From evidence to guidelines: the GSLC experience

EVIDENCE BASED VETERINARY MEDICINE E MEDICINA VETERINARIA
CENTRO COCHRANE ITALIANO
FACOLTÀ DI MEDICINA VETERINARIA – UNIVERSITÀ DI BOLOGNA

Luigi Gradoni

Research Director
Unit of Vector-borne Diseases & International Health
MIPI Department – Istituto Superiore di Sanità
Roma

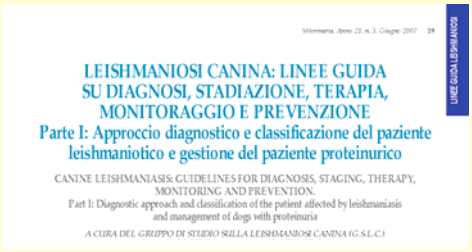
What is 'GSLC'?

GSLC = *Gruppo di Studio sulla Leishmaniosi Canina* (Canine Leishmaniasis Working Group, CLWG) is an expert panel established in November 2005 in collaboration with the Italian Society of Veterinarians of Companion Animals (SCIVAC).
The aim of the CLWG is to provide a scientific-based consensus approach for the management of CanL with regards to **diagnosis** and **clinical classification of disease**, **therapy** and **prevention**. The main outcome - but not unique –is the production of **guidelines** intended to assist veterinary practitioners

G.S.L.C. GRUPPO DI STUDIO SULLA LEISHMANIOSI CANINA

http://www.gruppoleishmania.org/

Published or 'in press' guidelines



LINEE GUIDA LEISHMANIOSI

LEISHMANIOSI CANINA: LINEE GUIDA SU DIAGNOSI, STADIAZIONE, TERAPIA, MONITORAGGIO E PREVENZIONE
Parte I: Approccio diagnostico e classificazione del paziente leishmaniotico e gestione del paziente proteinurico

CANINE LEISHMANIASIS: GUIDELINES FOR DIAGNOSIS, STAGING, THERAPY, MONITORING AND PREVENTION.
Part I: Diagnostic approach and classification of the patient affected by leishmaniasis and management of dogs with proteinuria

A CURA DEL GRUPPO DI STUDIO SULLA LEISHMANIOSI CANINA (G.S.L.C.)

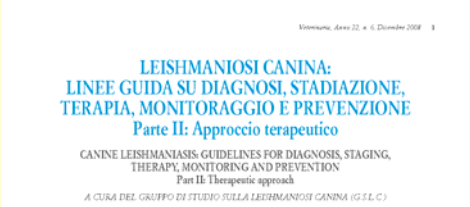
Published or 'in press' guidelines

Page 1 of 33 — Journal of the American Veterinary Medical Association
(accepted for publication)

Canine leishmaniasis: guidelines for diagnosis and clinical classification

Authors*: Saverio Paltrinieri (DVM, Prof, DECVCP), Laia Solano-Gallego (DVM, PhD),
DECVCP), Alessandra Fondati (DVM, PhD, DECVD), George Lubas (DVM, Prof, DECVIM),
Luigi Gradoni (BioSc, PhD), Massimo Castagnaro (DVM, Prof, DECVP), Alberto Cortese (DVM),
Michele Maroli (BioSc, PhD), Gaetano Oliva (DVM, Prof), Xavier Roura (DVM, PhD, DECVIM),
Andrea Zatelli (DVM), Eric Zini (DVM, PhD, DECVIM)

Published or 'in press' guidelines



LEISHMANIOSI CANINA:
LINEE GUIDA SU DIAGNOSI, STADIAZIONE, TERAPIA, MONITORAGGIO E PREVENZIONE
Parte II: Approccio terapeutico

CANINE LEISHMANIASIS: GUIDELINES FOR DIAGNOSIS, STAGING, THERAPY, MONITORING AND PREVENTION
Part II: Therapeutic approach

A CURA DEL GRUPPO DI STUDIO SULLA LEISHMANIOSI CANINA (G.S.L.C.)

DIAGNOSIS (I)
Search strategy for identification of studies

✓ **A search strategy for MEDLINE following Cochrane Reviewers' Handbook (Alderson 2004) was attempted (however this is most relevant for drug/vaccine intervention trials)**

✓ **Search for relevant citations in international conference proceedings**

✓ **Where inadequate or incomplete, information was supplemented with the experience of CLWG members**

DIAGNOSIS (II)
Limitations of EBVM approach in literature review and guideline generation

✓ Almost no 'ring trials among diagnostic centres' were available in literature for any of the diagnosis tools employed in canine leishmaniasis

✓ A large variety of methods were developed in the categories of 'serology' and 'molecular methods', however only a few studies were available on comparative diagnostic performances within each category

One serological technique (IFAT) is universally taken as reference method because of … tradition?

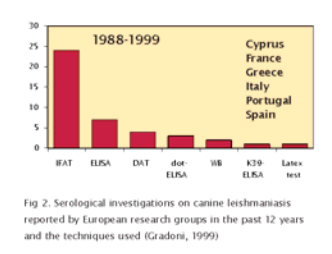


Fig 2. Serological investigations on canine leishmaniasis reported by European research groups in the past 12 years and the techniques used (Gradoni, 1999)

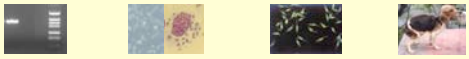
DIAGNOSIS (III)
Limitations of EBVM approach in literature review and guideline generation

✓ Very few studies were available on prospective comparative evaluation of diagnostic tools in naturally infected dogs at well-defined infection stages

✓ Conversely, most of the studies were performed using cross-sectional samples from dogs at different (unknown) infection stages

In a chronic progessive infection like leishmaniasis, after a long pre-patent period (4-7 months) the diagnostic markers convert to positive according to the following sequence:

PCR → Culture/Microscopy → Serology → Clinical evidence



0-22 months (m: 8.5)

0-2 months (m: 1.5)

3-14 months (m: 7.0)

(m= median)

Ideally, an EB approach in laboratory diagnosis methods should include the following:

PCR → Culture/Microscopy → Serology → Clinical evidence

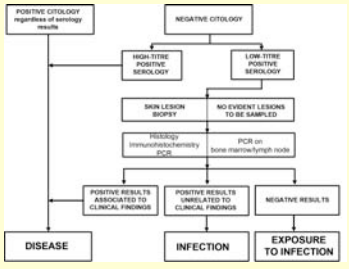
Compare:
- Tissues sampled
- Genome targets
- Techniques (Conv., Nested, Real-time)

Compare:
- Tissues sampled
- Staining/Immuno-
- Medium (Blood-agar, Liquid, Nutrients)

Compare:
- Antigens
-Techniques (IFAT, ELISAs, WB, DAT, Latex)
- Cut-off, Se, Sp

- Early/late lab changes
- Early/late signs
- Common to species/breed
- Individual

A GSLC consensus was reached about staging the infection/disease according to conversion of the main diagnostic markers



DRUG THERAPY (I)
Search strategy for identification of studies and assessment of methodological quality

✓ A search strategy for MEDLINE following Cochrane Reviewers' Handbook (Alderson 2004)

✓ Search for relevant citations in international conference proceedings

✓ Studies were rated as 'adequate' or 'inadequate' depending on the quality of methodology

✓ Where inadequate, information was supplemented with the experience of CLWG members

DRUG THERAPY (II)
Drugs evaluated for anti-leishmanial activity were reported in 62 studies

Pentavalent antimony:	34
Allopurinol:	19
Aminosidine:	4
Amphotericin B:	3
Miltefosine:	3
Pentamidine:	1
Spiramicin/metronidazole:	1
Enrofloxacin:	1
Marbofloxacin:	1
Domperidone:	1

DRUG THERAPY (III)
Limitations of EBVM approach in literature review and guideline generation

✓ Despite the (relative) high number, the large majority of studies were considered 'inadequate'

✓ Main limitations were:

- Non-randomised/non-controlled trials
- Unmasked allocations for observer/owner
- Variable criteria for initial diagnosis and efficacy evaluation
- Insufficient follow-up period
- Low number of enrolled patients, low/no significance

DRUG THERAPY (IV)
Basically, only one drug combination reached EBVM standards to be considered adequate for recommendation:

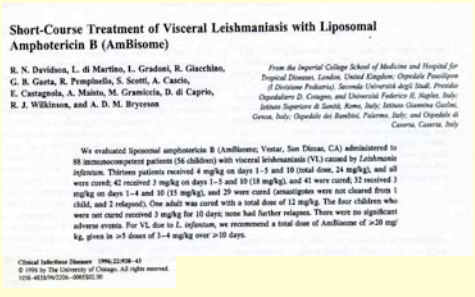
Meglumine antimoniate (MA) administered sc for at least 4 weeks at the dose of 100 mg/kg/d, plus oral allopurinol at the dose of 10 mg/kg bid for 6 months

The following variations, although suggested in guidelines, were not validated by EB criteria:

- 100 mg MA/kg/d *vs* 50 mg MA/kg/bid
- MA administered for 4 weeks *vs* 8 weeks
- Allopurinol administered for 6 months *vs* 12 months, or *vs* 'for life'

What about the EB approach in human visceral leishmaniasis?

Example of a single-drug dose-ranging trial: Liposomal amphotericin B



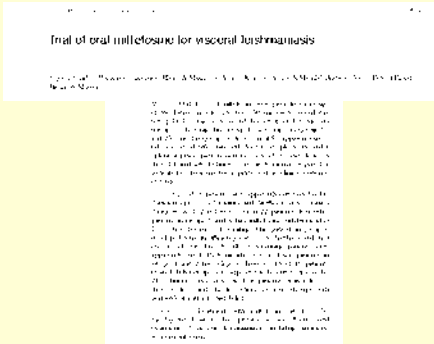
Short-Course Treatment of Visceral Leishmaniasis with Liposomal Amphotericin B (AmBisome)

R. N. Davidson, L. di Martino, L. Gradoni, R. Giacchino, G. B. Gaeta, R. Pempinello, S. Scotti, A. Cascio, E. Castagnola, A. Maisto, M. Gramiccia, D. di Caprio, R. J. Wilkinson, and A. D. M. Bryceson

From the Imperial College School of Medicine and Hospital for Tropical Diseases, London, United Kingdom; Ospedale Pausilipon (I Divisione Pediatria), Seconda Università degli Studi, Presidio Ospedaliero D. Cotugno, and Università Federico II, Naples, Italy; Istituto Superiore di Sanità, Rome, Italy; Istituto Giannina Gaslini, Genoa, Italy; Ospedale dei Bambini, Palermo, Italy; and Ospedale di Caserta, Caserta, Italy

We evaluated liposomal amphotericin B (AmBisome; Vestar, San Dimas, CA) administered to 88 immunocompetent patients (56 children) with visceral leishmaniasis (VL) caused by *Leishmania infantum*. Thirteen patients received 4 mg/kg on days 1–5 and 10 (total dose, 24 mg/kg), and all were cured; 42 received 3 mg/kg on days 1–5 and 10 (18 mg/kg), and 41 were cured; 32 received 2 mg/kg on days 1–4 and 10 (15 mg/kg), and 29 were cured (amastigotes were not cleared from 1 child, and 2 relapsed). One adult was cured with a total dose of 12 mg/kg. The four children who were not cured received 3 mg/kg for 10 days; none had further relapses. There were no significant adverse events. For VL due to *L. infantum*, we recommend a total dose of AmBisome of >20 mg/kg, given in >5 doses of 3–4 mg/kg over >10 days.

Example of a single-drug dose-ranging trial: Miltefosine

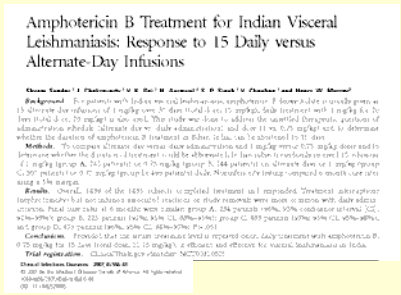


Trial of oral miltefosine for visceral leishmaniasis

Example of a combined-drug dose-ranging trial: Liposomal amphotericin B plus Miltefosine

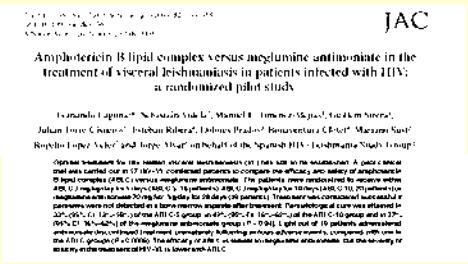
New Treatment Approach in Indian Visceral Leishmaniasis: Single-Dose Liposomal Amphotericin B Followed by Short-Course Oral Miltefosine

Example of a single-drug dose/frequency-ranging trial: Amphotericin B 1mg/kg *vs* 0.75 mg/kg, and 15d *vs* 30d on alternate days



Amphotericin B Treatment for Indian Visceral Leishmaniasis: Response to 15 Daily versus Alternate-Day Infusions

Example of a randomized comparative trial: Amphotericin B *vs* Antimony



JAC

Amphotericin B lipid complex versus meglumine antimoniate in the treatment of visceral leishmaniasis in patients infected with HIV: a randomized pilot study

CONCLUSIONS

✓ **Because approaches to canine leishmaniasis management are still very heterogeneous in clinical practice, generation of Guidelines is urgently needed**

✓ **Unfortunately, available studies are largely inadequate to meet EBVM quality standards, so that most information requires to be supplemented by individual experiences of expert panels**

✓ **High-quality studies meeting EBVM standards, like those developed in the field of human visceral leishmaniasis, should be strongly encouraged**