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Intravenous liposomal amphotericin B efficacy and safety for cutaneous and mucosal leishmaniasis: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction Treatment of cutaneous and mucosal leishmaniasis (CL and ML, respectively) must be individualised as there is no universal therapeutic approach. Intravenous liposomal amphotericin B (L-AmB) is an accessible and relatively safe treatment that has been increasingly used for the treatment of CL and ML. While several descriptive studies have been published on the efficacy and safety of L-AmB, there are no interventional studies. Moreover, the findings from published studies have not yet been integrated and synthesised. Therefore, we aim to evaluate and consolidate the descriptive evidence on the efficacy and the safety of Intravenous L-AmB treatment for CL and ML in both the New and Old World.

Methods and analyses A systematic review of all relevant study types with no restriction on date or language of publication will be conducted. Online databases including MEDLINE, The Cochrane Library, EMBASE, EBSCO, Scopus, Ovid and WHO databases were searched on 3 April 2020. The search included all study types that assess Intravenous L-AmB treatment for CL and ML in humans. The Population, Intervention, Comparison, Outcome and Study Design strategy and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines will be used to determine which studies will be selected for final inclusion. The quality of included case series and case reports will be assessed using modified quality assessment tools. A narrative synthesis of the findings will be provided and the primary outcome and secondary outcome of interest, response rate and adverse events rate, respectively, and the 95% CI will be ascertained. Estimates from individual studies will be pooled using random-effects model.

Ethics and dissemination This systematic review does not require formal ethical approval since no primary data will be collected. Findings will be disseminated through a peer-reviewed publication and relevant conferences.

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Strengths and limitations of this study

- This systematic review will help increase the body of knowledge on the efficacy and safety of intravenous liposomal amphotericin B (L-AmB) treatment for cutaneous and mucosal leishmaniasis (CL and ML, respectively).
- Inclusion of all study types with no restrictions on date and language of publication will ensure a comprehensive review of the evidence available.
- This systematic review expects to highlight the need for high-quality clinical trials to determine how L-Amb compares to the other therapeutic options for the treatment of CL and ML.
- Heterogeneity among studies with different human populations, parasite species, clinical presentations and varying definitions of cure/response rates as a result of intravenous L-AmB treatment may pose an obstacle in consolidating the evidence gathered from this review.

BACKGROUND

Leishmaniasis is a neglected tropical disease caused by *Leishmania* parasites transmitted through the bite of female sandflies. Close to 20 different species of *Leishmania* are involved in human cutaneous leishmaniasis (CL) and the geographical distribution of this parasitic infection is often divided between the Old World (Mediterranean basin, the Middle East, the Horn of Africa and South and Central Asia) and the New World (Americas), which largely correlates with aetiological species. With approximately 0.7–1.2 million new cases of CL estimated to occur annually worldwide, the disease is of global importance.[1] Ecosystem changes due to global warming, increased migration, political instability, war zones and growing numbers of travellers in endemic areas have the potential of significantly increasing the number of incident cases of leishmaniasis globally and altering epidemiologic characteristics.

The clinical manifestations of CL and mucosal leishmaniasis (CL and ML, respectively) vary, depending on many factors including the acquired species, strains, and virulence factors as well as host

characteristics.[2 3] The variety of clinical manifestations and lack of awareness in primary care settings may impede accurate diagnosis. Diagnosis of CL and ML can be achieved through a number of laboratory tests including amastigote visualisation on microscopy, histopathological examination of tissue specimens, culture and nucleic acid amplification-based methods with PCR being the most commonly used. Identifying the species of *Leishmania* is recommended by the Infectious Diseases Society of America to improve case management.[4]

The treatment of leishmaniasis remains challenging as there is no ideal and universally applicable therapeutic approach. Treatment for leishmaniasis may either be local or systemic. Patients who are at an increased risk of acquiring ML (for living or travelling in endemic areas); patients who present with larger and more complex lesions; those with subcutaneous nodules; and those who are immunocompromised typically receive systemic treatment. Suboptimal management could lead to superinfections, chronic wounds or increased scarring, with attendant disfigurement and functional limitations.[5] Systemic use of antimonial compounds has served as principal antileishmanial treatment for both Old and New World parasites for decades and has been considered the gold standard against which all other treatments are assessed.[4 6] The predominant shortcomings of antimonial therapy include their toxicity and limited accessibility in some locations. In Canada and the USA, these compounds are only accessible through the Health Canada Special Access Programme and the Center for Disease Control and Prevention (CDC) Programme, respectively.

Amphotericin B deoxycholate has been administered as an alternative therapy for CL. However, newer lipid formulations of this agent are better tolerated and are much less nephrotoxic than conventional amphotericin B and antimonial agents. Liposomal amphotericin B (L-AmB) is a widely used agent, mainly for fungal infections and is the treatment of choice for visceral leishmaniasis (VL) in many regions. While L-AmB had not been indicated as official treatment for tegumentary leishmaniasis, it has proven efficacy over time in the treatment of VL since its approval by the Food and Drug Administration in 1997.[7 8] Since then, L-AmB has also been used to treat both CL and ML based on its efficacy in treating VL. However, caution should be taken when extrapolating L-AmB efficacy from VL studies; skin penetration of L-AmB is not well studied and species-related differences in L-AmB susceptibility are also important considerations.

There are no published interventional studies that assess the efficacy of L-AmB in the treatment of CL and ML. During our initial literature search, we found that the data available on treatment efficacy are not only heterogeneous, but they are solely based on descriptive studies. Well cited examples include a study by Wortmann and colleagues conducted in 2010 which demonstrated a response rate of 84% in a group of 20 patients diagnosed with CL caused by a variety of strains of parasites, using a regimen of 3 mg/kg/day of L-AmB for up to 10 doses over a period of 21 days.[9] Subsequent studies have shown similar response rates in the range of 83%–88%, which is within the range reported for other commonly used treatments.[10–13] A study by Guery *et al* retrospectively analysed the efficacy of L-AmB in patients with CL and ML using a French database and demonstrated a 46% response rate after a single course treatment.[14] The response rate was 63% when they included patients with delayed healing and patients who required a second course of L-AmB.[14] More recent findings from Senchaya *et al* demonstrated a 72% cure rate in CL patients on short-term treatment with L-AmB. Their findings also suggest the potential for shorter hospitalisation periods as a result of CL treatment with L-AmB.[15] Our experience at the J.D. MacLean Centre for Tropical Diseases at McGill University demonstrated a cure rate of 69% when L-AmB was used as a first-line agent for CL and 75% when L-AmB was used either as first or second-line treatment.[16] Adverse event rates have been reported between 30% and 53%.[11 14 16] Such differences between studies may result from the diversity of species that are capable of causing CL and ML, treatment regimens, diversity of populations studied and clinical manifestations. Moreover, the heterogeneity in response rates highlight the need for high-quality clinical trials to better assess L-AmB efficacy and safety for the treatment of CL and ML.

Given the global burden of leishmaniasis coupled with limited options and availability of treatment, there is a pressing need for increasing evidence on the efficacy and safety of L-AmB to better inform therapeutic management. With a potentially safer toxicity profile and overall greater accessibility in some regions, L-AmB presents as an appealing option. Nevertheless, better data on efficacy and safety are paramount when it comes to therapeutic choices. Through this systematic review, we aim to consolidate the descriptive evidence specifically on the efficacy and safety of intravenous L-AmB treatment for CL and ML acquired by travellers, migrants and residents of both the New and Old World regions.

METHODS AND DESIGN

Search strategy and study selection

This systematic review was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[17] The search strategy was developed with the assistance of a medical librarian and consisted of text words and relevant indexing to identify studies treating CL and ML with L-AmB. The following databases were searched for relevant studies on 3 April 2020: MEDLINE (via Ovid and via PubMed); The Cochrane CENTRAL Register of Controlled Trials & Cochrane Database of Systematic Reviews (via Wiley); Embase (via Ovid); Africa-Wide Information (via EBSCO); Global Health (via Ovid); Global Index Medicus (via WHO); Scopus (via Elsevier). On 20 April 2020, we searched clinical trials registries (ClinicalTrials.gov, International Clinical Trials Registry Platform). No

Table 1 Population, Intervention, Comparison, Outcome and Study Design (PICOS) strategy and inclusion and exclusion criteria

PICOS item	Inclusion criteria	Exclusion criteria
Population	All individuals being treated for CL/ML of varying immune status who travelled to or are residents of leishmaniasis-endemic areas, as well as migrants with no restrictions on age and geography; Patients being treated for CL/ML (simple or complex), diffuse, disseminated CL and/or leishmania recidivans.	Patients with visceral leishmaniasis and the post-kala-azar dermal leishmaniasis; Animals.
Intervention	Intravenous Liposomal Amphotericin B (IV L-AmB) (alone or as part of combination therapy).	Intralesional and topical amphotericin B and any other local or systemic treatments including any other lipid formulations of amphotericin B for CL and ML.
Comparator	Other treatment regimens or controls that do not include IV L-AmB as presented in interventional/observational studies. If included studies do not consist of interventional/observational studies, a comparator is not applicable.	
Outcomes	The efficacy and potential toxicity/adverse effects (safety) of IV L-AmB treatment against CL and ML.	Studies that do not report the efficacy or safety from IV L-AmB treatment for CL and ML. Studies that fail to follow-up participants for at least 4 weeks will be included only in the safety analysis.
Study Design	Case reports, case-series, observational and interventional studies (if any).	Animal and in vitro studies

CL, cutaneous leishmaniasis; IV L-AmB, intravenous liposomal amphotericin B; ML, mucosal leishmaniasis.

restrictions on date and language of publication were applied in effort to optimise the evidence to be captured. The MEDLINE search strategy was applied to all databases with appropriate modifications (online supplemental appendix 1). In addition, further studies will be identified in Web of Science and Scopus by carrying out citation searches for the reference lists of included studies. The MEDLINE search strategy will be rerun prior to submission to capture studies published in the intervening time interval. The bibliographic software EndNote will be used for the purposes of citation management and storage. The implementation of the search strategy occurred prior to the selection of relevant studies and data extraction as per the PRISMA guidelines.[17] Additionally, the Population, Intervention, Comparison, Outcome and Study Design strategy was used to formulate the research question, the inclusion and exclusion criteria and to guide the overall review process (table 1).[18]

Table 1 provides a summary of the studies considered relevant for this review. In our review, we will include all studies with the exception of in-vitro and animal studies that assess the efficacy of intravenous L-AmB treatment for CL and ML. The included studies may be performed on children (less than 18 years of age) and/or adults who are migrants, travellers and residents of CL/ML-endemic areas. The populations under review will also include individuals of varying immune status. Studies that assess patients with VL and the post-kala-azar dermal leishmaniasis will be excluded. We intend to include all studies that use intravenous L-AmB treatment for CL and ML while studies focusing solely on the use of intralesional or topical amphotericin B treatment or other forms of systemic treatment including other lipid formulations of amphotericin B will be excluded. Diagnosis of CL/ML must be confirmed through either visualisation of amastigotes on a smear or on histopathology of lesion biopsy, a positive culture or nucleic acid amplification testing such as PCR. The primary outcome of interest is the efficacy of intravenous L-AmB in the healing of cutaneous or mucosal lesions. Treatment outcomes will be classified at three timepoints: 28–83 days for 'initial response'; 84–179 days for 'initial cure' and 180–360 days for 'definitive cure'.[19] Cure will be defined as an ulcer that is completely reepithelialised on both days 84 and 180–360.[19] Studies vary with respect to the timepoints used and our systematic review will reflect this variation. A secondary outcome of interest is the toxicity profile and adverse events (safety) associated with intravenous L-AmB treatment for CL and ML. We aim to consolidate all side effects reported during and following treatment with intravenous L-AmB. Upon consolidation, we will categorise the adverse effects based on degree of severity (mild, moderate, or severe). Studies that fail to report the efficacy or response rate of intravenous L-AmB treatment for CL/ML and those that do not follow-up study participants for a minimum of 4 weeks will not be analysed based on the primary outcome of treatment efficacy but will be included in the analysis of adverse events regardless of the length of the follow-up. Finally, a variety of study designs will be incorporated in our review, including case reports, case series, observational and interventional studies (if any) and conference abstracts.

Screening and data extraction

Titles and abstracts of studies retrieved using the predefined search strategies and those from additional sources (eg, clinical trials registries, Web of Science and Scopus) will be screened independently by two review authors (KN and JC) to identify studies that meet the inclusion criteria. Inclusion of an article will be re-evaluated among the two reviewers if there is a disagreement. If the disagreement persists, an expert reviewer (SB) will make the final decision. Next, the full text of potential eligible studies will be independently assessed by the two review authors (KN and JC). Articles that meet all of the inclusion criteria will be submitted for data extraction by one of the three review authors who will read the full-text articles. Relevant data from the studies that meet the inclusion criteria will be extracted and incorporated into three separate standard data extraction forms by three reviewers (KN, JC and FN). These three extraction forms will be merged once complete. Extracted data will include: general and methodological study characteristics and more specific variables including, but not limited to: baseline population characteristics (eg, age, sex, ethnicity, immune status), number of patients, country of acquisition, type of leishmaniasis (CL/ML), method of diagnosis, species identified, specific details on treatment regimen, previous treatment (if applicable), efficacy definition, efficacy results, follow-up duration, toxicity and adverse reactions, authors conclusion and any reported biases. In case any data is unclear or unavailable, the corresponding author for the study may be contacted for further clarification. Prior to full extraction, the reviewers (KN, JC and FN) will perform a pilot data extraction using a small random sample of the included studies. The expert reviewer (SB) will assess the pilot data extraction for quality control and concordance purposes. Cohen's kappa (κ) will be calculated based on the initial pilot data extraction to assess inter-reviewer concordance.

Risk of bias and quality assessment

Study quality and risk of bias (RoB) assessment will be performed by the three review authors (KN, JC and FN) using modified quality assessment tools. The quality assessment tools for case series and observational studies are a modified adaptation of the study quality assessment tool developed by the National Heart, Lung and Blood Institute, NIH.[20] The quality of case reports will be assessed using an adaptation of the CARE guidelines.[21] The second version of the Cochrane RoB 2 tool for randomised trials will be used to assess the quality of any potential randomised trials.[22] Any uncertainties will be addressed by the expert reviewer (SB).

Descriptive and statistical analyses

A narrative synthesis will be carried out for all studies included in our review. The response rate following treatment with intravenous L-AmB for CL and ML will be used to determine its efficacy. The timepoints at which treatment outcomes are ascertained vary between studies. Our review will consider and reflect the variation in timepoints at which outcomes are reported. The primary outcome of interest, response rate at the different timepoints mentioned above and the 95% CI will be estimated. The second outcome which consists of the rate of adverse events will be reported alongside appropriate 95% CIs. In addition to reporting the numerical rates of adverse events, we will also compile and report the specific adverse effects in our review descriptively. Response rates and adverse event rates will be presented in the form of proportions (with associated precision) for case reports and case series and in the form of effect sizes (odds ratio, hazard ratio, relative risk) for interventional/observational studies. Treatment outcomes reported at the same timepoints among the articles with the same study design will be pooled using a random-effects model.

Amendments

In the case of any amendments to the present protocol, specific details and justifications will be provided through PROSPERO prior to the publication of this review.

Patient and public involvement

Patients nor the public were involved in the design, conduct, reporting, or dissemination plans of our research.

CONCLUSION

The increasing global burden of leishmaniasis demands the need for effective, safe and accessible treatment. Intravenous L-AmB holds great potential in serving as optimal treatment for CL and ML. While a number of individual studies have reported on the efficacy and safety of intravenous L-AmB treatment, evidence on these outcomes has not yet been consolidated. Through our comprehensive systematic review, we aim to fill this evidence gap and increase the body of knowledge on leishmaniasis treatment by including all of the relevant literature. Not only will this review compile the available evidence, it will also shed light on the need for further, high-quality clinical trials on intravenous L-AmB treatment for CL/ML.

Contributors FN and SB designed, drafted and reviewed the initial manuscript while KN, JC, TE and ML provided further review. The search strategy was developed and executed by TE, SB, KN and JC. SB planned quality assessment and statistical analyses. All authors approved and contributed to the final written manuscript.

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terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

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