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ORDINI MEDICI VETERINARI
PIEMONTE E VALLE D' AOSTA

CONF PROFESSIONI
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Leishmaniosi canina: apparentemente semplice, maledettamente complicata

Prof. Gaetano Oliva

Dipartimento
Medicina Veterinaria
Produzioni Animali

PREVENIRE E’ MEGLIO CHE CURARE

Drugs for CanL therapy

Oliva G.,
DNDi forum
Ginevra, 2014

Drugs	Mechanism	Time treatment	Side effects	Time to relapse	Drug Resistance (dog)
Meglumine antimoniate	Poor understood (Drug *vs* Pro-drug)	4 -8 weeks	Local pain Pancreatic damage (renal damage ?)	6-12 months	Reported
Amphotericin B	Interference with membrane sterols	8 weeks	Nephrotoxicity	12-18 months	Not reported
Liposomed Amph B	Same (with reduction of nephrotoxicity)	5 days	Nephrotoxicity	6-8 months	Not reported
Paromomycin	Interference with mitochondrial and induction of respiratory dysfunction	3 weeks	Nephrotoxicity	3-4 months	Not reported
Allopurinol	Interference on purine pathway	24 months	Xantinuria (stones)	No clinical relapse (?)	Low suscepibility
Meg Antimoniate + Allopurinol	Combination of both	4 weeks (MA) + several months (ALL)	Sum of side effects		Reported (MA)
Miltefosine (+ Allopurinol)	Impairment of signaling pathways and cell membrane synthesis	4 weeks (MILT) + several months (ALL)	Gastrointestinal SE (MILT) + Xantinuria (ALL)	< 1 year (Anecdotal)	Not reported
Marbofloxacin	Inhibition of DNA gyrase	4 weeks	None	5-6 months	Not reported

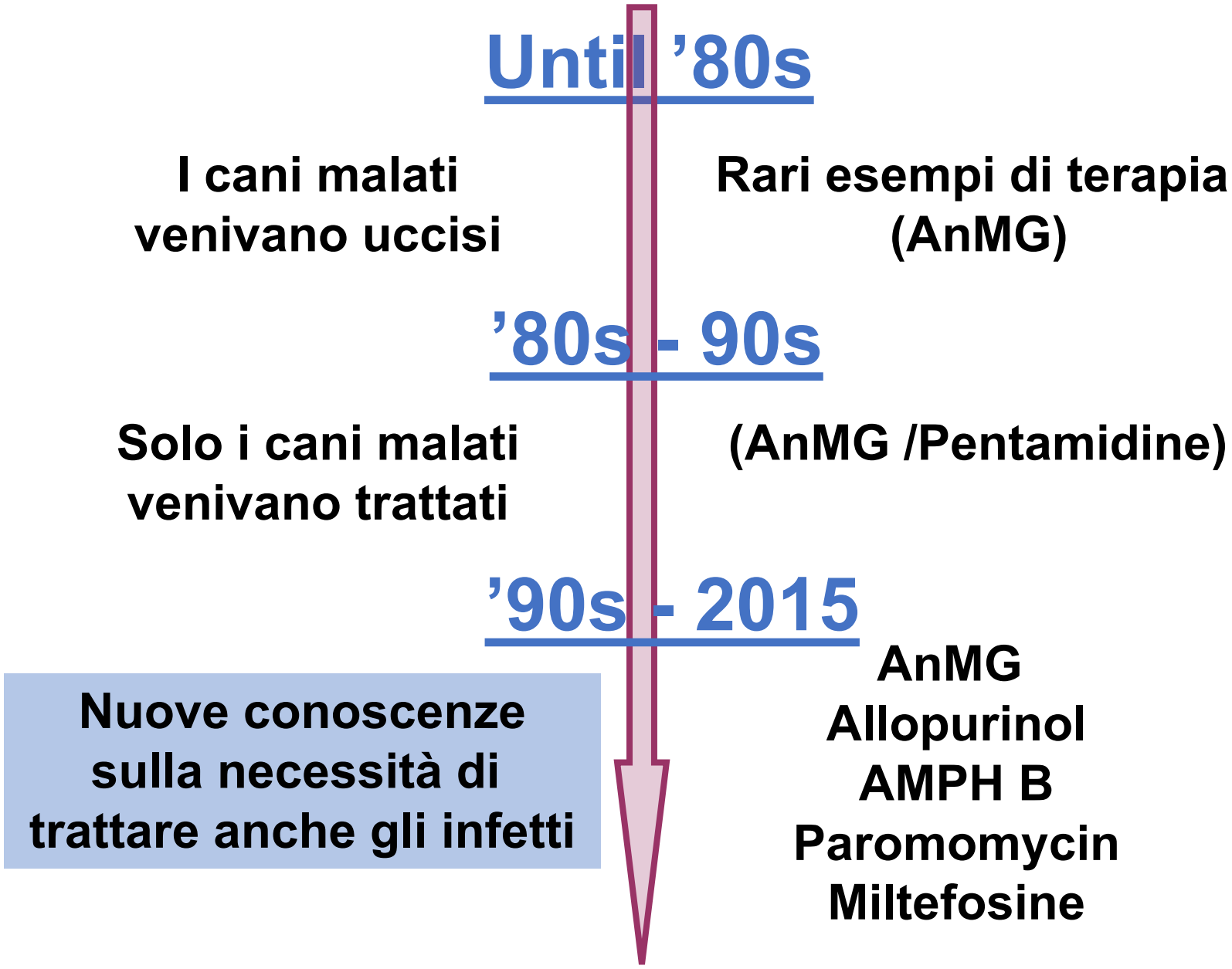
Problemi legati alla terapia della CanL:

1) Qual è il protocollo ideale?

2) Recidive (quante volte può essere ripetuto lo stesso trattamento ?)

3) Qual è il ruolo epidemiologico (reservoir) dei cani sottoposti a terapia?

? Resistenza ai farmaci anti-*Leishmania*?


Until ’80s
I cani malati venivano uccisi
Rari esempi di terapia (AnMG)
’80s - 90s
Solo i cani malati venivano trattati
(AnMG /Pentamidine)
’90s - 2015
Nuove conoscenze sulla necessità di trattare anche gli infetti
AnMG
Allopurinol
AMPH B
Paromomycin
Miltefosine
……

Punto n. 1

Situazione attuale

- Molti cani ancora trattati con protocolli non standardizzati

- EBM:

Antimoniali + Allopurinolo

Miltefosina + Allopurinolo

Allopurinolo

limiti degli studi eseguiti ad oggi :

- studi non «in cieco»;
- assenza di gruppo controllo;
- scarso numero di cani arruolati;
- assenza di criteri standard per la diagnosi;
- assenza di criteri standard per la definizione dello «score» clinico;
- assenza di criteri standard per la definizione di «guarigione»;
- insufficiente follow up;
- grande variabilità di dosaggi adoperati e di tempi di trattamento

Oliva et al., JAVMA, 2010

Olías-Molero *et al. Parasites Vectors* (2021) 14:36
https://doi.org/10.1186/s13071-020-04544-x

RESEARCH Open Access

Scientometric analysis of chemotherapy of canine leishmaniasis (2000–2020)

A. I. Olías-Molero[1,2], E. Fontán-Matilla[1], M. Cuquerella[1,2] and J. M. Alunda[1,2*]

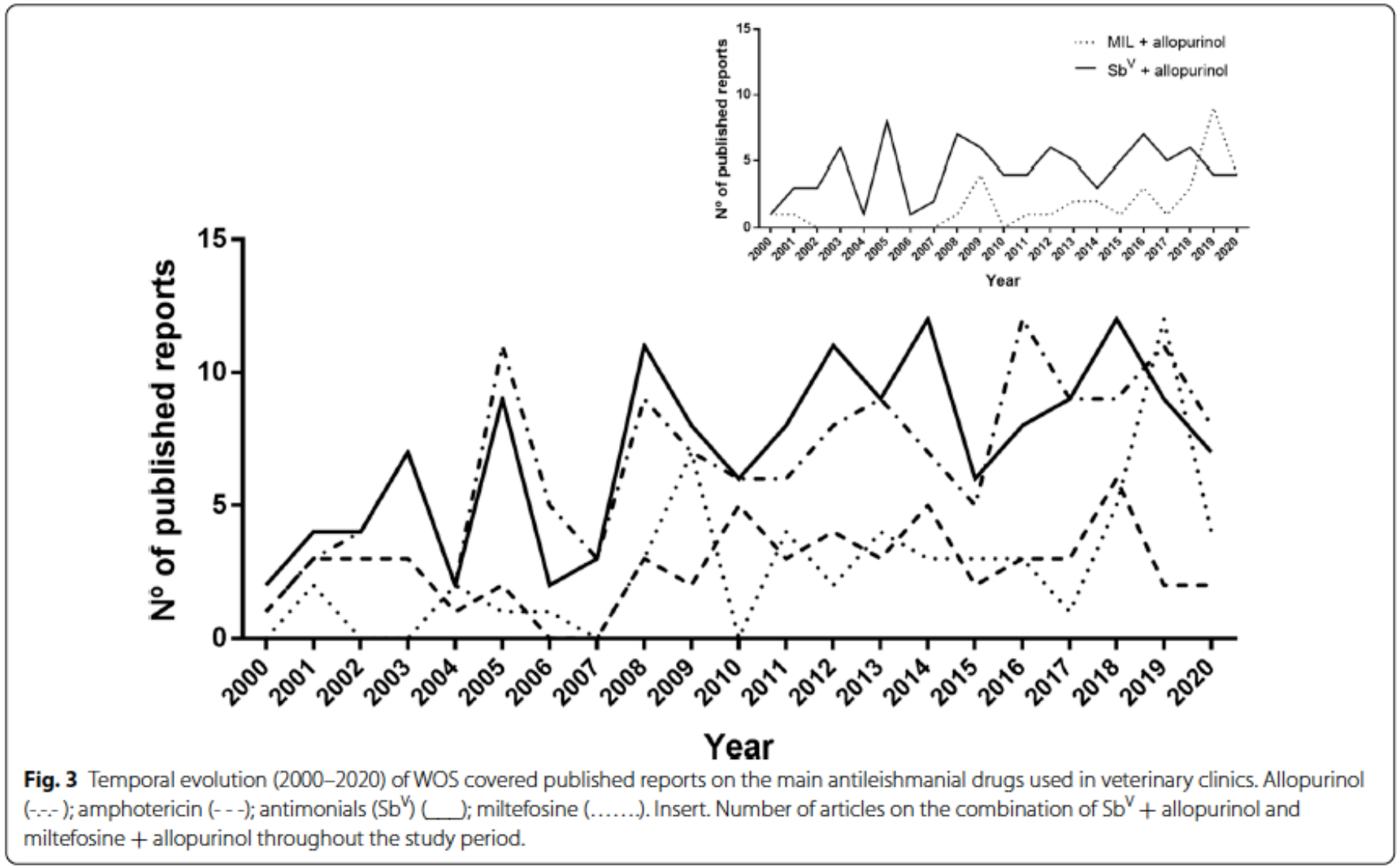


Fig. 3 Temporal evolution (2000–2020) of WOS covered published reports on the main antileishmanial drugs used in veterinary clinics. Allopurinol (-.-.-); amphotericin (- - -); antimonials (Sb^V) (___); miltefosine (.....). Insert. Number of articles on the combination of Sb^V + allopurinol and miltefosine + allopurinol throughout the study period.

EBM reference protocol:

Meglumine antmoniate + allopurinol

100 mg/kg q24h SC/IM 4-8 weeks

+

10 mg kg BID PO x 6 months or more

Meglumine antimoniate + allopurinol

- Reduction of the parasite load in infected/ill dogs (ok)
- Treatment of the organ’s damages (+/-)
- Restoration of the immunological response (ok)
- Stabilization of the dog during the time (ok)
- Relapses treatment (ok)

limits :

- compliance of the owner;
- pain at the injection site, abscesses;
- potential renal damage;
- chemo-resistance

MILTEFOSINA: dosaggio : 2 mg/kg per os, SID, per 28 gg

Recentemente: nuovo schema terapeutico proposto:
1,2 mg/kg per 5 gg, quindi 2,5 mg/kg per 25 gg (Iarussi et al., 2021)

Maneggevolezza	**Effetti gastroenterici (limitati)**
Compliance proprietari	**Non adeguata rapidità di risultati**
Efficacia	**Lentezza di normalizzazione parametri ematobiochimici**
Tollerabilità (anche in nefropatici)	**Recidive**
Costo	**Resistenza ?????**

Punto n. 2: PROGNOSI E RECIDIVE (Roura et al., 2013)

Il destino dei cani malati è legato al mantenimento della funzione renale

In assenza di danno renale, il 75% dei cani trattati sopravvive per più di 4 anni

Anche in presenza di danno renale (IRIS 1 and 2) la prognosi è buona con lunghi periodi di sopravvivenza

Le recidive sono stimate tra il 20 e il 50%, più frequenti e gravi nei cani che in prima visita mostrano titoli Ac elevati e patologie da immunocomplessi

Summary of treatments options for dogs with clinical leishmaniosis and concomitant allergic or immune-mediated diseases.

Courtesy: Prof. L. Ferrer
University Autonoma de Barcelona

Clinical situation	Safe treatments	Contra-indicated treatments	Moderate risk/ Data lacking
Atopic dermatitis and clinical leishmaniosis	Topical treatments: shampoos, moisturizing creams, EFA spot-ons. Topical tacrolimus. Essential fatty acids. Antihistamines (1st and 2nd generation). Allergen specific immunotherapy. Monoclonal anti IL-31 antibody. Low dose/frequency topical steroids.	Oral/Injectable steroids. Oral ciclosporin (5 mg/kg/q 24h or higher dose).	Low dose/low duration oral steroids. Oclacitinib (not recommended, but data lacking).
Autoimmune or immune-mediated disease (PF, IMHA, IMPA, IMT…) and clinical leishmaniosis	Topical tacrolimus. Topical steroids. Tetracycline – Nicotinamide. Intravenous immunoglobulins.	Azathioprine (allopurinol interaction, thiopurine methyl transferase). Glucocorticoids (at high dose: > 2mg/kg). Ciclosporin (at high dose).	Glucocorticoids (anti-inflammatory dose). Mycophenolate mofetil (1 case report in humans).

NELLA PRATICA…….

- Necessità di **terapie collaterali** derivanti da diagnostica appropriata
- Ragioni economiche/compliance
- Necessità di alternare i protocolli in caso di recidive

CANINE LEISHMANIOSIS: UP-DATE ON THERAPEUTIC APPROACH VERSUS STAGING AND EMERGENCE OF ALLOPURINOL RESISTANCE

M. Saridomichelakis & G. Oliva

World Leish 6, Toledo Spain, 2017

NATURAL EVOLUTION

Histologic lesions precede clinical manifestations:

- Skin
- Masticatory muscles
- Large intestine
- Liver
- Joints
- Kidneys

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Veterinary Immunology and Immunopathology 104 (2005) 227–237
Veterinary immunology and immunopathology
www.elsevier.com/locate/vetimm

Cellular immunophenotyping of exfoliative dermatitis in canine leishmaniosis (*Leishmania infantum*)

E.I. Papadogiannakis[a], A.F. Koutinas[a,*], M.N. Saridomichelakis[a], J. Vlemmas[b], S. Lekkas[b], A. Karameris[c], A. Fytianou[d]

22 dogs with CanL without skin lesions
Histologic lesions in the skin of 11/22 (50%)

Masticatory and skeletal muscle myositis in canine leishmaniasis (*Leishmania infantum*)

C. D. VAMVAKIDIS, A. F. KOUTINAS, G. KANAKOUDIS, G. GEORGIADIS, M. SARIDOMICHELAKIS

Veterinary Record (2000)
146, 698-703

C. D. Vamvakidis, DVM,
A. F. Koutinas, DrMedVet,
M. Saridomichelakis,

8 dogs with CanL without masticatory muscle atrophy
Histologic lesions in the masticatory muscles of 6/8 (75%)

J. Comp. Path. 2005, Vol. 132, 145–152

Available online at www.sciencedirect.com

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Chronic Hepatitis Associated with Canine Leishmaniosis (*Leishmania infantum*): a Clinicopathological Study of 26 Cases

T. Rallis, M. J. Day*, M. N. Saridomichelakis, K. K. Adamama-Moraitou, L. Papazoglou†, A. Fytianou‡ and A. F. Koutinas

26 dogs with CanL without clinical signs of liver disease

Histologic lesions in the liver of 26/26 (100%)

Saturday 6 April
Abstract 73 1150 Telford Room

Prevalence of arthritis in naturally infected leishmanial dogs: a prospective study

N. Soubasis[1], K. Theodorou[2], D. Kasabalis[3], M. Mylonakis[2], C. Koutinas[2], I. Kalli[2], M. Ntargara[2], K. Sideri[3], M. Patsikas[2], Z. Polyzopoulou[2], M. Saridomichelakis[3], D. Psalla[4], M. Kritsepi-Konstantinou[5], A. Galatos[3] and A. Koutinas[2]

10 dogs with CanL without clinical signs of arthritis
Cytological evidence of arthritis in 10/10 (100%)

J Vet Intern Med 2006;20:228–233

Effects of Allopurinol Treatment on the Progression of Chronic Nephritis in Canine Leishmaniosis (*Leishmania infantum*)

K. Plevraki, A.F. Koutinas, H. Kaldrymidou, N. Roumpies, L.G. Papazoglou, M.N. Saridomichelakis, I. Savvas, and L. Leondides

22 dogs with CanL without azotemia: 12 without proteinuria and 10 with proteinuria

Histologic lesions in the kidneys of 22/22 (100%)

Clinical staging of canine leishmaniosis

Clinical staging of canine leishmaniosis based on serological status, clinical signs, laboratory findings, and type of therapy and prognosis for each clinical stage.

Clinical stages	Serology[a]	Clinical signs	Laboratory findings	Therapy	Prognosis
Stage I: mild disease	Negative to low positive antibody levels	Dogs with mild clinical signs such as peripheral lymphadenopathy, or papular dermatitis (Ordeix et al., 2005; Bottero et al., 2006)	Usually no clinicopathological abnormalities observed; normal renal profile: creatinine < 1.4 mg/dl; non-proteinuric: UPC < 0.5	Scientific neglect/ allopurinol alone/ allopurinol + meglumine antimoniate or miltefosine	Good
Stage II: moderate disease	Low to high[b] positive antibody levels	Dogs, which apart from the signs listed in stage I, may present: diffuse or symmetrical cutaneous lesions such as exfoliative dermatitis/onychogryphosis, ulcerations (planum nasale, footpads, bony prominences, mucocutaneous junctions), anorexia, weight loss, fever, and epistaxis (Petanides et al., 2008)	Clinicopathological abnormalities such as mild non-regenerative anemia, hypergammaglobulinemia, hypoalbuminemia, serum hyperviscosity syndrome (Petanides et al., 2008). Substage—(a) normal renal profile: creatinine < 1.4 mg/dl; non-proteinuric: UPC < 0.5. (b) Creatinine < 1.4 mg/dl; UPC = 0.5–1	Allopurinol + meglumine antimoniate or miltefosine	Good to guarded
Stage III: severe disease	Medium to high positive antibody levels	Dogs, which apart from the signs listed in stages I and II, may present signs originating from immune-complex lesions: vasculitis, arthritis, uveitis and glomerulonephritis	Clinicopathological abnormalities listed in stage II Chronic kidney disease (CKD) IRIS stage I with UPC > 1 or stage II (creatinine 1.4–2 mg/dl) (IRIS, 2006a)	Allopurinol + meglumine antimoniate or miltefosine Follow IRIS guidelines for CKD (IRIS, 2006b)	Guarded to poor
Stage IV: very severe disease	Medium to high positive antibody levels	Dogs with clinical signs listed in stage III. Pulmonary thromboembolism, or nephrotic syndrome and end stage renal disease	Clinicopathological abnormalities listed in stage II CKD IRIS stage III (creatinine 2–5 mg/dl) and stage IV (creatinine > 5 mg/dl) (IRIS, 2006a) Nephrotic syndrome: marked proteinuria UPC > 5	Allopurinol (alone) Follow IRIS guidelines for CKD (IRIS, 2006b)	Poor

[a] Dogs with negative to medium positive antibody levels should be confirmed as infected with other diagnostic techniques such as cytology, histology/ immunohistochemistry and PCR.

[b] High levels of antibodies are conclusive of a diagnosis of CanL and are defined as three- to four fold increase of a well established laboratory reference cut-off.

LeishVet

Veterinary Immunology and Immunopathology 219 (2020) 109958

Contents lists available at ScienceDirect

Veterinary Immunology and Immunopathology

journal homepage: www.elsevier.com/locate/vetimm

Research paper

Comparison of acute phase proteins in different clinical classification systems for canine leishmaniosis

Luis Pardo-Marin[a], Jose J. Ceron[a], Fernando Tecles[a], Gad Baneth[b], Silvia Martínez-Subiela[a,*]

[a] Interdisciplinary Laboratory of Clinical Analysis (Interlab-UMU), Veterinary School, Campus of Excellence Mare Nostrum, University of Murcia, 30100 Espinardo, Murcia, Spain

[b] Koret School of Veterinary Medicine, Hebrew University, Rehovot, Israel

IRIS International Renal Interest Society

www.iris-kidney.com

Treatment Recommendations for CKD in Dogs (2015)

TABLE 2. IRIS stage of CKD in dogs

Stage	Creatinine (mg/dL)	SDMA (µg/dL)	Description
1	<1.4	<18	No azotaemia
2	1.4-2.8	18-35	Mild azotaemia
3	2.9-5.0	36-54	Moderate azotaemia
4	>5.0	>54	Severe azotaemia
Sub-stage proteinuria (UPC)	Nonproteinuric <0.2	Borderline proteinuric 0.2-0.5	Proteinuric >0.5
Sub-stage blood pressure (mmHg)	Normotensive <140 Hypertensive 160-179	Prehypertensive 140-159 Severely hypertensive ≥180	

CKD Chronic kidney disease, IRIS International renal interest society, SDMA Symmetric dimethylarginine, UPC Urinary protein creatinine ratio. Adapted from IRIS (2019).

Proteinuria:

Dogs in Stage 2 with UP/C >0.5 should be investigated for the disease processes leading to proteinuria (see 1 and 2 below) and treated with anti-proteinuric measures (see 3, 4, 5 and 6 below).
Those with borderline proteinuria (0.2 to 0.5) require close monitoring (see 1 and 6 below).

Look for any concurrent associated disease process that may be treated/corrected.

Consider kidney biopsy as a means of identifying underlying disease
(see Appendix 2 and/or consult experts if unsure of indications for kidney biopsy).

Administer an ACEI and feed a clinical renal diet

Combine ACEI and diet with an angiotensin receptor blocker (ARB) if proteinuria is not controlled.

Low-dose acetylsalicylic acid (1 to 5 mg/kg once daily) if serum albumin is <20 g/l (2.0 g/dl).

Monitor response to treatment / progression of disease:

……

REVIEW

Canine leishmaniosis and kidney disease: Q&A for an overall management in clinical practice

X. Roura [1,*], O. Cortadellas[†], M. J. Day[‡], S. L. Benali[§], Canine Leishmaniosis Working Group[a] and A. Zatelli[¶]

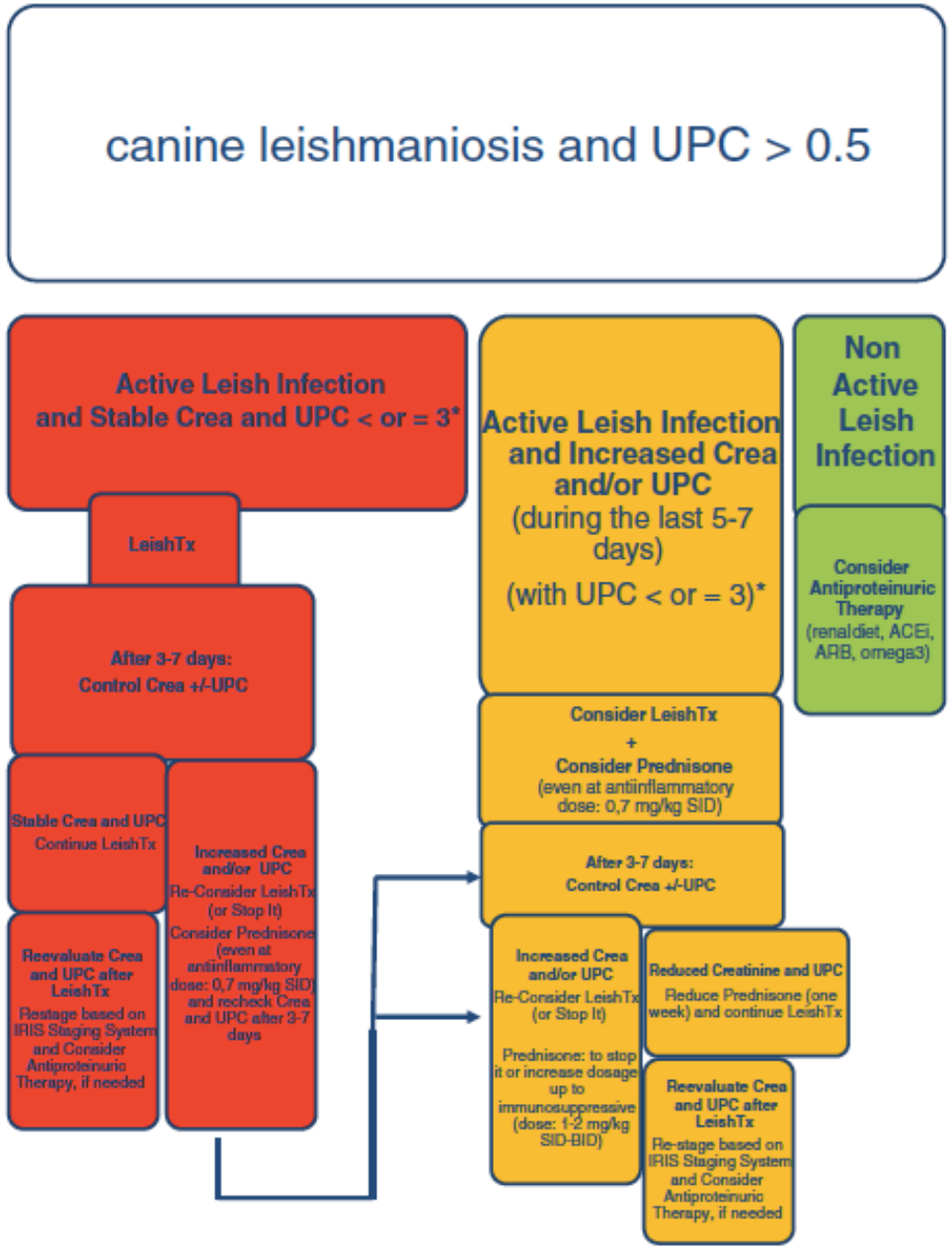


FIG 1. Flow-chart of clinical management of dogs with leishmaniosis and proteinuria (UPC >0.5). Leish *Leishmania* spp., UPC urine protein creatinine ratio, LeishTx leishmanicide treatment, ACEI angiotensin-converting enzyme inhibitors, ARB angiotensin-receptor blockers. *With UPC >3, the antiproteinuric therapy could also be instituted at the same time of leishmanicide treatment.

Punto n.3: ruolo dei cani trattati
In termini di infettività per i flebotomi

Infectivity to *Phlebotomus perniciosus* of dogs naturally parasitized with *Leishmania infantum* after different treatments

Guadalupe Miró[1*], Rosa Gálvez[2], Cristeta Fraile[1], Miguel A Descalzo[3] and Ricardo Molina[2]

Miró *et al. Parasites & Vectors* 2011, 4:52

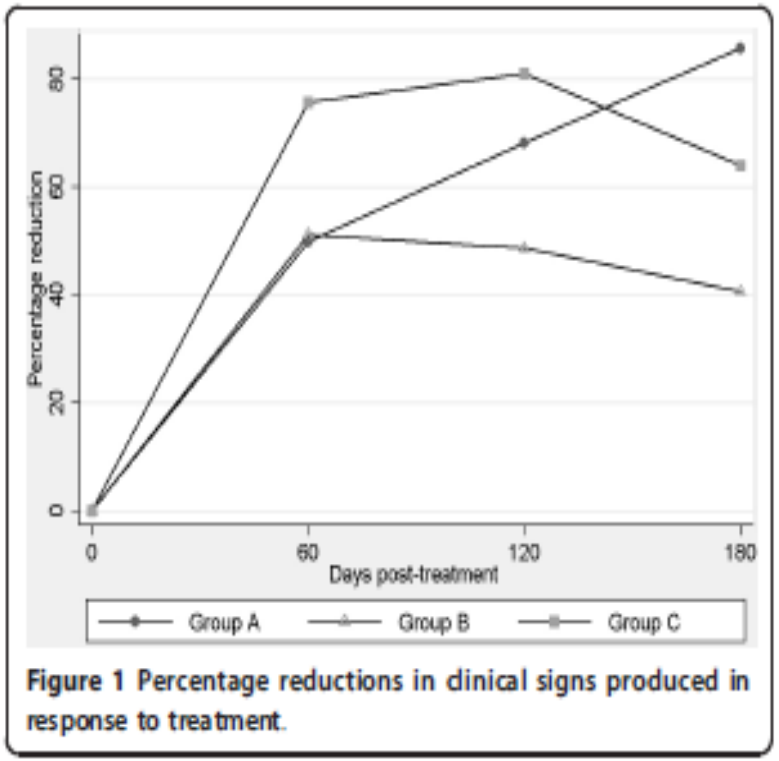


Figure 1 Percentage reductions in dinical signs produced in response to treatment.

Table 3 Bone-marrow culture and xenodiagnosis results recorded before and after starting treatment in each dog

Dog	Bone narrow culture				Xenodiagnosis			
	D0	D60	D120	D 180	D0	D60	D120	D 180
A1	+	+	+	+	+	-	+	-
A2	+	-	-	+	+	-	-	-
A3	-	-	-	-	+	-	-	-
A4	+	-	-	-	-	-	-	-
A5	+	-	-	-	-	-	-	-
A6	-	-	-	-	+	-	-	-
A7	+	-	-	-	+	-	-	-
A8	-	-	-	-	+	-	-	-
A9	+	-	-	-	-	-	-	-
A10	-	-	-	-	+	-	-	-
A11	+	-	-	-	+	+	-	-
A12	+	-	-	+	-	-	-	-
B1	+	-	-	-	+	-	-	-
B2	+	-	-	-	+	+	-	-
B3	+	-	-	-	+	-	-	-
B4	+	-	-	+	-	-	-	+
B5	+	-	-	-	+	-	-	-
B6	+	-	-	-	-	-	-	-
B9	+	-	-	-	-	-	-	-
B10	+	-	-	-	+	-	-	-
B11	+	-	-	-	+	-	-	-
C1	-	-	-	-	+	-	-	-
C3	+	+	+	+	+	-	-	-
C5	+	+	-	-	+	-	-	-
C7	+	-	+	-	-	-	-	-
C9	+	-	+	-	-	-	-	-

+ indicates positive culture result or infectious dog.

D0, D60, D120 and D180 indicate the time points before treatment and after 60, 120 or 180 days of treatment respectively.

frontiers in Veterinary Science

ORIGINAL RESEARCH
published: 04 May 2021
doi: 10.3389/fvets.2021.667290

Examining the Relationship of Clinical and Laboratory Parameters With Infectiousness to *Phlebotomus perniciosus* and Its Potential Infectivity in Dogs With Overt Clinical Leishmaniasis

Manuela Gizzarelli[1], Antonio Bosco[2], Valentina Foglia Manzillo[1], Gioia Bongiorno[2], Riccardo Bianchi[2], Daniela Giaquinto[1], Nour El Houda Ben Fayala[1], Marie Varloud[3], Alessia Crippa[3], Luigi Gradoni[1], Giuseppe Cringoli[1], Maria Paola Maurelli[1], Laura Rinaldi[1] and Gaetano Oliva[1]*

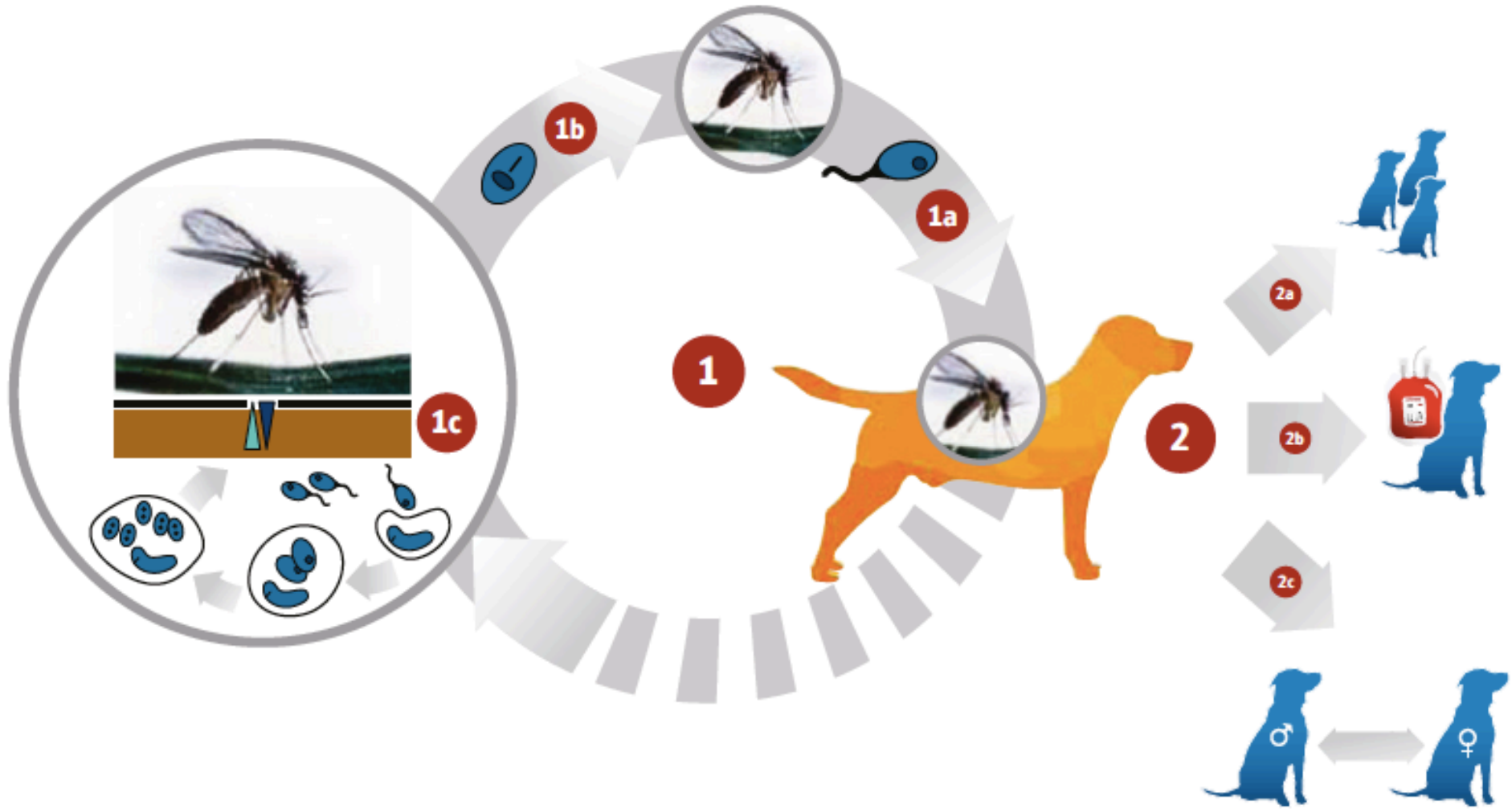
[1] Department of Veterinary Medicine and Animal Production, University of Naples Federico II, Naples, Italy, [2] Unit of Vector-Borne Diseases, Istituto Superiore di Sanità, Rome, Italy, [3] Ceva Santé Animale, Libourne, France

OPEN ACCESS

Edited by:
Simona Gabrielli,
Sapienza University of Rome, Italy

- La gravità dei segni clinici può influenzare il pasto di sangue e il rilevamento dei promastigoti nei flebotomi
- Il "Promastigote burden" è correlato al titolo IFAT, alle lesioni cutanee e alla gravità clinica
- Questo studio conferma che sia l'infezione sia l'infettività di *P. perniciosus* sono influenzate dalle condizioni cliniche del cane

PROFILASSI



1. Classical life cycle of *Leishmania infantum*

1a. Promastigote
1b. Amastigote
1c. Parasite dissemination to organs in macrophages

2. Other unusual modes of transmission

2a. Vertical
2b. Blood transfusion
2c. Venereal transmission
Other (unproven): Dog to dog (bites, wounds)

Strategie di prevenzione in aree non endemiche

Geographic area	Clinical status	Different scenarios	Travel history	Lifestyle	Preventative applications	Additional recommendations
Nonendemic areas	Any	0	Local (negligible)	Any	None	Avoid breeding with, or blood transfusion from dogs belonging to scenarios 3–5 (and 1–2, if possible)
		1	Occasional travel to endemic fringe or endemic areas	Any	Repellents: Cover the entire period of travelling/exposure including the delay for activity	See scenario 0 If travel once and less than 3 weeks, topical insecticide spot-on formulations applied at least 2 days before travelling/ exposure. For longer periods of travel, repeated spot on or collars. Test for *L. infantum* infection (6 months post- travel, via quantitative serology)
		2	Frequent (or long) travel to endemic fringe/ endemic areas	Breeding, frequently outdoors	Repellents: cover the period of travelling including the delay for activity Vaccination[c] (optional)	See scenario 0 If long or frequent trips preventative measures should be the same as for Scenario 4 Test for *L. infantum* infection (6 months post last travel, via quantitative serology)
		3	Re-homing from an endemic area	Any	None	Test for *L. infantum* infection via quantitative serology If positive, do not breed, consider treatment (staging); ectoparasite control Testing of other household dogs

Strategie di prevenzione in aree endemiche

Geographic area	Clinical status	Different scenarios	Travel history	Lifestyle	Preventative applications	Additional recommendations
Endemic and fringe areas	Any Seronegative	4	Outdoors		Repellents all year round or during the known sand flies season. Vaccination[c] (optimal)	Domperidone could be considered (if not vaccinated) Periodic testing if breeding or blood donor
		5	Indoors		Repellents as in 4. Vaccination[c] (optional)	Domperidone could be considered (if not vaccinated) Periodic testing if breeding or blood donor
	Seropositive Healthy[a]	6a	Any		Repellents all year round	Do not use for breeding or as blood donor Periodic check Test other household dogs.
	Seropositive Sick[b]	6b				Do not use for breeding or blood transfusion to other dogs. Staging Treatment as needed. Test other household dogs.

Table 1. Insecticide Molecules with Efficacy to Prevent Sand Fly Bite[a]

Active ingredient	Pyrethroid (range)	Type	Onset	Duration	Brand name (Company)	Refs
Permethrin Indoxacarb	48 mg/kg (48–96)	Spot-on	24–48 h	3–4 weeks	Activyl® Plus (MSD)	[25]
Permethrin Imidacloprid	50 mg/kg (50–125)	Spot-on	24–48 h	3–4 weeks	Advantix® (BAYER)	[23]
Permethrin	–	Spray	Instant	2–3 days	Duowin® (VIRBAC)	[8]
Permethrin Fipronil	60 mg/kg (60–160)	Spot-on	24–48 h	4 weeks	Effitix® (VIRBAC)	[27]
Permethrin	47.6 mg/kg	Spot-on	24–48 h	2 weeks	Ex-spot ® (MSD)	[28]
Permethrin Fipronil	50.48 mg/kg (50.5–101)	Spot-on	24–48 h	4 weeks	Frontline Tri-Act® (MERIAL)	[26]
Deltamethrin	40 mg/g	Collar	7 days	6 months	Scalibor® (MSD)	[12]
Flumethrin Imidacloprid	56 mg/g	Collar	–		Seresto® (BAYER)	
Permethrin Dinotefuran Piriproxyfen	46.6 mg/kg (46.6–158.8)	Spot-on	24–48 h	4 weeks	Vectra 3D® (CEVA)	[11]

[a]The focus of this table are products licenced in Europe; however, certain products are also available on other continents.

Mirò et al., 2017. Trends in Parasitol;

Commercial name (manufacturer)	Composition		Availability	Vaccine protocol	Primary outcome	Vaccine efficacy	Diagnostic interference associated w/vaccine
	Antigen	Adjuvant					
Leishmune® (Zoetis)	Fucose-mannose ligand (FML)	QuilA	Brazil[a]	Three primary vaccination doses (SC), 21-day intervals; one annual booster	Clinical disease	80%	Detection of vaccinal antibodies with official tests (DPP®, ELISA, IFAT). Antibodies not detected after 45 days of first annual booster by FAST or DAT
CaniLeish® (Virbac Santé Animale)	LiESP	QA-21	Europe; Argentina; Paraguay	Three primary vaccination doses (SC), 21-day intervals; one annual booster	Active infection[b]	68.4%	Detection of vaccinal antibodies with quantitative tests (ELISA, IFAT). Rare detection of vaccinal antibodies with Speed Leish K™
Leish-Tec® (Hertape Calier Saúde Animal)	A2	Saponin	Brazil	Three primary vaccination doses (SC), 21-day intervals; one annual booster	Parasite detection	71.4%	Detection of vaccinal antibodies with official ELISA
Letifend® (Laboratorios Leti)	Q-protein	None	Europe	One primary vaccination dose (SC); one annual booster	Clinical disease	72%	No detection of vaccinal antibodies by quantitative tests (IFAT, ELISA) or rapid tests

Abbreviations: DAT, direct agglutination test; ELISA, enzyme-linked immunosorbent assay; FAST, fast agglutination screening test; IFAT, immunofluorescence antibody test; LiESP, Leishmania infantum excreted-secreted proteins; SC, subcutaneous.

[a] To date not on the market.

[b] Active infection was defined as the detection of parasite growth in tissue culture from PCR-positive dogs, shortly followed by the elevation of IFAT titers.

Commercial name (manufacturer)	Composition		Availability	Vaccine protocol	Primary outcome	Vaccine efficacy	Diagnostic interference associated w/vaccine
	Antigen	Adjuvant					
Leishmune® (Zoetis)	Fucose-mannose ligand (FML)	QuilA	Brazil[a]	Three primary vaccination doses (SC), 21-day intervals; one annual booster	Clinical disease	80%	Detection of vaccinal antibodies with official tests (DPP®, ELISA, IFAT). Antibodies not detected after 45 days of first annual booster by FAST or DAT
CaniLeish® (Virbac Santé Animale)	LiESP	QA-21	Europe; Argentina; Paraguay	Three primary vaccination doses (SC), 21-day intervals; one annual booster	Active infection[b]	68.4%	Detection of vaccinal antibodies with quantitative tests (ELISA, IFAT). Rare detection of vaccinal antibodies with Speed Leish K™
Leish-Tec® (Hertape Calier Saúde Animal)	A2	Saponin	Brazil	Three primary vaccination doses (SC), 21-day intervals; one annual booster	Parasite detection	71.4%	Detection of vaccinal antibodies with official ELISA
Letifend® (Laboratorios Leti)	Q-protein	None	Europe	One primary vaccination dose (SC); one annual booster	Clinical disease	72%	No detection of vaccinal antibodies by quantitative tests (IFAT, ELISA) or rapid tests

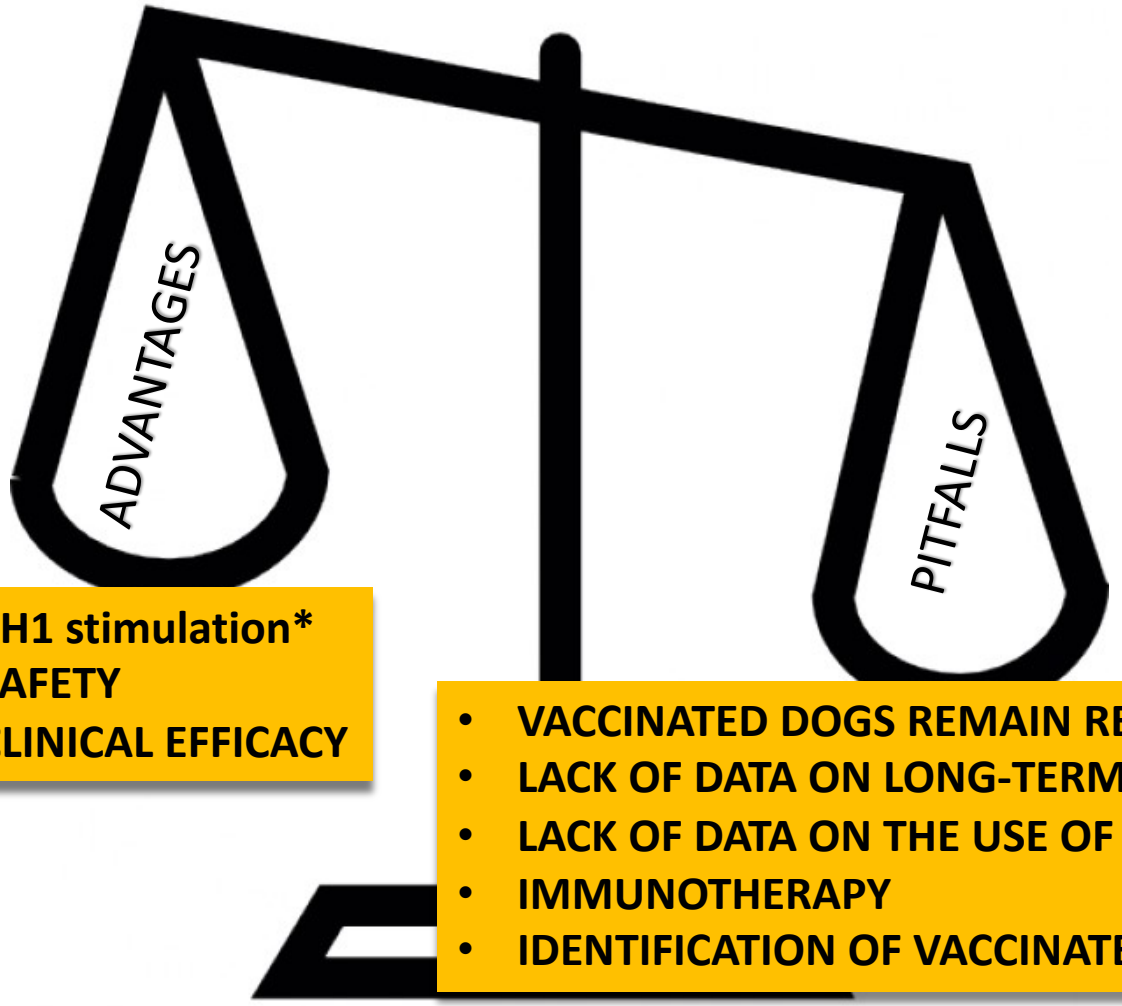
Abbreviations: DAT, direct agglutination test; ELISA, enzyme-linked immunosorbent assay; FAST, fast agglutination screening test; IFAT, immunofluorescence antibody test; LiESP, Leishmania infantum excreted-secreted proteins; SC, subcutaneous.

[a] To date not on the market.

[b] Active infection was defined as the detection of parasite growth in tissue culture from PCR-positive dogs, shortly followed by the elevation of IFAT titers.

LeishVet

INDIVIDUAL PROTECTION



PUBLIC HEALTH APPROACH

- TH1 stimulation*
- SAFETY
- CLINICAL EFFICACY

- VACCINATED DOGS REMAIN RESERVOIRS
- LACK OF DATA ON LONG-TERM CLINICALEFFICACY
- LACK OF DATA ON THE USE OF VACCINES AS
- IMMUNOTHERAPY
- IDENTIFICATION OF VACCINATED DOGS

*Lack of data for Letifend