretation
High	The GDG is very confident that the true effect lies close to that of the estimate of the effect.
Moderate	The GDG is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	The GDG's confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low	The GDG has very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

For the GRADE methodology *(17)*, controlled clinical trials represent, in principle, high-certainty evidence; however, confidence in the effect (certainty) can be affected by the presence of serious or very serious limitations in the design or conduct of the study (risk of bias); serious or very serious limitations in consistency in results; serious or very serious limitations when

analyzing the applicability of the evidence or in assessing the accuracy of the results; and finally, when the presence of publication bias is strongly suspected. Although non-randomized controlled studies (e.g., cohort studies or case–control studies) start being catalogued as "low certainty" evidence within this methodology, confidence in the effect can be increased (even becoming "high certainty" evidence) if gradient dose response is observed; whether the magnitude of the effect is strong or very strong (in terms of the magnitude of the measure of association) or whether all plausible biases could have decreased the magnitude of the effect.

Formulation of recommendations

As for the strength of the recommendation, GRADE proposes two grades of recommendation "Strong" or "Conditional." When the desirable effects of an intervention clearly outweigh the undesirable effects, the guideline panel issued a "Strong" recommendation. On the other hand, when the balance between the desirable and undesirable effects of the intervention is less clear either by virtue of the low or very low certainty of the evidence, the uncertainty or variability in the values and preferences of patients, the concern that the intervention demands a wide consumption of resources, or, because the evidence suggests little or narrow differences between the desirable and undesirable effects of the intervention, or equity effects are found, the panel issued a "Conditional" recommendation. The AMSTAR-2 assessment for each of the included systematic reviews is presented within the body of evidence, and GRADE evidence profiles can be found in Annex 5.

This guideline follows the methodology proposed by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system where the following levels of evidence and degrees of recommendation are implemented:

Strength of the GRADE methodology recommendation	
Strength of recommendation	**Meaning**
Strong in favor	The desirable effects clearly outweigh the undesirable effects. **IT IS RECOMMENDED TO DO SO**
Conditional in favor	The desirable effects probably outweigh the undesirable effects. **IT IS SUGGESTED TO DO SO**
Conditional against	The undesirable effects probably outweigh the desirable effects. **IT IS SUGGESTED NOT TO DO SO**
Strong against	The undesirable effects clearly outweigh the desirable effects. **IT IS RECOMMENDED NOT TO DO SO**

Once the elaboration of the different evidence profiles was completed, the main substrate for the formulation of the recommendations was available. In this way, the different GRADE evidence profiles were presented at the virtual GDG meeting to generate the recommendations of the guideline. Each recommendation, accompanied by its respective synthesis of evidence, was presented to the group of regional clinical and research experts who determined the strength and direction of each recommendation by implementing the GRADE methodology, which weighs the certainty of the evidence, the risk–benefit balance, the costs, and the preferences of the patients as a primary input when defining the strength and direction of the recommendations. Each recommendation presents the strength of the recommendation according to the GRADE approach that is interpreted according to Table 1.

TABLE 1

Definition of recommendations according to the GRADE system

	Strong recommendations	Conditional recommendations
For patients	Most individuals in this situation would like the recommended course of action and only a small proportion would not.	Most individuals would like the suggested course of action, but many would not accept it.
For users	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as certainty criteria or a performance indicator.	Recognize what different options would be appropriate for different patients, and that it should help each patient reach a management decision consistent with their values and preferences. Decision collaborations can be useful in assisting individuals in making decisions consistent with their values and preferences. Doctors should know that they will spend more time with patients in the decision-making process.
	Collaboration in formal decisions is unlikely to be needed to help individuals make decisions consistent with their values and preferences.	
For policy developers	The recommendation can be adapted as a policy in most situations, including its use as a performance indicator.	Policy formulation would require major discussions and the participation of many stakeholders. Policies are likely to vary between regions. Performance indicators should focus on the fact that proper deliberation has taken place on management options.

Source: World Health Organization. WHO handbook for guideline development – 2nd ed. Geneva; WHO; 2014. 179 [Internet]. Available from: https://apps.who.int/iris/handle/10665/145714

At the end of each discussion that gave rise to the recommendations, it was verified that the panel agreed with the meaning and strength of the recommendations, while its content was specific and directed. For each recommendation, the panel members had the opportunity to discuss the evidence, present their opinions and implementation issues, and propose changes to the recommendations. The panel was able to vote on each recommendation using a cell-phone app and we reached consensus when more than 70% was obtained. The deliberative and voting process, as well as the results, were recorded on a virtual platform designed for this purpose and the audio of the discussion was saved as a later support.

In addition, the tables of evidence to the recommendation were developed, which present the value judgments that led to the formulation of the recommendations. The evidence to recommendation tables are found in the online annex and present the decision about desirable effects, undesirable effects, certainty of evidence, quality of evidence, variability, risk benefit balance, resources, cost effectiveness, equity, acceptability, and feasibility.

Best practice statements

During the consensus meeting, best practice statements were also formulated and updated from the previous guideline by consensus of experts in order to support patient management and provide information for the management of special situations for which there is no evidence, as the regional experts considered that it was essential that the Guideline present guidance in this regard. These statements can be found next to the recommendations.

Incorporating the perspective of patients

To incorporate patients' perspectives, we searched the literature and experiences of the GDG panel, which provide the patient perspective needed in order to support the recommendations.

Incorporation of costs

For the incorporation of cost aspects, we evaluated whether the recommended interventions were available to the countries of the Region; the costs of their acquisition and possible costs for patients, based on PAHO's Strategic Fund; and literature from published studies in Latin America.

Implementation and adaptation considerations

For each question, relevant aspects are presented for the implementation of the recommendations in relation to barriers related to physicians, patients, the health system, costs, and access. Additionally, in order to facilitate the administration of medications in an effective and safe way, the updating of the doses table and level of care were developed for each recommended medication and includes special situations. These tables were validated virtually by the development group and were based on evidence and GDG experience when data were not available. This information can be found in the Implementation and Adaptation section.

Recommendations for the treatment of leishmaniasis in the Americas

Recommendations for the treatment of leishmaniasis in the Americas

Recommendations will be presented by clinical form of leishmaniasis, stratified by the degree of evidence and strength of the recommendation. In addition, for the cutaneous form, the recommendations are presented according to the classification of the patient's age and the *Leishmania* species presumably involved. Despite the effort to gather the evidence in a systematized and complete manner, in several clinical situations no studies were found to support the recommendations. In these cases, the best practice statements were updated from the previous guideline and present considerations that were extracted from the discussions of the GDG panel based on the safety profile of the drugs, studies in other populations, and clinical experience. Likewise, there is a small number, or nonexistence, of randomized controlled studies identified for the different clinical forms, which reinforces the importance of using these guidelines as the collection of the currently available evidence and reference in the therapeutic definition, and it is up to the prescriber to carefully analyze the application of the evidence to individual patients, considering their specificities and respecting their autonomy. Similarly, the availability of the various therapeutic alternatives varies between countries, requiring critical discernment from both managers and professionals to provide medication and have more than one treatment option available in each country.

The therapeutic schemes with the administration routes, doses, and more details by intervention, species of *Leishmania*, and treatment location according to the level of complexity of the care unit, are detailed in Tables 2 to 11 in the Implementation, Adaptation, Dissemination, and Pharmacological Interventions section.

Cutaneous leishmaniasis

Question 1

Cutaneous leishmaniasis

What is the efficacy and safety of the different systemic and local treatments for the management of patients diagnosed with cutaneous leishmaniasis in the Americas?

RECOMMENDATIONS
Cutaneous leishmaniasis in adult patients
The application of intralesional pentavalent antimonials is recommended in patients with localized cutaneous leishmaniasis caused by *L. braziliensis* and *L. amazonensis*. **Strong recommendation, low certainty evidence**
The use of miltefosine is recommended in adult patients diagnosed with cutaneous leishmaniasis caused by *L. panamensis*, *L. mexicana*, *L. guyanensis*, and *L. braziliensis*. **Strong recommendation, low certainty evidence**
The administration of pentamidine isethionate is suggested in patients diagnosed with cutaneous leishmaniasis caused by *L. guyanensis*. **Conditional recommendation, low certainty evidence**
The application of thermotherapy is suggested in patients with localized cutaneous leishmaniasis caused by *L. braziliensis*, *L. panamensis*, and *L. mexicana*. **Conditional recommendation, very low certainty evidence**
The use of paromomycin is suggested in patients with cutaneous leishmaniasis caused by *L. panamensis*, *L. braziliensis*, and *L. mexicana*. **Conditional recommendation, very low certainty evidence**
The use of pentavalent antimonials is suggested in adult patients diagnosed with cutaneous leishmaniasis caused by *L. braziliensis*, *L. panamensis*, *L. amazonensis*, *L. peruviana*, and *L. mexicana*. **Conditional recommendation, moderate to low certainty evidence**

RECOMMENDATIONS

Cutaneous leishmaniasis in pediatric patients

The use of miltefosine is recommended in pediatric patients diagnosed with cutaneous leishmaniasis caused by *L. panamensis*, *L. guyanensis*, and *L. braziliensis*.

Strong recommendation, low certainty evidence

The use of paromomycin is suggested in pediatric patients with cutaneous leishmaniasis caused by *L. panamensis*, *L. braziliensis*, and *L. mexicana*.

Conditional recommendation, low certainty evidence

The use of pentavalent antimonials is suggested to treat pediatric patients diagnosed with cutaneous leishmaniasis when no other alternative is available.

Conditional recommendation, low certainty evidence

Note: The treatment scheme, administration route, and indications are found in the Implementation, Adaptation, Dissemination, and Pharmacological Interventions section (Tables 2, 3, 5, and 8).

BEST PRACTICE STATEMENTS

Treatment of any species of *Leishmania* in pediatric and adult patients with cutaneous leishmaniasis

Decision-making about the therapeutic strategy to be used in patients diagnosed with leishmaniasis should be shared with patients based on a clear explanation of the risks and benefits of the available alternatives.

It is not imperative to identify the species to initiate treatment, but if the most prevalent species in the region is known, treatment should be initiated according to the clinical condition, availability of the medication, and considering the risk–benefit balance.

Patients diagnosed with leishmaniasis should be guided about the hygienic care of skin or mucosal lesions; recognition of clinical manifestations, presence of concomitant infections, signs of non-response to treatment, and occurrence of toxicity caused by drugs.

To treat the following special cases of patients with cutaneous leishmaniasis, it is suggested:

- **Pregnant women:** Thermotherapy and cases requiring systemic treatment should be referred to the reference center. The suggested indicated medication is liposomal amphotericin B or other formulations of amphotericin B. The use of pentavalent antimonials, miltefosine, and pentamidine is contraindicated.
- **Breastfeeding women:** Intralesional antimonials, or thermotherapy, or amphotericin B, guaranteeing contraception.
- **Patients with alterations in the electrocardiogram:** Local treatment with thermotherapy or systemic with miltefosine or liposomal amphotericin B. The use of systemic pentavalent antimonials and pentamidine isethionate is contraindicated.
- **Patients with kidney disease, liver disease, heart disease:** Local treatments or the use of liposomal amphotericin B. Caution and frequent monitoring is suggested for the use of intralesional treatment with pentavalent antimonial in patients with heart disease.
- **Comorbidity with tuberculosis:** Take special care in monitoring adverse events, especially when deciding to use the two treatments concomitantly (tuberculosis and leishmaniasis).
- **Patients with HIV and other causes of immunosuppression:** Liposomal amphotericin B or amphotericin B deoxycholate and perform treatment in reference center.
- **Patients over 50 years of age:** Perform a careful clinical evaluation of each case considering the comorbidities and the possibility of therapeutic toxicities. The use of pentavalent antimonials should be avoided in patients over 50 years of age.
- **Patients with therapeutic failure:** Administer any of the recommended treatments other than the one initially used.
- **Patients with disseminated cutaneous leishmaniasis:** Use of liposomal amphotericin B, miltefosine, or pentavalent antimonials and perform treatment in reference center.
- **Patients with diffuse cutaneous leishmaniasis:** It is suggested to use pentavalent antimonials, pentamidine isethionate, or miltefosine and perform treatment in reference center.
- **Patients with atypical cutaneous leishmaniasis caused by *L. infantum:*** The use of intralesional or systemic pentavalent antimonials is suggested.

Note: The treatment scheme, administration route, and indications are found in the Implementation, Adaptation, Dissemination, and Pharmacological Interventions section (Tables 4 and 8).

Evidence

Two SR were selected for answering the question: one Cochrane SR from 2020 that evaluated all pharmacological interventions for the treatment of patients diagnosed with cutaneous leishmaniasis in the Americas, and another SR that evaluated interventions in children. Below, we present the evidence reported in the randomized controlled trials of the SR with respect to the critical outcomes selected by drug and population group *(20)*. An update of the SR was made without finding new studies. The Cochrane SR identified 67 studies evaluating cutaneous leishmaniasis with patients aged between 2 and 87 years. The studies did not perform analysis by gender. The participants' lesions were mainly located in the upper and lower extremities, and to a lesser extent on the neck and torso. The main species evaluated were *L. braziliensis*, *L. panamensis*, *L. mexicana*, and *L. guyanensis*.

Adult population

Local and systemic pentavalent antimonials

No. studies (sample) Species	Intervention	Comparator	Cure at least 3 months after treatment	Recurrence	Side effects (SE)	Evidence certainty (reference of the study included in the SR)
1 (60) *L. braziliensis* and *L. amazonensis*	Intralesional antimony 1, 3, 5 days	Placebo	RR 5.00; 95% CI (1.94, 12.89)	Does not report	No participant reported SE	Low Due to risk of bias and imprecision *(21)*
2 (157) *L. braziliensis* and *L. panamensis*	IM meglumine antimoniate (20 mg/kg/day) 20 days	Placebo for 28 days	No differences were reported. RR 4.23; 95% CI (0.84, 21.38)	No differences were reported. RR 1.79; 95% CI (0.17, 19.26)	Severe SE in meglumine antimoniate group RR 1.51; 95% CI (1.17, 1.96) 134 patients. No differences in mild SE were reported.	Moderate Due to imprecision (cure for at least 3 months after treatment and side effects) Low for recurrence due to risk of bias and imprecision *(22, 23)*

No. studies (sample) Species	Intervention	Comparator	Cure at least 3 months after treatment	Recurrence	Side effects (SE)	Evidence certainty (reference of the study included in the SR)
2 (177) *L. braziliensis*, *L. panamensis*, and *L. mexicana*	IM meglumine antimoniate 20 days (20 mg/kg/day)	IM meglumine antimoniate 10 days	No differences were reported. RR 0.91; 95% CI (0.69, 1.21)		No differences were reported between groups in terms of anorexia, myalgias, headache, malaise occurred more frequently than arthralgias. RR 0.36; 95% CI (0.14, 0.94).	Low Due to risk of bias, heterogeneity, and imprecision *(24, 25)*
1 (50) *L. panamensis*	IV meglumine antimoniate for 15 days (20 mg/kg/day)	No treatment	No effect was reported. RR 13.24; 95% CI (0.83, 210.87)	No differences were reported between groups. RR 1.55; 95% CI (0.35, 6.85)		Very low Due to risk of bias and imprecision *(26)*
1 (61) *L. braziliensis* and *L. panamensis*	IV meglumine antimoniate 20 days	IV meglumine antimoniate 7 days + topical placebo	Greater effect on treatment at 20 days RR 0.64; 95% CI (0.44, 0.92)	Does not report	Does not report	Low Due to risk of bias and imprecision *(27)*
1 (90) *L. braziliensis*	IV meglumine antimoniate at 20 mg/kg/day for 20 days plus anthelmintic treatment: albendazole (400 mg), ivermectin (200 µg/kg), and praziquantel (50 mg/kg) in an oral formulation at days 0 and 30 and at day 60	IV meglumine antimoniate at 20 mg/kg/day for 20 days plus placebo	No differences were reported between treatments. RR 0.77; 95% CI (0.48, 1.25)		60% of participants reported some SE (muscle pain, headache, leg pain, fever, dizziness) with the first group	Very low Due to risk of bias and imprecision *(28)*
7 (510) *L. braziliensis*	Sodium stibogluconate	Placebo, meglumine antimoniate, other regimens	No differences between treatments were reported	No differences between treatments were reported	No differences between treatments were reported	Very low Due to risk of bias and imprecision *(22, 29–34)*

No. studies (sample) Species	Intervention	Comparator	Cure at least 3 months after treatment	Recurrence	Side effects (SE)	Evidence certainty (reference of the study included in the SR)
1 (38) *L. braziliensis*	Oral tamoxifen (40 mg/day for 20 days) or topical (0.1% tamoxifen citrate for 20 days) combined with meglumine antimoniate (20 mg Sb^{+5}/kg/day for 20 days)	Meglumine antimoniate (20 mg/kg/day for 20 days)	No differences were reported. RR 1.25; 95% CI (0.67, 2.32)	No differences were reported in oral (RR 0.59; 95% CI [0.05, 7.43]) and topical (RR 0.68; 95% CI [0.07, 6.61])	Mild side effects (arthralgia, myalgia) were reported at a similar frequency between groups	Very low Due to risk of bias and imprecision *(35)*

Miltefosine

No. studies	Intervention	Comparator	Cure at least 3 months after treatment	Recurrence	Side effects	Evidence certainty (Reference of the study included in the SR)
1 (133) *L. braziliensis*, *L. panamensis* and *L. mexicana*.	Oral miltefosine for 28 days (50 mg)	Placebo	Miltefosine in Colombian population probably cures lesions. RR 2.18, 95% CI (1.28, 3.71) and RR 2.50; 95% CI (0.99, 6.33) for population in Guatemala.	Recurrence at 6 months was lower in the miltefosine group	Miltefosine probably produced more SE. RR 3.96; 95% CI (1.49, 10.48)	Very low Due to risk of bias and imprecision *(36)*
6 (626)	Oral miltefosine for 28 days	Meglumine antimoniate	No differences were presented. RR 1.16; 95% CI (0.91, 1.48)		Increased frequency of nausea (RR 2.45; 95% CI [1.72, 3.49]) and vomiting (RR 4.76; 95% CI [1.82, 12.46]) with miltefosine	Low Due to very serious imprecision *(37–41)*

Pentamidine isethionate

No. studies	Intervention	Comparator	Cure at least 3 months after treatment	Recurrence	Side effects	Certainty of evidence
1 (80) *L. braziliensis*	IV pentamidine isethionate 2mg/kg (7 doses)	IV meglumine antimoniate (20 mg/kg/day)	Probably favors IV meglumine antimoniate RR 0.45; 95% CI (0.29, 0.71)	No differences were reported at 6 months (p > 0.05)	No differences in gastrointestinal or musculoskeletal events (p > 0.05). More patients with headache in the meglumine antimoniate group RR 0.61; 95% CI (0.43, 0.85)	Low Due to very serious imprecision (42)
3 (226) *L. braziliensis*	IV or IM pentamidine isethionate	IM meglumine antimoniate	No differences were reported RR 0.95; 95% CI (0.81, 1.13)		More arthralgias were reported for antimoniate RR 0.27; 95% CI (0.11, 0.69). No differences were reported in others.	Cure: Low Due to risk of bias and imprecision (43–45) SE: Very low due to risk of bias and serious imprecision
1 (159) *L. guyanensis*	IM pentamidine isethionate single dose of 7 mg/kg bodyweight	IV or IM pentamidine isethionate 2 or 3 doses	Probably favors pentamidine 2 or 3 doses 96.2% RR 0.47; 95% CI (0.35, 0.64)		No differences were reported in SE	Low Due to risk of bias and imprecision (46)

Physical therapies

Thermotherapy

No. studies	Intervention	Comparator	Cure at least 3 months after treatment	Recurrence	Side effects	Certainty of evidence
1 (44) *L. braziliensis* and *L. mexicana*	Thermotherapy: Three localized heat treatments at 50 °C for 30 seconds, at 7 day intervals	Placebo	Complete cure occurred in 73% (16/22) and 27% (6/22) of participants in the respective groups 2 months after treatment		Four participants developed moderately severe local cellulitis	Very low Due to risk of bias and imprecision (47)
1 (292) *L. panamensis* and *L. braziliensis*	Three localized heat treatments at 50 °C for 30 seconds, at 7 day intervals	IM meglumine antimoniate for 15 days	Favors meglumine antimoniate RR 0.80; 95% CI (0.68, 0.95)		All the participants reported pain at the area up to 4 days after treatment.	Moderate Due to imprecision (41)
1 (294) *L. panamensis* and *L. braziliensis*	Single thermotherapy session that included the application of 50 °C for 30 seconds on the lesion and the surrounding area of each lesion	Oral miltefosine administered for 28 days	There were no differences RR 0.98; 95% CI (0.81, 1.20)		Pain at the site of treatment with thermotherapy and gastrointestinal SE for miltefosine	High (41)

Non-antimonial topical or intralesional therapies

Paromomycin

No. studies	Intervention	Comparator	Cure at least 3 months after treatment	Recurrence	Side effects	Certainty of evidence
1 (76) *L. braziliensis* and *L. mexicana*	Topical paromomycin 15% in 12% methylbenzethonium chloride	Placebo	Favors paromomycin. RR 2.38; 95% CI (1.50, 3.80)	One RCT reported that 3.1% of paromomycin participants experienced reactivation and 0% of the placebo group	It was reported that 58% of participants who received topical paromomycin had SE which disappeared 1 week after treatment	Low Due to very serious imprecision *(49)*
2 (429) *L. panamensis*	Topical paromomycin 15% plus gentamicin 0.5% for 20 days	Paromomycin 15% for 20 days	Differences were not reported. RR 1.19; 95% CI (0.74, 1.91)		Patients on combination therapy had higher SE	Very low Due to risk of bias, indirectness, and heterogeneity *(50, 51)*
1 (80) *L. braziliensis*	Aquaphilic paromomycin applied topically daily for 20 days	Intralesional pentamidine administered on days 1, 3, and 5, and vehicular aquaphilic for 20 days	Cure rates were higher for aquaphilic paromomycin (77.5%: 31/40) than for aquaphilic vehicle. RR 7.75; 95% CI (2.06, 29.17). No differences were reported with the other comparisons.		Grade 1 SE was reported. Intralesional pentamidine was the least tolerated.	Very low Due to risk of bias and imprecision *(52)*

Oral pentoxifylline

No. studies	Intervention	Comparator	Cure at least 3 months after treatment	Recurrence	Side effects	Certainty of evidence
1 (70) *L. braziliensis*	IM meglumine antimoniate (20 mg/kg/day x 20 days) plus oral pentoxifylline 400 mg 3 times daily	IM meglumine antimoniate plus placebo	No differences were reported RR 0.86; 95% CI (0.63, 1.18)		No differences were reported for SE	Low Due to very serious imprecision *(53)*
2 (197) *L. braziliensis*	Pentavalent antimonial administered at a dose of 20 mg/kg daily plus oral pentoxifylline (400 mg)	Pentavalent antimonial administered at a dose of 20 mg/kg daily plus placebo	No differences were reported RR 1.08; 95% CI (0.80, 1.47)		More side effects with pentoxifylline were reported (37.8% vs 23%). Myalgia headache, nausea, and arthralgia	Low Due to risk of bias and imprecision *(54)*

*No evidence was identified for the other prioritized outcomes

Pediatric population

One SR evaluated the efficacy and safety of pharmacological interventions for the treatment of cutaneous leishmaniasis in children over 2 years of age and younger than 12 years (*L. panamensis* and *L. guyanensis*). We included four RCTs and one non-randomized study evaluating patients with cutaneous leishmaniasis in Latin America. No serious adverse events were reported. Three studies (130 patients) evaluated miltefosine at doses of 2.5 mg/kg/day for 28 days divided into three doses for adult and pediatric patients with *L. panamensis*, *L. guyanensis*, and *L. braziliensis*, reporting efficacy between 63.1% to 82.8% regarding complete epithelialization and absence of inflammatory signs for all lesions at day 210 of treatment. Four studies evaluated the efficacy of meglumine antimoniate with 164 patients. The most frequent dose was 20 mg/day IM/IV for 20 days. Efficacy was identified between 55.5% and 75% with high heterogeneity in the population. The certainty of the evidence is very low due to risk of bias and heterogeneity *(56)*.

The Cochrane SR identified two studies *(37, 39)* that evaluated oral miltefosine compared with MA in participants aged between 2 and 12 years old, presenting no differences between groups (RR 1.19; 95% CI [0.98, 1.46], 2 studies, 144 patients). The group of patients receiving miltefosine had more moderate gastrointestinal side effects than patients receiving MA ($p < 0.05$). The certainty of the evidence is low *(20)*. A study from Peru *(57)* that evaluated imiquimod combined with IM/IV MA compared with IM/IV MA for 20 days in pediatric and adult patients (*L. peruviana* and *L. braziliensis*) found no difference in cure at three months (RR 0.87; 95% CI [0.58, 1.30], 40 participants). The certainty of the evidence is very low due to risk of bias, imprecision, and indirect evidence. Another study from the SR *(51)* evaluated topical paromomycin 15% plus gentamicin 0.5% for 20 days with paromomycin 15% for 20 days. No differences were reported in children under 12 years old (RR 0.86; 95% CI [0.74, 1.01]) and between 12 to 17 years old (RR 1.16; 95% CI [0.95, 1.43]) in relation to cure at three months *(50)*. When analyzing meglumine antimoniate 20mg/kg/day for 20 days compared to 10 days, no differences were reported in the subgroup analysis of children under 5 years of age (RR 0.44; 95% CI [0.05, 4.02], 17 patients, 1 study) nor between 5 and 15 years old (RR 0.89%; 95% CI [0.59, 1.34], I^2 55%, 37 patients, 1 study). Lower frequency of arthralgias was reported in the 10-day group (RR 0.34; 95% CI [0.14, 0.81], I^2 0%, 2 studies) and no difference in other side effects. The certainty of the evidence is very low due to risk of bias, imprecision, and heterogeneity for cure rate and low certainty for side effects *(20)*.

Special groups

We identified no evidence for women of childbearing age, pregnancy, immunocompromised, and breastfeeding women.

Factors that improve adherence to treatment of cutaneous leishmaniasis

A clinical trial evaluated the factors associated with adherence to therapy in patients with meglumine antimoniate (MA) in the treatment of cutaneous leishmaniasis in the state of Rio de Janeiro, Brazil. The study included patients with a mean age of 40 years, predominantly men (68.4%), white (61.4%), and resident of endemic areas of Rio de Janeiro (86%). Greater adherence to treatment was reported in the group of patients receiving low doses compared with patients receiving high-dose, consecutive and intermittent schedules, due to easier administration, fewer side effects and, consequently, less modification of daily life. The good relationship of patients with health professionals is also reported as a factor of adherence and explaining the reasons for selecting a treatment with its risks and benefits *(58)*.

Value judgements for the formulation of recommendations

Evidence certainty: The overall certainty of evidence is low and very low due to the risk of bias of the studies (selection bias, lack of blinding, detection bias), very serious imprecision (small sample sizes and confidence intervals exceeding 25% of the estimator), and inconsistency in the findings. Only moderate certainty was reported for the comparison of MA with placebo for the outcome of cure of at least three months. The included studies in the SR *(20)* did not find mortality and loss to follow-up. Even though intralesional antimonial and miltefosine has low certainty evidence, the panel decided to formulate a strong recommendation because other alternatives (such as pentavalent antimonials with moderate certainty) can cause more secondary side effects to the patients and are more painful, whereas intralesional antimonial and miltefosine may be more easily accepted by the patients because of its easier administration (topical and oral).

Benefits and harms: The GDG panel reviewed the different doses used in the Region, the duration of treatment, side effects, and the probability of high adherence by patients. Experts expressed the importance of the safe use of pentavalent antimonials in order to reduce side effects and possible drug resistance; therefore, follow-up and supervision of patients should be a priority. The evidence reports several treatment schemes, and experts agree that they can be used in individualized situations taking into account the risk–benefit and patients' preferences. The use of MA for 20 days or 10 days shows the same efficacy and lower SE, so it

can be a scheme to use in remote areas, where short schemes may have better adherence, making it easier to complete treatment and follow patients.

Regarding miltefosine, in terms of effectiveness, it is very similar to MA and has the fundamental advantage of being oral and more accepted by adult and pediatric patients. The only point that requires monitoring is its use in women of childbearing age (which is a minority group in the total patients with CL), seeing that the drug must be administered with contraception methods and safety needs to be evaluated, as it is a teratogenic drug.

Local treatment of CL patients should be the first option, especially for the pediatric population, because systemic treatments can be more painful. Thermotherapy and cryotherapy are available, which can be used by trained personnel maintaining the recommended scheme to ensure their effectiveness and safety.

Use of resources: The panel reports that the management of leishmaniasis can involve significant costs for patients due to multiple and expensive trips to the health service for the administration of medications given the long duration of treatment. In rural health centers, sometimes, systemic treatment is not administered, so patients and their companions must incur higher costs and therefore this could lead to less adherence to treatment. For institutions providing health services, costs arise in the payment of fees for trained personnel, or investment in training, as well as inputs such as syringes to provide adequate care to patients. It was identified that there is a high turnover of health personnel, so training of new professionals in necessary, increasing the costs of providing services.

Evidence was identified in the Cochrane SR for ketoconazole, fluconazole, and allopurinol. However, the clinical experts consider that those interventions are outdated, some of them are not available, and that there are other interventions to recommend to the patients.

A 2017 cost analysis study compared systemic pentavalent antimonials with intralesional antimonials as the first line of CL treatment in Bolivia. Intralesional pentavalent antimonials presented a saving of US$ 248 per patient treated according to the payment made by the Ministry of Health and US$ 688 saved from the society point of view *(59)*. Another cost-effectiveness study evaluated intralesional MA therapy compared to intravenous therapy in the Brazilian health system, reporting that the costs per cured patient were US$ 330.81 for intralesional and US$ 494.16 for intravenous per patient in 2018. The incremental cost-effectiveness ratio showed that intralesional MA can result in a US$ 864.37 saving for each additional patient cured *(60)*. One study evaluated the cost-effectiveness of thermotherapy compared to MA in CL treatment. It was found that the cost of MA per patient was $66,807 Colombian pesos compared to $14,079 for thermotherapy *(61)*.

Patient preference: A qualitative study in three Colombian cities near the Amazon reported that more than 60% of the population had scars consistent with cutaneous leishmaniasis and

had not sought treatment in health centers because of lack of knowledge about the possibility of obtaining adequate treatment in a health service institution; they went to pharmacies or neighbors to use topical creams; or the belief, in conflict zones, that leishmaniasis is the "guerrilla's disease" and that, therefore, the treatment is controlled by the army or they may have problems with the authorities *(62)*. Another study reports that since cutaneous leishmaniasis is not a disabling disease, and the injury usually does not hurt (unless infected), affected people do not seek medical attention *(63)*. Several studies also report that many patients go to healers or use traditional medicine with plants or caustic remedies as the first option for cutaneous leishmaniasis treatment, because there is a negative perception of treatment with pentavalent antimonials due to pain, fear of injections, and side effects; also, they suffer the consequences of social stigma due to their association of leishmaniasis with armed conflict and contexts of poverty and social vulnerability. It is also reported that patients can self-medicate when they have access to medications, which can lead to using ineffective therapeutic doses and to increased side effects *(63)*. Another reason for not attending health services as a first option is the difficulty of access in terms of distance, costs, and bad experiences reported by family members or neighbors *(62)*.

Experts report that children present pain, fear of injections, and crying, so it is recommended that the first option is oral treatment and not to use systemic treatments *(63)*.

Applicability and impact on equity: It is deemed, among the experts of the Region, important to start treatment quickly (considering the local epidemiology) in order not to lose the opportunity for treatment, especially for patients who attend health services far from their home; however, diagnosis should be made. Difficulties of access and follow-up in remote areas are reported, which can have an impact on equity.

The panel discussed that it is not possible to obtain pentamidine in several countries of the Region, and it is reported that it can be acquired through PAHO's Strategic Fund. Furthermore, it was mentioned that miltefosine is an expensive medication, seeing that it is the only oral alternative and produced by a single laboratory. Currently there is no agreement between the provider and WHO to reduce its cost for use in public health programs. On the other hand, despite the recommendation of use of paromomycin cream by the experts, that alternative is currently commercially unavailable for purchase.

Mucosal or mucocutaneous leishmaniasis

Question 2

Mucosal or mucocutaneous leishmaniasis

What is the efficacy and safety of the different pharmacological treatments for the management of patients diagnosed with mucosal leishmaniasis in the Americas?

RECOMMENDATION

The use of pentavalent antimonials with or without oral pentoxifylline is recommended to treat patients with mucosal or mucocutaneous leishmaniasis.

Strong recommendation, low and very low certainty evidence

Note: The treatment scheme, administration route, and indications are found in the Implementation, Adaptation, Dissemination, and Pharmacological Interventions section (Tables 6 and 8).

BEST PRACTICE STATEMENTS

Decision-making about the therapeutic strategy to be used in patients diagnosed with mucosal or mucocutaneous leishmaniasis should be shared with the patients based on the clear explanation of the risks and benefits of the available alternatives.

The clinical course of mucosal or mucocutaneous leishmaniasis is complex and requires care and follow-up during and after treatment. Health personnel should monitor the treatment of patients and side effects.

BEST PRACTICE STATEMENTS

To treat the following special cases of patients with mucosal or mucocutaneous leishmaniasis, it is suggested:

- **Pregnant women:** Refer to the reference center. The medication suggested is liposomal amphotericin B or other formulations of amphotericin B. The use of pentavalent antimonials, miltefosine, and pentamidine is contraindicated.
- **Breastfeeding women:** Use of liposomal amphotericin B and pentavalent antimonials, ensuring contraception.
- **Patients with electrocardiogram alteration:** Administer treatments with miltefosine or amphotericin B. The use of pentavalent antimonials and pentamidine isethionate is contraindicated.
- **Patients with kidney disease, liver disease, heart disease:** The use of liposomal amphotericin B is suggested.
- **Comorbidity with tuberculosis:** It is suggested to take special care in monitoring adverse events, especially when deciding to use the two treatments concomitantly (tuberculosis and leishmaniasis).
- **Patients with HIV and other causes of immunosuppression:** Liposomal amphotericin B or other formulations of amphotericin B are suggested.
- **Patients over 50 years old:** Perform a careful clinical evaluation of each case. The use of pentavalent antimonials should be avoided in patients over 50 years old.
- **Patients with therapeutic failure:** Administer any of the recommended treatments other than the one initially used, by assessing the risk–benefit on an individualized basis.

Note: The treatment scheme, administration route, and indications are found in the Implementation, Adaptation, Dissemination, and Pharmacological Interventions section (Tables 7 and 8).

Evidence

We identified a Cochrane SR that evaluated all pharmacological interventions for the treatment of patients diagnosed with mucosal or mucocutaneous leishmaniasis (ML) from the Americas. We updated the RCTs without finding new studies. The SR by Pinart et al. (2000) included eight randomized controlled trials evaluating ML in ages 22 to 77 years. The lesions were mainly found in the nose or oral cavity. The lesions were mainly ulcerative or infiltrated. Below, we present the evidence reported in the SR by type of intervention *(20).*

Pentavalent antimonials

An SR evaluated the different intravenous N-methyl-glucamine antimoniate regimens (14 mg/kg/day in two 20-day series for the cutaneous leishmaniasis form or three 30-day series in the mucocutaneous form). We identified two studies with 89 participants with no differences in cure rates, doses, or effect on any form of leishmaniasis ($p > 0.05$). An RCT of 40 participants from Peru compared intravenous sodium stibogluconate (IV SS) for 28 days with IV SS for 40 days. One year after the treatment, there was no clear difference between cure rates (RR 0.83; 95% CI [0.47, 1.47]) in infections caused by *L. braziliensis*. No discontinuation of treatment was reported. Side effects were arthralgias, myalgias, itching, rash, nausea, anorexia, abdominal pain, cough, and headache in patients treated for 40 days *(33)*. The overall certainty of the evidence is very low due to the risk of bias and imprecision *(20).*

Non-antimonial systemic treatments

The SR identified an RCT that included 81 participants with mucocutaneous leishmaniasis from Peru which compared oral allopurinol (20 mg/kg/day) combined with IV SS versus IV SS only for 28 days. One year after treatment, there was a probably higher cure rate at least three months after treatment in patients receiving allopurinol and IV SS (RR 0.62; 95% CI [0.38, 1.03]). No differences in recurrence were reported. The most frequent SE were headache (81.5% of the participants), arthralgia (75.3%), myalgia (67.9%), chills (42%), fever (39.5%), abdominal pain (33.3%), and anorexia (25.9%) *(63).* Two studies evaluated oral miltefosine versus pentavalent antimonials in participants with mucosal leishmaniasis without reporting differences in cure rates at three months (RR 1.04; 95% CI [0.81, 1.34]; 40 participants; I^2 0%). Gastrointestinal effects (nausea, vomiting, and epigastric pain) were higher in patients receiving miltefosine (RR 2.97; 95%CI [1.05, 8.38]) *(64, 65).* The certainty of the evidence is low due to imprecision and the risk of bias.

Another RCT from the SR compared intramuscular aminosidine sulfate (IM AS) for 28 days with meglumine antimoniate for 28 days in patients with *L. braziliensis*. One year after treatment, IM AS 14 mg/kg/day for 28 days had significantly lower cure rates than MA 20 mg/kg/day for 28 days (RR 0.05; 95% CI [0.00, 0.78]). Participants in the IV MA group had mild transient electrocardiogram abnormalities that did not require therapeutic intervention. Fever, chills, arthralgia, anorexia, and myalgia were observed equally in both treatment groups *(63).*

Another RCT compared the addition of an oral rehydration solution (ORS) with the addition of intravenous saline solution (SAS) to the intravenous amphotericin B treatment, to prevent nephrotoxicity. No differences were reported in cure rates. No differences were found in serum creatinine, creatinine clearance, urea, and sodium values during treatment, but serum potassium

values were lower in the SAS group than in the ORS group. Hypokalemia was much less frequent in the oral rehydration solution group (RR 0.39; 95% CI [0.18, 0.85]; 48 patients) *(66)*. The first version of the guideline makes recommendations for special cases or patients with therapeutic failure based on very low certainty evidence for IV amphotericin B deoxycholate, IM pentamidine isethionate, IV liposomal amphotericin B, amphotericin B deoxycholate, and oral miltefosine *(15)*.

The overall certainty of the evidence is low and very low due to risk of bias and imprecision.

Immunochemotherapy

An RCT from the SR evaluated oral pentoxifylline combined with IV SS with IV SS for 30 days in patients with *L. braziliensis*. Four months after treatment, oral pentoxifylline had a significant synergistic effect with IV SS of 20 mg/kg/day for 30 days in *L. braziliensis* (RR 1.66; 95% CI [1.03, 2.69]; 23 patients). Mild adverse effects were most frequently observed in the pentoxifylline group. Healing speed was shorter in the pentoxifylline group combined with IV SS (MD −62.00; 95% CI [−121.92, −2.08]) *(67)*. The certainty of the evidence is very low due to risk of bias and imprecision.

Special groups

We identified no evidence for women of childbearing age, pregnancy, immunocompromised, breastfeeding women; nor by age group.

Value judgements for the formulation of recommendations

Evidence certainty: The overall certainty of evidence is low and very low due to the risk of bias of the studies (selection bias, lack of blinding, detection bias), and very serious imprecision (small sample sizes and confidence intervals exceeding 25% of the estimator). Even though pentavalent antimonials with or without oral pentoxifylline have low and very low certainty, the panel formulated a strong recommendation because it is the only available therapeutic option, and the panel wanted to ensure that the patients received the recommended treatment.

Benefits and harms: Mucosal or mucocutaneous leishmaniasis is a disease that has a high degree of relapse, regardless of the medication used, so the GDG panel reiterates the importance of proper follow-up and use of the therapeutic scheme that is well tolerated by patients. Experts considered the combination of pentavalent antimonials with pentoxifylline to be a good alternative for patients. Also, it is recognized that there is very little evidence in

ML, but the therapeutic options are those currently used in the Region with better results. Considering that most cases occur among patients between the sixth and seventh decade of life, liposomal amphotericin B, despite efficacy sustained by small series of cases, has been considered the alternative with the best benefit–risk ratio.

Use of resources: Experts report that liposomal amphotericin B is expensive in the countries of the Region, when not acquired with subsidized prices from the agreement with WHO; therefore, along with the availability of other alternatives and evidence, it is currently not recommended for patients with mucosal leishmaniasis. Pentavalent antimonials and pentamidine isethionate are included in the benefit plans of most countries. Costs may be incurred for patients, especially in rural areas because they must make several trips outside their geographic area to receive the treatment that generally requires hospitalization.

Patient preference: Patients with mucosal or mucocutaneous leishmaniasis report feeling low self-esteem because this clinical form can cause deformities or mutilations, so they prefer treatments that are shorter, and it is important to consider the patient's acceptance so that adherence to treatment is increased. A few studies also report that many patients go to healers or use traditional medicine with plants or caustic remedies as the first option of leishmaniasis treatment, because there is a negative perception of pentavalent antimonials treatment due to pain, fear of injections, and side effects *(61, 68).*

Applicability and impact on equity: It is reported that in most countries of the Region, pentavalent antimonial is the first choice of treatment in cases of mucosal or mucocutaneous leishmaniasis, so the recommendation can be easily accepted by health professionals, and, seeing that it is easily available in the Region, the recommendations do not have an impact on equity.

Visceral leishmaniasis

Question 3

Visceral leishmaniasis in non-immunocompromised patients

What is the efficacy and safety of the different pharmacological treatments for the management of non-immunocompromised patients diagnosed with visceral leishmaniasis in the Americas?

RECOMMENDATIONS
The use of liposomal amphotericin B is recommended in pediatric and adult non-immunocompromised patients to treat visceral leishmaniasis. **Strong recommendation, low certainty evidence**
The administration of pentavalent antimonials or other formulations of amphotericin B is suggested in pediatric and adult non-immunocompromised patients to treat visceral leishmaniasis. **Conditional recommendation, low certainty evidence**
We recommend against the use of miltefosine in pediatric and adult patients to treat visceral leishmaniasis. **Strong recommendation against, very low certainty evidence**

Note: The treatment scheme, administration route, and indications are found in the Implementation, Adaptation, Dissemination, and Pharmacological Interventions section (Table 9).

BEST PRACTICE STATEMENTS

For the treatment of visceral leishmaniasis (VL), the selection of the drug should consider the toxicity profile and the risk of death associated with the disease.

Given the impossibility of using liposomal amphotericin B for the situations described below, the therapeutic alternative is the use of other lipid formulations of amphotericin B.

- Age over 50 and under 1 year old
- Kidney failure
- Liver failure
- Heart failure
- Corrected QT interval greater than 450 ms
- Concomitant use of drugs that alter the QT interval
- Hypersensitivity to pentavalent antimonials or other medication used for the treatment of VL
- Therapeutic failure to pentavalent antimonials or other drugs used for the treatment of VL
- Pregnant and breastfeeding women.

Note: If the use of liposomal or lipid amphotericin B formulations is not possible, administer amphotericin B deoxycholate, with strict monitoring of toxicity.

Note: When using liposomal amphotericin B, and other formulations, it is important to carry out strict monitoring of renal functions of non-immunocompromised VL patients.

The clinical course of patients with visceral leishmaniasis is complex and requires supportive measures and experience in managing complications and toxicity caused by treatment. Therefore, it is suggested that the treatment be carried out in hospital, allowing the appropriate interventions to improve the prognosis and avoid lethality due to the disease.

Note: The treatment scheme, administration route, and indications are found in the Implementation, Adaptation, Dissemination, and Pharmacological Interventions section (Table 9).

Evidence

Pentavalent antimonials, amphotericin B deoxycholate, and liposomal amphotericin B

No SR was identified to answer the question. We identified two RCTs that evaluated amphotericin B compared to pentavalent antimonials in adult and pediatric patients.

An open RCT evaluated the efficacy and safety of N-methyl glucamine antimoniate (20 mg/kg/day for 20 days) and amphotericin B deoxycholate (1 mg/kg/day for 14 days) in 101 pediatric patients (6 months to 12 years old) and adults newly diagnosed with VL without signs

of severe disease. No differences in complete cure were found between the groups (RR 1.00; 95% CI [0.91, 1.10]); nor relapse at 180 days (RR 7.54; 95% CI [0.15, 378]). The fever resolution time was shorter in the pentavalent antimonial group (43.1%) compared with the amphotericin B group (16%), $p < 0.01$. Differences were observed in the size of the spleen, 3 cm vs 3.75 cm, $p < 0.01$. No differences were found in the biochemical and hematological indicators normalization time. Side effects were similar between groups. Patients who received pentavalent antimonials had a higher frequency of serious side effects that resulted in treatment discontinuation. The certainty of the evidence is low due to risk of bias and imprecision *(69).*

An RCT developed in Brazil evaluated the efficacy and safety of amphotericin B deoxycholate (1 mg/kg/day for 14 days), liposomal amphotericin B (LAB) (3 mg/kg/day for 7 days), and combination of LAB (10 mg/kg single dose) plus meglumine antimoniate (20 mg Sb^{+5}/kg/day for 10 days) compared with meglumine antimoniate (20 mg/kg/day for 20 days) in 220 patients aged 6 months to 50 years old diagnosed with VL and without HIV coinfection. High toxicity was reported in the first group, which led to the end of the study for this group of patients. No differences were reported between the groups compared with MA: LAB (9.7%; 95% CI [−0.28, 19.68]), $p = 0.06$) and LAB+MA (6.4%; 95% CI [−3.93, 16.73] $p = 0.222$) regarding differences in cure rate. LAB monotherapy has a lower frequency of side effects. The certainty of the evidence is low *(70).*

Miltefosine

We identified an open phase II study that evaluated the efficacy and safety of oral miltefosine for VL in Brazil caused by *L. infantum*, using escalated doses in children aged 2 to 12 years old and 40 adolescents/adults between 13 and 60 years old, in two care settings. Complete cure was evaluated within six months of follow-up, finding a cure rate of 42% (14 patients) at 28 days of treatment and 68% (28 patients) at 42 days of treatment. There were no side effects. The certainty of the evidence is very low due to risk of bias and imprecision *(71).*

Special groups

We identified no evidence for women of childbearing age, pregnancy, immunocompromised, breastfeeding women; nor by age group. Given the scarce evidence, no best practice statements were formulated.

Value judgements for the formulation of recommendations

Evidence certainty: The overall certainty of evidence is low and very low due to the risk of bias of the studies (selection bias, lack of blinding, detection bias), and very serious imprecision (small sample sizes and confidence intervals exceeding 25% of the estimator). Even though the use of liposomal amphotericin B has low certainty, the panel formulated a strong recommendation because it is the safest therapeutic option compared with pentavalent antimonials, which present more adverse events in the patients, and the administration is more painful, so it is not the first choice for the patients.

Benefits and harms: The evidence supports the use of liposomal amphotericin B for its being safer, which also helps to decrease the number of treatment interruptions. It is important to note that, once toxicity has been overcome, patients are completely cured. In terms of management, it is known that the management of amphotericin B toxicity (liposomal/deoxycholate) is easier than pentavalent antimonials (PA) toxicity, and the duration of treatment with amphotericin B (liposomal/deoxycholate) is shorter than PA. There is no evidence of efficacy for miltefosine, and a study in the Brazilian population of Piauí and Minas Gerais showed a natural resistance to the drug, which explains its low effectiveness compared to India. Its efficacy is less than PA so it should not be used for VL in the Americas. The GDG panel generally considers that the risks outweigh the benefits of the recommendations.

Use of resources: The GDG panel considers that liposomal amphotericin B is expensive when acquired nationally and still of little access in the countries of the Region, but it is the best therapeutic strategy for adult and pediatric patients in the Americas; therefore, acquiring that drug through the PAHO Strategic Fund is the option, due to the subsidized price through the agreement between the provider and WHO. As a second option, there are the other formulations of amphotericin B (lipids and deoxycholate) and the PA, which are included in regional benefit plans.

A cost-effectiveness study conducted in Brazil evaluated meglumine antimoniate (MA), liposomal amphotericin B (LAB) and their combination for the treatment of visceral leishmaniasis. LAB was more cost effective, followed by the MA plus LAB combination. When comparing LAB and MA, a saving of US$ 278.56 was reported for LAB for each therapeutic failure avoided, US$ 26.88 for each day of hospitalization, and US$ 89.88 for each VL case cured *(72)*.

Patient preference: We found no evidence of VL patient preferences in non-immunocompromised patients in the Americas. The GDG panel considers that patients would prefer the most effective therapeutic alternative with fewer side effects and shorter treatment.

Applicability and impact on equity: It is considered that recommendations can be easily accepted by clinical experts and decisionmakers in the Region. The recommendations may have an impact on equity because it is assumed that all patients can receive treatment; however, given that it must be provided in a specialized setting, it is likely that the interventions would be more limited for people in remote areas.

Question 4

Visceral leishmaniasis in immunocompromised patients

What is the efficacy and safety of the different pharmacological treatments for the management of immunocompromised patients diagnosed with visceral leishmaniasis in the Americas?

RECOMMENDATIONS

The use of liposomal amphotericin B is recommended for the treatment of immunocompromised patients with visceral leishmaniasis.

Strong recommendation, very low certainty evidence

We recommend against the use of pentavalent antimonials for the treatment of immunocompromised patients with visceral leishmaniasis.

Strong recommendation against, very low certainty evidence

The use of amphotericin B lipid complex/deoxycholate is recommended when liposomal amphotericin B is not available for the treatment of immunocompromised patients with visceral leishmaniasis.

Strong recommendation, very low certainty evidence

Note: The treatment scheme, administration route, and indications are found in the Implementation, Adaptation, Dissemination, and Pharmacological Interventions section (Table 10).

BEST PRACTICE STATEMENT

The clinical course of patients with visceral leishmaniasis in immunocompromised patients is complex and requires supportive measures and experience in managing complications and toxicity caused by treatment. Therefore, it is suggested that the treatment be carried out in hospital, allowing the appropriate interventions to improve the prognosis and avoid lethality due to the disease.

Note: When using liposomal amphotericin B and other formulations, it is important to carry out strict monitoring of renal function of immunocompromised VL patients.

Evidence

Liposomal amphotericin B and pentavalent antimonials

No SR was identified that answered the question, nor were studies developed in the Region. We identified two clinical trials (CT) conducted in Spain. Two CTs evaluated high doses of liposomal amphotericin B (3 mg/kg/day) compared with standard doses of pentavalent antimonials in VL patients infected with HIV. No differences were reported in complete cure (RR 0.96; 95% [CI 0.72, 1.29]), treatment abandonment (RR 1.28; 95% CI [0.02, 69.15]), death (RR 0.57; 95% CI [0.10, 3.36]), side effects (RR 0.60; 95% CI [0.11, 3.39]), or relapses (RR 0.87; 95% CI [0.51, 1.48]). The certainty of the evidence is very low due to risk of bias, indirect evidence, heterogeneity, and imprecision *(73, 74)*.

We identified a retrospective cohort that evaluated the efficacy of liposomal amphotericin B in the treatment of visceral leishmaniasis in HIV-coinfected patients in Brazil, from January 2010 to June 2017. Evidence reports that at the end of treatment, 83.8% of participants showed clinical improvement (196/239), 3.8% (9/239) showed treatment failure, and 12.4% died (29/239), with no difference between treatment groups (p = 0.247). Of these 29 participants, 16 died without completing treatment, with the majority (11 or 68.7%) in the treatment group <20 mg/kg, 3 in the treatment group from 20 to <30 mg/kg, and 1 in the groups from 30 to <40mg/kg and >40mg/kg (p = 0.125). There were also no differences in recurrence (p = 0.182), therapeutic failure (p = 0.816), and any unfavorable outcome (p = 0.356). The following risk factors for death were identified: time between the diagnosis of HIV and VL, presence of concomitant opportunistic infections, concomitant tuberculosis, absence of splenomegaly, absence of use of secondary prophylaxis, absence of use of blood products (p < 0.05). The certainty of the evidence is low.

Special groups

No evidence was identified for women of childbearing age, pregnancy, immunocompromised, breastfeeding women; nor by age group. Given the scarce evidence, no best practice statements were formulated.

Value judgements for the formulation of recommendations

Evidence certainty: The overall certainty of evidence is low and very low due to the risk of bias of the studies (selection bias, lack of blinding, detection bias) and very serious imprecision (small sample sizes and confidence intervals exceeding 25% of the estimator). It is also affected

by indirect evidence, because the studies were conducted in Spain, but the steering group considered that they can be extrapolated to the Latin American context, seeing that it is the same species of *Leishmania*. Even though liposomal amphotericin B and amphotericin B lipid complex/deoxycholate have very low certainty, the panel formulated a strong recommendation because is the only therapeutic option, and the panel wanted to ensure that the patients received the recommended treatment. Also, the panel considered that new evidence may not change the recommendation.

Benefits and harms: With respect to the evidence of coinfected patients, the two trials identified are European, and currently there are no comparative randomized trials to elucidate this issue in the Americas. The panel considers that amphotericin B has less toxicity than pentavalent antimonials, and so these should not be used in immunocompromised patients with VL. It is important to create a directive for immunosuppressed patients other than those with HIV infection, so a best practice statement was generated. When administering amphotericin B, it is important to review the safety profile and provide the lowest effective dose. It is recommended to take special care in patients with organ deficiencies, such as renal, where the toxicity profile of liposomal amphotericin B is increased. Given that there are few therapeutic options with very low certainty, the GDG decided to formulate strong recommendations because is neither safe nor ethical to provide no treatment.

Use of resources: The GDG considers that liposomal amphotericin B is expensive and difficult for the countries of the Region to access, but it is the best therapeutic strategy for immunocompromised adult and pediatric patients in the Americas. Gilead currently has an agreement with WHO on a grant for liposomal amphotericin B for the treatment of systemic VL and mycosis. Currently, the PAHO Strategic Fund makes it available to all countries with a price of US$ 16.50 per 50 mg vial, and this agreement remains in force for at least five more years. However, there is currently difficulty in the production of liposomals as there is only one supplier, which is in the process of building a new plant to produce the drug to serve the endemic countries. There is information that production will become regular by 2022. On the other hand, there is also an initiative for the development of generic liposomal amphotericin B from DNDi along with WHO.

Patient preference: We found no evidence of VL patient preferences in immunocompromised patients in the Americas. The GDG considers that patients would prefer the most effective therapeutic alternative with fewer side effects and shorter treatment.

Applicability and impact on equity: It is considered that recommendations can be easily accepted by clinical experts and decisionmakers in the region. Difficulties will be encountered in accessing liposomal amphotericin B, but it is hoped that access can be provided by strengthening drug production and distribution policies.

Question 5

Secondary prophylaxis for visceral leishmaniasis in immunocompromised patients

What is the efficacy and safety of secondary prophylaxis for the management of immunocompromised patients diagnosed with visceral leishmaniasis in the Americas?

RECOMMENDATION

The administration of liposomal amphotericin B is recommended for secondary prophylaxis in patients with HIV–visceral leishmaniasis coinfection after the first episode of visceral leishmaniasis, in all patients with a CD4 T-cell count less than 350 per mm^3.

Strong recommendation, very low certainty evidence

Note: The treatment scheme, administration route, and indications are found in the Implementation, Adaptation, Dissemination, and Pharmacological Interventions section (Table 11).

BEST PRACTICE STATEMENTS

For patients who are transplanted or have other immune-debilitating conditions not related to HIV, the indication of secondary prophylaxis after treatment of the first episode of visceral leishmaniasis should be evaluated on a case-by-case basis, based on the intensity of immunosuppression, and preferably in reference services. When secondary prophylaxis is not indicated, frequent clinical follow-up is recommended.

BEST PRACTICE STATEMENTS

The clinical course of patients with visceral leishmaniasis in immunocompromised patients is complex and requires supportive measures and experience in managing complications and toxicity caused by treatment. Therefore, it is suggested that the treatment be carried out in hospital, allowing the appropriate interventions to improve the prognosis and avoid lethality due to the disease.

Note: When using liposomal amphotericin B, and other formulations, it is important to carry out strict monitoring of renal function of immunocompromised VL patients.

Evidence

Liposomal amphotericin B and amphotericin B lipid complex

No SR were identified. We selected one clinical trial that evaluated the efficacy of liposomal amphotericin B (3 mg/kg/day) compared with not performing secondary prophylaxis treatment in 17 Spanish patients with VL–HIV coinfection. In the trail, 50% of participants remained free of VL events at one year of follow-up (95% CI [15.7, 84.3]) in the amphotericin B group and 22.2% in the untreated group (95% CI [2.8, 60]) (p = 0.141). The amphotericin B group had more mild side effects (88%) which were tolerated by participants compared to the control group (33%) (p = 0.0032). The certainty of the evidence is very low due to risk of bias and inaccuracy *(75)*.

We also identified one study, developed in Spain, without a control group, which evaluated the efficacy of liposomal amphotericin B 4 mg/kg/day for 5 consecutive days and once a week for 5 weeks for secondary VL prophylaxis in 15 VL–HIV coinfected patients who have received at least one dose of amphotericin B as treatment. The probability of remaining relapse-free at 6 months was 89.7% (95% CI [76.2, 100]), at 12 months it was 79.1% (95% CI [61, 97.2]), and 24–36 months was 55% (95% CI [30.5, 81.3]); 20% of the patients presented a moderate deficiency of renal function without the need for modification of treatment. The study was conducted in Spain. The certainty of the evidence is very low due to high risk of bias and indirect evidence *(76)*.

Special groups

No evidence was identified for women of childbearing age, pregnancy, immunocompromised, breastfeeding women; nor by age group. Given the scarce evidence, no best practice statements were formulated.

Value judgements for the formulation of recommendations

Evidence certainty: The overall certainty of evidence is low and very low due to the risk of bias of the studies (selection bias, lack of blinding, detection bias), and very serious imprecision (small sample sizes and confidence intervals exceeding 25% of the estimator). It is also affected by indirect evidence, because the studies were conducted in Spain, but the steering group considered that it can be extrapolated to the Latin American context, seeing that it is the same species of *Leishmania*. Even though liposomal amphotericin B has very low certainty, the panel formulated a strong recommendation because it is the only therapeutic option, and the panel wanted to ensure that the patients received the recommended treatment. Also, the panel considered that new evidence may not change the recommendation.

Benefits and harms: The GDG considers that the benefit of the intervention is greater than the risk; therefore, a strong recommendation was formulated. There was no evidence for immunocompromised patients due to HIV, so the GDG updated the best practice statements of the previous version of the guideline.

Use of resources: The GDG considers that liposomal amphotericin B is expensive and difficult for the countries of the Region to access, but it is the best therapeutic strategy for immunocompromised adult and pediatric patients in the Americas. Gilead currently has an agreement with WHO on a grant for liposomal amphotericin B for prophylaxis. Currently, the PAHO Strategic Fund makes it available to all countries with a price of US$ 16.50 per 50 mg vial, and this agreement remains in force for at least five more years. However, there is currently difficulty in the production of liposomals as there is only one supplier, which is in the process of building a new plant to produce the drug to serve the endemic countries. There is information that production will become regular by 2022. On the other hand, there is also an initiative for the development of generic liposomal amphotericin B from DNDi with WHO.

Patient preference: We found no evidence of VL patient preferences in immunocompromised patients in the Americas. The GDG considers that patients would prefer the most effective therapeutic alternative with fewer side effects and shorter treatment.

Applicability and impact on equity: It is considered that recommendations can be easily accepted by clinical experts and decisionmakers in the Region. Difficulties will be encountered in accessing liposomal amphotericin B, but it is hoped that access can be provided by strengthening drug production and distribution policies.

Implementation, **adaptation, dissemination,** and pharmacological interventions

Implementation, adaptation, dissemination, and pharmacological interventions

Implementation and adaptation

The ministries of health or their equivalents may incorporate current therapeutic recommendations for leishmaniasis in the Americas, considering the local context, treatment accessibility, operational capacity of health services, and the risks and benefits of interventions, according to the clinical status of the patient. On the other hand, PAHO will work with the national staff of the Evidence-Informed Policy Network, which promotes national mechanisms to facilitate the use of evidence obtained through research to support the decision-making process, facilitating the incorporation of medicines and implementation of recommendations.

Adherence by patients is decisive for the success of treatment; therefore, it is important that health professionals reinforce that the treatment is followed as recommended and that health policies are strengthened to provide access to medicines at no cost, as well as to facilitate the mobilization of the patients to receive the prescribed treatment scheme, offer oral treatment for the pediatric population and patients living in remote areas, as well as have available therapeutic alternatives for patients in special situations.

PAHO, through the Strategic Fund, works together with countries to provide technical advice and support in the provision of the medicines needed for the management of leishmaniasis in the Americas. Except for paromomycin, the other recommended antileishmanial medicines are incorporated in the Strategic Fund. Furthermore, the drug acquisition process by the countries was reviewed in 2020, and currently there are annual planning mechanisms for regional demands to guarantee the supply of products and meet national needs in quantity and time, which also results in the reduction of cost and availability to the Region. Despite being an excellent support

mechanism for the countries, the implementation of therapeutic recommendations for leishmaniasis will be incorporated gradually and differently between countries, especially when there still are products with high prices, such as oral medicines.

It is important to promote training in the management of leishmaniasis for health professionals who provide care in endemic areas, and in medical and nursing schools so that professionals have the appropriate knowledge.

Health services can demystify perceptions about leishmaniasis and promote seeking medical attention as a first option when an individual finds lesions on the body, and thus conduct the laboratory diagnosis and, if confirmed, start treatment early. In addition, it is important to monitor and evaluate treatment (cure/therapeutic failure), as many patients receive treatment but do not have a follow-up visit to assess the clinical outcome.

In several countries, joint work is being done with community leaders and health services to provide information on what to do with possible emerging cases, what strategies for therapeutic interventions exist, and how they can access them. There is also joint work with scientific societies and support organizations to disseminate and train health personnel who care for patients, seeking to provide adequate management, as well as strengthen national programs.

It is important to encourage identification and research in post-kala-azar and para-kala-azar dermal leishmaniasis in the Region to generate evidence on the efficacy and safety of pharmacological interventions for its treatment.

Experts report that it is important to mention in the recommendations that drugs such as pentamidine isethionate and pentavalent antimonials, should not be used in remote areas and primary care centers, but in second-level or specialized services that may have trained personnel to provide specialized care to ensure the safety of patients. Also, it is essential to have the knowledge on the most effective treatment schemes and types of *Leishmania* in order to maximize the effectiveness of the treatment. To this end, tables were constructed that present the effective and safe therapeutic doses and guidelines for their use by level of care, type of *Leishmania*, and other special considerations. These tables were constructed from the evidence and experience of the panel.

Dissemination

The Guideline for the Treatment of Leishmaniasis in the Americas in its updated version will be published in English, Spanish, and Portuguese, as these are the official languages of the countries in which this disease is endemic in the Region. Its dissemination and availability will be made only in the electronic version, complying with the current internal policies of the Organization to eliminate printed publications, moving toward digital information products.

As a strategy to disseminate this guideline, PAHO will be widely disseminating it on social networks, to regional partners, including the offices of the PAHO Representation in each country, the ministries of health of the Member States, the collaborating centers and reference services for leishmaniasis, universities and research centers, and nongovernmental organizations, among others.

Through the Regional Leishmaniasis Program, these guidelines will be presented to the countries at regional leishmaniasis meetings, technical and scientific seminars, national and regional congresses on parasitology, tropical medicine, and infectious diseases, as well as the World Congress on Leishmaniasis.

Other strategies for disseminating the therapeutic recommendations are through training of health professionals using face-to-face or distance modalities. With the support of the Latin American and Caribbean Center on Health Sciences Information (BIREME, PAHO/WHO Specialized Center), and the PAHO/WHO Virtual Campus for Public Health, the online virtual courses on Leishmaniasis in the Americas: Diagnosis and Treatment will be reviewed, revised to include the updated recommendations, and made available on the Virtual Campus for Public Health. In addition, technical documents prepared by PAHO/WHO that include the treatment recommendations will be updated, such as the Manual of Procedures for Surveillance and Control of Leishmaniasis in the Americas and the Interactive Atlas of Leishmaniasis in the Americas: Clinical Aspects and Differential Diagnosis.

Implementation of pharmacological interventions

It is important to know the recommendation, dosage, administration route, and level of care in order to provide effective treatment to the leishmaniasis patients in the Americas. The following tables present this information as a tool for health care professionals, patients, and policymakers in different settings. The tables were based on the experience of the guideline development group and the evidence available.

TABLE 2

Local treatments for the management of adult patients with cutaneous leishmaniasis

The criteria for indication of local treatment are: 1 to 3 lesions up to 900 mm^2 (largest diameter 3 cm). Lesions located in any location, except head and periarticular regions, absence of immunosuppression, and possibility of follow-up.

Intervention	Form of administration	Scheme	Species	Certainty of evidence References
Intralesional antimonials	Subcutaneous injection	3–5 infiltrations of 1–5 ml per lesion (depending on the size of the lesion; the amount used is what is needed to cover each lesion). Interval of 3–7 days between sessions. Classically, the infiltration technique described requires the volume necessary to achieve the saturation of the lesion, which is understood as complete swelling of the lesion. It is suggested not to exceed the total volume of 15 ml infiltrated/day considering all lesions.	*L. braziliensis* *L. amazonensis*	Low *(21, 77)*
Thermotherapy	Application of local heat with electromagnetic device generating high frequency waves	After local anesthesia, the electrode is applied at 50 °C for periods of 30 seconds, in the center and at the edge of the lesion. One session with the number of applications needed to cover the entire lesion.	*L. braziliensis* *L. mexicana* *L. panamensis*	Very low *(41, 47, 48)*
Paromomycin	Topical cream 15%	Application to the affected area once a day for 20 days	*L. panamensis* *L. braziliensis* *L. mexicana*	Very low *(49–51)*

TABLE 3

Systemic treatments for the management of adult patients with cutaneous leishmaniasis

Intervention	Form of administration	Scheme	Species	Certainty of evidence References
Miltefosine	Oral	2.5 mg/kg/day, with a maximum dose of 150 mg/day, for 28 days. It is suggested to divide the doses, to be taken after meals to reduce gastrointestinal side effects.	*L. panamensis* *L. guyanensis* *L. mexicana* *L. braziliensis*	Low *(36–41)*
Pentamidine isethionate	Intramuscular	The studies report the following doses: 4–7 mg/kg/day in 3 doses applied every 72 hours	*L. guyanensis*	Low *(42, 43, 45, 46, 81)*
Pentavalent antimonials (for 20 days)	Intravenous or intramuscular	20 mg Sb^{+5}/kg/day of pentavalent antimony in single daily dose for **20 days.** • Maximum dose of 1,215 mg Sb^{+5}/kg/day or 3 ampoules of AP to reduce adverse effects (expert opinion). • Indication of doses (5, 10, 15 mg Sb^{+5}/kg/day) must be according to the risk–benefit and/or local evidence. • The dose indication of 5 mg Sb^{+5} is only for Rio de Janeiro, Brazil. • In areas with circulation of *L. braziliensis* consider the local evidence, due to the different therapeutic responses observed for that species according to geographical location.	*L. braziliensis* *L. panamensis* *L. amazonensis* *L. peruviana* *L. mexicana* • PA can be used in all types of *Leishmania* considering the risk–benefit in each case	Moderate and low *(19, 36–40, 82, 83)* Expert opinion

Pentavalent antimonials (for 10 days)	Intravenous or intramuscular	20 mg Sb^{+5}/kg/day pentavalent antimony in single daily dose for **10 days**. • Maximum dose of 1,215 mg Sb^{+5}/kg/day or 3 ampoules of PA to reduce side effects (expert opinion). • In areas with circulation of *L. braziliensis*, consider the local evidence due to the different therapeutic responses observed for that species according to geographical location.	*L. braziliensis* *L. panamensis*	Very low *(24, 25)*

TABLE 4

Treatment of special cases in adults with cutaneous leishmaniasis

Case	Intervention	Form of administration	Scheme	Certainty of evidence References
Pregnancy	**Thermotherapy	Application of local heat with electromagnetic device generating high frequency waves	After local anesthesia, the electrode is applied at 50 °C for periods of 30 seconds, in the center and at the edge of the lesion. One session with the number of applications needed to cover the entire lesion.	Very low *(41, 47, 78)* Expert opinion
	Liposomal amphotericin B	Intravenous	2–3 mg/kg/day up to 20–40 mg/kg total cumulative dose, divided into the following days, interspersed and up to 2 times a week *Intervals greater than 24 hours between doses may be necessary in case of creatinine elevation.	Series of cases *(84, 85)* Expert opinion

Breastfeeding women*	**Thermotherapy	Application of local heat with electromagnetic device generating high frequency waves	After local anesthesia, the electrode is applied at 50 °C for periods of 30 seconds, in the center and at the edge of the lesion. One session with the number of applications needed to cover the entire lesion.	Very low *(41, 47, 78)* Expert opinion
	**Intralesional antimonials	Subcutaneous injection	3–5 infiltrations of 1–5 ml per lesion (depending on the size of the lesion. The amount used is what is needed to cover each lesion). Interval between sessions of 3–7 days. Classically, the infiltration technique described requires the volume necessary to achieve the saturation of the lesion, which is understood as complete swelling of the lesion. It is suggested not to exceed the total volume of 15 ml infiltrated/day considering all lesions.	Low *(21, 77)* Expert opinion
	Liposomal amphotericin B	Intravenous	2–3 mg/kg/day up to 20–40 mg/kg total cumulative dose, divided into the following days, interspersed and up to 2 times a week *Intervals greater than 24 hours between doses may be necessary in case of creatinine elevation.	Case series *(84, 85)* Expert opinion

Patients with electrocardiogram alterations	**Thermotherapy	Application of local heat with electromagnetic device generating high frequency waves	After local anesthesia, the electrode is applied at 50 °C for periods of 30 seconds, in the center and at the edge of the lesion. One session with the number of applications needed to cover the entire lesion.	Very low *(41, 47, 78)* Expert opinion
	Miltefosine	Oral	2.5 mg/kg/day, with a maximum dose of 150 mg/day, for 28 days. It is suggested to divide the doses, to be taken after meals to reduce gastrointestinal side effects.	Low *(36–41)* Expert opinion
	Liposomal amphotericin B	Intravenous	2–3 mg/kg/day up to 20–40 mg/kg of total cumulative dose, divided into the following days, interspersed and up to 2 times a week. *Intervals greater than 24 hours between doses may be necessary in case of creatinine elevation.	Series of cases *(84, 85)* Expert opinion

Patients with kidney, liver, and/or heart disease	**Local treatments for skin lesions**			
	Intralesional antimonial** *Caution and frequent monitoring are suggested for the use of intralesional treatment with pentavalent antimonial in patients with heart disease	Subcutaneous injection of pentavalent antimonials	3–5 infiltrations of 1–5 ml per lesion (depending on the size of the lesion; the amount used is what is needed to cover each lesion). Interval between sessions of 3–7 days. Classically, the infiltration technique described requires the volume necessary to achieve the saturation of the lesion, which is understood as complete swelling of the lesion. It is suggested not to exceed the total volume of 15 ml infiltrated/day considering all lesions.	Low *(21, 77)* Expert opinion
	Thermotherapy**	Application of local heat with electromagnetic device generating high frequency waves	After local anesthesia, the electrode is applied at 50 °C for periods of 30 seconds, in the center and at the edge of the lesion. One session with the number of applications needed to cover the entire lesion.	Very low *(41, 47, 78)*
	Systemic treatment: Liposomal amphotericin B (LAB)	Intravenous	2–3 mg/kg/day up to 20–40 mg/kg total cumulative dose. *Intervals greater than 24 hours between doses may be necessary in case of creatinine elevation.	Expert opinion
HIV patients and other causes of immunosuppression	Amphotericin B deoxycholate	Intravenous	0.5–0.7 mg/kg/day up to 1 and 1.5 g 0.7–1.0 mg/kg/day up to 25–30 doses (until it reaches the cure criteria) *Maximum dose of 50 mg/day. Intervals greater than 24 hours between doses may be necessary in case of creatinine elevation.	Very low Expert opinion

Disseminated cutaneous leishmaniasis	Liposomal amphotericin B	Intravenous	30–35 mg/kg total dose with time varying from 7 to 14 days *Intervals greater than 24 hours between doses may be necessary in case of creatinine elevation.	Very low *(86)* Expert opinion
	Miltefosine	Oral	2.5 mg/kg/day, with a maximum dose of 150 mg/day, for 28 days. It is suggested to divide the doses, to be taken after meals to reduce gastrointestinal side effects.	Low *(35–38, 40, 41)* Expert opinion
	Amphotericin B deoxycholate	Intravenous	0.7–1.0 mg/kg day, for 30 days *Maximum dose of 50 mg/day. Intervals greater than 24 hours between doses may be necessary in case of creatinine elevation.	Expert opinion
	Pentavalent antimonials (PA)	Intravenous or intramuscular	20 mg Sb^{+5}/kg/day of pentavalent antimony in single daily dose for 30 days. **Maximum dose of 1,215 mg Sb^{+5}/day or 3 ampoules of PA to reduce side effects (expert opinion).	Moderate and low *(22, 23, 27, 35, 41, 86)* Expert opinion

Patients with diffuse cutaneous leishmaniasis	Pentavalent antimonials (PA)	Intravenous or intramuscular	20 mg Sb^{+5}/kg/day of pentavalent antimony in single daily dose for 20 days. *Maximum dose of 1,215 mg Sb^{+5}/day or 3 ampoules of PA to reduce side effects (expert opinion).	Expert opinion
	Pentamidine isethionate	Intravenous	2 mg/kg/day in 3–4 doses on alternate days.	Expert opinion
	Miltefosine	Oral	2.5 mg/kg/day, with a maximum dose of 150 mg/day, for 28 days. It is suggested to divide the doses, to be taken after meals to reduce gastrointestinal side effects.	Expert opinion
Patients with atypical cutaneous leishmaniasis caused by *L. infantum*	**Local pentavalent antimonials	Intralesional: subcutaneous injection	3–5 infiltrations of 1–5 ml per lesion (depending on the size of the lesion; the amount used is what is needed to cover each lesion). Interval between sessions of 3–7 days. Classically, the infiltration technique described requires the volume necessary to achieve the saturation of the lesion, which is understood as complete swelling of the lesion. It is suggested not to exceed the total volume of 15 ml infiltrated/day considering all lesions.	Very low *(87)*
	Systemic pentavalent antimonials (PA)	Intravenous or intramuscular	20 mg Sb^{+5}/kg/day of pentavalent antimony in a single daily dose for 20 days. *Maximum dose of 1,215 mg Sb^{+5}/day or 3 ampoules of PA to reduce side effects (expert opinion).	Very low *(87)*

*Based on developer group experience and indirect evidence
**The criteria for indication of local treatment are: 1 to 3 lesions up to 900 mm^2 (largest diameter 3 cm). Lesions located in any location, except head and periarticular regions, absence of immunosuppression, and possibility of follow-up.

TABLE 5

Treatments for the management of pediatric patients with cutaneous leishmaniasis

Intervention	Form of administration	Scheme	Species	Certainty of evidence References
Miltefosine	Oral	1.5–2.5 mg/kg/day for 28 days. It is suggested to divide the doses, to be taken after meals to reduce gastrointestinal side effects.	*L. panamensis* *L. guyanensis* *L. braziliensis.*	Low *(37-39, 56)*
Paromomycin	Topical cream 15%	Application to the affected area for 20 days	*L. panamensis* *L braziliensis* *L. mexicana*	Very low *(50, 51)*
Pentavalent antimonials for 20 days)	Intravenous or intramuscular	20 mg Sb^{+5}/kg/day of pentavalent antimony in a single daily dose for **20 days.** • Maximum dose of 1,215 mg Sb^{+5}/kg/day or 3 ampoules of PA to reduce side effects (expert opinion). • The indication of doses (5, 10, 15 mg Sb^{+5}/kg/day) should be according to the risk–benefit and/or local evidence. • The indication of the dose of 5 mg Sb^{+5} /kg is only for Rio de Janeiro, Brazil. • In areas with circulation of *L. braziliensis* consider local evidence, due to the different therapeutic responses observed for that species according to geographical location.	*L. braziliensis* *L. panamensis* *L. amazonensis* *L. peruviana* *L. mexicana*	Moderate and low *(37–39)* Expert opinion *(83)*

Pentavalent antimonials (for 10 days)	Intravenous or intramuscular	20 mg Sb^{+5}/kg/day pentavalent antimony in single daily dose for **10 days.** • Maximum dose of 1,215 mg Sb^{+5}/kg/day or 3 ampoules of PA to reduce side effects (expert opinion). • In areas with circulation of *L. braziliensis* consider the local evidence, due to the different therapeutic responses observed for that species according to geographical location.	*L. braziliensis* *L. panamensis*	Very low *(24, 25)*

TABLE 6

Treatments for the management of patients with mucosal or mucocutaneous leishmaniasis

Intervention	Form of administration	Scheme	Species	Certainty of evidence References
Pentavalent antimonials	Intravenous or intramuscular	20 mg Sb^{+5}/kg/day of pentavalent antimony in a single daily dose for 30 continuous days.	Any species of *Leishmania*	Very low *(10, 33, 64, 65, 67, 79)*
Pentavalent antimonial (Sb^{+5}) + oral pentoxifylline	Sb^{+5} intramuscular or intravenous. Preferably use the intravenous route and if not possible, use the intramuscular route. Oral pentoxifylline	20 mg Sb^{+5}/kg/day for 30 days + 400 mg pentoxifylline every 8 hours for 30 days.	Any species of *Leishmania*	Low *(67)*

TABLE 7

Treatment of special cases* in adults with mucosal or mucocutaneous leishmaniasis

Case	Intervention	Form of administration	Scheme	Certainty of evidence References**
Pregnancy	Liposomal amphotericin B	Intravenous	2–3 mg/kg/day up to 20–40 mg/kg total cumulative dose. *Intervals greater than 24 hours between doses may be necessary in case of creatinine elevation.	Expert opinion
Breastfeeding women	Liposomal amphotericin B	Intravenous	2–3 mg/kg/day up to 20–40 mg/kg total dose. *Intervals greater than 24 hours between doses may be necessary in case of creatinine elevation.	*(88, 89)* (Evidence available for general population) Expert opinion

Patients with electrocardiogram alterations	Miltefosine	Oral	2.5 mg/kg/day, with a maximum dose of 150 mg/day, for 28 days. It is suggested to divide the doses, to be taken after meals to reduce gastrointestinal side effects.	Low *(64, 65)* Expert opinion
	Liposomal amphotericin B	Intravenous	2–3 mg/kg/day up to 20–40 mg/kg total dose. Intervals greater than 24 hours between doses may be necessary in case of creatinine elevation.	Expert opinion
Patients with kidney, liver, and/or heart disease	Liposomal amphotericin B	Intravenous	2–3 mg/kg/day up to 20–40 mg/kg total dose. Intervals greater than 24 hours between doses may be necessary in case of creatinine elevation.	Expert opinion
HIV patients and other causes of immunosuppression	Liposomal amphotericin B	Intravenous	2–3 mg/kg/day up to 20–40 mg/kg total dose. Intervals greater than 24 hours between doses may be necessary in case of creatinine elevation.	Expert opinion
	Amphotericin B deoxycholate	Intravenous	0.7–1.0 mg/kg/day up to 25–30 doses. Maximum dose of 50 mg/day. Intervals greater than 24 hours between doses may be necessary in case of creatinine elevation.	Expert opinion

*Studies with special populations are not available. In this case, the evidence for the general population is applied with attention to the risk of drug interaction and the worsening toxicity of available drugs, in particular pentavalent antimony.

**Based on experience of the developer group and evidence available to the general population

TABLE 8

Therapeutic options for cutaneous and mucosal leishmaniasis in the Americas, presented according to clinical presentation and level of complexity of the care unit suggested for the management of cases

	Treatment	
Description	**Therapeutic interventions**	**Level of complexity**
Localized cutaneous leishmaniasis • 1 to 3 lesions up to 900 mm^2 (the largest diameter 3 cm). Lesions located in any location, except head and periarticular regions, absence of immunosuppression, and possibility of follow-up	Local treatment (choices by certainty of evidence) • Intralesional pentavalent antimonials • Thermotherapy • Paromomycin	First or second level of care
	Systemic treatment • Miltefosine • Pentavalent antimonials • Pentamidine isethionate	First or second level of care. It is suggested to administer pentamidine isethionate only at the second level of care due to possible acute events of hypoglycemia or hypotension.
	Special cases. Treatment is indicated according to the patient's condition and/or clinical status. • The treatments already mentioned above, augmented by: • Amphotericin B deoxycholate (expert opinion) • Liposomal amphotericin B (expert opinion)	From the second level or reference center

Localized cutaneous leishmaniasis • Lesion(s) of more than 900 mm^2 in any location, or • Lesion(s) of any size, head or periarticular region, or • Multiple lesions • Unique lesions previously treated locally that did not respond or relapse	Systemic treatment • Miltefosine • Pentavalent antimonials • Pentamidine isethionate	First or second level of care. It is suggested to administer pentamidine isethionate only at the second level of care due to possible acute events of hypoglycemia or hypotension.
	Special cases: Treatment is indicated according to the patient's condition and/or clinical status. • The treatments already mentioned above, augmented by: • Amphotericin B (expert opinion) • Liposomal amphotericin B (expert opinion)	From the second level or reference center
Disseminated cutaneous leishmaniasis	Systemic treatment (expert opinion) • Liposomal amphotericin B • Miltefosine • Pentavalent antimonials	From the second level or reference center
Diffuse cutaneous leishmaniasis	Systemic treatment (expert opinion) • Pentavalent antimonials • Pentamidine isethionate • Miltefosine	Reference center
Mucosal leishmaniasis	Systemic treatment (choices by certainty of evidence) • Pentavalent antimonials + pentoxifylline • Pentavalent antimonials (expert opinion) • Liposomal amphotericin B • Miltefosine • Amphotericin B deoxycholate	Reference center

TABLE 9

Treatments for the management of non-immunocompromised patients with visceral leishmaniasis

Intervention	Form of administration	Scheme	Certainty of evidence	Level of complexity	References
Liposomal amphotericin B	Intravenous	3 mg/kg/day for 7 days up to 20 mg/kg total dose. *Intervals greater than 24 hours between doses may be necessary in case of creatinine elevation.	Low	Third level of care or reference center	*(69)*
Amphotericin B deoxycholate	Intravenous	Children: 1 mg/kg/day for 14 days up to a total dose of 800 mg Adults: 1 mg/kg/day for 14–21 days. Total daily dose of 50 mg. *Maximum dose of 50 mg/day. Intervals greater than 24 hours between doses may be necessary in case of creatinine elevation.	Low	Third level of care or reference center	*(70)* For children only Expert opinion
Pentavalent antimonials	Intravenous	20 mg Sb^{+5}/kg/day for 20 days	Low	Third level of care or reference center	*(69, 70)*

*Based on experience of the developer group and evidence available to the general population.

TABLE 10

Treatments for the management of immunocompromised patients with visceral leishmaniasis

Intervention	Form of administration	Scheme	Level of care	References
Liposomal amphotericin B	Intravenous	3 mg/kg/day up to 20–40 mg/kg total dose. *Intervals greater than 24 hours between doses may be necessary in case of creatinine elevation.	Reference center	Very low *(76)*
Amphotericin B lipid complex	Intravenous	Total dose of 30 mg/kg, 3 mg/kg/day for 10 days. *Intervals greater than 24 hours between doses may be necessary in case of creatinine elevation.	Reference center	*(75)* Expert opinion
Amphotericin B deoxycholate	Intravenous	0.7 mg/kg/day for 28 days *Maximum dose of 50 mg/day. Intervals greater than 24 hours between doses may be necessary in case of creatinine elevation.	Reference center	*(73, 74)* Expert opinion

*Based on experience of the developer group and evidence available to the general population.

TABLE 11

Treatments for secondary prophylaxis for the management of immunocompromised patients with visceral leishmaniasis

Intervention	Form of administration	Scheme	Certainty of evidence	Level of care	References
Liposomal amphotericin B	Intravenous	3 mg/kg/dose every 2–3 weeks	Very low	Reference center	*(75, 76)*

Research agenda to support future updates

Discussions between the members of the Guideline Development Group highlighted the limited evidence available in some knowledge areas relevant to this Guideline. These areas require further research to inform future updates to the Guideline:

Efficacy and safety

1. High quality randomized controlled trials to document the efficacy and safety of the different drugs and doses for all species of cutaneous leishmaniasis in the Americas.
2. Specification of optimal observation time for accurate reporting of adverse events and toxicity.
3. Randomized controlled trials to document the efficacy and safety of the different drugs and doses for mucosal and disseminated cutaneous leishmaniasis.
4. Randomized controlled trials to verify the efficacy and safety of treatments for HIV–visceral leishmaniasis coinfections and other immunosuppression.
5. To document the diagnosis and treatment of post-kala-azar and para-kala-azar dermal leishmaniasis in the Americas.

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ANNEXES

ANNEX 1
Contributors

The members of the guideline development group are presented below.

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Annex 2
Declaration of interest

Below is the analysis of the declaration of interest that each member of the development group fulfilled, as well as the decision of the leaders.

A. Specific or non-specific personal economic interest
B. Specific or non-specific non-personal economic interest
C. Personal non-economic interest
D. Specific or non-specific personal economic interest of a family member

Name	Role	A	B	C	D	Decision
Alejandro Llanos-Cuentas	Thematic expert	No	No	Yes	No	Partial participation. He did not participate in Question 1. Studies developed by the researcher were included in the guideline.
Dorcas Lamounier Costa	Thematic expert	No	No	No	No	Full participation
Glaucia Fernandes Cota	Thematic expert	No	No	Yes	No	Partial participation. She did not participate in Question 1. Studies developed by the researcher were included in the guideline.
Gustavo Adolfo Sierra Romero	Thematic expert	No	No	Yes	No	Partial participation. He did not participate in Question 1. Studies developed by the researcher were included in the guideline.

A. Specific or non-specific personal economic interest

B. Specific or non-specific non-personal economic interest

C. Personal non-economic interest

D. Specific or non-specific personal economic interest of a family member

Name	Role	A	B	C	D	Decision
Ivan Dario Velez Bernal	Thematic expert	No	No	No	No	Full participation
Jaime Soto	Thematic expert	No	No	No	No	Partial participation. He did not participate in Question 1. Studies developed by the researcher were included in the guideline.
José Angelo Lauletta Lindoso	Thematic expert	No	No	No	No	Full participation
José Antonio Suárez Sancho	Thematic expert	No	No	No	No	Full participation
Marcia Hueb	Thematic expert	No	No	No	No	Full participation
Marco Romano Quintanilla Cedillo	Thematic expert	No	No	No	No	Full participation
Nancy Gore Saravia	Thematic expert	No	No	Yes	No	Partial participation. She did not participate in Question 1. Studies developed by the researcher were included in the guideline.
Sandra Muvdi Arenas	Thematic expert	No	No	No	No	Full participation
Tomás Agustín Orduna	Thematic expert	No	No	No	No	Full participation

Name	Role	A	B	C	D	Decision
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Paulo R. Machado	Peer reviewer	No	No	No	No	Full participation
Rodrigo Pardo	Peer reviewer	No	No	No	No	Full participation
Sara Robledo	Peer reviewer	No	No	No	No	Full participation

Annex 3
Search strategy

Note: When developing guidelines, searches are performed with high sensitivity, so no relevant studies are lost, and by clinical aspect. Therefore, search terms for specific outcomes or medications are not included, nor are search strategies performed for each specific question. The strategies are developed globally, without restrictive terms, and during the selection of studies the evidence found is assigned to each question of the guideline. First, searches for systematic reviews (SR) are conducted; if no updated SR is found, randomized controlled trials (RCT) are searched given the type of question (efficacy of interventions). We used the following filters: leishmaniasis, treatment, RCT and SR validated by Cochrane (https://training.cochrane.org/handbook), and Medline (https://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx).

MEDLINE via Ovid

1. exp Leishmaniasis, Mucocutaneous/ or mucosal
2. espundia.mp.
3. exp Leishmaniasis, Cutaneous/
4. leish$.mp.
5. (mucocutan$ or mucos$ or american or new world or nose$ or nariz or naso$ or pharyn$ or faring$ or laring$ or laryn$ or paladar$ or palat$ or cartila$ or ear$ or oreja$ or orelha$ or tegument$).mp.

6. exp Leishmaniasis, visceral/
7. exp Leishmania
8. exp Leishmania infantum/
9. Kala azar OR kala-azar ti, ab
10. Visceral leishmania* ti, ab
11. (solitary or limited or localized or diffuse or cutaneous).mp.
12. leishmania$.mp.
13. (leishmani$ or kala-azar or kalaazar).mp.
14. (clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]
15. search*[Title/Abstract] OR meta-analysis[Publication Type] OR metaanalysis[Publication Type] OR meta analysis[Title/Abstract] OR meta analysis[MeSH Terms] OR meta-analysis[pt] OR meta-analysis[pt] OR meta analy*[tw] OR or systematic review*[tiab] OR technology assessment*[tiab] OR "Technology Assessment, Biomedical"[mh] OR HTA[tiab] OR HTAs[tiab] OR comparative efficacy[tiab] OR comparative effectiveness[tiab] OR outcomes research[tiab] OR indirect comparison*[tiab] OR ((indirect treatment[tiab] OR mixed-treatment[tiab]) AND comparison*[tiab]) OR Embase*[tiab] OR Cinahl*[tiab] OR systematic overview*[tiab] review[Publication Type] OR systematic[sb]
16. cost effective[Title/Abstract] OR sensitivity analys*[Title/Abstract]
17. "Case-Control Studies"[Mesh:noexp] OR "retrospective studies"[mesh:noexp] OR "Control Groups"[Mesh:noexp] OR (case[TIAB] AND control[TIAB]) OR (cases[TIAB] AND controls[TIAB]) OR (cases[TIAB] AND controlled[TIAB]) OR (case[TIAB] AND comparison*[TIAB]) OR (cases[TIAB] AND comparison*[TIAB]) OR "control group"[TIAB] OR "control groups"[TIAB])
18. cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR retrospective studies[mesh:noexp] OR cohort[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB]

19. (“antimony”[MeSH Terms] OR “antimony sodium gluconate/adverse”[MeSH Terms]) OR “antiprotozoal agents”[MeSH Terms] OR “meglumine [MeSH Terms] OR “paromomycin “[MeSH Terms] OR “pentamidine”[MeSH Terms] OR “organometallic compounds “[MeSH Terms] OR “[MeSH Terms] OR “trypanocidal agents”[MeSH] Terms OR therapeutic use[MeSH Subheading] OR (pentamidine OR ambisome OR amphotericin OR paromomycin OR miltefosine OR pentavalent OR sodium OR aminosidine sulphate OR Aminoglycosides) OR thermotherapy OR cryotherapy OR intralesional Granulocyte-Macrophage Colony-Stimulating Factor OR Mefloquine OR Immunotherapy)
20. Human NOT animal

Embase via Ovid

1. exp skin leishmaniasis/
2. leish$.mp.
3. (mucocutan$ or mucos$ or american or new world or nose$ or nariz or naso$ or pharyn$ or faring$ or laring$ or laryn$ or paladar$ or palat$ or cartila$ or ear$ or oreja$ or orelha$ or tegument$).mp.
4. espundia.mp.
5. systematic review.sh
6. crossover procedure.sh.
7. double-blind procedure.sh.
8. single-blind procedure.sh.
9. (crossover$ or cross over$).tw.
10. placebo$.tw.
11. (doubl$ adj blind$).tw.
12. trial.ti.
13. randomized controlled trial.sh.
14. random$.tw.

15. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/

16. human/ or normal human/

CINAHL via EBSCO

S1 TI espundia OR AB espundia

S2 TI mucocutaneous leishmaniasis or AB mucocutaneous leishmaniasis

S3 TI leish* OR AB leish*

S4 TI ((mucocutan* or mucos* or american or new world or nose* or nose or naso* or pharyn* or faring* or laring* or laryn* or paladar* or palat* or cartila* or ear* or oreja* or orelha* or tegument*)) OR AB ((mucocutan* or mucos* or american or new world or nose* or nariz or naso* or pharyn* or faring* or laring* or laryn* or paladar* or palat* or cartila* or ear* or ear* or orelha* or tegument*))

S5 (TI ((mucocutan* or mucos* or american or new world or nose* or nose or naso* or pharyn* or faring* or laring* or laryn* or paladar* or palat* or cartila* or ear* or ear* or orelha* or tegument*)) OR AB ((mucocutan* or mucos* or american or new world or nose* or nariz or naso* or pharyn* or faring* or laring* or laryn* or paladar* or palat* or cartila* or ear* or ear* or orelha* or tegument*))) AND (S3 AND S4) S6 ((TI ((mucocutan* or mucos* or american or new world or nose* or nose or naso* or pharyn* or faring* or laring* or laryn* or paladar* or palat* or cartila* or ear* or ear* or orelha* or tegument*)) OR AB ((mucocutan* or mucos* or american or new world or nose* or nose or naso* or pharyn* or faring* or laring* or laryn* or paladar* or palat* or cartila* or ear* or oreja* or orelha* or tegument*))) AND (S3 AND S4)) AND (S1 OR S2 OR S5)

S7 (MH "Clinical Trials+") S8 PT clinical trial

S9 TX (clinic* n1 trial*)

S10 (MH "Random Assignment") S11 TX random* allocat*

S12 TX placebo*

S13 (MH "Placebos")

S14 (MH "Quantitative Studies") S15 TX allocat* random*

S16 "randomi#ed control* trial*"

S17 TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX (doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*))

or TX ((trebl* n1 blind*) or (trebl* n1 mask*))

Lilacs

(cutaneous and leishmaniasis) or (cutanea and leishmaniasis) or (new world and leish man$) or ((solitar$ or locali$ or limited) and leishman$) OR (“kala-azar” or “kalaazar”9

It is complemented by the RS and ECA filter of LILACS

MEDLINE (Ovid) Adverse effects search strategy

1. exp product surveillance, postmarketing/ or exp adverse drug reaction reporting systems/ or exp clinical trials, phase iv/
2. adverse events.mp.
3. adverse eEects.mp.
4. exp hypersensitivity/ or exp drug hypersensitivity/ or exp drug eruptions/ or exp hypersensitivity, delayed/ or exp hypersensitivity, immediate/
5. exp hypersensitivity, immediate/ or exp anaphylaxis/ or exp conjunctivitis, allergic/ or exp dermatitis, atopic/ or exp food hypersensitivity/ or exp respiratory hypersensitivity/ or exp urticaria/
6. side eEect$.mp.
7. exp Poisoning/
8. exp Substance-Related Disorders/
9. exp Drug Toxicity/
10. exp Abnormalities, Drug-Induced/
11. exp Teratogens/
12. exp Mutagens/
13. exp Carcinogens/
14. exp dermatitis, contact/ or exp dermatitis, allergic contact/ or exp dermatitis, irritant/ or exp dermatitis, phototoxic/
15. reactions.mp photoallergic.
16. exp dermatitis, allergic contact/ or exp dermatitis, photoallergic/
17. sensitization.mp.

18. fetal abnormalities.mp.
19. exp Drug Monitoring/
20. harm$ eEects.mp.
21. (toxic eEects or drug eEects).mp.
22. undesirable eEect$.mp.
23. (safe or safety).mp.
24. toxicity.mp.
25. noxious.mp.
26. serious reaction$.mp.
27. complication$.mp.
28. tolerability.mp.
29. (adverse adj3 (eEect$ or reaction$ or event$ or outcome$)).mp.
30. Tachyphylaxis/ci, from [Chemically Induced, Drug EEects]
31. *Itraconazole/
32. *Ketoconazole/
33. *Paromomycin/
34. *Allopurinol/
35. *Amphotericin B/
36. aminosidine sulphate.mp.
37. pentamidine isethionate.mp. or *Pentamidine/
38. *Aminoglycosides/
39. miltefosine.mp.
40. thermotherapy.mp.
41. *Granulocyte-Macrophage Colony-Stimulating Factor/
42. *Mefloquine/
43. *Immunotherapy/

44. *BCG Vaccine/ or bacillus calmette guerin.mp.
45. *Meglumine/
46. sodium stibogluconate.mp.
47. meglumine antimoniate.mp.
48. imiquimod.mp.
49. IFN-gamma.mp.
50. new world.mp.
51. American.mp.
52. exp Leishmaniasis, Cutaneous/
53. exp Leishmaniasis, Mucocutaneous/
54. exp Leishmaniasis, visceral/
55. exp Leishmania
56. exp Leishmania infantum/
57. Kala azar OR kala-azar ti, ab
58. therapeutic use [MeSH Subheading]

CENTRAL (Cochrane Library)

#1 MeSH descriptor: [Leishmaniasis, Mucocutaneous] explode all trees

#2 espundia:ti,ab,kw

#3 #1 or #2

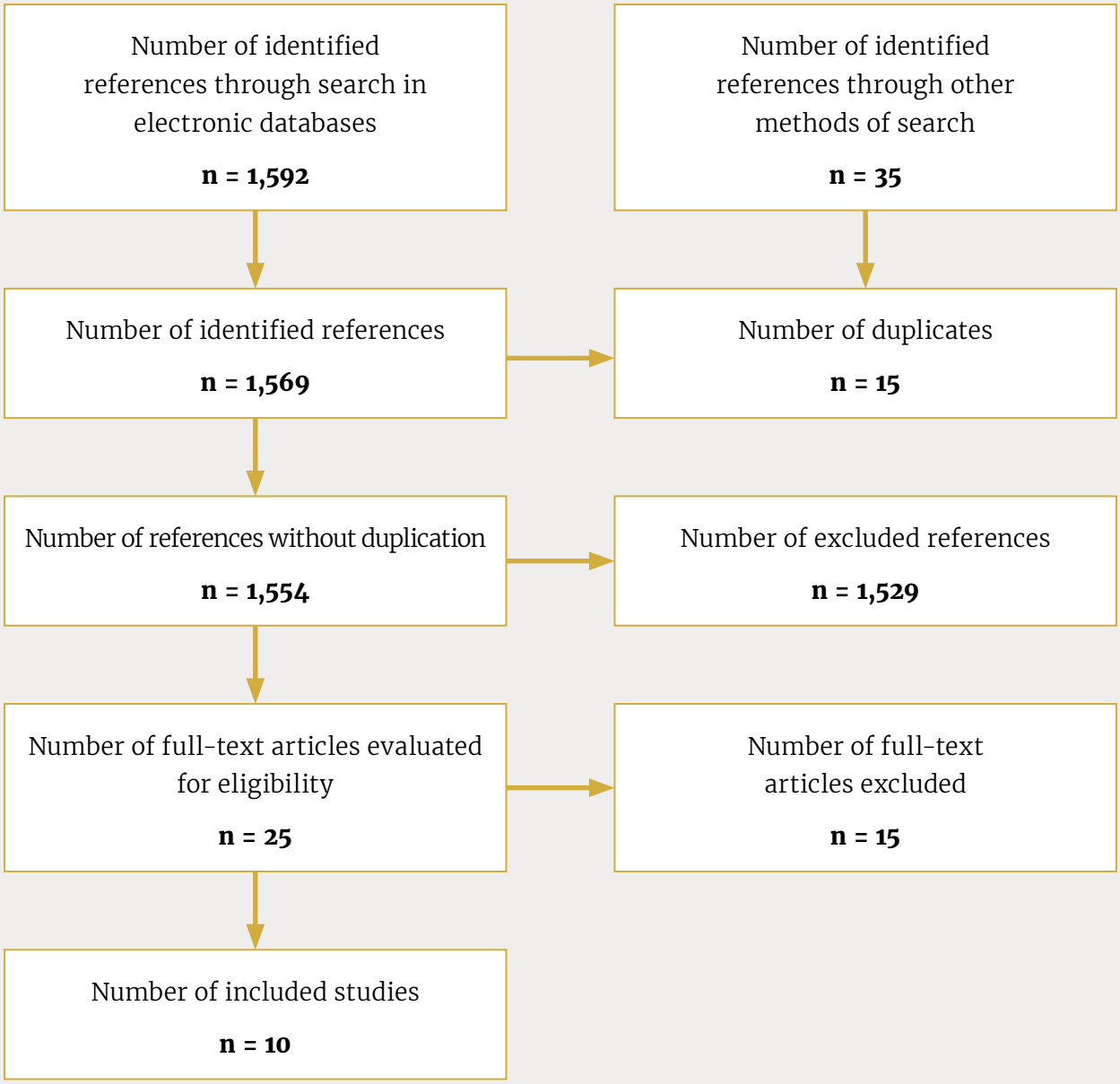
#4 MeSH descriptor: [Leishmaniasis, Cutaneous] explode all trees

#5 leish*:ti,ab,kw

#6 #4 or #5

#7 (mucocutan* or mucos* or american or new world or nose* or nose* or pharyn* or faring* or laring* or laryn* or paladar* or palat* or cartila* or ear* or oreja* or orelha* or tegument*):ti,ab,kw

Annex 4
Prisma diagram



Excluded studies

Reference	Reason
Iranpour S, Hosseinzadeh A, Alipour A. Efficacy of miltefosine compared with glucantime for the treatment of cutaneous leishmaniasis: a systematic review and meta-analysis. Epidemiol Health. 2019;41:e2019011. doi: 10.4178/epih.e2019011. Epub 2019 Mar 31. PMID: 30999735; PMCID: PMC6635659	Included in the Pinart et al. 2020 SR
Brito NC, Rabello A, Cota GF. Efficacy of pentavalent antimoniate intralesional infiltration therapy for cutaneous leishmaniasis: A systematic review. PLoS One. 2017 Sep 19;12(9): e0184777. doi: 10.1371/journal.pone.0184777. PMID: 28926630; PMCID: PMC5604971.	Included in the Pinart et al. 2020 SR
Wolf Nassif P, DE Mello TFP, Navasconi TR, Mota CA, Demarchi IG, Aristides SMA, Lonardoni MVC, Teixeira JJV, Silveira TGV. Safety and efficacy of current alternatives in the topical treatment of cutaneous leishmaniasis: a systematic review. Parasitology. 2017 Jul;144(8):995-1004. doi: 10.1017/S0031182017000385. Epub 2017 Apr 3. PMID: 28367792.	Included in the Pinart et al. 2020 SR
Cota GF, de Sousa MR, Fereguetti TO, Saleme PS, Alvarisa TK, Rabello A. The Cure Rate after Placebo or No Therapy in American Cutaneous Leishmaniasis: A Systematic Review and Meta-Analysis. PLoS One. 2016 Feb 19;11(2):e0149697. doi: 10.1371/journal.pone.0149697. PMID: 26894430; PMCID: PMC4760744.	Does not meet the inclusion criteria
Wolf Nassif P, De Mello TFP, Navasconi TR, Mota CA, Demarchi IG, Aristides SMA, Lonardoni MVC, Teixeira JJV, Silveira TGV. Safety and efficacy of current alternatives in the topical treatment of cutaneous leishmaniasis: a systematic review. Parasitology. 2017 Jul;144(8):995-1004. doi: 10.1017/S0031182017000385. Epub 2017 Apr 3. PMID: 28367792	Included in the Pinart et al. 2020 SR
Gadelha EPN, Ramasawmy R, da Costa Oliveira B, Morais Rocha N, de Oliveira Guerra JA, Allan Villa Rouco da Silva G, Gabrielle Ramos de Mesquita T, Chrusciak Talhari Cortez C, Chrusciak Talhari A. An open label randomized clinical trial comparing the safety and effectiveness of one, two or three weekly pentamidine isethionate doses (seven milligrams per kilogram) in the treatment of cutaneous leishmaniasis in the Amazon Region. PLoS Negl Trop Dis. 2018 Oct 31;12(10):e0006850. doi: 10.1371/journal.pntd.0006850. PMID: 30379814; PMCID: PMC6231690.	Included in the Pinart et al. 2020 SR
López L, Vélez I, Asela C, Cruz C, Alves F, Robledo S, Arana B. A phase II study to evaluate the safety and efficacy of topical 3% amphotericin B cream (Anfoleish) for the treatment of uncomplicated cutaneous leishmaniasis in Colombia. PLoS Negl Trop Dis. 2018 Jul 25;12(7):e0006653. doi: 10.1371/journal.pntd.0006653. PMID: 30044792; PMCID: PMC6078324. .	Included in the Pinart et al. 2020 SR

Reference	Reason
Ramalho DB, Silva RED, Senna MCR, Moreira HSA, Pedras MJ, Avelar DM, Saraiva L, Rabello A, Cota G. Meglumine antimoniate intralesional infiltration for localised cutaneous leishmaniasis: a single arm, open label, phase II clinical trial. Mem Inst Oswaldo Cruz. 2018 Jun 21;113(9):e180200. doi: 10.1590/0074-02760180200. PMID: 29947651; PMCID: PMC6012678.	Included in the Pinart et al. 2020 SR
Machado PRL, Ribeiro CS, França-Costa J, Dourado MEF, Trinconi CT, Yokoyama-Yasunaka JKU, Malta-Santos H, Borges VM, Carvalho EM, Uliana SRB. Tamoxifen and meglumine antimoniate combined therapy in cutaneous leishmaniasis patients: a randomised trial. Trop Med Int Health. 2018 Sep;23(9):936-942. doi: 10.1111/tmi.13119. Epub 2018 Jul 11. PMID: 29924907.	Included in the Pinart et al. 2020 SR
Francesconi VA, Francesconi F, Ramasawmy R, Romero GAS, Alecrim MDGC. Failure of fluconazole in treating cutaneous leishmaniasis caused by Leishmania guyanensis in the Brazilian Amazon: An open, nonrandomized phase 2 trial. PLoS Negl Trop Dis. 2018 Feb 26;12(2):e0006225. doi: 10.1371/journal.pntd.0006225. PMID: 29481560; PMCID: PMC5854414	Included in the Pinart et al. 2020 SR
Sampaio RNR, Silva JSFE, Paula CDR, Porto C, Motta JOCD, Pereira LIA, Martins SS, Barroso DH, Freire GSM, Gomes CM. A randomized, open-label clinical trial comparing the long-term effects of miltefosine and meglumine antimoniate for mucosal leishmaniasis. Rev Soc Bras Med Trop. 2019 Mar 28;52:e20180292. doi: 10.1590/0037-8682-0292-2018. PMID: 30942258.	Included in the Pinart et al. 2020 SR
Garcia Bustos MF, Barrio A, Parodi C, Beckar J, Moreno S, Basombrio MA. Miltefosina versus meglumine antimoniate in the treatment of mucosal leishmaniasis. Medicine (B Aires). 2014;74(5):371-7. English. PMID: 25347898.	Included in the Pinart et al. 2020 SR
Shahian M, Alborzi A. Effect of meglumine antimoniate on the pancreas during treatment of visceral leishmaniasis in children. Med Sci Monit. 2009 Jun;15(6):CR290-3. PMID: 19478699.	Does not include participants from Latin America
Kurizky PS, Marianelli FF, Cesetti MV, Damiani G, Sampaio RNR, Gonçalves LMT, Sousa CAF, Martins SS, Vernal S, Mota LMHD, Gomes CM. A comprehensive systematic review of leishmaniasis in patients undergoing drug-induced immunosuppression for the treatment of dermatological, rheumatological and gastroenterological diseases. Rev Inst Med Trop Sao Paulo. 2020;62:e28. doi: 10.1590/s1678-9946202062028. Epub 2020 May 11. PMID: 32401957; PMCID: PMC7232954	Presents no evidence of treatment effectiveness
Bush JT, Wasunna M, Alves F, Alvar J, Olliaro PL, Otieno M, Sibley CH, Strub Wourgaft N, Guerin PJ. Systematic review of clinical trials assessing the therapeutic efficacy of visceral leishmaniasis treatments: A first step to assess the feasibility of establishing an individual patient data sharing platform. PLoS Negl Trop Dis. 2017 Sep 5;11(9):e0005781. doi: 10.1371/journal.pntd.0005781. PMID: 28873394; PMCID: PMC5600407.	Includes a Brazil-Harhay study that is included in the previous version of the guideline.

Annex 5
Meta-analysis

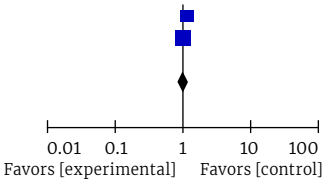
Meta-analyses were performed when we found clinical trials that provide answer to the PICO question. The risk of bias was independently assessed for each study included using the Cochrane risk of bias tool. Disagreements were resolved through discussion. The collected information was entered in the Review Manager 5 program in a paired manner to verify the certainty of the information. Given the nature of the outcomes (dichotomous data), the risk ratio (RR) was implemented as a summary measure of effect along with its 95% confidence interval (CI). The level of data was assessed for the studies included, and for all outcomes, intention-to-treat analysis was performed, if possible, regardless of whether they received the assigned intervention/test. Statistical heterogeneity was assessed in each meta-analysis using statistic I^2 and Chi^2 test values, considering substantial heterogeneity such as the presence of an I^2 statistic greater than 40% or the presence of a p-value, in the hypothesis test, smaller than 0.10 (Chi^2 heterogeneity test). Finally, we performed the construction of forest plots, using the Review Manager 5 program, implementing the fixed effects approach to combine the data when it was reasonable to assume that the studies estimated the same underlying effect of the treatment (from the clinical and methodological perspective). Conversely, if the clinical or methodological group or statistical evidence detected the presence of substantial heterogeneity, random effects meta-analyses were performed to produce an overall summary of whether the average treatment effect in all trials was considered clinically significant *(18)*.

What is the efficacy and safety of the different pharmacological treatments for the management of non-immunocompromised patients diagnosed with visceral leishmaniasis in the Americas?

Amphotericin vs pentavalent antimonial for the treatment of non-immunocompromised visceral leishmaniasis patients

Figure A1. Cure at 6 months

	Amphotericin		Antimonials			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**	**A B C D E F G**
Romero 2017	95	109	86	111	46.0%	1.12 (0.99, 1.27)		+ + + + ? + ?
Borges 2017	47	50	48	51	54.0%	1.00 (0.91, 1.10)		+ − − − + −
Total (95% CI)		**159**		**162**	**100.0%**	**1.05 (0.92, 1.20)**		
Total events	142		134					

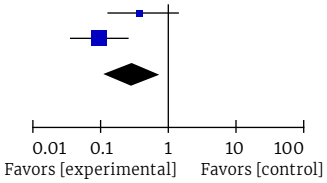


Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 2.85$; df = 1 (P = 0.09); $I^2 = 65\%$
Test for overall effect Z = 0.79 (P = 0.43)

Risk of bias legend:

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure A2. Discontinuation of therapy

	Amphotericin		Antimonials			Peto Odds Radio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95%CI	M-H, Random, 95% CI	A B C D E F G
Borges 2017	2	50	3	51	24.4%	0.67 [0.11 , 4.03]		
Romero 2017	1	109	15	111	75.6%	0.16 [0.06 , 0.43]		
Total (95% CI)		**159**		**162**	**100.0%**	**0.22 [0.09, 0.54]**		
Total events	3		18					

Heterogeneity: Chi² = 1.94, df = 1 (P=0.16%); I²=49%
Test for overall effect Z = 3.34 (P = 0.0009)

Risk of bias legend:

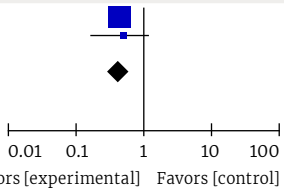
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Question 4

What is the efficacy and safety of the different pharmacological treatments for the management of immunocompromised patients diagnosed with visceral leishmaniasis in the Americas?

Amphotericin vs pentavalent antimonial for immunocompromised visceral leishmaniasis patients

Figure A3. Global Cure

	Amphotericin B		Antimonials			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	A B C D E F G
Laguna 1999	28	45	29	44	86.7%	0.94 [0.69, 1.29]		
Laguna 2003	8	20	7	19	13.3%	1.09 [0.49, 2.41]		
Total (95% CI)		**65**		**63**	**100.0%**	**0.96 [0.72, 1.29]**		
Total events	36		36					

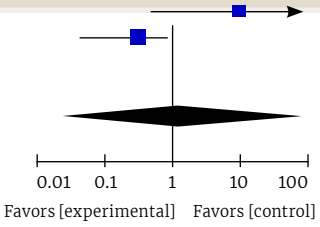
Heterogeneity: Tau² = 0.00; Chi²= 0.11, df = 1 (P=0.74); I²=0%
Test for overall effect Z = 0.26 (P = 0.79)

Risk of bias legend:

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure A4. Abandonment of treatment

	Amphotericin B		Antimonials			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	A B C D E F G
Laguna 1999	5	45	0	44	45.1%	10.76 [0.61, 188.98]		
Laguna 2003	2	20	9	20	54.9%	0.22 [0.05, 0.90]		
Total (95% CI)		**65**		**64**	**100.0%**	**1.28 [0.02, 69.15]**		
Total events	7		9					



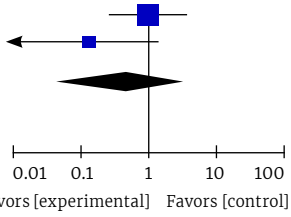
Heterogeneity: Tau² = 7.04; Chi² = 6.31; df = 1 (P=0.01); I²=84%
Test for overall effect Z = 0.12 (P = 0.90)

Risk of bias legend:

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure A5. Death

	Amphotericin B		Antimonials			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI	A B C D E F G
Laguna 1999	5	45	5	44	72.2%	0.98 [0.30, 3.14]		
Laguna 2003	0	20	3	19	27.8%	0.14 [0.01, 2.47]		
Total (95% CI)	**65**			**63**	**100.0%**	**0.57 [0.10, 3.36]**		
Total events	5		8					

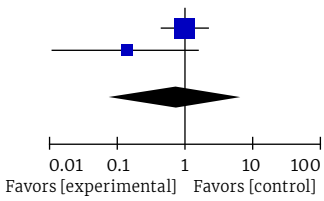


Heterogeneity: Tau² = 0.79; Chi² = 1.62 df = 1 (P=0.20); I²=38%
Test for overall effect Z = 0.63 (P = 0.53)

Risk of bias legend:

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure A6. At least one side effect

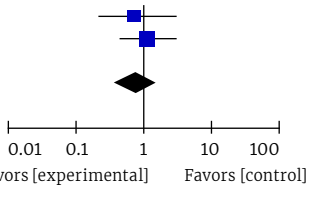
	Amphotericin B		Antimonials			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**	**A B C D E F G**
Laguna 1999	27	45	24	44	65.4%	1.10 [0.77, 1.58]		
Laguna 2003	1	20	5	19	34.6%	0.19 [0.02, 1.48]		
Total (95% CI)		**65**		**63**	**100.0%**	**0.60 [0.11, 3.39]**		
Total events	28		29					

Heterogeneity: Tau² = 1.16; Chi² = 3.05; df = 1 (P=0.08); I²=67%
Test for overall effect Z = 0.58 (P = 0.56)

Risk of bias legend:

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure A7. Relapse

	Amphotericin B		Antimonials			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**	**A B C D E F G**
Laguna 1999	8	24	11	24	55.5%	0.73 [0.36, 1.48]		
Laguna 2003	8	20	7	19	44.5%	1.09 [0.49, 2.41]		
Total (95% CI)		**44**		**43**	**100.0%**	**0.87 [0.51, 1.48]**		
Total events	16		18					

Heterogeneity: Tau² = 0.00; Chi² = 0.54; df = 1 (P=0.46); I²=0%
Test for overall effect Z = 0.52 (P = 0.61)

Risk of bias legend:

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Annex 6
GRADE evidence profiles

Question 1

What is the efficacy and safety of the different systemic and local treatments for the management of patients diagnosed with cutaneous leishmaniasis in the Americas?

Question: Intralesional antimoniate (1, 3, and 5 days) compared to placebo for leishmaniasis caused by *L. braziliensis*, *L. amazonensis*, *L. guyanensis*, and *L. lainsoni*.

Bibliography: Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub3

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Intralesional antimoniate	Placebo	Relative (95% CI)	Absolute (95% CI)		
Complete cure (follow-up: 6 months)												
1	Randomized trials	Serious[a]	Not serious	Not serious	Very serious[b]	None	20/30 (66.7%)	4/30 (13.3%)	RR 5.00 (1.94, 12.89)	533 more per 1,000 (from 125 more to 1,000 more)	⨁⨁◯◯ Low	Critical

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Blinding of personnel and patients was not performed when administering the intervention or measuring outcomes. No masking was performed.

b. Sample size is not optimal for finding differences, wide confidence intervals that exceed 25% of the estimator.

Question: Meglumine antimoniate (20 mg/kg/day plus tamoxifen 40 mg/day) for 20 days compared to meglumine antimoniate alone for leishmaniasis caused by *L. braziliensis*.

Bibliography: Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub3

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Meglumine antimoniate (20 mg/kg/day plus tamoxifen 40 mg/day)	Meglumine antimoniate alone	Relative (95% CI)	Absolute (95% CI)		
Complete cure (follow-up: 6 months)												
1	Randomized trials	Serious[a]	Not serious	Not serious	Serious[b]	None	15/24 (62.5%)	14/30 (46.7%)	RR 1.33 (0.82, 2.16)	154 more per 1,000 (from 84 less to 541 more)	⨁⨁◯◯ Low	Critical
Recurrence (follow-up: 6 months)												
1	Randomized trials	Not serious	Not serious	Not serious	Very serious[b]	None	1/12 (8.3%)	2/15 (13.3%)	RR 0.63 (0.06, 6.09)	49 less per 1,000 (from 125 less to 679 more)	⨁⨁◯◯ Low	Critical

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Low power of the study to see differences between groups

b. Sample size is not optimal for finding differences, wide confidence intervals that exceed 25% of the estimator.

Question: Meglumine antimoniate (low dose: 5 mg/kg/day, 20 to 30 days) compared to high doses (20–30 mg/kg/day, 20 to 30 days) for the treatment of leishmaniasis caused by *L. braziliensis*.

Bibliography: Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub3

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Meglumine antimoniate (low dose: 5 mg/kg/day, 20–30 days)	High doses (20–30 mg/kg/day, 20–30 days)	Relative (95% CI)	Absolute (95% CI)		
Complete cure (follow-up: range 12 months to 45 months)												
2	Randomized trials	Serious[a]	Serious[b]	Not serious[b]	Serious[c]	None	39/44 (88.6%)	35/45 (77.8%)	RR 1.10 (0.77, 1.58)	78 more per 1,000 (from 179 less to 451 more)	⨁◯◯◯ Very low	Critical
Side effects (follow-up: range 12 months to 45 months)												
1	Randomized trials	Serious[a]	Not serious	Not serious	Serious[c]	None	6/11 (54.5%)	2/12 (16.7%)	RR 3.27 (0.83, 12.95)	378 more per 1,000 (from 28 less to 1,000 more)	⨁⨁◯◯ Low	Critical

CI: Confidence interval; RR: Risk ratio

Explanations

a. Possible selection and detection bias

b. Moderate heterogeneity is reported; I^2 47%

c. Sample size is not optimal for finding differences, wide confidence intervals that exceed 25% of the estimator.

Question: Meglumine antimoniate (20 mg/kg/day) for 20 days compared to placebo for the treatment of cutaneous and mucocutaneous leishmaniasis caused by *L. braziliensis* and *L. panamensis*.

Bibliography: Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub3

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Meglumine antimoniate	Placebo	Relative (95% CI)	Absolute (95% CI)		
Complete cure at least 3 months (follow-up: median 1 year)												
2	Randomized trials	Serious[a]	Not serious	Not serious	Serious[b]	None	65/86 (75.6%)	17/71 (23.9%)	RR 4.23 (0.84, 21.38)	773 plus per 1,000 (from 38 minus to 1,000 plus)	⨁⨁◯◯ Low	Critical
Side effects (follow-up: median 1 year)												
1	Randomized trials	Not serious	Not serious	Not serious	Serious[b]	None	53/67 (79.1%)	35/67 (52.2%)	RR 1.51 (1.17, 1.96)	266 more per 1,000 (from 89 more to 501 more)	⨁⨁⨁◯ Moderate	Critical
Recurrence (follow-up: median 1 year)												
1	Randomized trials	Not serious	Not serious	Not serious	Serious[b]	None	2/67 (3.0%)	1/60 (1.7%)	RR 1.79 (0.17, 19.26)	13 more per 1,000 (from 14 less to 304 more	⨁⨁⨁◯ Moderate	Critical

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. One included study (Saenz, 1990) reported no masking or blinding of personnel.

b. Sample size is not optimal for finding differences.

Question: IV meglumine antimoniate plus anthelmintic compared to IV MA plus placebo for leishmaniasis caused by *L. braziliensis*.

Bibliography: Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub3

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	IV meglumine antimoniate plus anthel-mintic	MA IV plus placebo	Relative (95% CI)	Absolute (95% CI)		
Complete cure (follow-up: 90 days)												
1	Randomized trials	Not serious	Not serious	Not serious	Very serious[a]	None	17/45 (37.8%)	22/45 (48.9%)	RR 0.77 (0.48, 1.25)	112 less per 1,000 (from 254 less to 122 more)	⨁⨁◯◯ Low	Critical

Explanations

a. Sample size is not optimal for finding differences, wide confidence intervals that exceed 25% of the estimator.

Question: Sodium stibogluconate 20 mg/kg/day for 20 days compared to meglumine antimoniate 20 mg/kg for 20 days for treatment of *L. panamensis*.

Bibliography: Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub3

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Sodium stibogluconate 20 mg/kg/day for 20 days	Meglumine antimoniate 20 mg/kg for 20 days	Relative (95% CI)	Absolute (95% CI)		
Complete cure												
1	Randomized trials	Serious[a]	Not serious	Not serious	Very serious[b,c]	None	52/64 (81.3%)	38/50 (76.0%)	RR 1.07 (0.88, 1.30)	53 more per 1,000 (from 91 less to 228 more)	⨁◯◯◯ Very low	Critical
Side effects												
1	Randomized trials	Very serious[a]	Not serious	Not serious	Very serious[b,c]	None	19/30 (63.3%)	15/29 (51.7%)	RR 1.22 (0.78, 1.91)	114 more per 1,000 (from 114 less to 471 more)	⨁◯◯◯ Very low	Critical
Recurrence												
1	Randomized trials	Very serious[a]	Not serious	Not serious	Very serious[b,c]	None	20/89 (22.5%)	7/30 (23.3%)	RR 0.96 (0.45, 2.05)	9 less per 1,000 (from 128 less to 245 more)	⨁◯◯◯ Very low	Critical

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. It is unclear whether randomization, masking, or blinding of outcome measurement was performed.

b. The sample size is not optimal to see statistically significant differences and the confidence interval exceeds 25% of the estimator.

c. It is unclear whether randomization, masking, blinding of personnel, and measurement of outcomes were performed, and losses to follow-up are reported.

Question: Meglumine antimoniate 20 mg/kg/day for 10 days compared to meglumine antimoniate 20 mg/kg/day for 20 days for complete cure in minors.

Bibliography: Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub3

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Meglumine antimoniate 20 mg/kg/day for 10 days	Meglumine antimoniate 20 mg/kg/day for 20 days	Relative (95% CI)	Absolute (95% CI)		
Full cure under 5 years old												
1	Randomized trials	Very serious[a]	Not serious	Not serious	Very serious[b]	None	1/9 (11.1%)	2/8 (25.0%)	RR 0.44 (0.05, 4.02)	140 less per 1,000 (from 238 less to 755 more)	⨁◯◯◯ Very low	Critical
Full cure 5 to 15 years												
1	Randomized trials	Very serious[a]	Not serious	Not serious	Very serious[b]	None	14/21 (66.7%)	15/30 (50.0%)	RR 0.89 (0.59, 1.34)	55 less per 1,000 (from 205 less to 170 more)	⨁◯◯◯ Very low	Critical

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. It is not clear that masking was performed, attrition bias is reported due to lack of data.

b. The sample size is not optimal to see differences and the confidence interval exceeds 25% of the estimator.

Question: 20 mg/kg/day of meglumine antimoniate for 10 days compared to 20 mg/kg/day of meglumine antimoniate for 20 days for at least a 3-month cure.

Bibliography: Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub3

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	20 mg/kg/day of MA for 10 days	20 mg/kg/day of MA for 20 days	Relative (95% CI)	Absolute (95% CI)		
Cure												
2	Randomized trials	Not serious	Serious[a]	Not serious	Serious[b]	None	49/88 (55.7%)	58/89 (65.2%)	RR 0.91 (0.69, 1.21)	59 less per 1,000 (from 202 less to 137 more)	⨁⨁◯◯ Low	Critical

Explanations

a. Moderate heterogeneity is reported; I^2:50%.

b. Confidence intervals exceed 25% of the estimator.

Question: Meglumine antimoniate 20 mg/kg/day for 15 days compared to no treatment for the management of patients with *L. panamensis*.

Bibliography: Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub3

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Meglumine antimoniate 20 mg/kg/day	No treatment	Relative (95% CI)	Absolute (95% CI)		
Cure at least 3 months												
1	Randomized trials	Serious[a]	Not serious	Not serious	Very serious[b]	None	12/33 (36.4%)	0/17 (0.0%)	RR 13.24 (0.83, 210.87)	0 minus per 1,000 (from 0 minus to 0 minus)	⨁◯◯◯ Very Low	Critical

CI: Confidence Interval; **RR:** Risk ratio

Explanations

a. Risk of detection bias

b. Sample size is not optimal to see differences; confidence intervals exceed the estimator.

Question: Meglumine antimoniate for 7 days plus placebo compared to MA for 20 days standard dose plus topical placebo for patients diagnosed with *L. braziliensis* and *L. panamensis*.

Bibliography: Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub3

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Meglumine antimoniate for 7 days plus placebo	Meglumine antimoniate for 20 days plus topical placebo	Relative (95% CI)	Absolute (95% CI)		
Complete cure												
1	Randomized trials	Serious[a]	Not serious	Not serious	Serious[b]	None	16/30 (53.3%)	26/31 (83.9%)	RR 0.64 (0.44, 0.92)	302 less per 1,000 (from 470 less to 67 less)	⨁⨁◯◯ Low	Critical

Explanations

a. Lack of masking is reported and it is unclear whether outcome measurement was blinded.

b. The confidence interval exceeds 95% of the estimator.

Question: Meglumine antimoniate (20 mg/kg/day) plus tamoxifen 40 mg/day compared to meglumine antimoniate (20 mg/kg/day) for the treatment of *L. braziliensis*.

Bibliography: Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub3

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Meglumine antimoniate (20 mg/kg/day) plus tamoxifen 40 mg/day	Meglumine antimoniate (20 mg/kg/day)	Relative (95% CI)	Absolute (95% CI)		
3-month cure												
1	Randomized trials	Serious[a]	Not serious	Not serious	Very serious[b]	None	8/12 (66.7%)	8/15 (53.3%)	RR 2.25 (1.42, 3.58)	133 more per 1,000 (from 176 less to 704 more)	⨁◯◯◯ Very low	Critical
6-month cure												
1	Randomized trials	Serious[a]	Not serious	Not serious	Very serious[b]	None	7/12 (58.3%)	6/15 (40.0%)	RR 1.46 (0.67, 3.19)	184 more per 1,000 (from 132 less to 876 more)	⨁◯◯◯ Very low	Critical
Total cure												
1	Randomized trials	Serious[a]	Not serious	Not serious	Very serious[b]	None	15/24 (62.5%)	14/30 (46.7%)	RR 1.33 (0.82, 2.16)	154 more per 1,000 (from 84 less to 541 more)	⨁◯◯◯ Very low	Critical

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Biases associated with sample size are reported.

b. Very serious imprecision due to suboptimal sample size to see statistically significant differences and wide confidence intervals.

Question: Oral miltefosine 50 mg for 28 days compared to placebo for leishmaniasis caused by *L. braziliensis*, *L. panamensis*, and *L. mexicana*.

Bibliography: Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub3

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Miltefosine oral 50 mg for 28 days	Placebo	Relative (95% CI)	Absolute (95% CI)		
Complete cure (follow-up: 6 months)												
1	Randomized trials	Serious[a]	Not serious	Not serious	Serious[b]	None	60/89 (67.4%)	13/44 (29.5%)	RR 2.25 (1.42, 3.58)	369 more per 1,000 (from 124 more to 762 more)	⨁⨁◯◯ Low	Critical
Side effects (follow-up: 6 months)												
1	Randomized trials	Serious[a]	Not serious	Not serious	Serious[b]	None	9/89 (10.1%)	5/44 (11.4%)	RR 0.89 (0.32, 2.50)	12 less per 1,000 (from 77 less to 170 more)	⨁⨁◯◯ Low	Critical
Recurrence (follow-up: 6 months)												
1	Randomized trials	Serious[a]	Not serious	Not serious	Serious[b]	None	6/89 (6.7%)	1/44 (2.3%)	RR 2.97 (0.37, 23.89)	45 more per 1,000 (from 14 less to 520 more)	⨁⨁◯◯ Low	Critical

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Possible selection bias due to lack of masking and randomization is not described. Blinding is not described. The power of the study is low.

b. Sample size is not optimal for finding differences; wide confidence intervals that exceed 25% of the estimator.

Question: Oral miltefosine compared to meglumine antimoniate for leishmaniasis by species.

Bibliography: Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub3

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Miltefosine oral	Meglumine antimoniate	Relative (95% CI)	Absolute (95% CI)		
Complete cure (follow-up: range 6 months to 12 months)												
7	Randomized trials	Serious[a]	Serious	Not serious	Not serious	None	271/380 (71.3%)	205/296 (69.3%)	RR 1.05 (0.90, 1.23)	35 more per 1,000 (from 69 less to 159 more)	⨁⨁◯◯ Low	Critical
Complete cure in children aged 2 to 12 years (follow-up: range 6 months to 12 months)												
2	Randomized trials	Not serious	Not serious	Not serious	Serious[b]	None	60/77 (77.9%)	45/67 (67.2%)	RR 1.19 (0.98, 1.46)	128 more per 1,000 (from 13 less to 309 more)	⨁⨁⨁◯ Moderate	Critical
Side effects: Nausea (follow-up: range 6 months to 12 months)												
3	Randomized trials	Serious[a]	Not serious	Not serious	Serious[b]	None	92/246 (37.4%)	32/218 (14.7%)	RR 2.45 (1.72, 3.49)	213 more per 1,000 (from 106 more to 366 more)	⨁⨁◯◯ Low	Critical
Side effects: Vomiting (follow-up: range 6 months to 12 months)												
3	Randomized trials	Serious[a]	Serious[d]	Not serious	Serious[c]	None	84/246 (34.1%)	19/218 (8.7%)	RR 4.76 (1.82, 12.46)	328 more per 1,000 (from 71 more to 999 more)	⨁◯◯◯ Very low	Critical
Healing speed												
1	Randomized trials	Very serious[a]	Not serious	Not serious	Serious [b, c]	None	31/44 (70.5%)	16/16 (100.0%)	RR 0.72 (0.59, 0.89)	280 minus per 1,000 (from 410 minus to 110 minus)	⨁◯◯◯ Very low	Critical

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Some included studies do not report masking and may have detection bias due to lack of blinding of staff and patients

b. Sample size is not optimal for finding differences.

c. Confidence intervals are wide.

d. Moderate heterogeneity is present; I^2: 48%.

e. High risk of bias due to selection, detection, and performance biases.

Question: 7 doses of pentamidine (2 mg/kg) compared to meglumine antimoniate 20 mg/kg for 20 days for patients with *L. braziliensis*.

Bibliography: Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub3

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other consider-ations	7 doses of pentamidine (2 mg/kg)	Meglumine antimoniate 20 mg/kg for 20 days	Relative (95% CI)	Absolute (95% CI)		
Complete cure (follow-up: 4 months)												
1	Randomized trials	Not serious	Not serious	Not serious	Very serious[a]	None	14/40 (35.0%)	31/40 (77.5%)	RR 0.45 (0.29, 0.71)	426 less per 1,000 (from 550 less to 225 less)	⨁⨁◯◯ Low	Critical
Headache												
1	Randomized trials	Not serious	Not serious	Not serious	Very serious[a]	None	20/40 (50.0%)	33/40 (82.5%)	RR 0.61 (0.43, 0.85)	322 less per 1,000 (from 470 less to 124 less)	⨁⨁◯◯ Low	Critical

CI: Confidence Interval; **RR:** Risk ratio

Explanations

a. The sample size is not optimal to see the expected effect. The confidence interval exceeds 95% of the estimator.

Question: IM pentamidine compared to IM meglumine antimoniate 20 days for patients diagnosed with *L. braziliensis*.

Bibliography: Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub3

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Pentamidine IM	Meglumine antimoniate IM 20 days	Relative (95% CI)	Absolute (95% CI)		
Complete cure												
3	Randomized trials	Serious[a]	Not serious	Not serious	Serious[b]	None	71/111 (64.0%)	77/115 (67.0%)	RR 0.95 (0.81, 1.13)	33 less per 1,000 (from 127 less to 87 more)	⨁⨁◯◯ Low	Critical
Arthralgia												
2	Randomized trials	Serious[a]	Not serious	Not serious	Very serious[b,c]	None	5/77 (6.5%)	20/79 (25.3%)	RR 0.27 (0.11, 0.69)	185 less per 1,000(from 225 less to 78 less)	⨁◯◯◯ Very low	Critical

CI: Confidence Interval; **RR:** Risk ratio

Explanations

a. It is unclear whether randomization, masking, and blinding were performed.

b. The sample size is not optimal to find the expected differences.

c. The confidence interval exceeds 25% of the estimator.

Question: Pentamidine 7 mg/kg single dose compared to pentamidine three doses for patients with *L. guyanensis*.

Bibliography: Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub3

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Pentamidine 7 mg/kg single dose	Pentamidine three doses	Relative (95% CI)	Absolute (95% CI)		
Cures at least 6 months												
1	Randomized trials	Not serious	Not serious	Not serious	Very serious[a]	None	24/53 (45.3%)	51/53 (96.2%)	RR 0.47 (0.35, 0.64)	510 minus per 1,000 (from 625 minus to 346 minus)	⨁⨁◯◯ Low	Critical

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. The sample size is not optimal for finding differences. The confidence interval exceeds 25% of the estimator.

Question: Thermotherapy compared to placebo for patients with *L. braziliensis*.

Bibliography: Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub3

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Thermotherapy	Placebo	Relative (95% CI)	Absolute (95% CI)		
Cures at least 3 months												
1	Randomized trials	Serious[a]	Not serious	Not serious	Very serious[b]	None	16/22 (72.7%)	6/22 (27.3%)	RR 2.67 (1.29, 5.53)	455 plus per 1,000 (from 79 plus to 1,000 plus)	⨁◯◯◯ Very low	Critical

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. It is not clear that randomization, masking, blinding was performed for the measurement of outcomes.

b. The sample size is not optimal to see expected differences, and the confidence interval exceeds 25% of the estimator.

Question: Thermotherapy compared to meglumine antimoniate 20 mg/kg for 15 days IM for patients diagnosed with *L. braziliensis* and *L. panamensis.*

Bibliography: Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub3

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Thermotherapy	Meglumine antimoniate 20 mg/kg for 15 days IM	Relative (95% CI)	Absolute (95% CI)		
Complete cure												
1	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	86/149 (57.7%)	103/143 (72.0%)	RR 0.80 (0.68, 0.95)	144 minus per 1,000 (from 230 minus to 36 minus)	⨁⨁⨁◯ Moderate	Critical

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. The confidence interval exceeds 25% of the estimator.

Question: Paromomycin 15% plus gentamicin 0.5% compared to topical paromomycin 15% alone for patients with *L. panamensis*.

Bibliography: Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub3

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Paromomycin 15% plus gentamicin 0.5%.	Paromomycin topical 15% alone	Relative (95% CI)	Absolute (95% CI)		
Complete cure (adults and pediatric population)												
2	Randomized trials	Serious[a]	Very serious[b]	Serious[c]	Serious[d]	None	164/216 (75.9%)	159/213 (74.6%)	RR 1.19 (0.74, 1.91)	142 more per 1,000 (from 194 less to 679 more)	⨁◯◯◯ Very low	Critical
Cure in children under 12 years of age												
1	Randomized trials	Serious[a]	Not serious	Not serious	Very serious[d, e]	None	48/61 (78.7%)	42/46 (91.3%)	RR 0.86 (0.74, 1.01)	128 less per 1,000 (from 237 less to 9 more)	⨁◯◯◯ Very low	Critical
Cure in children from 12 to 17 years of age												
1	Randomized trials	Serious[a]	Not serious	Not serious	Very serious[d, e]	None	31/35 (88.6%)	32/42 (76.2%)	RR 1.16 (0.95, 1.43)	122 more per 1,000 (from 38 less to 328 more)	⨁◯◯◯ Very low	Critical

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. It is not clear whether masking or blinding for outcome measurement was performed.

b. High heterogeneity is reported; I^2:72%.

c. Data include pediatric and adult population.

d. Confidence intervals exceed 25% of the estimator.

e. The sample size does not allow us to see effect.

Question: Paromomycin topical for 20 days compared to placebo for patients diagnosed with *L. panamensis* and *L. mexicana*.

Bibliography: Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub3

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Paromomycin topical for 20 days	Placebo	Relative (95% CI)	Absolute (95% CI)		
Complete cure												
1	Randomized trials	Not serious	Not serious	Not serious	Very Serious[a]	None	31/38 (81.6%)	13/38 (34.2%)	RR 2.38 (1.50, 3.80)	472 more per 1,000 (from 171 more to 958 more)	⨁⨁◯◯ Low	Critical

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. The sample size is not optimal to find the expected differences. The confidence interval exceeds 25% of the estimator.

Question: Oral pentoxifylline (1,200 mg/day) plus MA compared to meglumine antimoniate 20 mg/kg plus placebo for patients with *L. braziliensis*.

Bibliography: Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub3

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Oral pentoxifylline (1,200 mg/day) plus MA	Meglumine antimoniate 20 mg/kg plus placebo	Relative (95% CI)	Absolute (95% CI)		
Complete cure												
1	Randomized trials	Not serious	Not serious	Not serious	Very serious[a]	None	22/34 (64.7%)	27/36 (75.0%)	RR 0.86 (0.63, 1.18)	105 less per 1,000 (from 277 less to 135 more)	⨁⨁◯◯ Low	Critical

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. The sample size is not optimal for finding differences. The confidence interval exceeds 25% of the estimator.

Question 2

What is the efficacy and safety of the different pharmacological treatments for the management of patients diagnosed with mucosal leishmaniasis in the Americas?

Question: Meglumine antimoniate (14 mg/kg/day) compared to meglumine antimoniate (28 mg/kg/day) for cutaneous or mucocutaneous leishmaniasis.

Bibliography: Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub3

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Meglumine antimoniate 14 mg/kg/day	Meglumine antimoniate 28 mg/kg/day	Relative (95% CI)	Absolute (95% CI)		
Complete cure (follow-up: 1 year)												
1	Randomized trials	Not serious	Not serious	Not serious	Very serious[a]	None	4/10 (40.0%)	4/7 (57.1%)	RR 1.43 (0.53, 3.86)	246 more per 1,000 (from 269 less to 1,000 more)	⨁⨁◯◯ Low	Critical

CI: Confidence interval**; RR:** Risk ratio

Explanations

a. Sample size is not optimal for finding differences; wide confidence intervals that exceed 25% of the estimator.

Question: Sodium stibogluconate for 28 days compared to sodium stibogluconate for 40 days for mucosal or mucocutaneous leishmaniasis.

Bibliography: Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub3

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Sodium stibogluconate for 28 days	Sodium stibogluconate for 40 days	Relative (95% CI)	Absolute (95% CI)		
Complete cure (follow-up: 1 year)												
1	Randomized trials	Serious[a]	Not serious	Not serious	Very serious[b]	None	12/20 (60.0%)	10/20 (50.0%)	RR 0.83 (0.47, 1.47)	85 less per 1,000 (from 265 less to 235 more)	⨁◯◯◯ Very low	Critical

Explanations

a. The study does not present sufficient power; no intention-to-treat analysis was performed.

b. Sample size is not optimal for finding differences; wide confidence intervals that exceed 25% of the estimator.

Question: Oral pentoxifylline with sodium stibogluconate compared to sodium stibogluconate for mucosal leishmaniasis, *L. braziliensis*.

Bibliography: Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub3

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Oral pentoxifylline with sodium stibogluconate	Sodium stibogluconate	Relative (95% CI)	Absolute (95% CI)		
Cure in 4 months of *L. braziliensis* (follow-up: 6 months)												
1	Randomized trials	Serious[a]	Not serious	Not serious	Very serious[b]	None	11/11 (100.0%)	7/12 (58.3%)	RR 1.66 (1.03, 2.69)	385 more per 1,000 (from 18 more to 986 more)	⨁◯◯◯ Very low	Critical

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. No mention is made of how the concealment was performed.

b. Sample size is not optimal for finding differences; wide confidence intervals that exceed 25% of the estimator.

Question: Allopurinol with IV SS compared to IV SS for mucosal or mucocutaneous leishmaniasis.

Bibliography: Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub3

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Allopurinol with SS IV	SS IV	Relative (95% CI)	Absolute (95% CI)		
Complete cure												
1	Randomized trials	Serious[a]	Not serious	Not serious	Very serious[b]	None	14/10 (140.0%)	23/41 (56.1%)	RR 0.62 (0.38, 1.03)	213 less per 1,000 (from 348 less to 17 more)	⨁◯◯◯ Very low	Critical

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Open study.

b. Sample size is not optimal for finding differences; wide confidence intervals that exceed 25% of the estimator.

Question: Oral miltefosine compared to meglumine antimoniate for mucosal or mucocutaneous leishmaniasis.

Bibliography: Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub3

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Oral miltefosine	Meglumine antimoniate	Relative (95% CI)	Absolute (95% CI)		
Complete cure												
2	Randomized trials	Very serious[a]	Not serious	Not serious	Serious[b]	None	-/20	-/20	RR 1.04 (0.81, 1.34)	0 minus per 1,000 (from 0 minus to 0 minus)	⨁◯◯◯ Very low	Critical
Side effects												
1	Randomized trials	Very serious[a]	Not serious	Not serious	Serious[b]	None	-/10	-/10	RR 2.97 (1.05, 8.38)	0 minus per 1,000 (from 0 minus to 0 minus)	⨁◯◯◯ Very low	Critical

Explanations

a. No blinding was performed; no intention-to-treat analysis was performed.

b. Sample size is not optimal for finding differences; wide confidence intervals that exceed 25% of the estimator.

Question: Oral pentoxifylline 400 mg 3 times daily for 30 days with SS compared to SS for mucosal or mucocutaneous leishmaniasis.

Bibliography: Pinart M, Rueda J-R, Romero GAS, Pinzón-Flórez CE, Osorio-Arango K, Silveira Maia-Elkhoury AN, et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub3

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Oral pentoxifylline 400 mg 3 times a day for 30 days with SS	SS	Relative (95% CI)	Absolute (95% CI)		
Complete cure (follow-up: 4 months)												
1	Randomized trials	Serious[a]	Not serious	Not serious	Very serious[b]	None	11/11 (100.0%)	7/12 (58.3%)	RR 1.66 (1.03, 2.69)	385 more per 1,000 (from 18 more to 986 more)	⨁◯◯◯ Very low	Critical
Improvement rate at 4 months												
1	Randomized trials	Serious[a]	Not serious	Not serious	Very serious[b]	None	11	12	-	MD 62 less (121.92 less than 2.08 less)	⨁◯◯◯ Very low	Critical

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. The type of *Leishmania* is not specified and no sample calculation was performed.

b. Sample size is not optimal for finding differences; wide confidence intervals that exceed 25% of the estimator.

Question 3

What is the efficacy and safety of the different pharmacological treatments for the management of non-immunocompromised patients diagnosed with visceral leishmaniasis in the Americas?

Question: Amphotericin B compared with antimonials for VL in pediatric population.

Bibliography: Borges MM, da Silva Pranchevicius MC, Noronha EF, Romero GAS, Carranza-Tamayo CO. Efficacy and safety of amphotericin B deoxycholate versus N-methylglucamine antimoniate in pediatric visceral leishmaniasis: An open-label, randomized, and controlled pilot trial in Brazil. Rev Soc Bras Med Trop 2017;50(1):67-74

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Amphotericin B	Antimonials	Relative (95% CI)	Absolute (95% CI)		
6-month cure												
1	Randomized trials	Very serious[a]	Not serious	Not serious	Serious[b,c]	None	95/109 (87.2%)	86/111 (77.5%)	RR 1.00 (0.91, 1.10)	93 more per 1,000 (from 8 less to 209 more)	⨁⨁◯◯ Low	Critical
Discontinuation due to side effects												
1	Randomized trials	Very serious[a]	Not serious	Not serious	Serious[b]	None	2/50 (4.0%)	3/51 (5.9%)	RR 0.68 (0.12, 3.90)	19 less per 1,000 (from 52 less to 171 more)	⨁⨁◯◯ Low	Critical
180-day relapse												
1	Randomized trials	Very serious[a]	Not serious	Not serious	Serious[c]	None	1/50 (2.0%)	0/51 (0.0%)	RR 7.54 (0.15, 378)	0 minus per 1,000 (from 0 minus to 0 minus)	⨁⨁◯◯ Low	Critical

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Selection bias, detection, attrition, low power to see differences.

b. Small sample size.

b. Wide confidence intervals exceeding 25% of the estimator.

Question: Miltefosine oral for VL

Bibliography: Carnielli JBT, Monti-Rocha R, Costa DL, Molina Sesana A, Pansini LNN, Segatto M, et al. Natural Resistance of Leishmania infantum to Miltefosine Contributes to the Low Efficacy in the Treatment of Visceral Leishmaniasis in Brazil. Am J Trop Med Hyg. 2019 Oct;101(4):789-794. doi: 10.4269/ajtmh.18-0949. PMID: 31436148; PMCID: PMC6779219.

Certainty assessment							Impact	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations			
Percentage of patients free of VL events (follow-up: 1 year).									
1	Randomized trials	Very serious[a]	Not serious	Not serious	Very serious[b]	None	Definitive cure was evaluated at 6 months follow-up, finding a 42% (14 patients) cure rate at 28 days of treatment and a 68% (28 patients) cure rate at 42 days of treatment.	⨁◯◯◯ Very low	Critical
Side effects									
1	Randomized trials	Very serious[a]	Not serious	Not serious	Very serious[b]	None	No adverse events occurred	⨁◯◯◯ Very low	Critical

CI: Confidence interval

Explanations

a. Selection and detection bias due to lack of blinding; expected sample size was not reached.

b. Sample size is not optimal for finding differences; wide confidence intervals that exceed 25% of the estimator.

Question 4

What is the efficacy and safety of the different pharmacological treatments for the management of immunocompromised patients diagnosed with visceral leishmaniasis in the Americas?

Question: Liposomal amphotericin B compared with antimonials for the treatment of VL in HIV coinfected patients.

Bibliography: Meta-analysis available in Figures A3,A4,A5,A6 and A7

Laguna F. Treatment of leishmaniasis in HIV-positive patients. Ann Trop Med Parasitol. 2003;97(Suppl 1):135-42

Laguna F, López-Vélez R, Pulido F, Salas A, Torre-Cisneros J, Torres E, et al. Treatment of visceral leishmaniasis in HIV-infected patients: a randomized trial comparing meglumine antimoniate with amphotericin B. Spanish HIV-Leishmania Study Group. AIDS. 1999 Jun.18;13(9):1063-9. doi: 10.1097/00002030-199906180-00009. PMID: 10397536.s

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Liposomal amphotericin B	Antimonials	Relative (95% CI)	Absolute (95% CI)		
Global cure at least one year												
2	Randomized trials	Very serious[a]	Not serious	Serious[b]	Serious[c]	None	36/65 (55.4%)	36/63 (57.1%)	RR 0.96 (0.72, 1.29)	23 less per 1,000 (from 160 less to 166 more)	⨁◯◯◯ Very low	Critical
Treatment abandonment												
2	Randomized trials	Very serious[a]	Very serious[d]	Serious[b]	Serious[c]	None	7/65 (10.8%)	9/64 (14.1%)	RR 1.28 (0.02, 69.15)	39 plus per 1,000 (from 138 minus to 1,000 plus)	⨁◯◯◯ Very low	Critical
Death												
2	Randomized trials	Very serious[a]	Not serious	Serious[b]	Serious[c]	None	5/65 (7.7%)	8/63 (12.7%)	RR 0.57 (0.10, 3.36)	55 less per 1,000 (from 114 less to 300 more)	⨁◯◯◯ Very low	Critical
At least one side effect												

2	Randomized trials	Very serious[a]	Not serious	Serious[b]	Serious[c]	None	28/65 (43.1%)	29/63 (46.0%)	RR 0.60 (0.11, 3.39)	184 less per 1,000 (from 410 less to 1,000 more)	⨁◯◯◯ Very low	Critical
Relapse												
2	Randomized trials	Very serious[a]	Not serious	Serious[b]	Serious[c]	None	16/44 (36.4%)	18/43 (41.9%)	RR 0.87 (0.51, 1.48)	54 less per 1,000 (from 205 less to 201 more)	⨁◯◯◯ Very low	Critical

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Selection and detection bias due to lack of blinding and masking.

b. The study was conducted in Spain. The GDG considers that the results can be extrapolated to VL in Latin America.

c. Sample size is not optimal for finding differences; wide confidence intervals that exceed 25% of the estimator.

d. An I^2 of 84% is reported.

e. I^2 of 67% is reported.

Question 5

What is the efficacy and safety of secondary prophylaxis for the management of immunocompromised patients diagnosed with visceral leishmaniasis in the Americas?

Question: Amphotericin B compared to no treatment for secondary prophylaxis of HIV and VL infected population.

Bibliography: López-Vélez R, Videla S, Márquez M, Boix V, Jiménez-Mejías ME, Górgolas M, et al. Amphotericin B lipid complex versus no treatment in the secondary prophylaxis of visceral leishmaniasis in HIV-infected patients. J Antimicrob Chemother. 2004 Mar;53(3):540-3. doi: 10.1093/jac/dkh084. Epub 2004 Jan 22. PMID: 14739148.

Certainty assessment							Impact	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations			
Percentage of patients free of VL events (follow-up: 1 year).									
1	Randomized trials	Very serious[a]	Not serious	Serious[b]	Very serious[c]	None	50% of participants remained free of VL events at 1-year follow-up (95% CI 15.7, 84.3) in the amphotericin group and 22.2% in the untreated group (95% CI 2.8, 60) (p = 0.141).	⨁◯◯◯ Very low	Critical
Side effects									
1	Randomized trials	Very serious[a]	Not serious	Serious[b]	Very serious[c]	None	The amphotericin group presented more mild side effects (88%) that were tolerated by the participants compared to the control group (33%) (p = 0.0032).	⨁◯◯◯ Very low	Critical

CI: Confidence interval

Explanations

a. Selection and detection bias due to lack of blinding. The expected sample size was not reached.

b. The study was conducted in Spain.

c. The sample size is too small to observe differences.

Question: Liposomal amphotericin B compared to no treatment for secondary prophylaxis of HIV and VL infected population.

Bibliography: Molina I, Falcó V, Crespo M, Riera C, Ribera E, Curran A, et al. J Antimicrob Chemother. 2007 Oct;60(4):837-42. doi: 10.1093/jac/dkm294.

Certainty							Impact	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations			
Probability of remaining free of relapse									
1	Observational study	Very serious[a]	Not serious	Serious[b]	Very serious[c]	None	At 6 months it was 89.7% (95% CI 76.2, 100), at 12 months it was 79.1% (95% CI 61, 97.2) and 24–36 months it was 55% (95% CI 30.5, 81.3).	⨁◯◯◯ Very low	Critical
Side effects									
1	Randomized trials	Very serious[a]	Not serious	Serious[b]	Very serious[c]	None	20% of patients had moderate renal function impairment without the need for treatment modification	⨁◯◯◯ Very low	Critical

CI: Confidence interval

Explanations

a. Selection bias, did not control for confounding factors, detection bias.

b. The study was conducted in Spain.

c. The sample size is too small to observe differences.

Guideline for the treatment of leishmaniasis

Leishmaniases are neglected infectious diseases of great importance in the Americas because of their morbidity, mortality, and wide geographical distribution. Out of the three main clinical forms of leishmaniasis, cutaneous leishmaniasis is the most common and the visceral form is the most severe, causing death in up to 90% of untreated people.

In 2013, the Pan American Health Organization (PAHO) developed recommendations for the treatment of leishmaniases in the Americas using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. However, given the new evidence that has accumulated since that time, there was a need to revise those recommendations. This second edition presents updated therapeutic recommendations for leishmaniases, detailing the treatment indications, criteria and schemes in the regional context.

These guidelines include several notable changes from the first edition. For cutaneous leishmaniasis, ketoconazole has been removed from the list of treatment options; the number of Leishmania species for which there is strong evidence for the efficacy of miltefosine has increased from two to four; and the recommendation for intralesional antimonials is now strong. For mucosal leishmaniasis there is now a strong recommendation for use of pentavalent antimonials with or without oral pentoxifylline. For visceral leishmaniasis, the strong recommendations for use of pentavalent antimonials and amphotericin B deoxycholate are now conditional. For miltefosine, there is strong evidence against its usage in patients with leishmaniasis caused by *Leishmania infantum*. Further important changes include the division of recommendations by adult and pediatric populations, the addition of *Leishmania* species, and for immunocompromised patients, a strong recommendation against the use of pentavalent antimonials.

PAHO
Pan American Health Organization
World Health Organization
REGIONAL OFFICE FOR THE Americas