

# Treatment of acute Old World cutaneous leishmaniasis: A systematic review of the randomized controlled trials

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**Background:** Cutaneous leishmaniasis (CL) is caused by different species of *Leishmania* and transmitted by the bite of infected sand flies. It is a health problem in many countries.

**Objective:** This study was performed to assess the evidence for the efficacy of different therapeutic modalities for acute Old World CL, which is usually caused by *L major* and *L tropica*.

**Methods:** Evidence was reviewed according to the hierarchy of evidence. Because there have been no published systematic reviews on this topic to date, the primary source of evidence was individual randomized controlled trials (RCTs). Multiple databases were systematically searched. Using independent double review and published quality review criteria, articles were rated as good, fair, or poor. Treatment benefit data were tabulated, and conclusions were based on the rated strength of published evidence.

**Results:** In all, 50 RCTs met inclusion criteria consisting of 5515 patients in 119 study arms. Reviewed trials were highly variable in quality and methods and generally provide weak evidence for treatment of acute Old World CL.

**Limitations:** The quality of included studies was generally poor.

**Conclusions:** Well-designed randomized, double-blind, controlled trials should be designed and conducted to find better evidence for the treatment of acute Old World CL. (J Am Acad Dermatol 2007; 335:e1-e29.)

Leishmaniasis are a group of diseases caused by several species of the genus *Leishmania*, a protozoan transmitted by the bite of a tiny insect vector, the sand fly. The 4 clinical patterns of the disease in the human host are cutaneous leishmaniasis (CL), diffuse cutaneous leishmaniasis, mucocutaneous leishmaniasis, and visceral leishmaniasis.<sup>1</sup> The prevalence of the disease is in excess

of 12 million cases and 350 million people in 88 countries are at risk. The annual incidence of CL is 1 to 1.5 million cases of which 90% occur in only 7 countries: Afghanistan, Algeria, Brazil, Iran, Peru, Saudi Arabia, and Syria.<sup>1</sup>

The causative agents of CL in the Old World are *L major*, *L tropica*, *L aethiops*, and, rarely, *L infantum*. Clinically, the disease is seen in dry

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Conflicts of interest: None declared.

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*Abbreviations used:*

ACL:	anthroponotic cutaneous leishmaniasis
ARR:	absolute risk reduction
CL:	cutaneous leishmaniasis
PDT:	photodynamic therapy
RCT:	randomized controlled trial
SSG:	sodium stibogluconate
ZCL:	zoonotic cutaneous leishmaniasis
Z-HE:	Zerehsaz herbal extract
ZnSO <sub>4</sub> :	zinc sulfate

and wet forms. Anthroponotic cutaneous leishmaniasis (ACL), the dry, urban, or late ulcerative form, is generally attributed to *L tropic*; the zoonotic cutaneous leishmaniasis (ZCL), the wet, rural, or early ulcerative form, is caused by *L major*. In human beings the initial sign of infection is the appearance of an erythematous papule or nodule at the feeding site of the insect. It develops into an ulcer with a violaceous border that heals spontaneously in several weeks to months, usually with scarring.<sup>2</sup> It should be mentioned that although CL is generally considered a self-healing disease, ZCL and ACL both can adversely affect the life of the patients. At its ulcerative stage, ZCL can result in discomfort and even disability, which can result in significant loss of working hours and wages. In addition, when ZCL lesions are allowed to self heal, they can result in disfiguring scars, lifelong stigmas usually on the exposed sites of skin. Generally, ACL lesions are more chronic and in the worst scenario, they can develop into a long-lasting, destructive, and disfiguring form, known as recidivans leishmaniasis, which is very difficult to treat.<sup>1</sup> It should be mentioned that the Old World and New World forms of CL are quite different in their epidemiology, causative parasites, vectors, reservoirs as well as their clinical presentation, treatment indications, and prognosis, so it is reasonable to consider them as different diseases.<sup>1</sup>

There are many treatment modalities for CL. Physical treatments include curettage, surgical removal, grenz ray (in the past), thermotherapy, cryotherapy, electrotherapy, and laser. Topical treatments include 15% paromomycin and intralesional injection of pentavalent antimonials. Systemic treatments include antimony compounds, pentamidine, interferon, allopurinol, rifampin, dapsone, azole antifungal drugs, and immunotherapy. In addition, efficacy of other therapeutic modalities such as photodynamic therapy (PDT), topical azole agents, herbal extracts, and zinc sulfate (ZnSO<sub>4</sub>) in the treatment of acute Old World CL have been studied in several clinical trials.<sup>3-7</sup> However, intralesional or systemic administration of antimonial compounds

(sodium stibogluconate, meglumine antimonials) are still considered to be the standard treatment of CL.<sup>8</sup>

A proposed mechanism of action for therapeutic modalities that have been used in the treatment of acute Old World CL is presented in Table I. This systematic review was performed to assess the evidence for the efficacy of different therapeutic modalities for acute Old World CL.

## METHODS

### Search strategy and selection criteria

Evidence was reviewed according to the hierarchy of evidence whereby systematic reviews of randomized controlled trials (RCTs) are accepted as the most robust evidence, followed by individual RCTs.<sup>9</sup> Since there has been no published systematic review on this topic to date, the primary source of evidence was individual RCTs. To locate all studies concerning treatment of CL, an initial search was performed (by A. K. and F. G.) using cutaneous AND leishman\$ AND treat\$ OR (therap\$ NOT treat\$) filter in the following databases: Cochrane Central Register of Controlled Trials (3rd quarter 2006), Ovid MEDLINE (1966 to July 2006), and EMBASE (1980 to July 2006). Early online and other electronic formats of articles were also searched and considered. The search was not limited to English-language articles. A manual search was also performed on all available issues of medical journals that were published in Iran up to June 2006 (by A. K. and A. F.) In addition, references of relevant articles and reviews were manually searched for additional sources. Bibliographies of retrieved publications were reviewed to identify sources not obtained in our search.

All searched studies were considered eligible if they were RCTs. All interventions were therapeutic, and vaccine or any other preventive trials were excluded before appraisal. The trial should be conducted in an area in which Old World CL was endemic unless the selected study confirmed that patients had Old World CL.

### Data extraction, quality assessment methods, and statistical analysis

The titles and abstracts (whenever available) of relevant articles, which remained after duplicated ones were omitted, were reviewed and those related to acute Old World CL were selected (by A. K., A. F., and F. G.). Among selected articles, RCTs were chosen for full text review. The authors independently reviewed all eligible articles and disagreements were solved by the consensus (all authors).

The data were extracted by using a modified version of a data extraction form suggested by the

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