

BRIEF COMMUNICATION

SYSTEMATIC REVIEWS ON LEPTOSPIROSIS

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SUMMARY

Objectives: To find the existing clinical evidence on interventions for leptospirosis. The objective is to evaluate the effectiveness and safety of any intervention on leptospirosis through systematic reviews of randomized controlled trials (RCTs).

Data source: The sources of studies used (where there were no limitations concerning language, date, or other restrictions) were: EMBASE, LILACS, MEDLINE, the Cochrane Controlled Clinical Trials Database, and the Cochrane Hepato-Biliary Group Randomized Trials register.

Selection of studies: *Type of Study:* All systematic reviews of randomized controlled trials. *Participants:* patients with clinical and/or laboratorial diagnosis of leptospirosis, and subjects potentially exposed to leptospirosis as defined by the authors *Interventions:* any intervention for leptospirosis (as antibiotics or vaccines for prevention or treatment).

Data collection: The assessment will be independently made by the reviewers and cross-checked. The external validity was assessed by analysis of: studies, interventions, and outcomes.

Data synthesis: Located 163 studies using the search strategy described above, at the electronic databases above. Only 2 hits were selected, which are protocols of systematic reviews of Cochrane Collaboration, and not full reviews. One of the protocols evaluates antibiotics for treatment, and the other evaluates antibiotics for prevention of leptospirosis.

Conclusions: There were not complete systematic reviews on interventions for leptospirosis. Any interventions for leptospirosis, such as prevention and treatment remains unclear for guidelines and practice.

KEYWORDS: Leptospirosis; Treatment; Prevention; Systematic review; Meta-analysis.

INTRODUCTION

Leptospirosis (International Code of Diseases: 07.079.0) is a worldwide zoonosis that is transmitted by rats, cats, dogs, and other animals to humans. In many countries (like USA, Italy, and other European countries), it is an occupational disease. It is endemic in Brazil and the incidence is highest during the summer between January and April, when heavy rains and floods occur in urban areas. The Brazilian government officially reported 2,634 new cases (range 2,396 to 4,138 cases) per year of the disease that were admitted to hospitals, and the mortality was 348 deaths (range 265 to 425 deaths) per year, during the period of 1990-95, remaining steady¹.

This acute infectious disease caused by a spirocheta of the leptospira gender is characterized by severe vasculitis. It affects any age, 75% of the infected are males and incubation period varies from 2 to 20 days. The most severe form of leptospirosis starts with jaundice, azotaemia, haemorrhages, anemia, consciousness disturbances, continuous fever, renal failure, and thrombocytopenia.

For prevention of this acute disease, the drug of choice is considered to be doxycycline, during the period of exposure². On the other hand, prevention can be made by vaccination. The drug of choice for treatment of leptospirosis is considered to be sodium penicillin, the alternative drugs are ampicillin, doxycycline, tetracycline and amoxicillin³.

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Systematic reviews of research evidence are invariable scientific activities. Systematic review efficiently integrate existing information and provide data for rational decision making, and establish whether scientific findings are consistent and can be generalized across populations, settings, and treatment variations, on whether findings vary significantly by particular subjects³.

The aim of this systematic review is to find the existing clinical evidence (systematic reviews of randomized controlled trials) in interventions on leptospirosis. The objective is to evaluate the effectiveness and safety of any intervention on leptospirosis through systematic reviews of randomized controlled trials.

METHODS

1. Design: Systematic review of RCTs.

2. Setting: Clinical Trials and Meta-Analysis Unit, Federal University of São Paulo, Brazil.

3. Sources of studies: The sources of studies used (where there were no limitations concerning language, date, or other restrictions) were: EMBASE, LILACS, MEDLINE, the Cochrane Controlled Clinical Trials Database, The Cochrane Hepato-Biliary Group Randomized Controlled Trials register, checking references list, and personal communication to the authors. The Cochrane Hepato-Biliary Group Randomized Controlled Trials register⁴ is a result of an international effort to searched for any trial or reference to a relevant trial (published, in-press, or in progress), through handsearching, electronic searching, and letters to pharmaceutical companies.

4. Study selection: Type of Study: All systematic reviews of Randomized Controlled Trials. **Participants:** patients with clinical and/or laboratorial diagnosis of leptospirosis, and subjects potentially exposed to leptospirosis as defined by the authors **Interventions:** with any intervention on leptospirosis (as antibiotics or vaccines for prevention or treatment).

5. Locating and selecting studies: Two reviewers (FG, AAC) independently selected the systematic reviews of RCTs which were

included in the review. Disagreements were resolved at a consensus meeting.

6. Critical appraisal of studies: The methodological quality of each systematic review of RCTs were assessed by the same two reviewers. **Details of the study valid?** 1. Did the overview address a focused clinical question? 2. Were the criteria used to select articles for inclusion appropriate? 3. Is it unlikely that important, relevant studies were missed? 4. Was the validity of the included studies appraised? 5. Were assessments of studies reproducible? 6. Were the results similar from study to study? **What are the results?** 1. What are the overall results of the review? 2. How precise were the results?

7. Collecting data: The assessment was independently made by the reviewers and cross-checked. The external validity was assessed by analysis of: **STUDIES:** inclusion criteria, exclusion criteria, category of disease (Weil disease or anicteric leptospirosis), type of intervention (treatment or prevention), type of prevention regimen (Antibiotics or vaccines), age, male and female, duration of follow-up, location of study, and presence of other illnesses. The calculation of the sample size and the sample representativity will be also appraised; **INTERVENTIONS:** besides the types of interventions described above; **OUTCOMES:** data from the studies published twice or more were extracted from the one offering the best description or after consultation with the authors.

RESULTS

163 studies were located using the search strategy described above, at the electronic databases above. Only 2 hits were selected, which are protocols of systematic reviews of Cochrane Collaboration, and not full reviews. One of the protocols evaluates antibiotics for treatment⁵, and the other evaluates antibiotics for prevention of leptospirosis⁶.

DISCUSSION

With the searching method that we used for this review, we could not find any systematic literature reviews on interventions for leptospirosis. If we could do so, systematic reviews including meta-analyses are invaluable scientific activities. The rationale for such reviews

Table 1
Search strategy for systematic reviews. Adapted for LILACS
(31st Edition, 1998)

Step	hits			
	MEDLINE (1966-1998)	LILACS 31 st edition 1998	The Cochrane Library Issue 1, 1999	EMBASE (1980-1999)
1. Pt meta-analysis OR Tw meta-anal\$ OR Tw metaanal\$ OR Tw metaanal\$ OR Tw metanal\$	5,361	10	not used	10,637
2. Tw Medline OR Tw system\$	631,441	11,405	not used	not used
3. Tw leptospir\$ OR Explode Mh leptospirosis	4,413	272	15	1479
4. (1 OR 2) AND 3	140	8	15	0

is well established³. It synthesizes an unmanageable amount of information and, efficiently integrates existing information and provide data for rational decision making for health care providers, policy makers, and customers. Systematic reviews establish whether scientific findings are consistent and can be generalized across populations, settings, and treatment variations, or whether findings vary significantly by particular subsets. Meta-analyses is the statistical method on which systematic reviews can increase power and precision of estimates of treatment effects and exposure risks. Finally, explicit methods used in systematic reviews limit bias and, hopefully, will improve reliability and accuracy of conclusions³. When the protocols⁵⁻⁶ turn into complete reviews, it can be a state-of-art on antibiotics for leptospirosis, and it will be the beginning for the struggle for evidences in others interventions on leptospirosis, like vaccines (for prevention).

CONCLUSIONS

There were not complete systematic reviews on interventions for leptospirosis. Any interventions for leptospirosis, such as prevention and treatment remain unclear for guidelines and practice.

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SUMMARY OF THESIS*

CARDOSO, André Gustavo Tempone – Ação do veneno de *Bothrops moojeni* e sua fração L-aminoácido oxidase, submetida ao tratamento com raios gama de ^{60}Co , em *Leishmania spp.* São Paulo, 1999. (Dissertação de Mestrado – Instituto de Pesquisas Energéticas e Nucleares da Universidade de São Paulo).

ACTION OF *Bothrops moojeni* VENOM AND ITS L-AMINO ACID OXIDASE FRACTION, TREATED WITH ^{60}Co GAMMA RAYS, IN *Leishmania spp.*

Bothrops moojeni venom showed an antileishmania activity *in vitro*, as determined by a cell viability assay using the reduction of MTT. After venom purification, by chromatography techniques, the fractions with antileishmania and L-amino acid oxidase activities, eluted in the same positions. The molecular weight of the enzyme was estimated to be 140 kDa by molecular exclusion chromatography, and 69 kDa, by SDS-PAGE, migrating as a single band, with an isoelectric point of 4.8 as determined by isoelectric focusing. The purified LAO from *B. moojeni* venom, 135-fold more active than crude venom, showed homodimeric constitution, and was active against *Leishmania spp* from the New World, with an effective concentration against *L.(L). amazonensis* of 1.80 mg/ml (EC_{50}), *L.(V.) panamensis* (0.78 mg/ml)

and *L.(L.) chagasi* (0.63 mg/ml). Ultrastructural studies of promastigotes affected by LAO demonstrated cell death, with edema in several organelles such as mitochondria and nuclear membrane, before cell disruption and necrosis. The action of LAO was demonstrated to be hydrogen peroxide-dependent. Studies with LLCMK-2 cells, treated with LAO, showed a toxic effect, with an EC_{50} of 11 mg/ml. Irradiation of LAO with ^{60}Co gamma rays, did not affect its whole oxidative activity, neither detoxified the enzyme. Amastigotes treated with LAO were not affected by its hydrogen peroxide, otherwise, the exogenous product, killed amastigotes with an EC_{50} of 0.67mM. These data could be of help in the development of alternative therapeutic approaches to the treatment of leishmaniasis.

*This thesis is available at the Library of the Instituto de Medicina Tropical de São Paulo