



CONVEGNO

GIORNATE INFETTIVOLOGICHE "LUIGI SACCO" 2022



HYBRID
EDITION

UNIVERSITÀ DEGLI STUDI
DI MILANO

Sistema Sanitario
Regione
Lombardia
ASST Fatebenefratelli Sacco

Milano, 14–15 Ottobre 2022

Sabato 15 Ottobre 2022

Ore 09.00-10.45 **MALATTIE TROPICALI NEGLETTE**
Moderatore: A. Bartoloni (Firenze)

Ore 09.00 **Italian Network on NTDs**
F. Bruschi (Milano)

Ore 09.15 **Leishmaniosi**
A. Cascio (Palermo)

Ore 09.35 **Malattia di Chagas**
S. Antinori (Milano)

Ore 09.55 **Strongiloidiasi**
D. Buonfrate (Negrar-VR)

Ore 10.15 **Schistosomiasi**
F. Gobbi (Negrar-VR)

Leishmaniosi

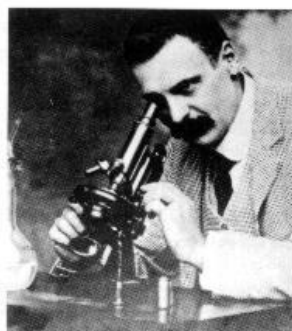
Antonio Cascio

Università di Palermo

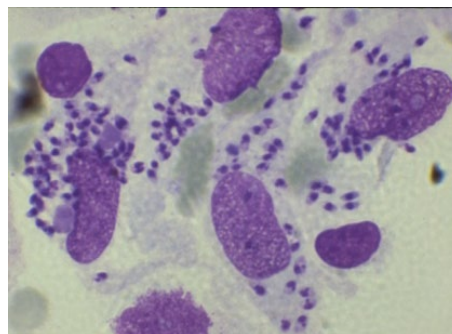


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promise
Dipartimento di Promozione della Salute, Materno-Infantile, Medicina Interna e Specialistica di Eccellenza "G. D'Alessandro"



Early twentieth century – discovery of the parasite



[THE BRITISH MEDICAL JOURNAL Nov. 14, 1903.]

NOTE ON THE BODIES RECENTLY DESCRIBED BY LEISHMAN AND DONOVAN.

BY MAJOR R. ROSS, F.R.S., F.R.C.S., C.B.,

Professor of Tropical Medicine, University of Liverpool.

(From the Johnston Tropical Laboratory, Liverpool.)

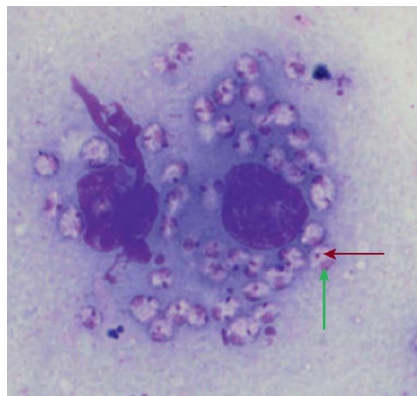
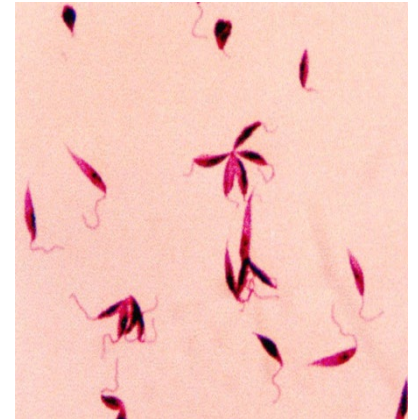
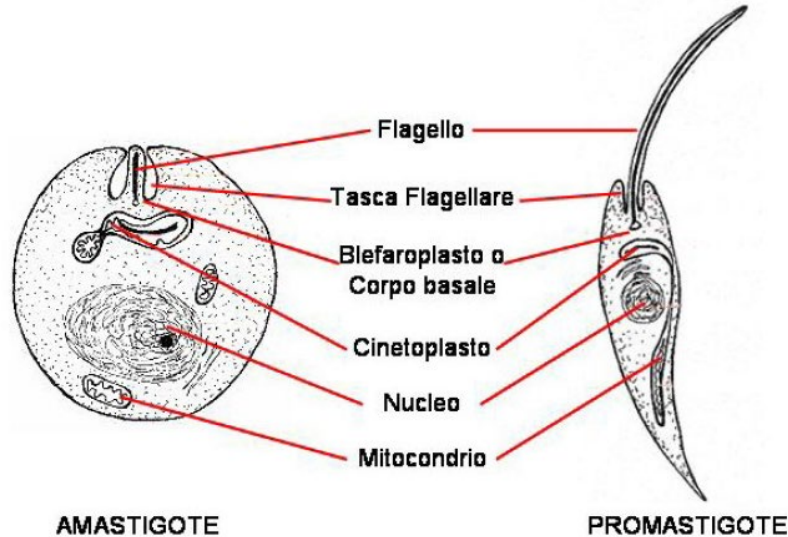
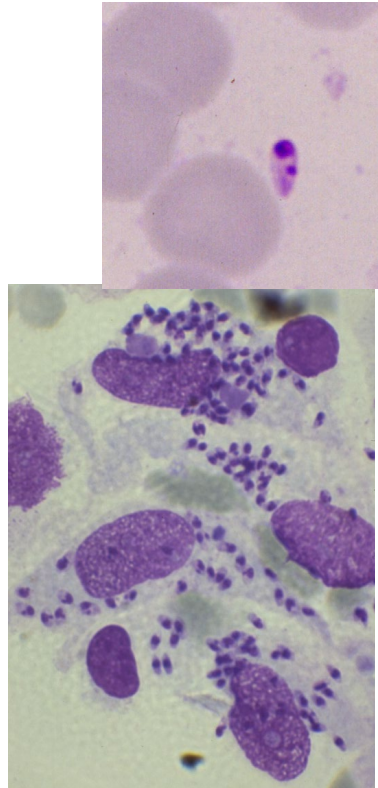
IN May, 1903, Major Leishman, R.A.M.C., described¹ certain small oval bodies occurring in smear preparations made *post mortem* from the spleen of a soldier suffering from low fever, chronic dysentery, and cachexia. The observation was made in London at the Military Hospital, and the patient had contracted his illness at Dum-Dum, near Calcutta. Leishman gave a very accurate description of these bodies. He said that they existed in large numbers among the spleen cells and red corpuscles; that they were round or oval, and $2\ \mu$ to $3\ \mu$ in diameter; that on staining with Romanowsky's method they were found to contain two masses of chromatin—a large circular mass or ring, and another smaller mass, “usually in the form of a short rod set perpendicularly or at a tangent to the circumference of the larger mass.” The outline of the bodies containing these two masses of chromatin was faintly visible with this stain. The bodies were usually isolated, but occasionally aggregated into “clumps composed of twenty to fifty members.” Regarding their nature, he thought it probable that they were the residue of trypanosomes of which the vibratile membrane had disappeared after death, leaving behind the nucleus and micronucleus shrunk together in a small mass, and quotes in support of this view the occurrence of similar *post-mortem* changes in the trypanosomes of dead rats.

IN July Captain Donovan, I.M.S., stated² that he had already found the same bodies on April 9th, 23rd, and 24th in *post-mortem* smears from the spleens of three consecutive cases said to have died from chronic malaria in Madras. At first he thought that the bodies represented the long-sought-for resting stage of the malaria parasite, but, after finding them in two other cases, began to think that they were *post-mortem* degenerations of spleen cells. On reading Leishman's paper he recognized their similarity to the bodies described by that observer; and next was able to recover them in blood taken *intra vitam* from the spleen of a boy suffering from irregular pyrexia (June 17th). He remarks that this case excludes the possibility of the bodies being due to *post-mortem* changes, and adds that nothing resembling trypanosomata could be found in the boy's blood.

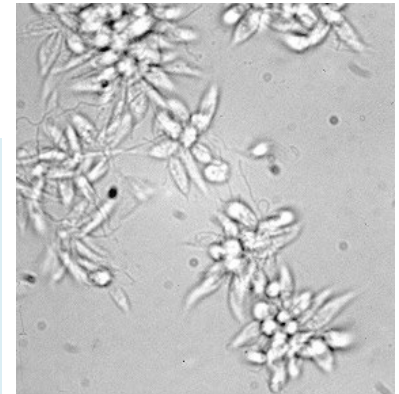
**Amastigote (2-3 μm) ,
intracellulare (cellule
monocito-macrofagiche)**

Leishmania

**Promastigote (15-26 μm di
lunghezza), extracellulare, mobile;
flagello polo anteriore (intestino
flebotomo femmina; coltura); T
22-26 $^{\circ}\text{C}$**



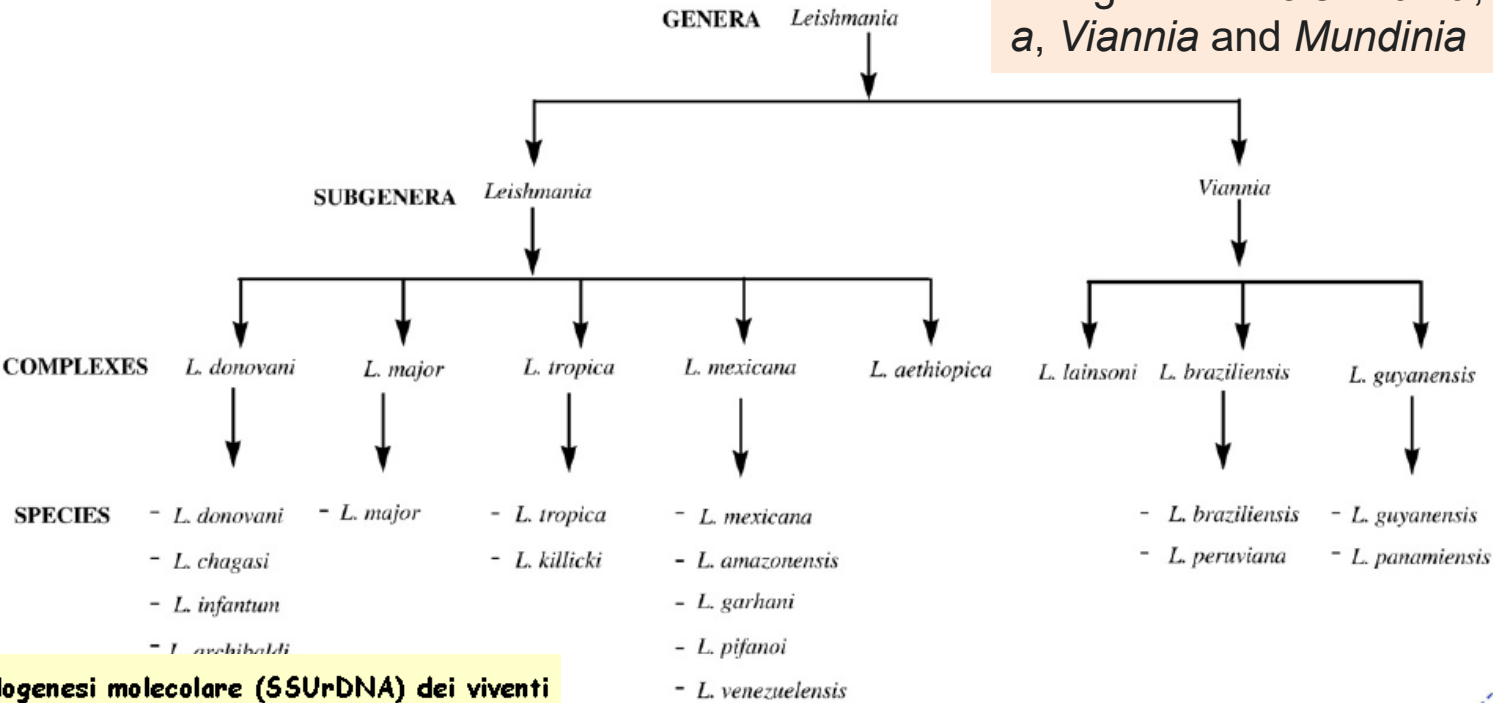
**Cinetoplasto (kinetoplasto,
DNA extranucleare)**
piriforme od a bastoncino,
spesso situato alla periferia del
corpo parassitario ed in
posizione antinucleare (spesso
perpendicolare al nucleo)



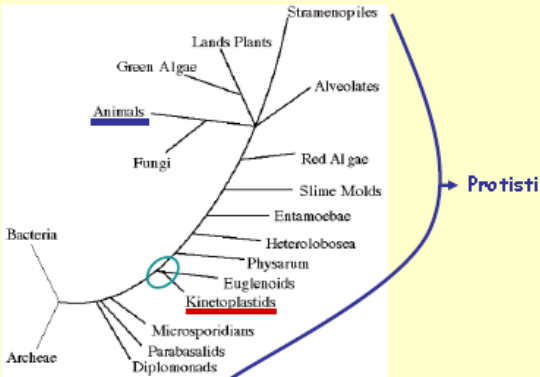
Subkingdom: Protozoa
Order: Kinetoplastida
Family: Trypanosomatidae

LEISHMANIOSI-tassonomia

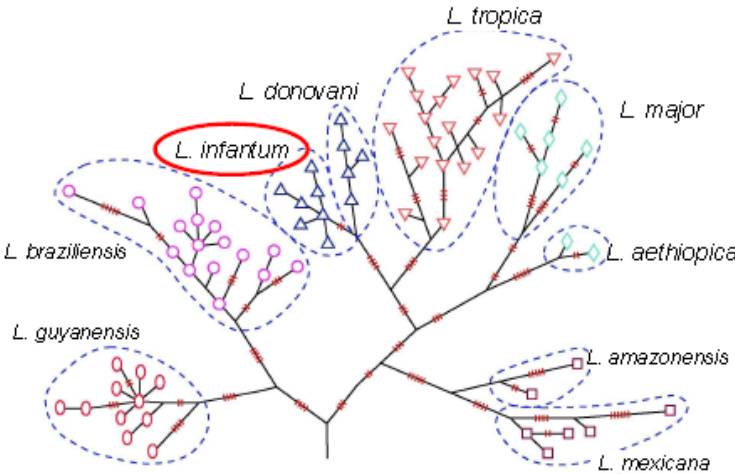
Four subgenera of *Leishmania* are now recognised *Leishmania*, *Sauroleishmania*, *Viannia* and *Mundinia*



Filogenesi molecolare (5SUrDNA) dei viventi

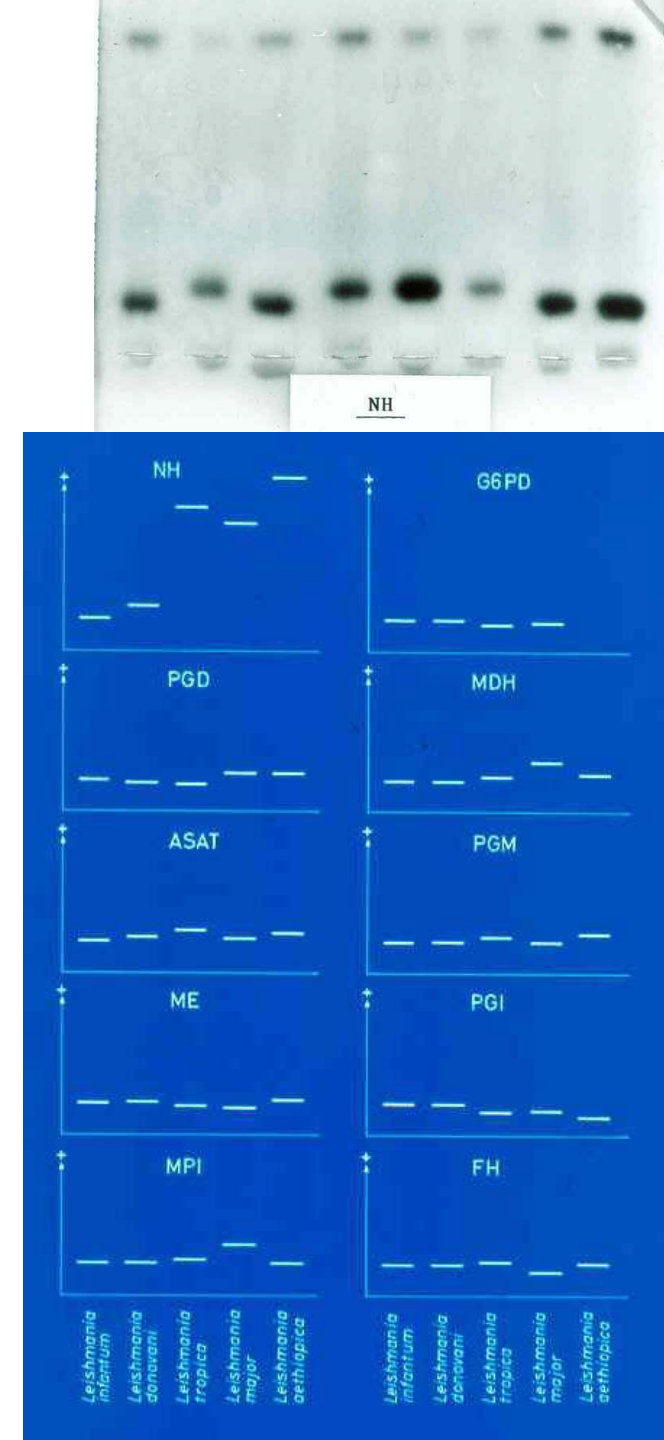


Evoluzione del genere in base all'analisi dei polimorfismi genetici



Analisi elettroforetica degli isoenzimi ($\Rightarrow$ zimodema)

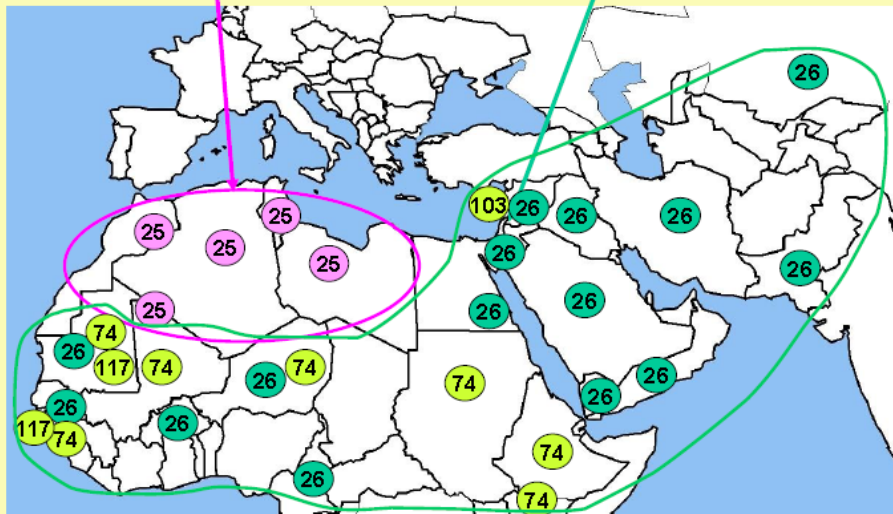
- Ogni zimodema comprende leishmanie con un uguale pattern isoenzimatico; i microrganismi che presentano modeste differenze sono ritenute appartenenti allo stesso complesso di zimodemi.
- I termini di “zimodema” e “complesso di zimodemi” tendono a sostituire quelli che in passato erano “specie” e “sottospecie”. I diversi zimodemi vengono indicati con il prefisso MON (Montpelier) o LON (London) seguito da un numero arabo: MON 1, MON 2, etc.



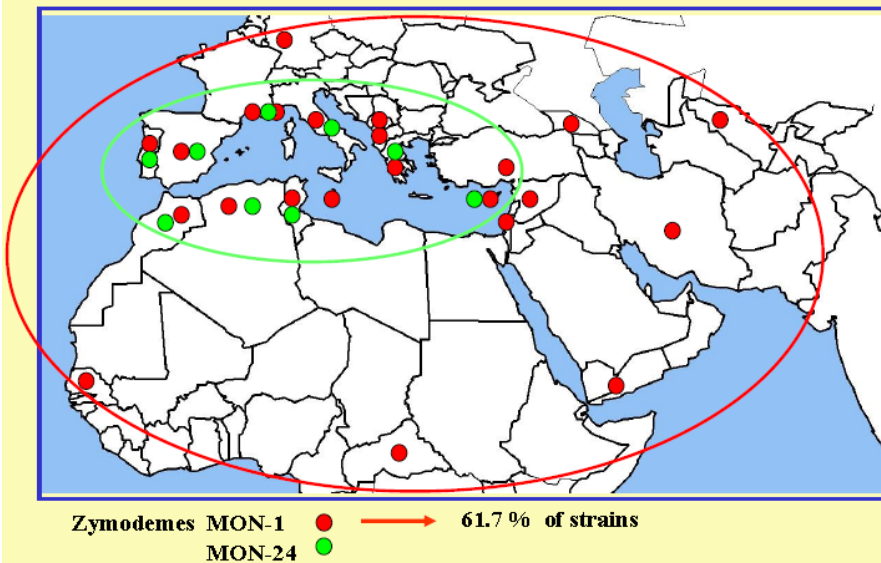
Distribution of the 12 *L. major* zymodemes

Maghreb : 1 zymodeme MON-25

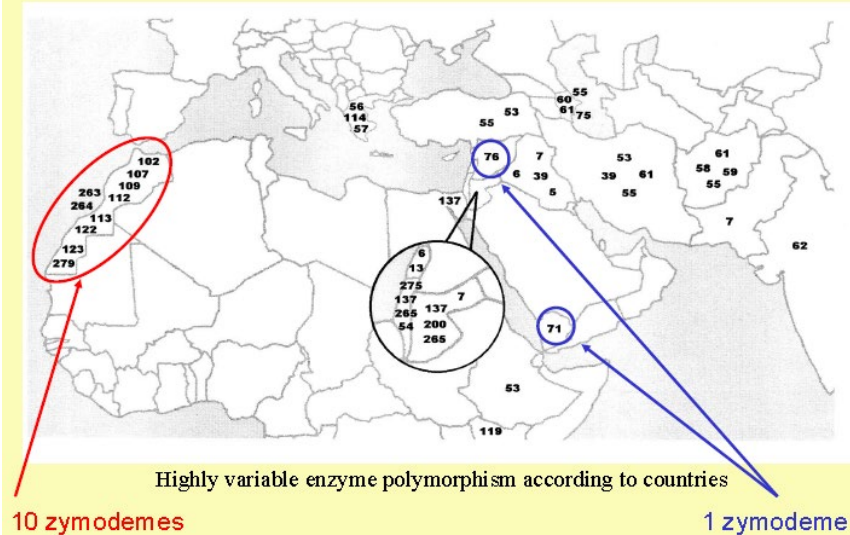
Israël/Palestine : 5 zymodemes



Distribution of *L. infantum* zymodemes (n=37)



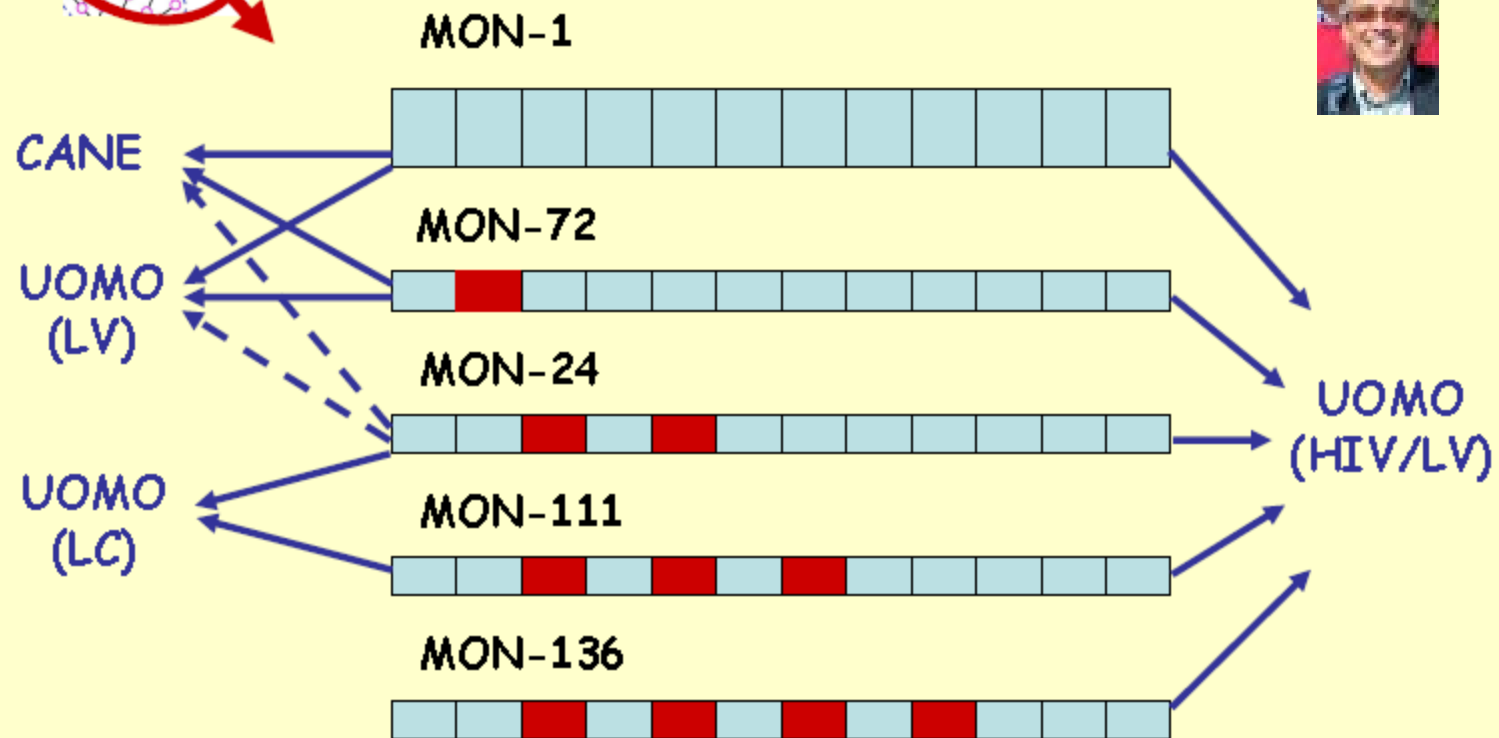
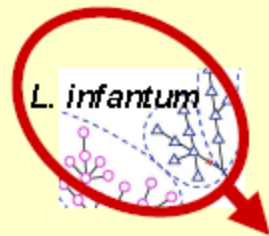
Distribution of the 35 *L. tropica* zymodemes (highly diversified electromorphs)



The *Leishmania* collection of Montpellier
(France),
a tool for studying taxonomy, phylogeography
and epidemiology.

Il polimorfismo di *Leishmania infantum* e relazioni con l'ospite mammifero

I PRINCIPALI ZIMODEMI IN ITALIA

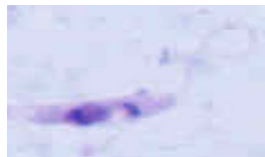


Leishmaniasis

- Group of diseases caused by protozoa of the genus *Leishmania*, hosts of various wild and domestic animals, occasionally transmitted to humans by vector insects of the genus *Phlebotomus* (in America by insects of the genus *Lutzomya*).
- Based on the clinical picture and geographical distribution they can be classified into:
 - **Visceral leishmaniasis** (in which we distinguish the Mediterranean form (also present in China and South America), the Indian form or Kala-azar, and the African Kala-azar);
 - **Old World cutaneous Leishmaniasis** (urban eastern button, rural eastern button, diffuse cutaneous leishmaniasis);
 - **New World Cutaneous Leishmaniasis** ("uta", "ulcera de los chicleros", "pian bois", mucocutaneous form "espundia", and diffuse cutaneous leishmaniasis).

Leishmania

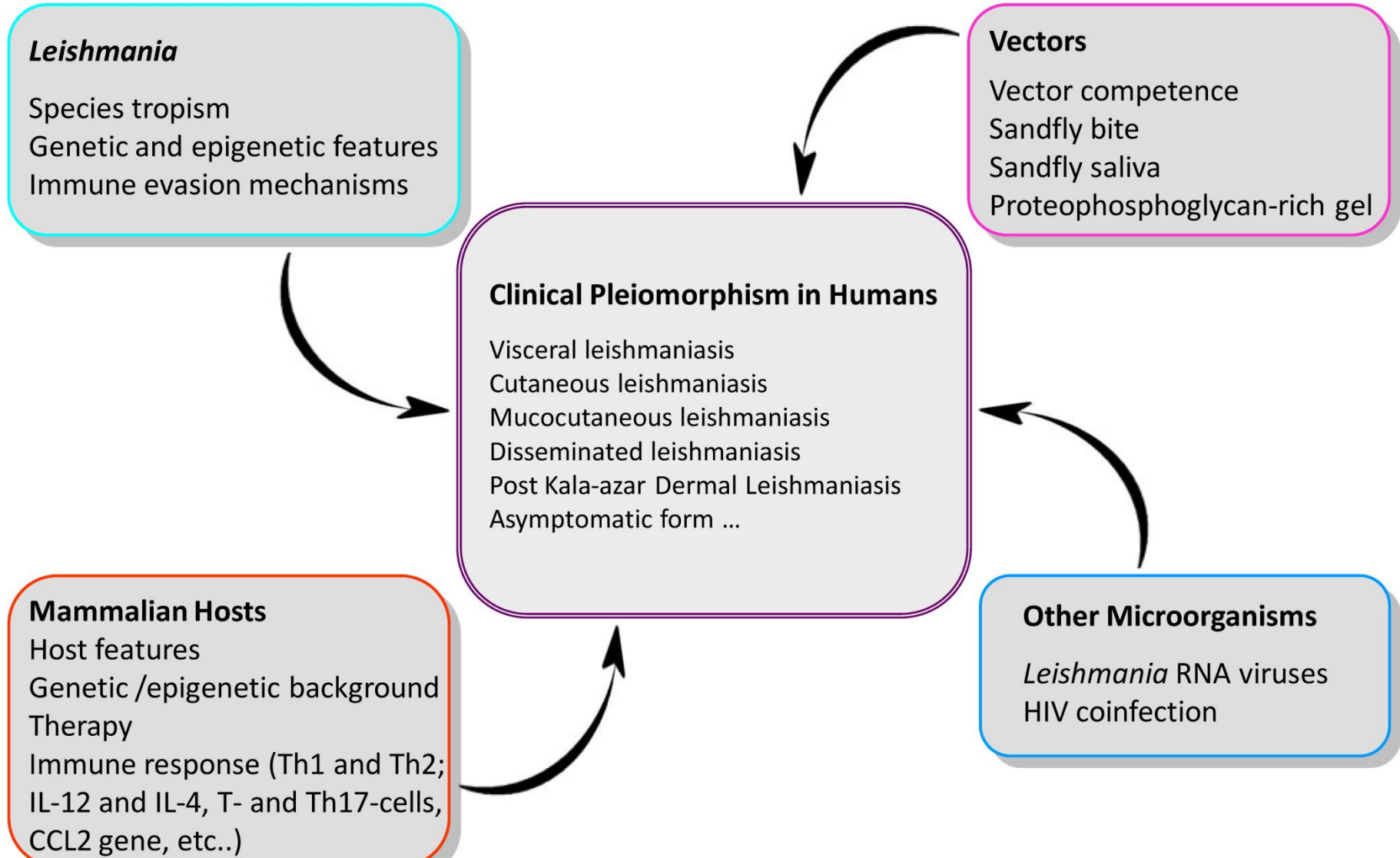
- There are at least 22 species of *Leishmania*, with a wide range of geographical distributions and hosts.
- They cause a spectrum of diseases ranging from self-healing ulcers to disseminated and often fatal infections, depending on the species involved and the host's cell-mediated immune response.



Clinical pleiomorphism in human leishmaniases, with special mention of asymptomatic infection

A. L. Bahuls^{1*}, P. Bastien^{1,2*}, C. Pomares^{3,4}, J. Arevalo⁵, R. Fisa⁶ and M. Hide¹

1) UMR MIVEGEC (IRD 224-CNRS 5290-Université Montpellier 1), 2) Université Montpellier 1 (UFR Médecine) and Centre Hospitalier Universitaire, Laboratoire de Parasitologie-Mycologie, National Reference Centre (CNR) for Leishmania, Montpellier, 3) INSERM U895, C3M, Bâtiment Universitaire Archimède, 4) Centre Hospitalier Universitaire de Nice, Laboratoire de Parasitologie-Mycologie, Nice, France, 5) Instituto de Medicina Tropical 'Alexander von Humboldt' y Departamento de Bioquímica, Biología Molecular y Farmacología, Universidad Peruana Cayetano Heredia, Lima, Peru and 6) Laboratori de Parasitologia, Facultat de Farmàcia, Universitat de Barcelona, Barcelona, Spain

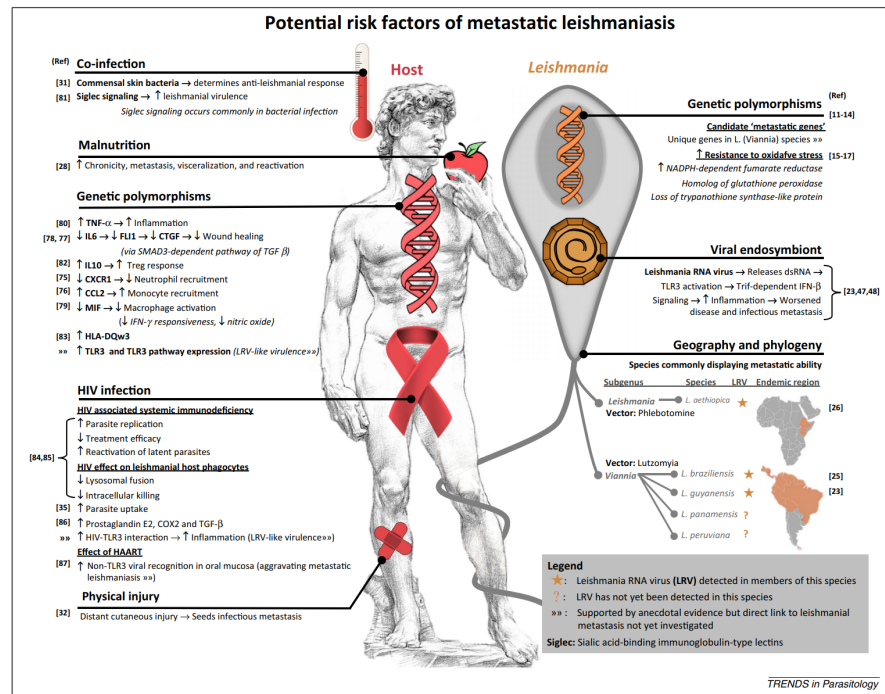


The immunological, environmental, and phylogenetic perpetrators of metastatic leishmaniasis

Mary-Anne Hartley¹, Stefan Drexler¹, Catherine Ronet¹, Stephen M. Beverley², and Nicolas Fasel¹

¹ Department of Biochemistry, University of Lausanne, 1066 Epalinges, Switzerland

² Department of Molecular Microbiology, Washington University School of Medicine, Saint Louis, MO, USA



(A) Endemic species of the Neotropics



↑ Metastatic potential

- L. (Viannia) subgenus*
- L. brasiliensis*
- L. guyanensis*
- L. panamensis*
- L. peruviana*
- L. Mexicana complex*
- L. amazonensis*

↓ Metastatic potential

- L. Mexicana complex*
- L. mexicana*
- L. venezuelensis*

The various phenotypic outcomes of cutaneous metastasis



1: Mucocutaneous leishmaniasis
— (a) Buccal
— (b) Septal
— (c) Classic 'tapir nose' after septal disease
Bolivia

2: Diffuse cutaneous leishmaniasis (DCL) of the trunk and limbs with multiple nodulated lesions
Brazil

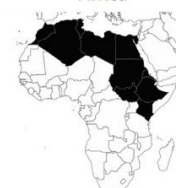
3: Facial CL with multiple lesions undergoing hyperkeratosis
Bolivia

4: Classic ulcerative lesions with raised edges and a clear exudate
Bolivia

5: Classic ulcerative scar that is smooth, shiny and centrally hypo-pigmented
Brazil

(B) Endemic species of the Paleotropics

Africa



↑ Metastatic potential

- L. (Leishmania) subgenus*
- L. aethiopica*
- L. tropica*
- Visceralizing**
- L. infantum*

↓ Metastatic potential

- L. (Leishmania) subgenus*
- L. major*

Eurasia



↑ Metastatic potential

- L. (Leishmania)*
- L. tropica*
- Visceralizing**
- L. infantum*
- L. donovani*

↓ Metastatic potential

- L. (Leishmania)*
- L. major*

The various phenotypic outcomes of cutaneous metastasis



6: DCL marked by non-ulcerating hyperpigmented papules
Kenya (*L. tropica*)

7: Leishmaniasis recidivans lupoid disfiguration after disease reactivates in periphery of previously healed leishmanial scars
Kenya (*L. tropica*)

8: Nasal CL where most of the infection is localized on the outer surface rather than in the mucosa
Eritrea (*L. aethiopica*)

9: Post Kala-Azar Dermal leishmaniasis (PKDL), presenting with depigmentation on the trunk and multiple papules on the face
Sudan (*L. infantum*)

10: Non-ulcerated cutaneous leishmaniasis typical of *L. infantum* infection before visceralization
Turkey (*L. infantum*)

11: Post Kala-Azar Dermal leishmaniasis (PKDL), presenting with peri-buccal macular depigmentation
India (*L. donovani*)

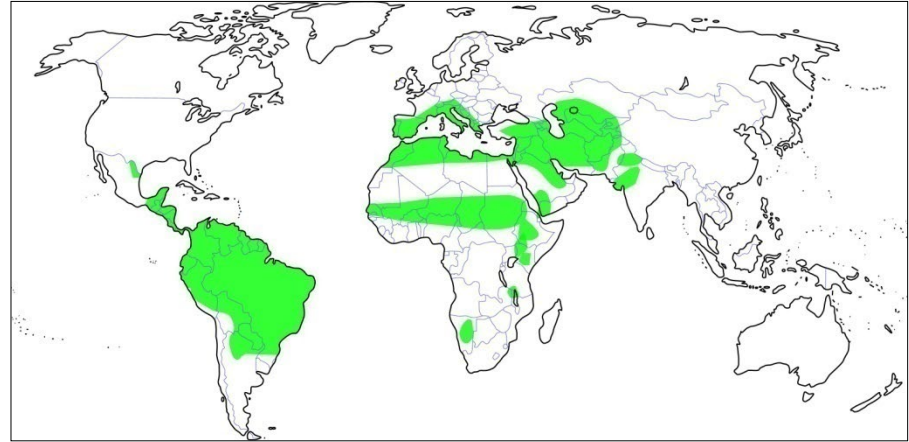
12: Leishmaniasis recidivans, reactivation of infection in the peripheral granulomatous scars of previously healed CL
Syria (*L. tropica*)

13: Zosteriform cutaneous leishmaniasis, multiple papules resembling herpes zoster
Jordan (*L. tropica*)

Leishmaniasis

Cutaneous leishmaniasis

$1.5-2 \times 10^6$ cases/y

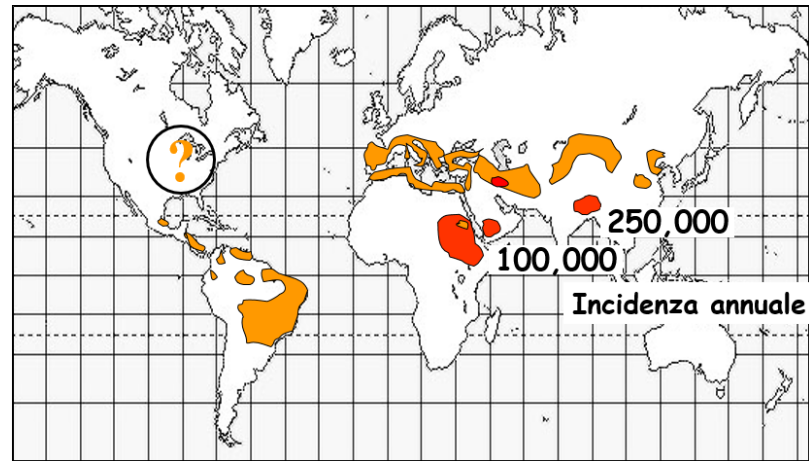


Visceral leishmaniasis

- Anthroponotic VL (*Leishmania donovani*)

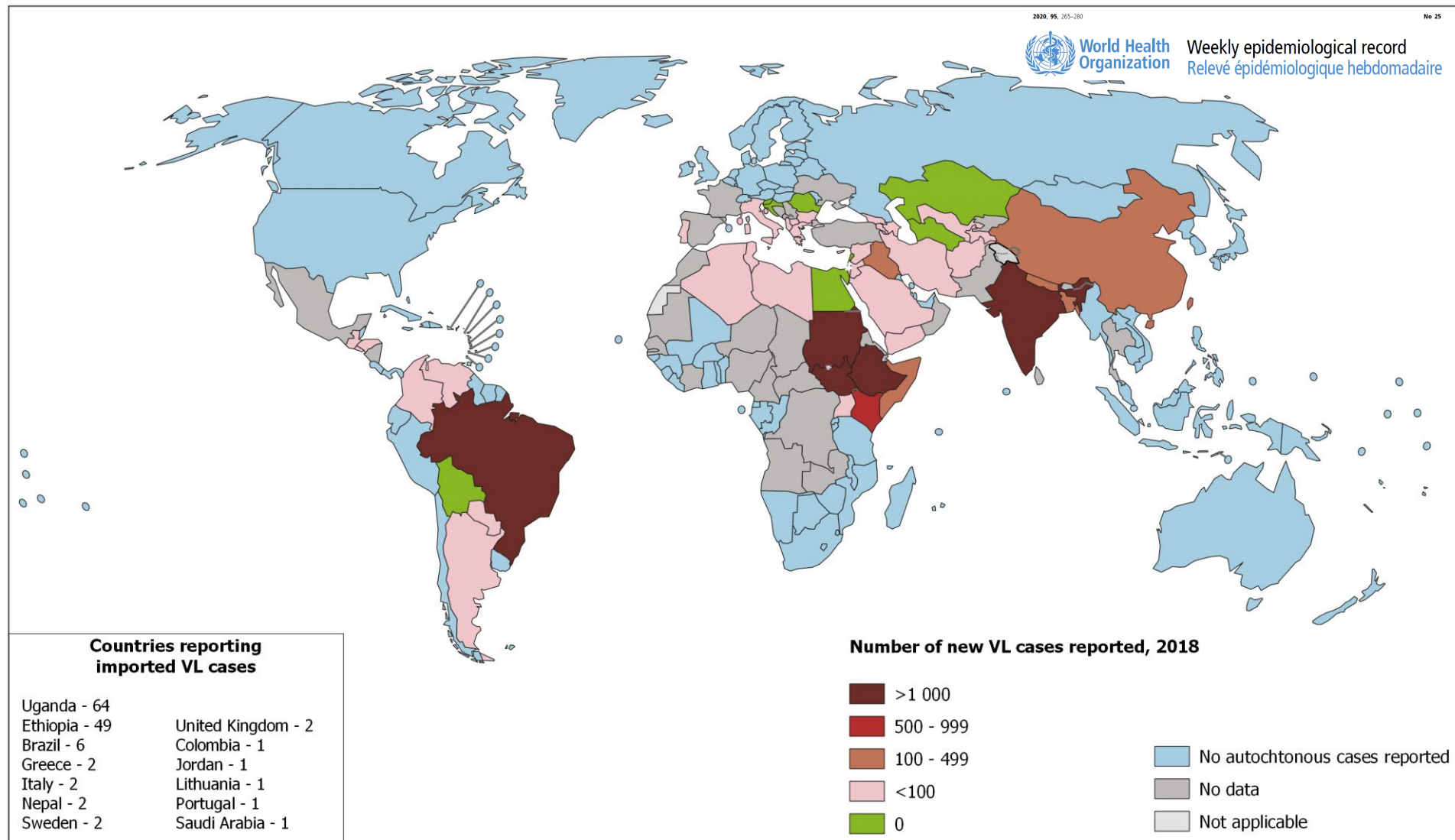
- Zoonotic VL *infantum* – sin.: *L. chagasi*)

500.000 cases/y



Marina Gramiccia ISS

Status of endemicity of visceral leishmaniasis worldwide, 2018

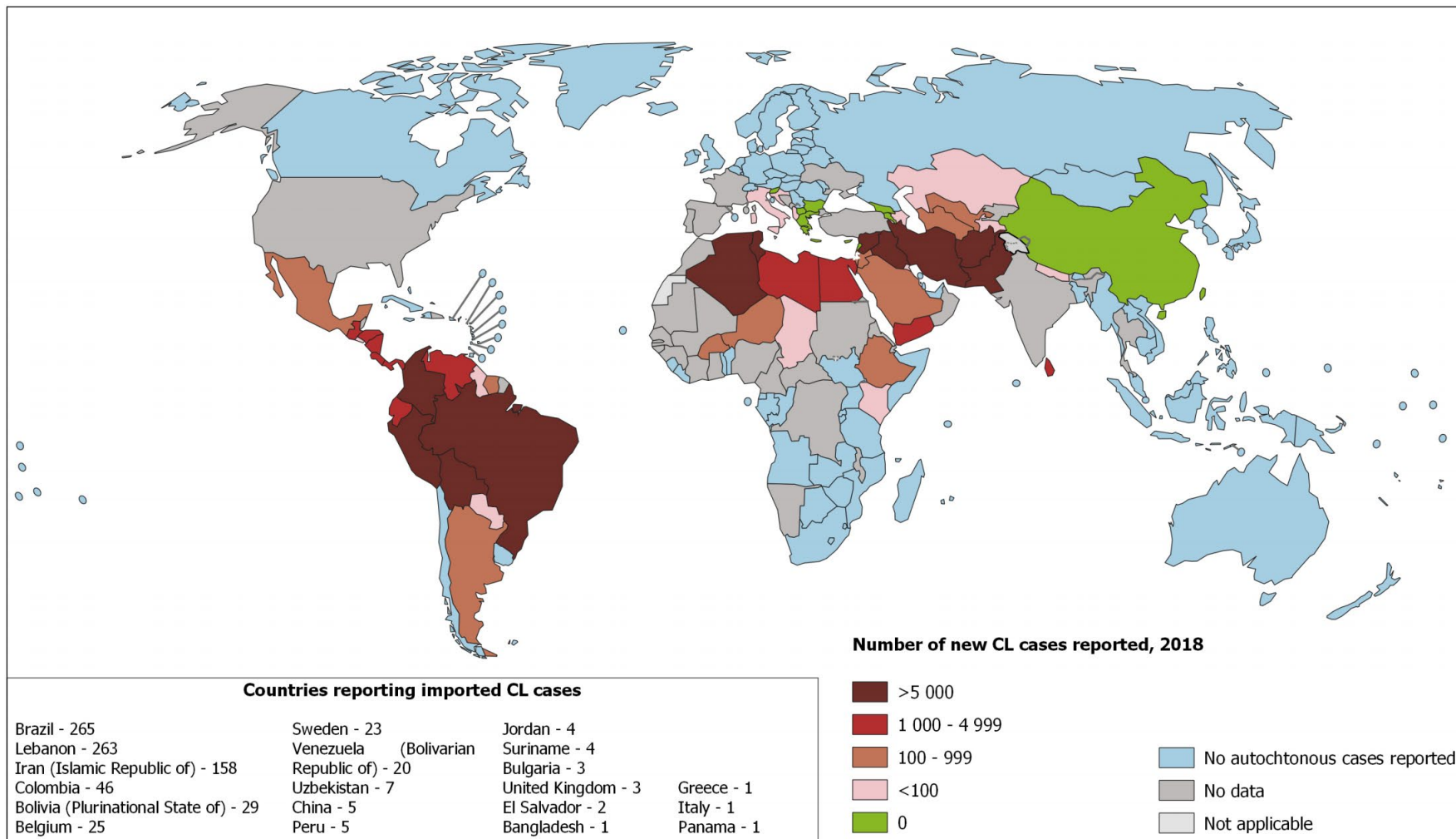


The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2019. All rights reserved

Data Source: World Health Organization
Map Production: Control of Neglected Tropical Diseases (NTD)
World Health Organization



Status of endemicity of cutaneous leishmaniasis worldwide, 2018



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2019. All rights reserved

Data Source: World Health Organization
Map Production: Control of Neglected Tropical Diseases (NTD)
World Health Organization

Figure 1b **Evolution of numbers of visceral leishmaniasis (VL) cases, by WHO region, 1998–2018**

Figure 1b **Évolution du nombre de cas de leishmaniose viscérale (LV), par Région de l'OMS, 1998–2018**

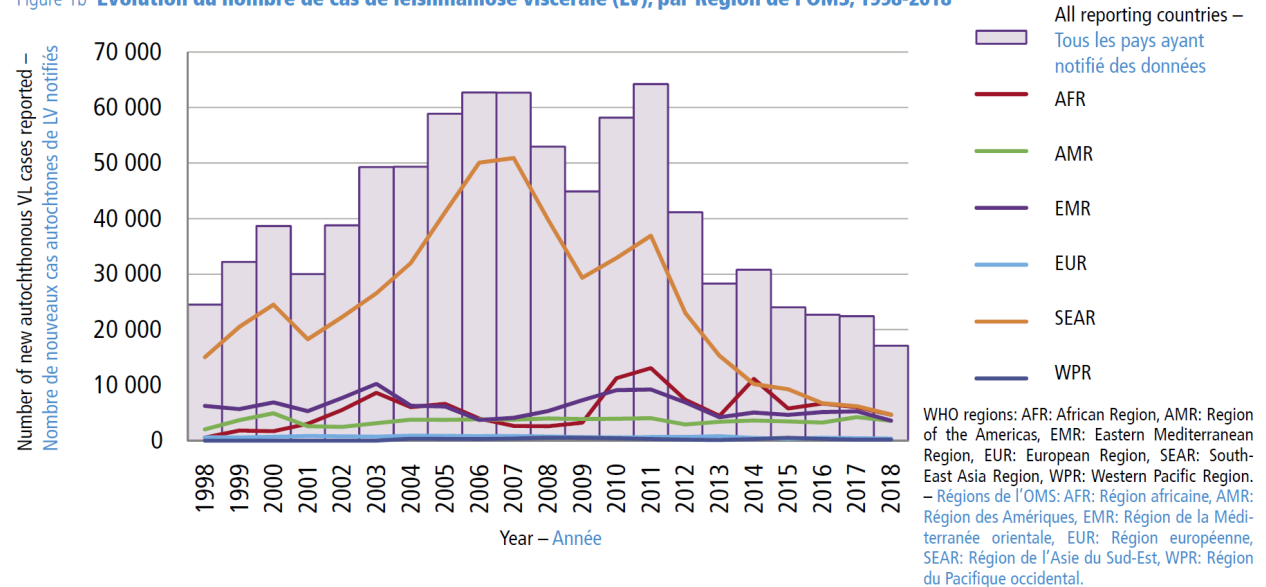
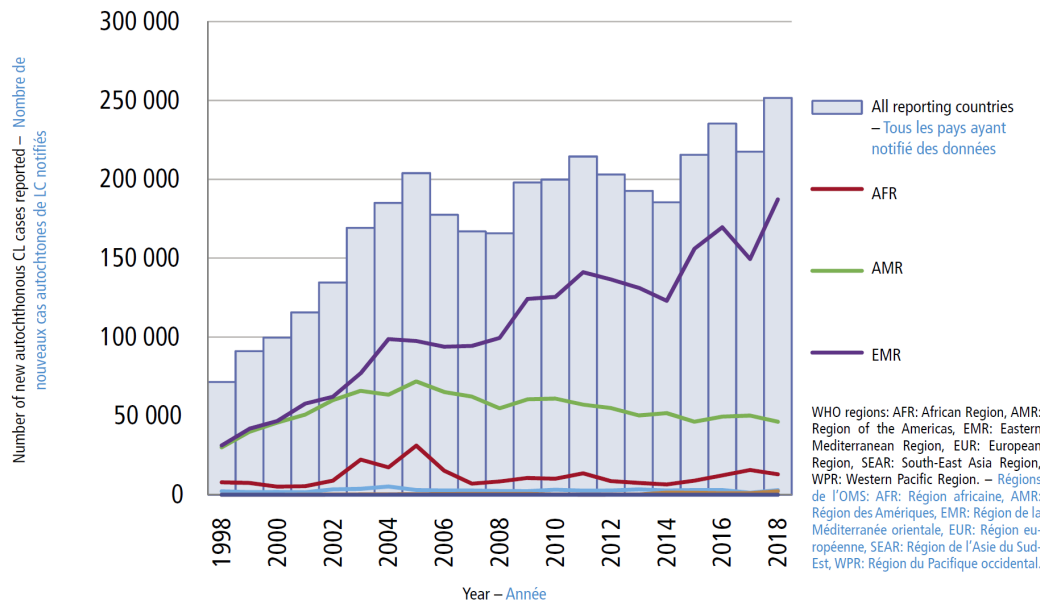


Figure 1a **Evolution of the numbers of cutaneous leishmaniasis (CL) cases, by WHO region, 1998–2018**

Figure 1a **Évolution du nombre de cas de leishmaniose cutanée (LC), par Région de l'OMS, 1998–2018**



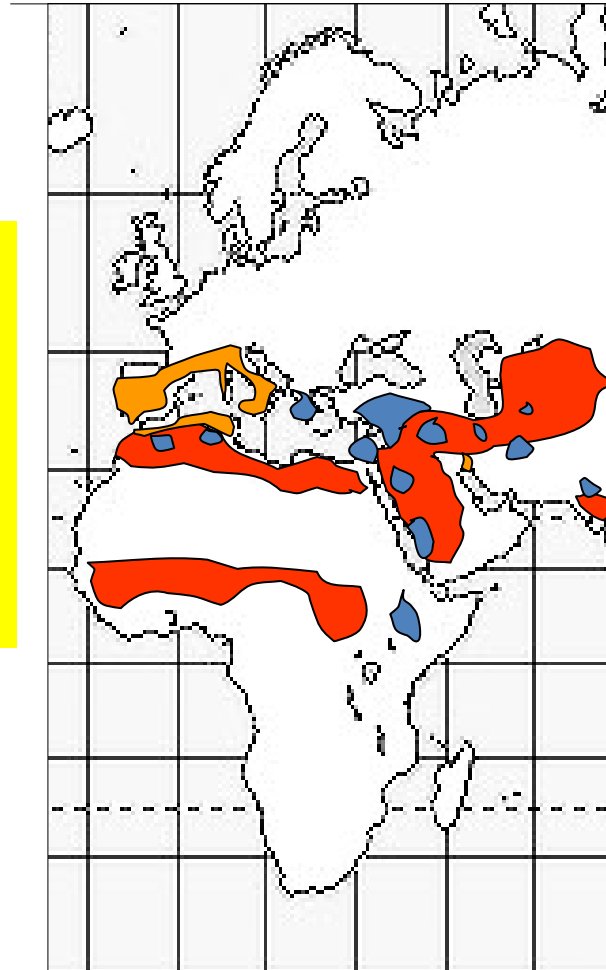
Old world cutaneous leishmaniasis

Leishmaniosi cutanea
zoonotica da *Leishmania major*



Il serbatoio: *Meriones shawi*
(Gerbillidae)

- Zoonotic LC (ZCL)
(*L. major*)
- Antroponotic CL
(*L. tropica*)
- Sporadic ZCL
(*L. infantum*)

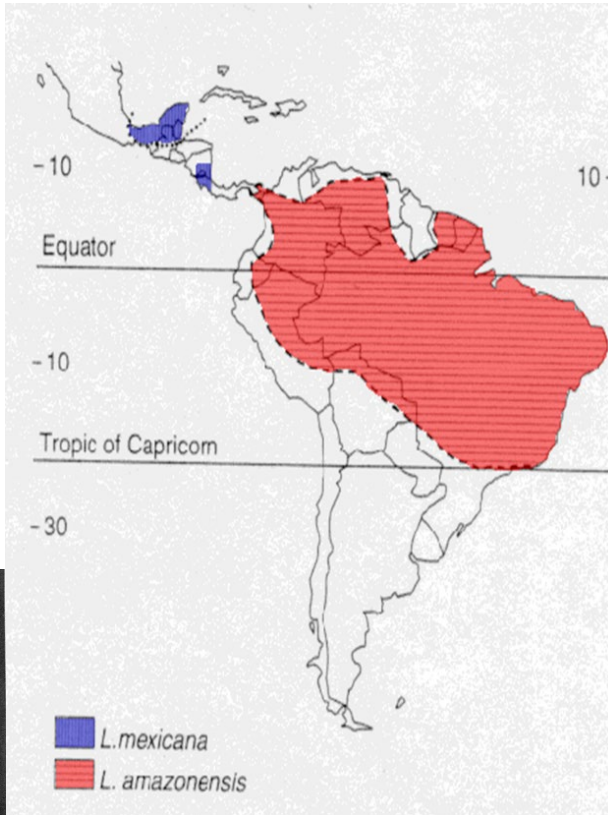


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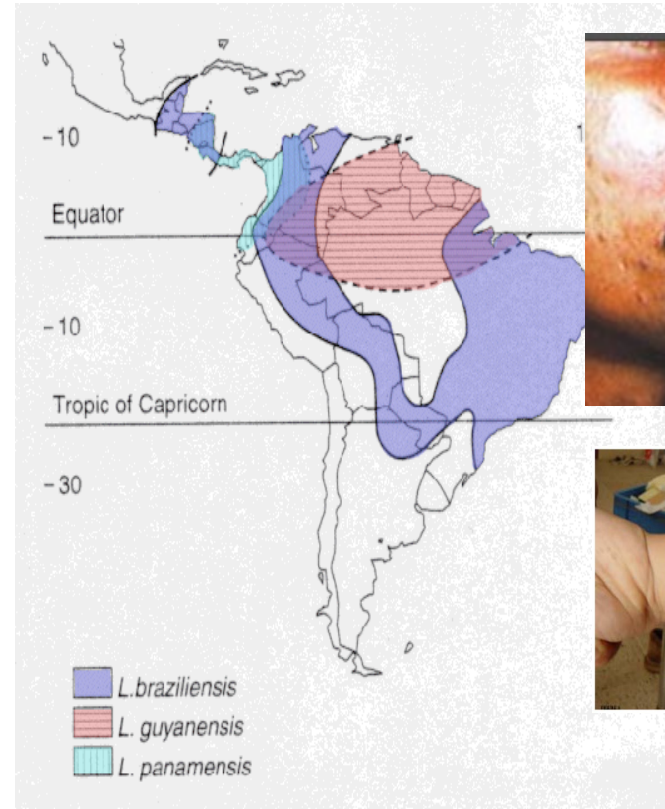


New world cutaneous and mucocutaneous leishmaniasis

Subgenus *Leishmania*



Subgenus *Viannia*



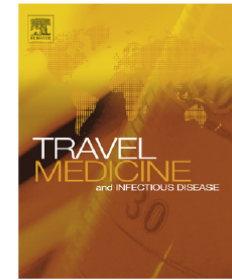
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REVIEW

Leishmaniasis in travelers: A literature review



Pasquale Mansueto ^{a,*}, Aurelio Seidita ^a, Giustina Vitale ^a,
Antonio Cascio ^b

EDITORIAL

10.1111/j.1469-0691.2004.01046.x

Cutaneous leishmaniasis: an increasing threat for travellers

S. Antinori¹, E. Gianelli¹, S. Calattini¹, E. Longhi¹, M. Gramiccia² and M. Corbellino¹

¹Istituto di Malattie Infettive e Tropicali, Università di Milano; ²Reparto di Malattie Trasmesse da Vettori e Sanità Internazionale, Dipartimento di Malattie Infettive, Parassitarie e Immunomediate, Istituto Superiore di Sanità, Roma, Italy

RESEARCH

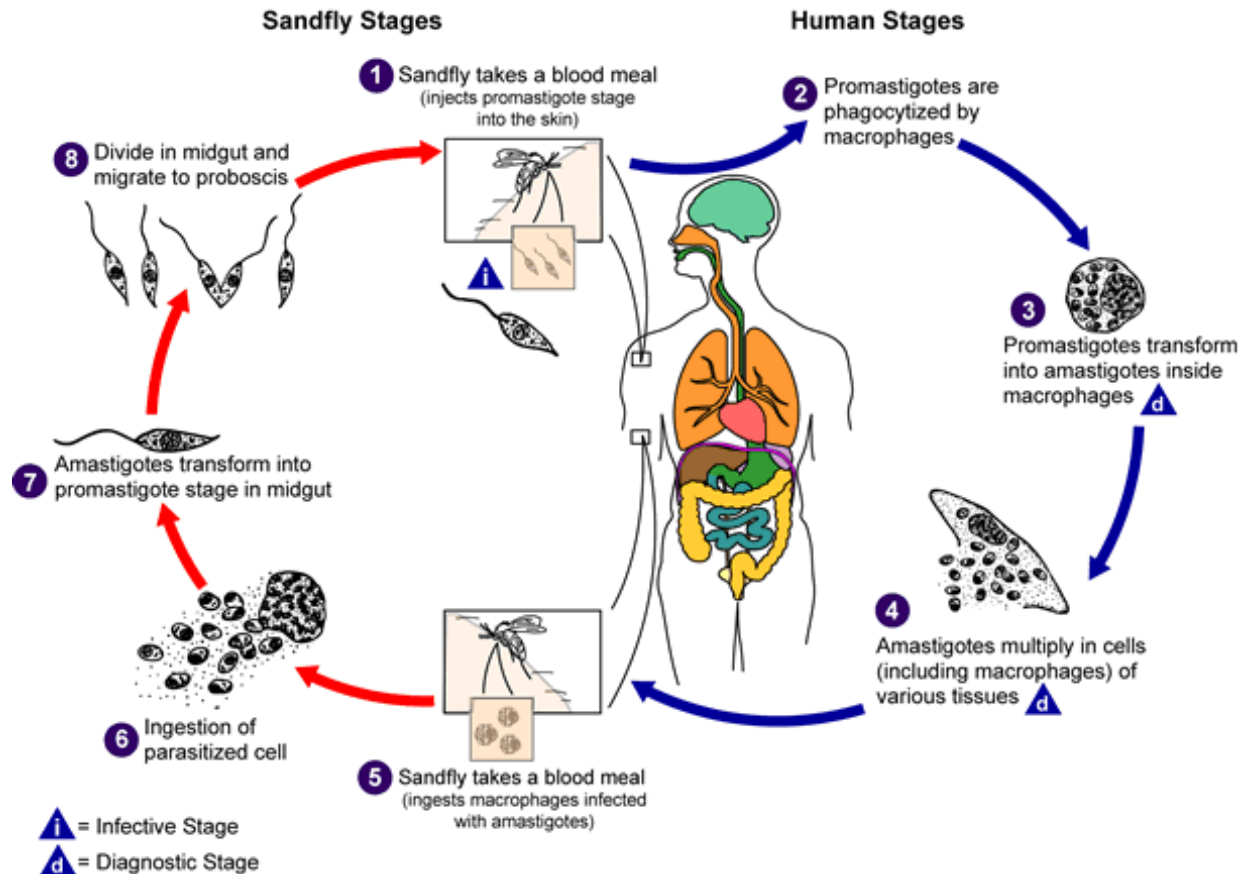
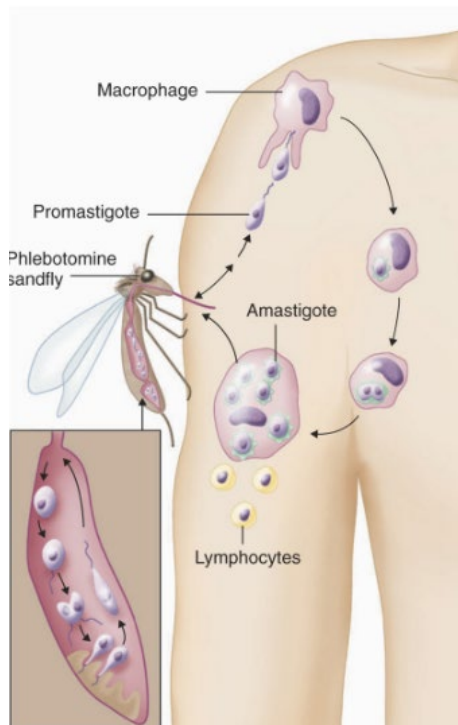
Open Access

Imported leishmaniasis in travelers: a 7-year retrospective from a Parisian hospital in France



Nesrine Aissaoui¹, Samia Hamane¹, Maud Gits-Muselli^{1,2}, Antoine Petit³, Mazouz Benderdouche¹, Blandine Denis⁴, Alexandre Alanio^{1,2}, Sarah Dellièvre^{1,2}, Martine Bagot^{3,5} and Stéphane Bretagne^{1,2*}

- **Methods:** We reviewed all consecutive leishmaniasis cases seen between September 2012 and May 2020. The diagnostic strategy included microscopy after May-Grünwald-Giemsa staining, a diagnostic quantitative PCR (qPCR) assay, and species identification based on sequencing of the cytochrome b gene. **Results: Eighty-nine patients had a definitive leishmaniasis diagnosis.**
- **Nine patients had VL with *Leishmania infantum*.**
- **Eighty patients had CL.**
 - Twelve patients acquired CL after trips in Latin America (7 *Leishmania guyanensis*, 2 *Leishmania braziliensis*, 2 *Leishmania mexicana*, and 1 *Leishmania panamensis*).
 - Species could be identified in 63 of the 68 CLs mainly after travel in North Africa (59%) with *Leishmania major* (65%), *Leishmania tropica/killicki* (24%), and *L. infantum* (11%), or in West Sub-Saharan Africa (32%), all due to *L. major*. The median day between appearance of the lesions and diagnosis was 90 [range 60–127].





- Alopecia simmetrica e iperpigmentazione in cane con CanL e dermatite atopica

- Ulcere all'arto inferiore

- Lesione da inoculazione



- onicogrifia

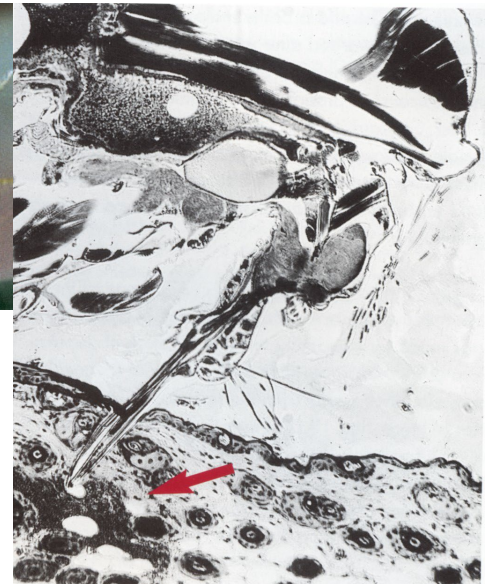
- Epistassi

- Uveite bollosa

- Glaucoma grave



Flebotomi

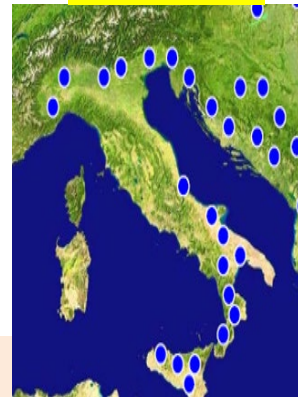


- Piccoli (1,5-2,5 mm) ditteri ematofagi appartenenti alla sottofamiglia Phlebotominae (Diptera: Psychodidae).
- Riconoscibili per:
 - il caratteristico movimento a “salto”,
 - per la posizione delle ali che vengono mantenute erette con una configurazione a V,
 - per il capo forma un angolo retto con il torace e
 - per la fitta peluria che ricopre addome torace ed ali
 - colorazione del corpo giallino vivace
- Meno del 10% delle specie conosciute sono coinvolte nella trasmissione di leishmanie
- Solo le femmine ematofaghe, i maschi si nutrono di pollini
- Sono in grado di trasmettere la leishmaniosi 7-10 giorni dopo essersi infettate e restano infettive per il resto della loro vita (poche settimane)
- La saliva contiene un potente vasodilatatore (maxadilan)
- L'intestino dei flebotomi infetti può essere parzialmente bloccato, il che li indurrebbe a nutrirsi ripetutamente aumentando le probabilità della trasmissione.

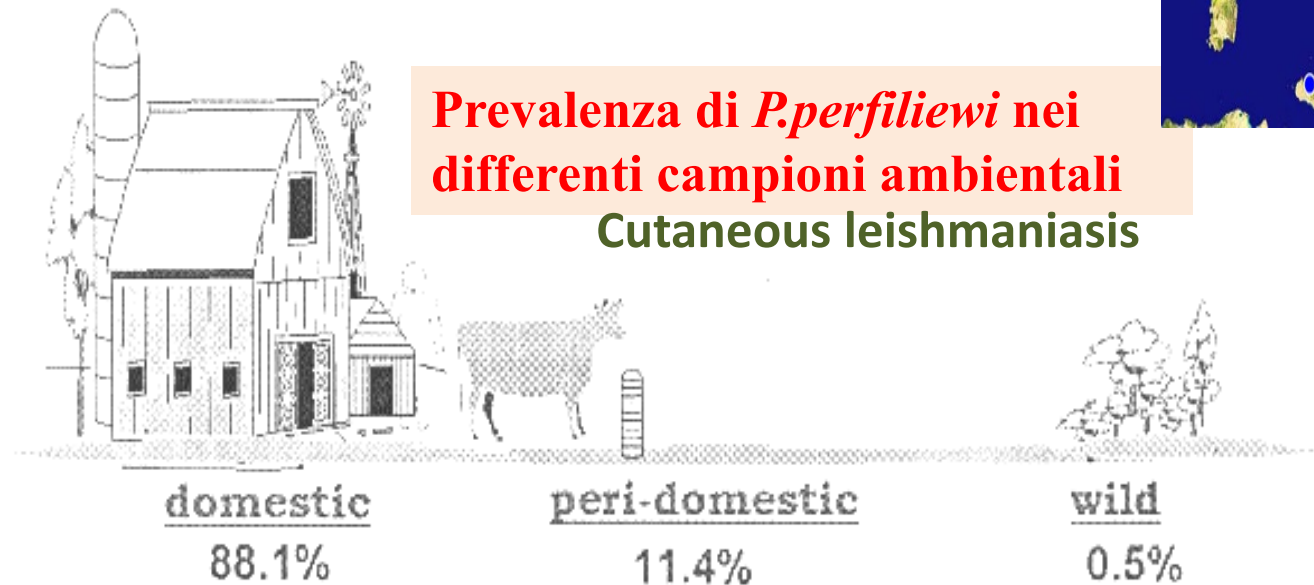
P. perniciosus



P. neglectus



P. perfliewi



Tissue granuloma structure-function in experimental visceral leishmaniasis

HENRY W. MURRAY

Department of Medicine, Weill College of Cornell University, New York, USA

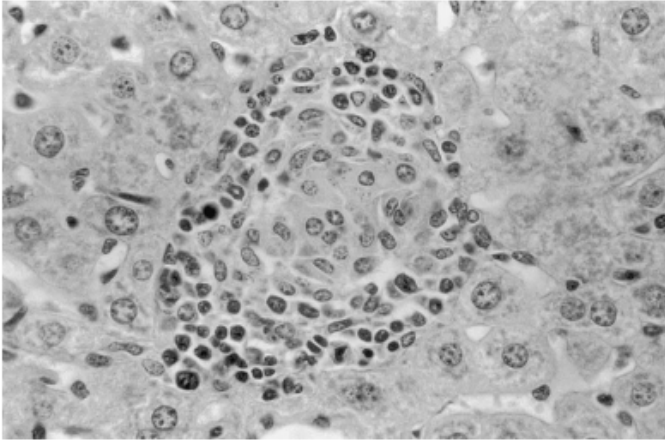


Figure 2. Mature liver granuloma 4 weeks after *L. donovani* infection in normal BALB/c mouse. Well-developed mononuclear cell mantle surrounds Kupffer cell core containing few residual amastigotes. ($\times 315$). Reproduced with permission (Squires *et al.* 1989).

- Leishmaniasis is a granulomatosis disease and granulomas represent the tissue expression of the successful T-cell-dependent immune response



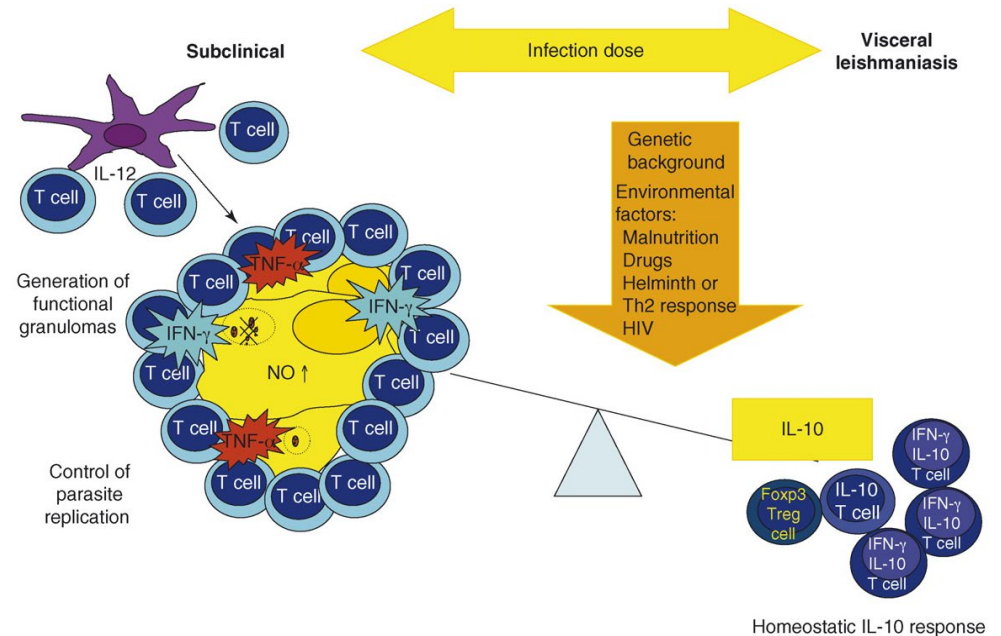
Review

TRENDS in Immunology Vol.28 No.9

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Interleukin-10 and the pathogenesis of human visceral leishmaniasis

Susanne Nylén and David Sacks



TRENDS in Immunology



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SHORT COMMUNICATION

Asymptomatic *Leishmania infantum/chagasi* infection in blood donors of western Sicily

Francesco Scarlata^a, Fabrizio Vitale^b, Laura Saporito^{a,*}, Stefano Reale^b,
Valentina Li Vecchi^a, Salvatore Giordano^a, Laura Infurnari^a,
Francesco Occhipinti^c, Lucina Titone^a

Journal of Infection 80 (2020) 116–120



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Asymptomatic *Leishmania infantum* infection in blood donors living in an endemic area, northeastern Italy

Margherita Ortalli^a, Alessandra Mistral De Pascali^a, Serena Longo^a, Nadia Pascarelli^b,
Andrea Porcellini^b, Deborah Ruggeri^b, Vanda Randi^b, Anna Procopio^c, Maria Carla Re^{a,d,1},
Stefania Varani^{a,d,1,*}



Leishmaniasis in Sardinia. 5. Leishmanin reaction in the human population of a focus of low endemicity of canine leishmaniasis

M. Gramiccia¹, S. Bettini², L. Gradoni¹, P. Ciarmoli¹, M. L. Verrilli³, S. Loddo² and C. Cicalò² ¹Laboratorio di Parassitologia, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Roma, Italy; ²Istituto di Genetica 'Carlo Jucchi', Università di Cagliari, Cagliari, Italy; ³Medical Officer, Soleminis (CS), Italy

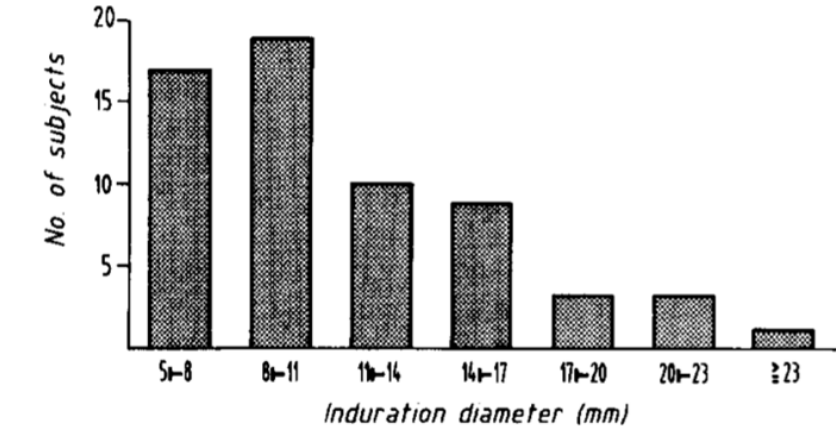


Fig. 2. Distribution of extent of reaction to leishmanin among the positive subjects in Soleminis, Sardinia.

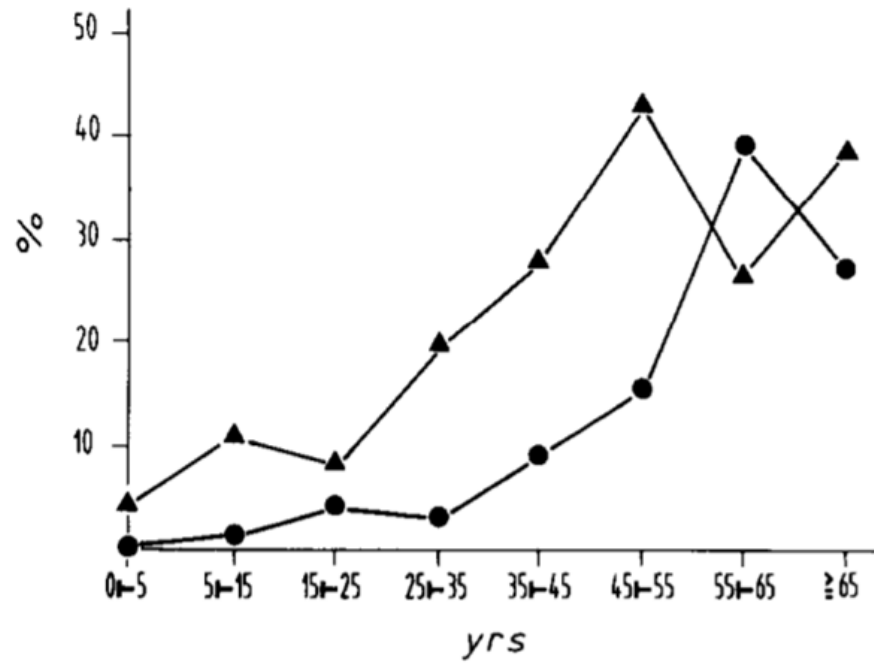


Fig. 1. Response to the leishmanin skin test according to age of 640 subjects in Soleminis, Sardinia (●) and of 1818 subjects in Monte Argentario, Tuscany (▲).

Congenital Leishmaniasis in a Newborn Infant Whose Mother was Coinfected With Leishmaniasis and HIV

Nicolas Argy,^{1,2,3*} Sylvie Lariven,⁴ Aline Rideau,⁵ Anais Lemoine,⁶ Agnès Bourgeois Moine,⁷ Lahcene Allal,⁷ Laurence Choudat,⁸ Christophe Ravel,⁹ Florence Michard,⁴ Pierre Buffet,¹⁰ Albert Faye,^{11,12,13} Sandrine Houze,^{1,2,3} and Yazdan Yazdanpanah^{4,12,14}

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We report here the occurrence, specific management, and monitoring of congenital leishmaniasis in a newborn infant whose mother was coinfectd with leishmaniasis and human immunodeficiency virus; transplacental transmission, confirmed by overt clinical disease at birth, was documented, which provides, to our knowledge, the first evidence of hepatic and neurologic impairment in an infant with congenital visceral leishmaniasis.

Forum

Sexual Transmission of Visceral Leishmaniasis: A Neglected Story

Diego L. Guedes ^{1,2,*}
Saskia van Henten,³
Lieselotte Cnops,³
Wim Adriaensen,³ and
Johan van Griensven³



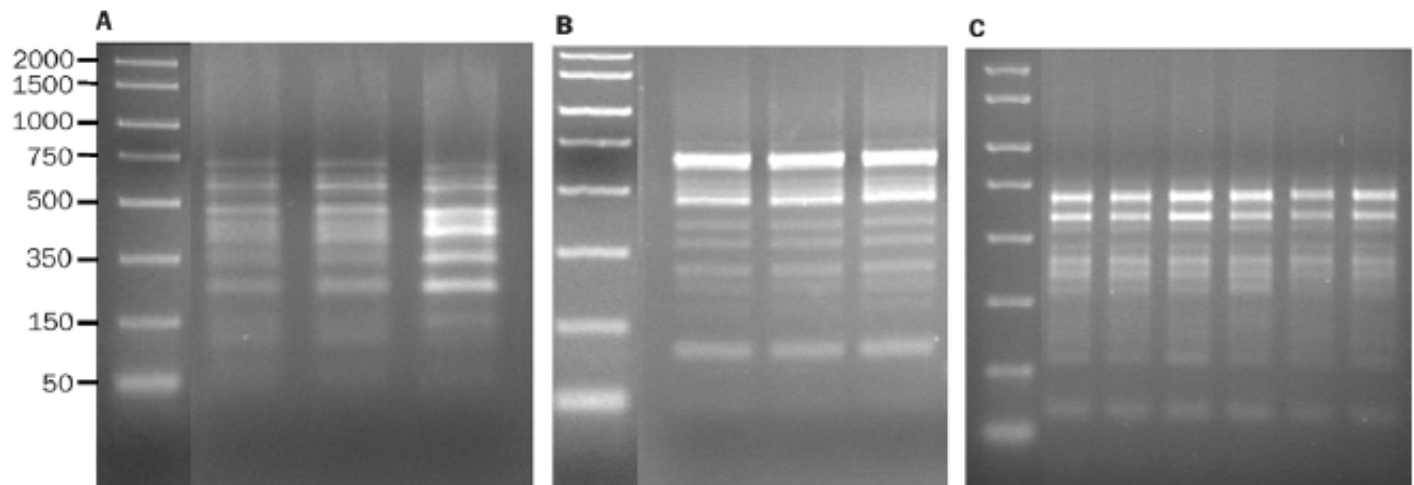
For visceral leishmaniasis (VL), a major vector-borne parasitic disease, an alternative sexual transmission route is well documented in dogs but evidence is lacking in humans. Here, we discuss the current knowledge and key questions to be answered as it may be an additional obstacle in ongoing VL elimination programs.

***Leishmania* in discarded syringes from intravenous drug users**

I Cruz, M A Morales, I Noguez, A Rodríguez, J Alvar

Needle sharing by intravenous drug users (IVDUs) has been proposed as providing an alternative, artificial, and anthroponotic cycle for leishmania transmission. We looked for parasites in syringes discarded by IVDUs using two different PCR techniques. *Leishmania* spp were detected in 65 (52%) of 125 syringes collected in southern Madrid, Spain, in 1998, and in 52 (34%) of 154 collected in southwestern Madrid in 2000–01. We found shared restriction fragment length polymorphisms in 12 of 65 positive samples tested, suggesting that syringe sharing can indeed promote the spread of leishmania clones among IVDUs.

Lancet 2002; **359**: 1124–25



Molecular characterisation of *Leishmania* spp detected in syringes discarded by intravenous drug users

From 65 syringes positive for *Leishmania* spp, the three genotypes shown (A, B, and C) were shared by three, three, and six syringes, respectively.



Research article

Leishmania infantum asymptomatic infection in inflammatory bowel disease patients under anti-TNF therapy



M. Carmen Guillén^a, M. Magdalena Alcover^a, Natalia Borrue^b, Elena Sulleiro^c, Fernando Salvador^d, Diana Berenguer^a, Claudia Herrera-de Guise^b, Verónica Rodríguez^b, Zaira Moure^c, Adrián Sánchez-Montalv^d, Israel Molina^d, Roser Fisa^a, Cristina Riera^{a,*}

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Journal of Microbiology, Immunology and Infection (2020) 53, 176–178



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journal homepage: www.e-jmii.com



Short Communication

Viability of Leishmania in blood donors: A tangible possibility of transfusion transmission



Adriana de Oliveira França^{a,*},
Luiza de Oliveira Ramos Pereira^b, Tayana Serpa Ortiz Tanaka^c,
Márcia Pereira de Oliveira^d,
Maria Elizabeth Cavalheiros Dorval^a



Asymptomatic *Leishmania infantum* infection in blood donors living in an endemic area, northeastern Italy

Margherita Ortalli^a, Alessandra Mistral De Pascali^a, Serena Longo^a, Nadia Pascarelli^b, Andrea Porcellini^b, Deborah Ruggeri^b, Vanda Randi^b, Anna Procopio^c, Maria Carla Re^{a,d,1}, Stefania Varani^{a,d,1,*}

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^c Istituto Zooprofilattico Sperimentale della Lombardia e dell'Emilia-Romagna, Brescia 25100, Italy

^d Unit of Clinical Microbiology, Regional Reference Centre for Microbiological Emergencies (CRREM), St. Orsola-Malpighi University Hospital, Bologna 40100, Italy

Table 1

Rates of asymptomatic *Leishmania* infection among blood donors ($n=240$) residing in the Bologna Province (northeastern Italy) by Western Blot and real time PCR.

Variables	Results							
	WB Pos		WB Neg		PCR Pos		PCR Neg	
	No.	%	No.	%	No.	%	No.	%
No. of subjects (240)	27	11.2	213	88.7	4	1.7	236	98.3
Sex								
Male (174)	21	12.1	153	87.9	4	2.3	170	97.7
Female (66)	6	9.1	60	90.9	0	0	66	100

WB; Western Blot. PCR; polymerase chain reaction. Pos; positive. Neg; negative. No.; number.

Country	Prevalence/year ^a			Reference	Study cohort
	Serology	PCR	T-cell memory response		
Spain			53%, LST (2002)	Moral et al. ²	General population (L'Alacantí region)
	5%, EIA (2004)			Garrote et al. ⁹	General population (Castilla-Leon region)
	2% EIA, 8% WB (2004)	22% (2004)	22%, LST (2004)	Riera et al. ¹⁰	Blood donors (Balearic Islands)
	3%, WB (2008)	6% (2008)	11%, LST (2008)	Riera et al. ¹¹	Blood donors (Balearic Islands)
	2%, EIA (2015)	8% (2015)		Pérez-Cutillas, ¹²	Blood donors (Murcia region)
	0.1% IFA, 1% DAT (2019)	0% (2019)	21%, WBA (2019)	Ibarra-Meneses et al. ¹³	Healthy individuals (Madrid province)
France	13%, WB (1999)			Le Fichoux et al. ¹⁴	Blood donors (Marseille province)
Italy	1%, IFA (2008)	36%, only IFA-positive ^b (2008)		Scarlata et al. ¹⁵	Blood donors (Sicily)
	7%, WB (2010)	4% (2010)		Biglino et al. ¹⁶	General population (Piedmont)
		8% (2018)		Maritati et al. ¹⁷	Healthy individuals (Emilia-Romagna region)
Greece	0%, EIA (2005)			Colomba et al. ¹⁸	Blood donors (Sicily)
	15%, IFA+WB (2003)	2% (2003)		Kyriakou et al. ¹⁹	Blood donors (Crete)
	3%, IFA (2008)			Diza et al. ²⁰	General population (northern Greece)
Balkans	11%, EIA (2013)			Sisko-Kraljevic et al. ²¹	General population (Croatia)

^a Year of the article's publication (only data published after 1999 are reported).

^b Only IFA positive samples were tested by PCR and leishmanial DNA was detected in 36% of this subgroup. DAT: direct agglutination test; EIA: enzyme immunoassay; IFA: immunofluorescent assay; LST: Leishmania skin test; Ref.: References; WB: Western Blot; WBA: whole blood stimulation with soluble *Leishmania* antigen.

RESEARCH ARTICLE

Leishmania tarentolae and *Leishmania infantum* in humans, dogs and cats in the Pelagie archipelago, southern Italy

Roberta Iatta^{1,2}, Jairo Alfonso Mendoza-Roldan¹, Maria Stefania Latrofa¹, Antonio Cascio³, Emanuele Brianti⁴, Marco Pombi⁵, Simona Gabrielli⁵, Domenico Otranto^{1,6*}

1 Department of Veterinary Medicine, University of Bari, Bari, Italy, **2** Department of Interdisciplinary Medicine, University of Bari, Bari, Italy, **3** Infectious and Tropical Diseases Unit, Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties "G. D'Alessandro", University of Palermo, Palermo, Italy, **4** Dipartimento di Scienze Veterinarie, Università degli Studi di Messina, Messina, Italy, **5** Dipartimento di Sanità Pubblica e Malattie Infettive, "Sapienza" Università di Roma, Rome, Italy, **6** Faculty of Veterinary Sciences, Bu-Ali Sina University, Hamedan, Iran

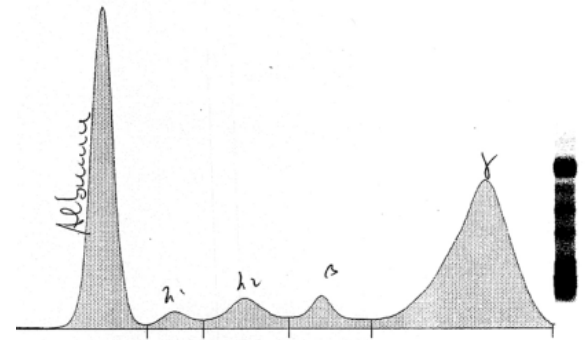
* domenico.otranto@uniba.it



- Humans, dogs, reptiles, and sand flies living in the same confined environment in small islands in the middle of the Mediterranean Sea may share *Leishmania* spp. including the non-pathogenic *L. tarentolae*.
- The presence of *L. tarentolae* in humans and dogs, undoubtedly raises many scientific questions about the potential beneficial effects this species of *Leishmania* may have in cross-protecting hosts infected by pathogenic *Leishmania* species.

Zoonotic visceral leishmaniasis (*L. infantum*)

- ✓ Long incubation period (2-7 mo)
- ✓ Triad of signs and symptoms (94-100%):
 - Splenomegaly
 - Irregular fever
 - Pallor
- ✓ Triad of biological parameters (94-100%):
 - Raised immunoglobulin levels
 - Pancytopenia
 - Raised ESR



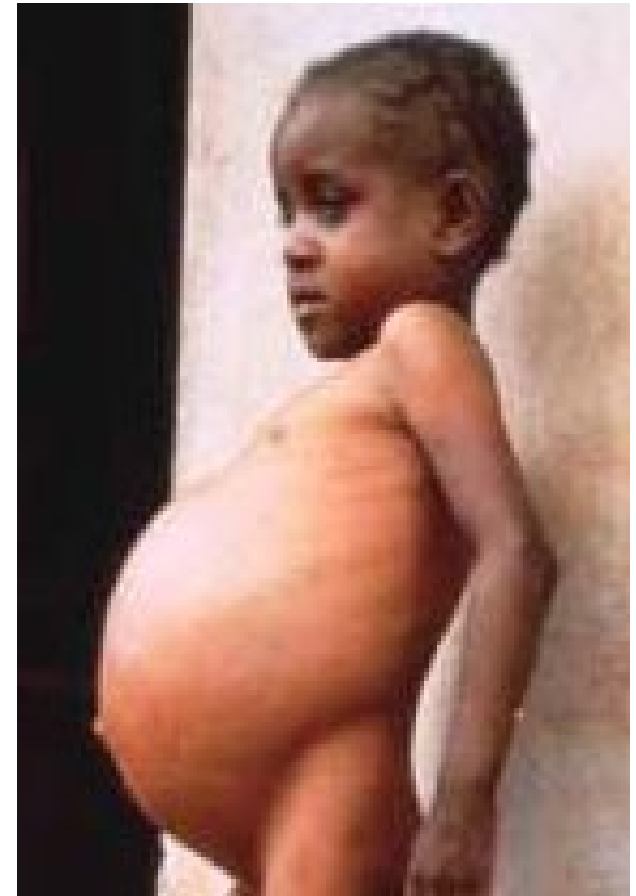


Kenya

South Ethiopia



Many children suffering from visceral leishmaniasis develop a noticeable thickening, stiffening and darkening of the eyelashes and eyebrows



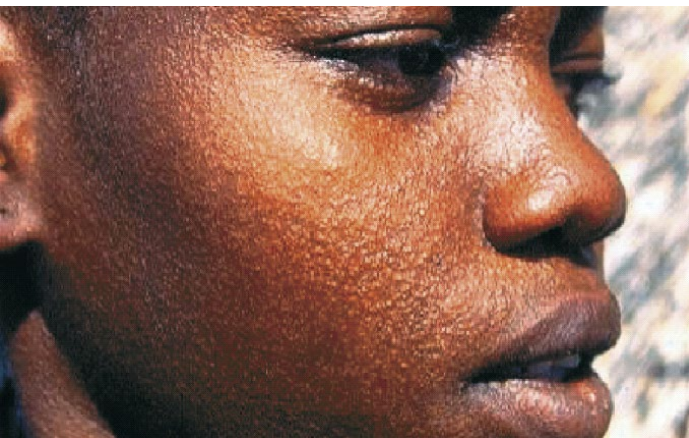
Profile view of a teenage boy suffering from visceral leishmaniasis.

The boy exhibits splenomegaly, distended abdomen and severe muscle wasting

kala-azar in *sanscrito*
significa “malattia nera”



PKDL



Post-kala-azar dermal leishmaniasis

THE LANCET Infectious Diseases Vol 3 February 2003 <http://infection.thelancet.com>

Table 1. Comparison of most important features of Sudanese and Indian PKDL

	Sudan	India
Clinical		
PKDL may occur in absence of previous VL	Yes	Yes
PKDL may occur while still on treatment for VL	Yes	No
PKDL may occur with evidence of visceralized disease (VL)	Yes	Yes
Most commonly described predilection over body	Face>trunk>arms>legs	Face>trunk>arms>legs
Type of rash	PN>MP>microP>M*	Erythema, induration M,P,N
Lymphadenopathy	Frequent	Rare
More severe disease found in	Young children, short interval after VL	Not known
Concomitant other post-kala-azar manifestations	Yes	Yes
Epidemiology		
Frequency of PKDL following VL	50–60%	5–10%
Highest prevalence reported in field study	4·8/100	4·8/1000
Interval between VL and PKDL		
most common	0–6 months	2–3 years
range	0–13 months†	6 months–32 years
Age distribution	Children, mean age 6 years	Young adults
Diagnosis		
Parasites may be demonstrated in smears	20–30%	20–40%
Parasites may be demonstrated by PCR	83%	94%
LST positive	16–65%	0–67%
Most difficult differential diagnosis	Leprosy	Leprosy
Treatment		
Treatment with stibogluconate	2–3 months	4 months
Spontaneous cure	The rule	Not reported, all cases are treated

*PN=papulo-nodular, MP=maculo-papular, MicroP=micropapular, M=macular, N=nodular. †In neighbouring Kenya, an interval of 30 years has been reported.



PKDL-India



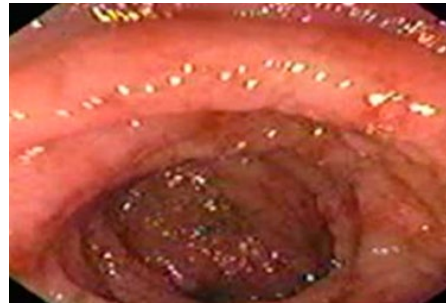
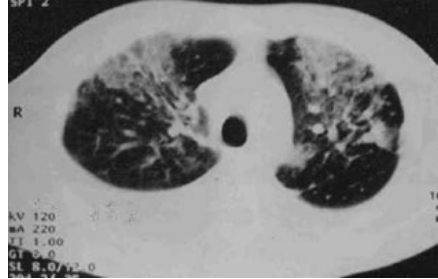
International Journal of STD & AIDS 2006; 17: 351-353

CASE REPORT

**Atypical disseminated leishmaniasis resembling
post-kala-azar dermal leishmaniasis
in an HIV-infected patient**

E Boumis MD¹, P Chinello MD¹, C Della Rocca MD², M G Paglia MD¹,
M F Proietti MD¹ and N Petrosillo MD¹

LEISHMANIASIS in HIV-Infected Patients

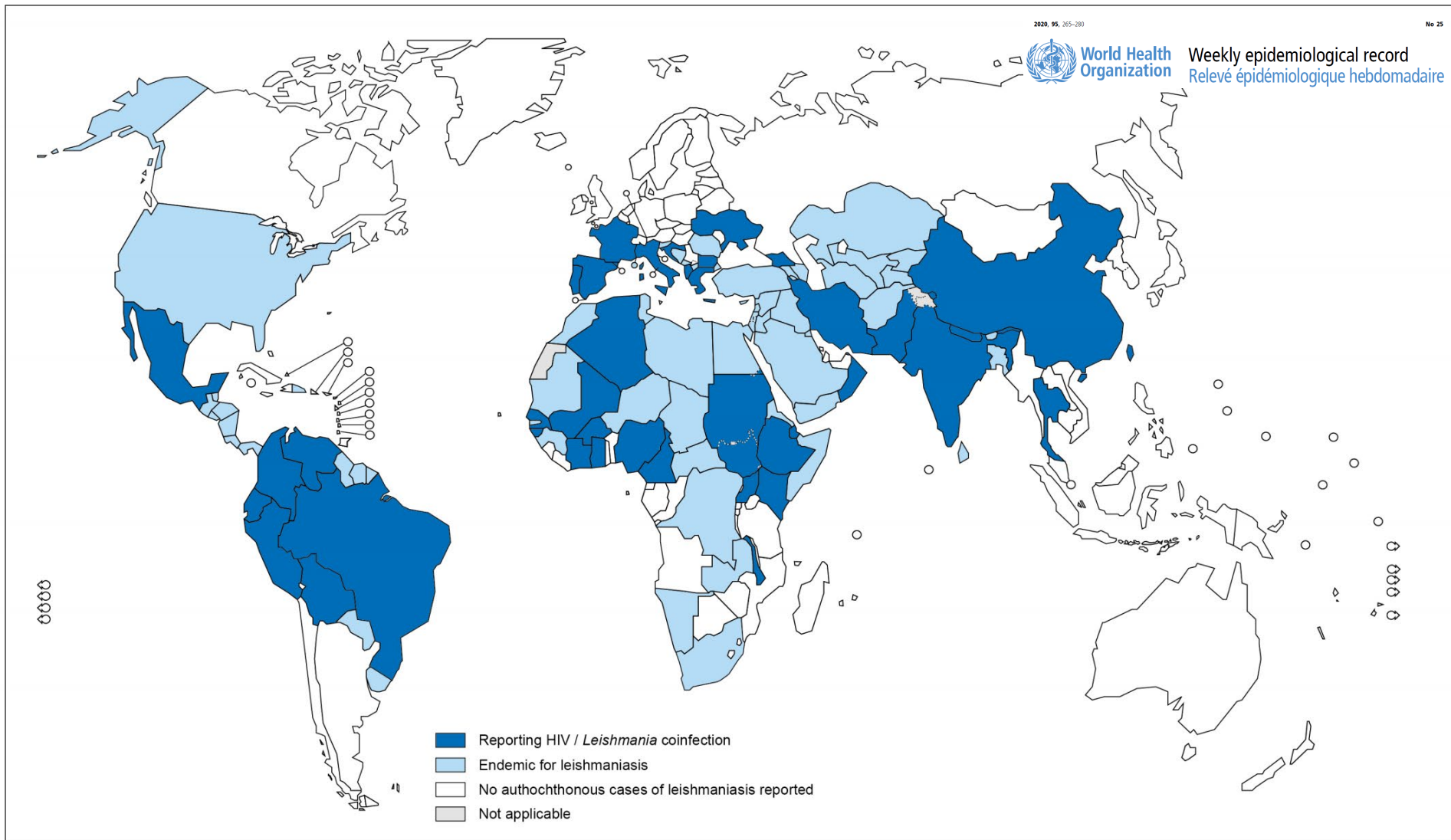


CD4	Number	Percentage
< 200/mm ³	624	91.50
200 to 499/mm ³	51	7.47
> 500/mm ³	7	1.03
total	682	100

Clinical features	number	%
Visceral - typical	736	84.89
Visceral - atypical	82	9.46
Cutaneous	36	4.15
Others	6	0.69
Mucocutaneous	4	0.46
Mixed	3	0.35
	n = 867	



Global distribution of leishmaniasis and countries reporting HIV/*Leishmania* coinfection



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2020. All rights reserved

Data Source: World Health Organization
Map Production: Control of Neglected
Tropical Diseases (NTD)
World Health Organization

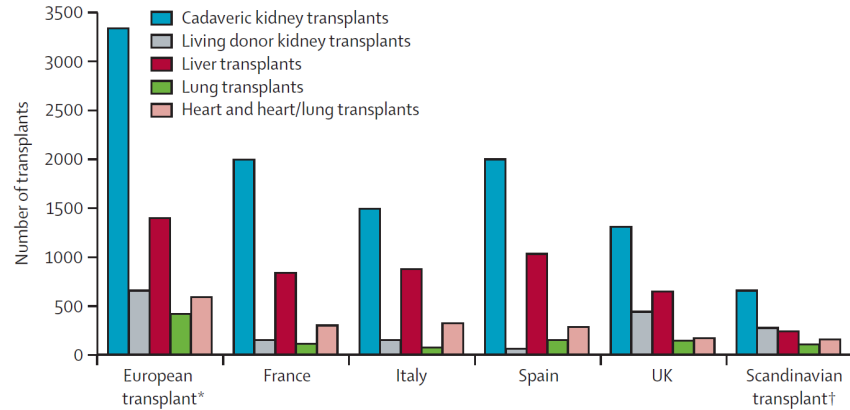


Leishmaniasis among organ transplant recipients

Spinello Antinori, Antonio Cascio, Carlo Parravicini, Roberto Bianchi, Mario Corbellino

Lancet Infect Dis 2008;
8: 191–99

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L Sacco, Section of Infectious
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(Prof S Antinori MD,
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of Infectious Diseases,
University of Messina, Messina,
Italy (A Cascio MD); and



Recurrent leishmaniasis in kidney transplant recipients: report of 2 cases and systematic review of the literature

I. Simon, K.M. Wissing, V. Del Marmol, S. Antinori, M. Remmelink, E. Nilufer Broeders, J.L. Nortier, M. Corbellino, D. Abramowicz, A. Cascio. Recurrent leishmaniasis in kidney transplant recipients: report of 2 cases and systematic review of the literature. *Transpl Infect Dis* 2011. All rights reserved

I. Simon¹, K.M. Wissing², V. Del Marmol³, S. Antinori⁴, M. Remmelink⁵, E. Nilufer Broeders¹, J.L. Nortier¹, M. Corbellino⁴, D. Abramowicz¹, A. Cascio⁶

¹Department of Nephrology, Erasme Hospital, Université



Mucocutaneous Leishmaniasis due to *Leishmania infantum* Infection

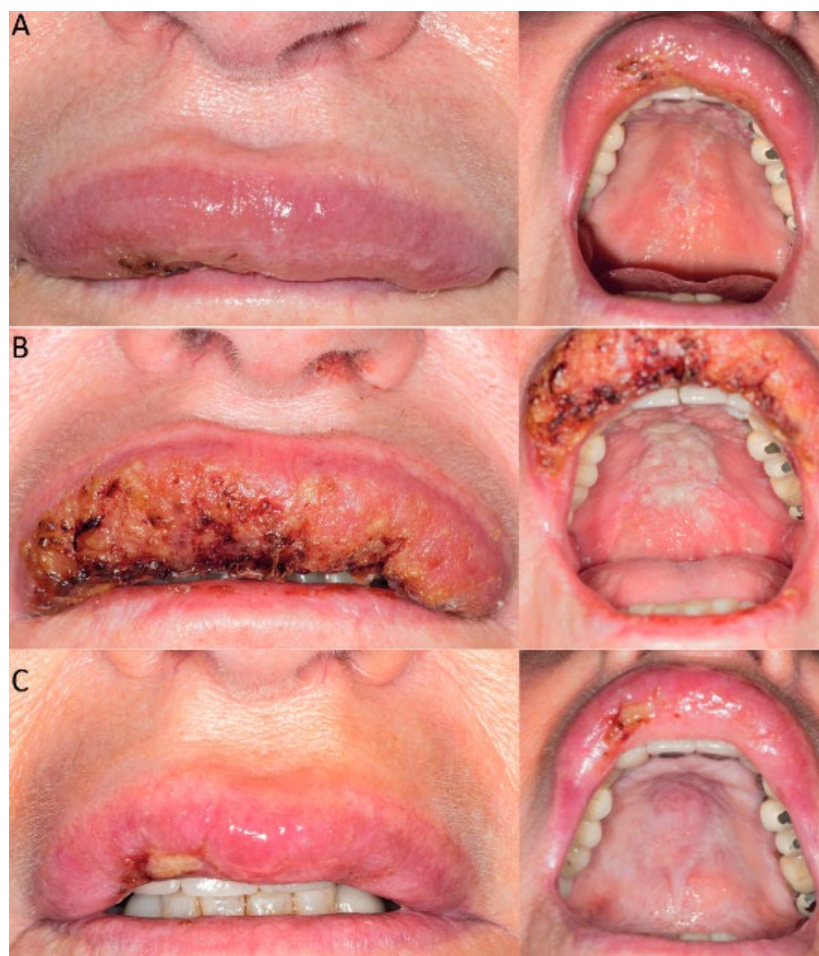
Kai-Philipp LINSE¹, Christian BOGDAN², Holger A. HAENSSLE^{1#} and Ferdinand TOBERER^{1#}

¹Department of Dermatology, University Hospital Heidelberg, Heidelberg, and ²Mikrobiologisches Institut – Klinische Mikrobiologie, Immunologie und Hygiene, Universitätsklinikum Erlangen und Friedrich-Alexander-Universität (FAU) Erlangen, Erlangen, Germany. E-mail: kai-philipp.linse@med.uni-heidelberg.de

#These authors contributed equally to this work.

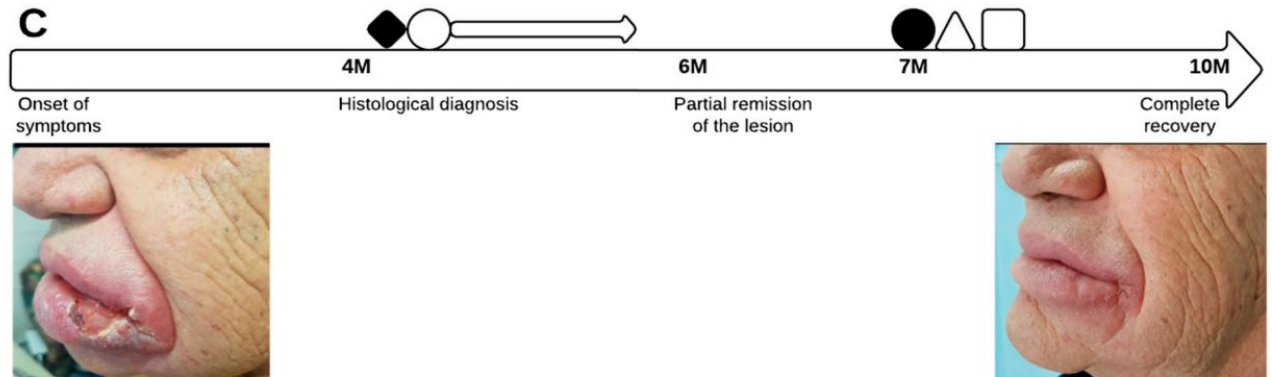
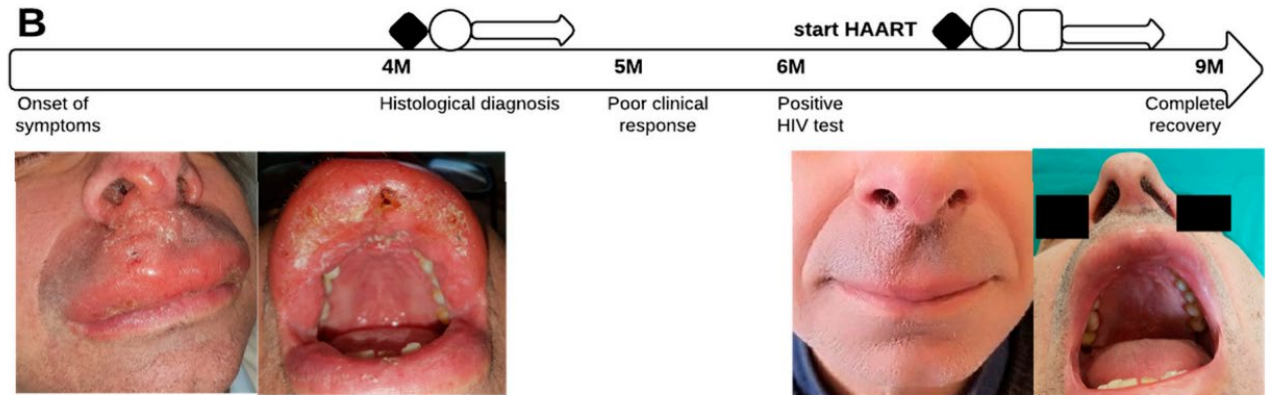
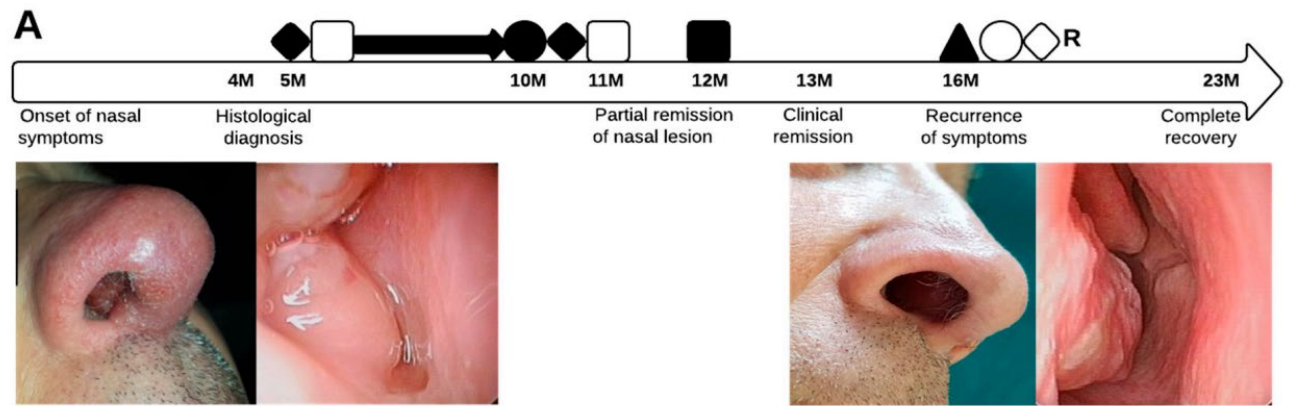
Accepted May 23, 2022; Epub ahead of print May 23, 2022

Acta Derm Venereol 2022; 102: adv00748. DOI: 10.2340/actadv.v102.2321

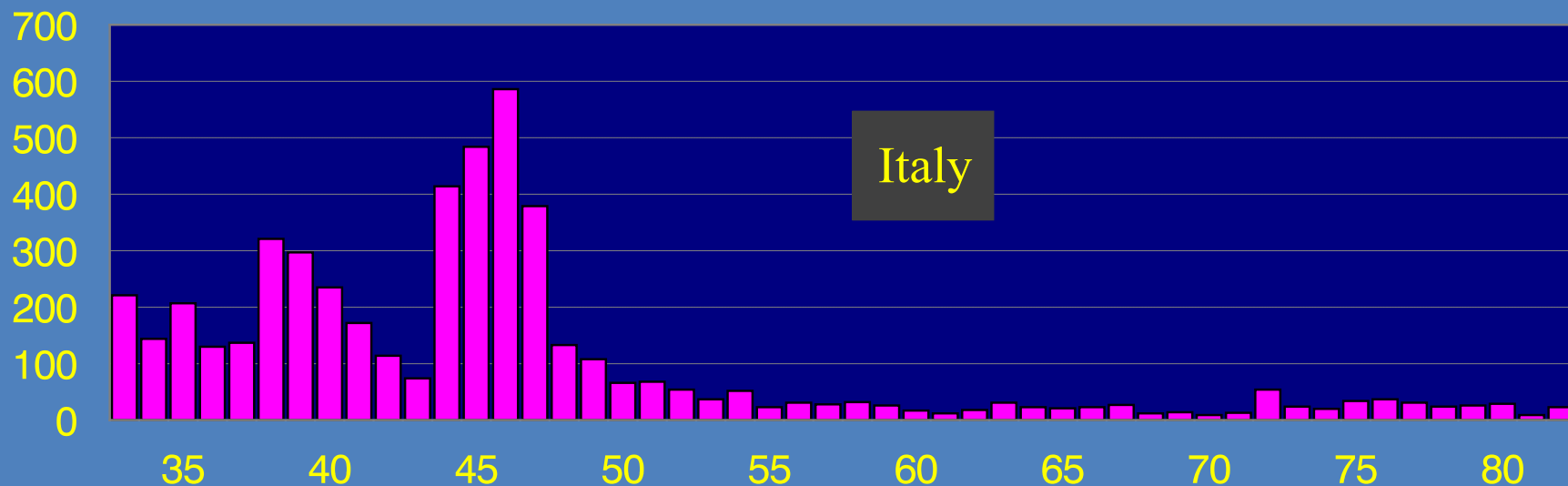
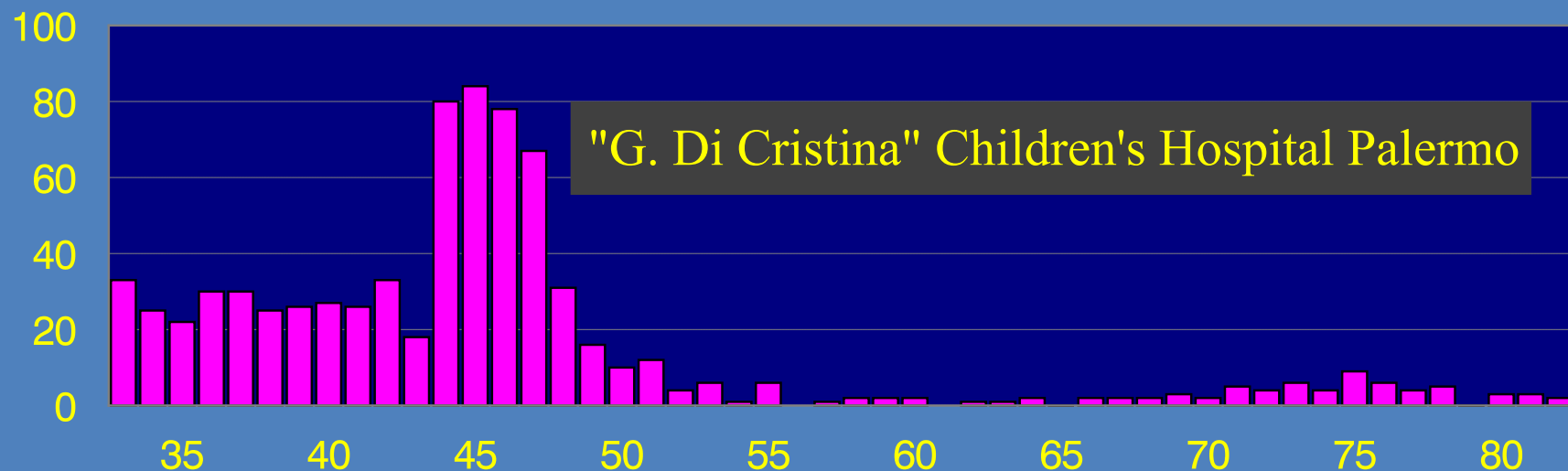


Autochthonous Cases of Mucosal Leishmaniasis in Northeastern Italy: Clinical Management and Novel Treatment Approaches

Valeria Gaspari ^{1,*}, Irene Zaghi ², Giovanni Macri ³, Annalisa Patrizi ^{1,4}, Nunzio Salvi ⁵, Francesca Locatelli ⁵, Elena Carra ⁶, Maria Carla Re ^{4,7} and Stefania Varani ^{4,7}



Visceral leishmaniasis cases from 1933 to 1982



Visceral leishmaniasis: adult cases reported in Sicily from 1939 to 1984

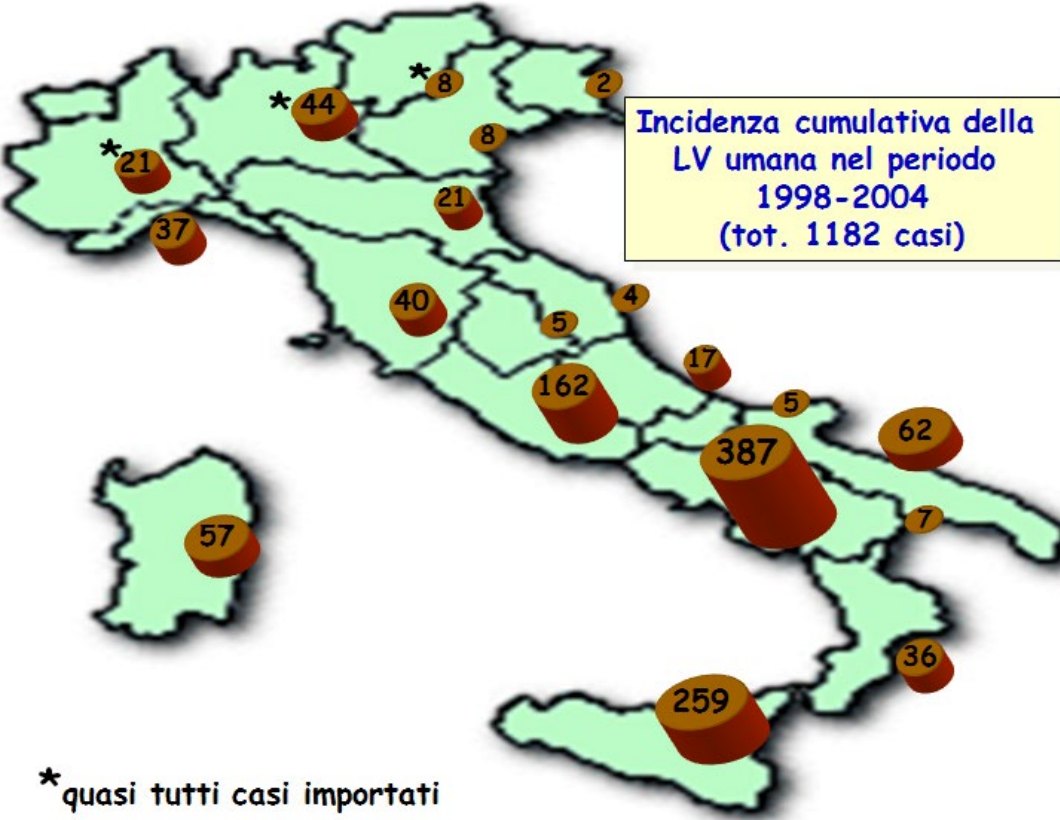


EPIDEMIOLOGIC SURVEILLANCE OF VISCERAL LEISHMANIASIS IN SICILY, ITALY

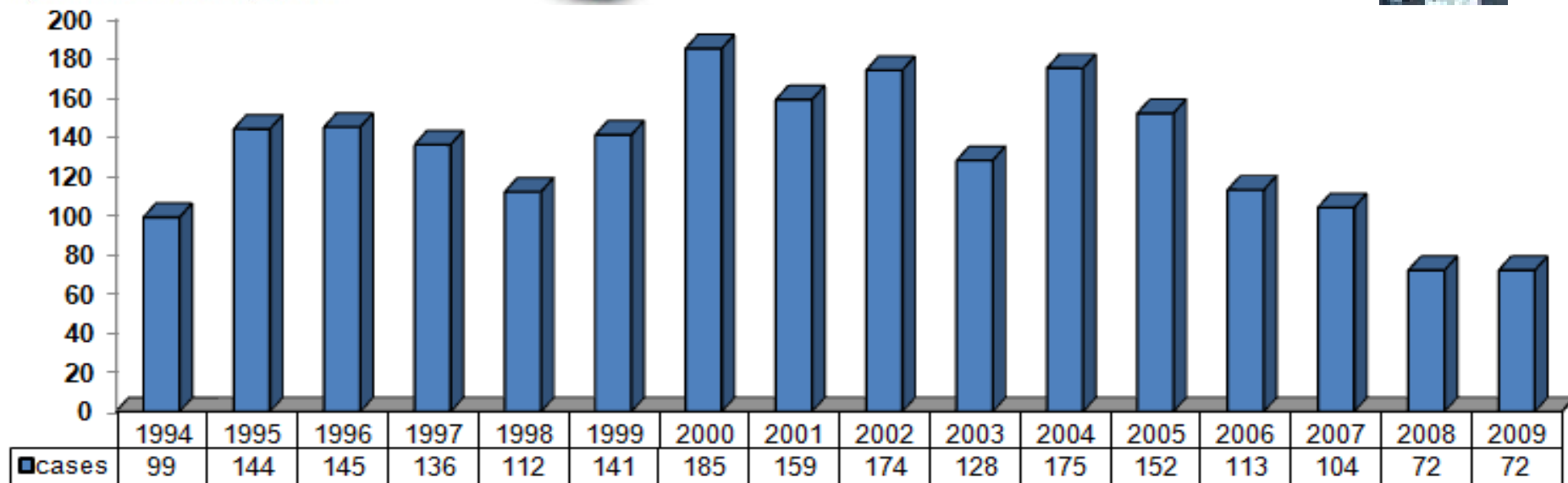
ANTONIO CASCIO, LUIGI GRADONI, FRANCESCO SCARLATA, MARINA GRAMICCIA, SALVATORE GIORDANO,
ROSARIO RUSSO, ALDO SCALONE, CESARE CAMMA, AND LUCINA TITONE

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Istituto Superiore di Sanità, Rome, Italy; Istituto di Malattie Infettive, Università di Catania, Catania, Italy;
Istituto di Parassitologia Medica, Università di Messina, Messina, Italy*

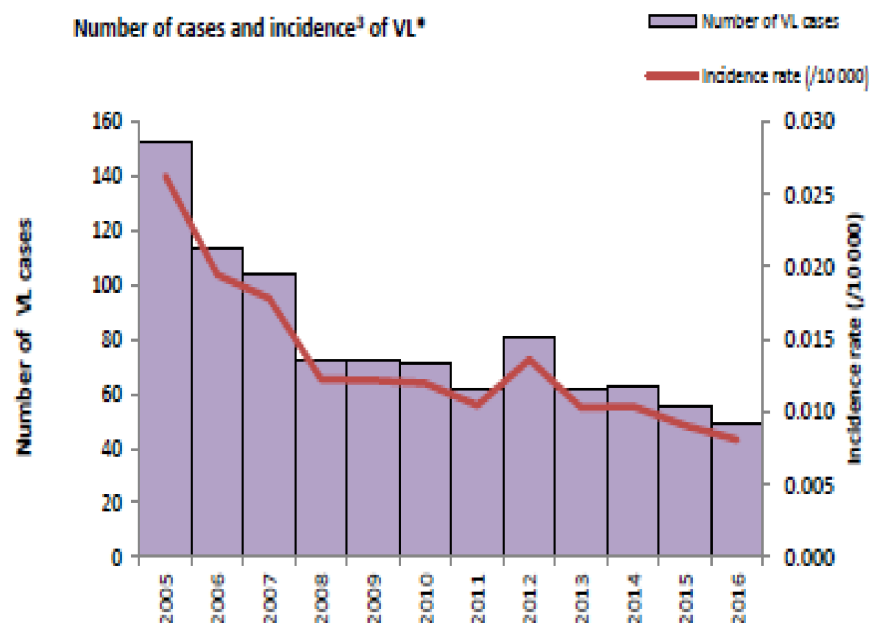
Abstract. Visceral leishmaniasis (VL) is endemic in Sicily. Although it is a notifiable disease, there is evidence that the actual number of cases is higher than that reported. In 1987, a regional reference center for active surveillance of VL was established and it recorded a total of 284 cases through 1995, a mean of 31.5 cases/year and about four-fold more than previously reported. Of the 284 cases, 150 (53%) were children (≤ 14 years of age), and of the 134 adults, 39 (29%) were coinfecting with human immunodeficiency virus (HIV). The commonest viscerotropic zymodeme of *Leishmania infantum*, MON 1, was identified in 40 (93%) of 43 HIV-negative and eight (57%) of 14 HIV-positive patients. Among 280 patients evaluated (i.e., all HIV-negative and 35 of 39 HIV-positive subjects), 254 (91%) were treated with meglumine antimoniate alone or in combination with other drugs; 23 (8%) received allopurinol or amphotericin B, either conventional or in liposomal form; and three terminally ill patients were not treated. Among the 245 HIV-negative patients, 236 (96%) were successfully cured, while nine (4%) (seven adults) died during the course of antimonial treatment. None of the 35 HIV-positive patients was definitively cured, although mortality was apparently associated with other opportunistic infections.



Sorveglianza della Leishmaniosi Viscerale umana in Italia



Number of cases and incidence³ of VL*



Infection (2020) 48:695–713
<https://doi.org/10.1007/s15010-020-01443-2>

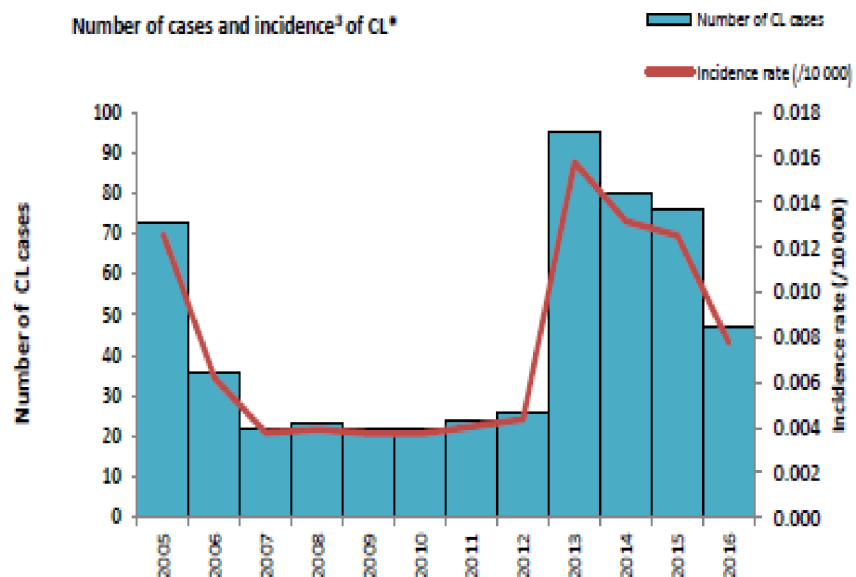
ORIGINAL PAPER



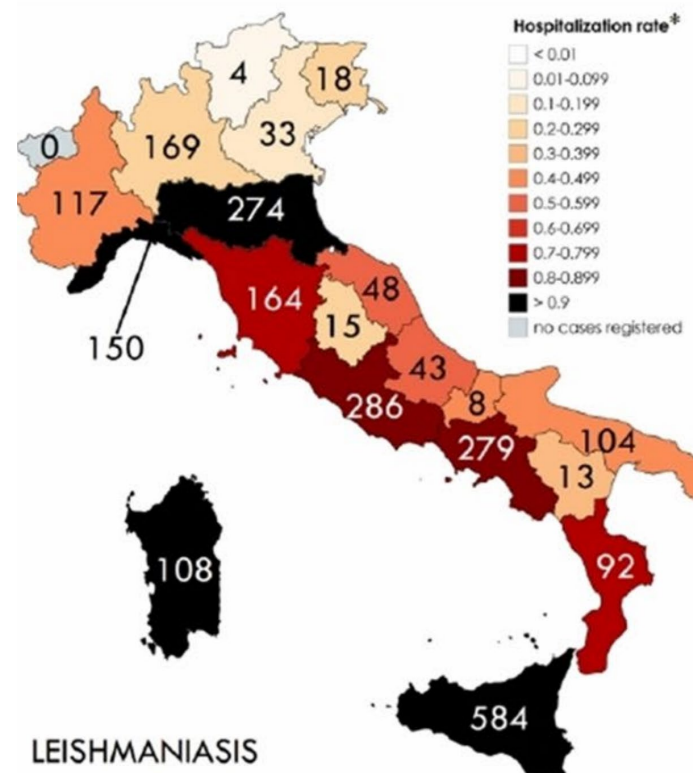
Hospitalization for Chagas disease, dengue, filariasis, leishmaniasis, schistosomiasis, strongyloidiasis, and *Taenia solium* taeniasis/ cysticercosis, Italy, 2011–2016

Marta Tili¹ · Annarita Botta¹ · Alessandro Bartoloni^{1,2,3} · Giampaolo Corti^{1,2} · Lorenzo Zammarchi^{1,2,3}

Number of cases and incidence³ of CL*



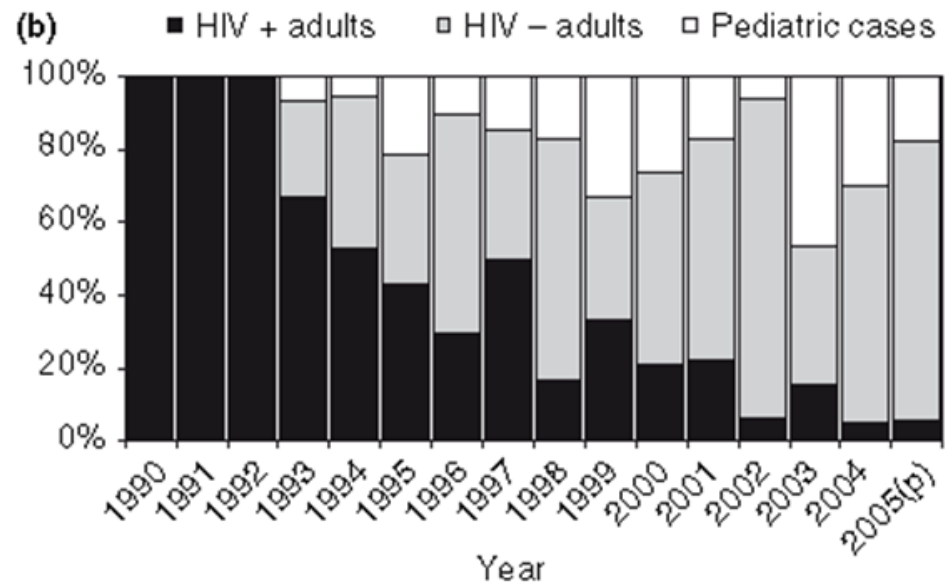
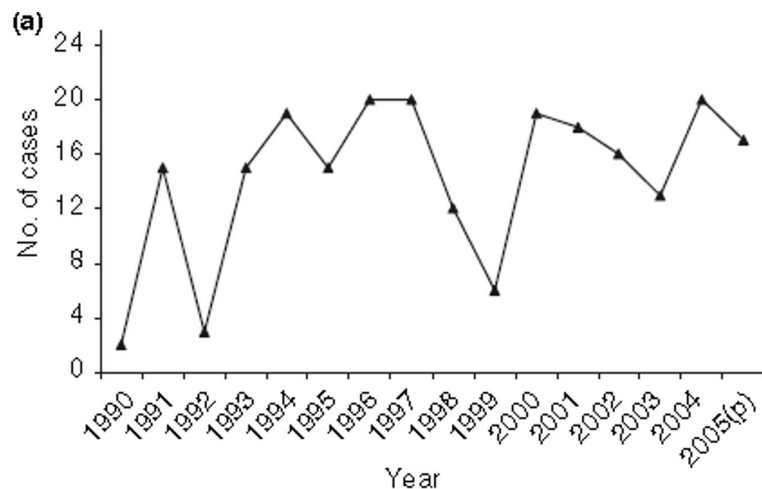
* Years with no cases or the number are years where data were not available



LEISHMANIASIS

The northward spread of leishmaniasis in Italy: evidence from retrospective and ongoing studies on the canine reservoir and phlebotomine vectors

Michele Maroli¹, Luca Rossi², Raffaella Baldelli³, Gioia Capelli⁴, Ezio Ferroglia², Claudio Genchi⁵, Marina Gramiccia¹, Michele Mortarino⁵, Mario Pietrobelli⁶ and Luigi Gradoni¹



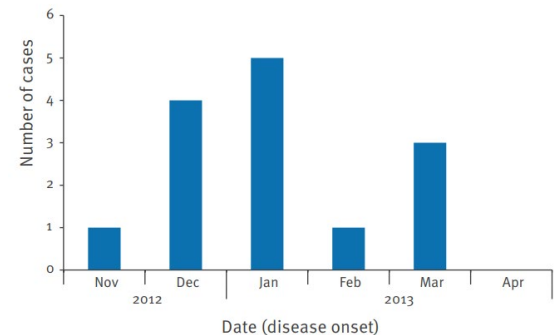
- Annual trend of 230 visceral leishmaniasis cases recorded in in region of northern continental Italy from 1990 to 2005

Ongoing outbreak of visceral leishmaniasis in Bologna Province, Italy, November 2012 to May 2013

S Varani (stefania.varani@unibo.it)¹, R Cagarelli², F Melchionda³, L Attard⁴, C Salvadori⁴, A C Finarelli², G A Gentilomi¹, R Tigani¹, R Rangoni⁵, R Todeschini⁶, A Scalone⁷, T Di Muccio⁷, M Gramiccia⁷, L Gradoni⁷, P Viale⁴, M P Landini¹

FIGURE 1

Epidemic curve of human cases of visceral leishmaniasis, Bologna Province, northern Italy, November 2012–May 2013 (n=14)



Hindawi Publishing Corporation
BioMed Research International
Volume 2016, Article ID 6481028, 7 pages
<http://dx.doi.org/10.1155/2016/6481028>



Clinical Study

Clinical and Microbiological Characteristics of Visceral Leishmaniasis Outbreak in a Northern Italian Nonendemic Area: A Retrospective Observational Study

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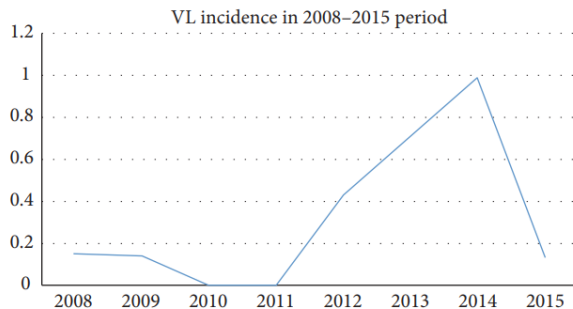
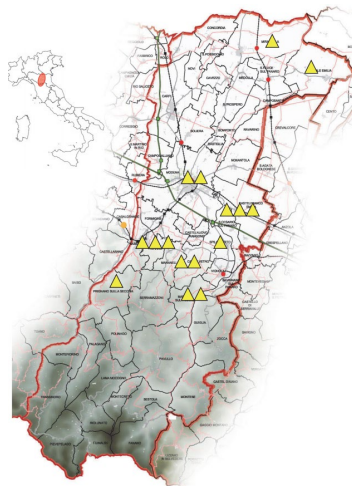


FIGURE 1: Visceral leishmaniasis incidence per 100,000 inhabitant in 2008–2015 period in the Modena province.



STUDIES ON MEDITERRANEAN LEISHMANIASIS

I. AN OUTBREAK OF VISCERAL LEISHMANIASIS IN NORTHERN ITALY

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Two patients displayed tonsillar hypertrophy with presence of *Leishmania* in the tonsils, and in a lateral cervical lymph node, without high rises of temperature.

The fatal cases were 13 (21,7%) all in adult males. **Most fatalities occurred before a correct diagnosis** was made and specific therapy could be used. **Death occurred in 11 patients who did not receive antimony** treatment while the remaining 2 had been partially treated

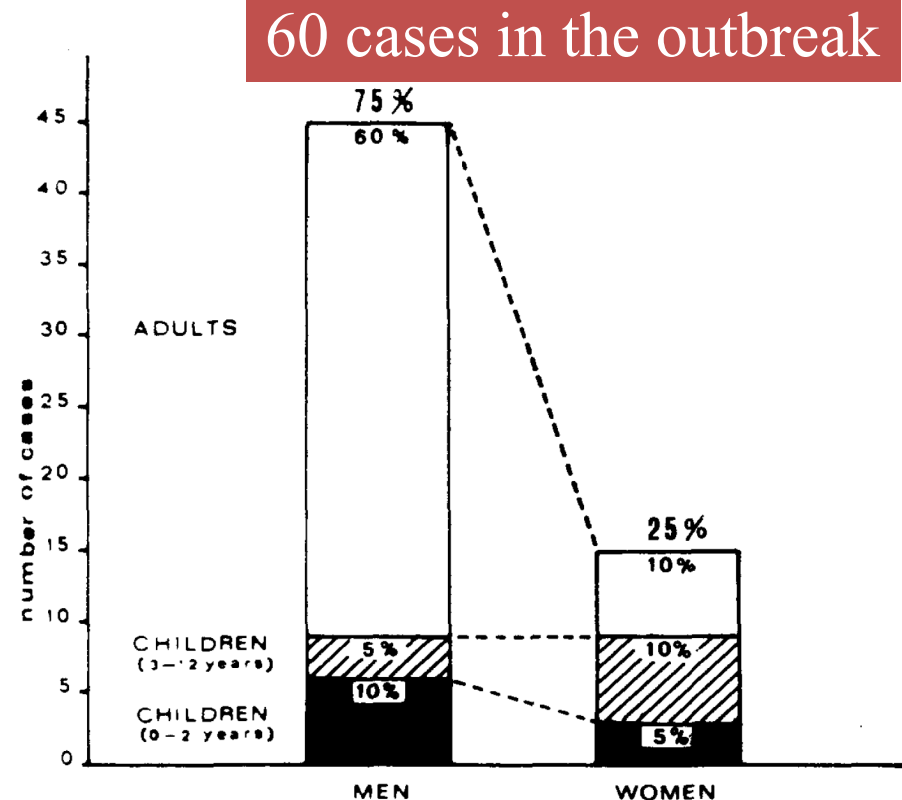
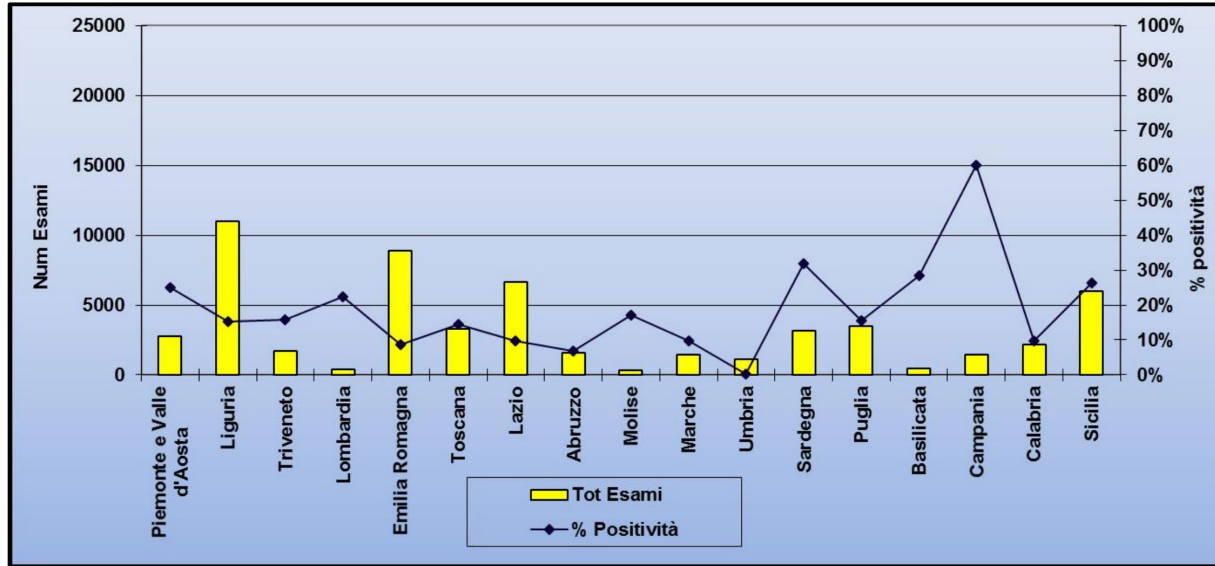


Figura 3. Leishmaniosi canina: numero di esami sierologici e tasso di positività in regioni italiane. Anno 2017 (Centro di Referenza Nazionale per le Leishmaniosi - C.Re.Na.L)

A. Italia



Original Article

Canine leishmaniosis in the Italian northeastern Alps: A survey to assess serological prevalence in dogs and distribution of phlebotomine sand flies in the Autonomous Province of Bolzano - South Tyrol, Italy

Giulia Morosetti^a, Marica Toson^b, Karin Trevisiol^c, Ilda Idrizi^c, Alda Natale^b, Laura Lucchese^b, Alice Michelutti^b, Piera Ceschi^a, Giovanni Lorenzi^a, Christian Piffer^a, Eleonora Fiorentino^d, Gioia Bongiorno^d, Luigi Gradoni^{d,*}

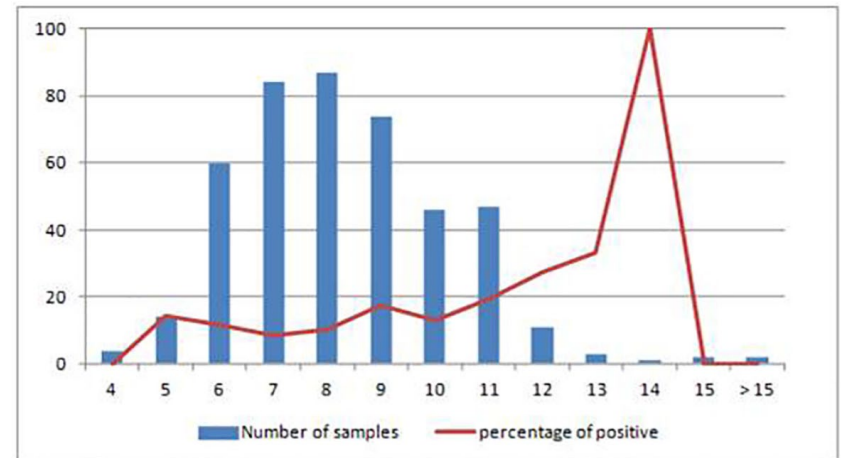


Fig. 5. Age distribution of examined dogs and respective proportion of *Leishmania* seropositives.

ARTICLE

A. Cascio · C. Colomba · S. Antinori · M. Orobello
D. Paterson · L. Titone

Pediatric Visceral Leishmaniasis in Western Sicily, Italy: A Retrospective Analysis of 111 Cases

Table 1 Clinical features of 111 children with visceral leishmaniasis

Clinical feature	Finding
Median duration of disease before admission (range)	15 days (2 days–7 months)
Fever [no. of cases (%)]	111 (100)
Splenomegaly [no. of cases (%)]	111 (100)
Extent of spleen enlargement [median distance below left costal margin (range)]	4 cm (2–13 cm)
Hepatomegaly [no. of cases (%)]	101 (91)
Extent of liver enlargement [median distance below the right costal margin (range)]	3 cm (0–11 cm)
Skin lesions (no. of cases)	2
Lymphadenopathy (no. of cases) ^a	0

^a Mild enlargement of the small lymph nodes in the cervical chain of 13 patients was not considered true lymphadenopathy related to visceral leishmaniasis

A. Cascio · C. Colomba · S. Antinori · M. Orobello
D. Paterson · L. Titone

**Pediatric Visceral Leishmaniasis in Western Sicily, Italy:
A Retrospective Analysis of 111 Cases**

Table 2 Hematological and biochemical features of 111 children with visceral leishmaniasis

Variable	Median value (range)
Erythrocyte count ($\cdot 10^6$ cells/ μ l)	3.7 (1.9–5)
Hemoglobin (g/dl)	7.8 (3.8–12.7)
Leukocyte count ($\cdot 10^3$ cells/ μ l)	4.3 (1.6–10.9)
Neutrophil count ($\cdot 10^3$ cells/ μ l)	1 (0.2–3.7)
Platelets ($\cdot 10^3$ cells/ μ l)	110 (12–362)
Erythrocyte sedimentation rate (mm/h)	73 (9–138)
C-reactive protein (mg/100 ml)	2.3 (0.3–18.2)
Total protein (g/dl)	7.3 (4.5–10.4)
Albumin (g/dl)	3.3 (1.4–5.3)
Gammaglobulin (g/dl)	2.3 (0.6–6.6)
Aspartate aminotransferase (IU/l)	53 (19–847)
Alanine aminotransferase (IU/l)	33 (8–497)

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D. Paterson · L. Titone

Pediatric Visceral Leishmaniasis in Western Sicily, Italy: A Retrospective Analysis of 111 Cases

Table 3 Treatment and outcome of the 111 children with visceral leishmaniasis

Drug and dosage	Duration of therapy	No. of courses of therapy	No. of cases	Clinical response	No. of relapses
Meglumine antimoniate; median Sb ^V 23.5 mg/kg/day (range, 14–30.2 mg/kg/day)	<18 days (median, 14.5; range, 2–17)	1 course, <i>n</i> =19 patients; 2 courses, <i>n</i> =2 patients	21	19/21 ^a	0
	18–24 days (median, 21; range, 18–24)	1 course, <i>n</i> =50 patients; 2 courses, <i>n</i> =15 patients	65	65/65	0
	>24 days (median, 28; range, 25–30)	1 course, <i>n</i> =8 patients; 2 courses, <i>n</i> =5 patients	13	13/13	2/13
Liposomal AmB; 3 mg/kg/day	5 days (4+1 on day 10)		2	2/2	0
	6 days (5+1 on day 10)		11 ^b	11/11	0
	10 days		3 ^c	3/3	0

^a Two patients were switched from meglumine antimoniate to liposomal amphotericin B: 1 on day 6 of meglumine antimoniate treatment because clinical and laboratory findings had worsened, and 1 because of adverse reaction to meglumine antimoniate (severe urticarial rash after the second dose)

^b Includes the two cases described above in footnote “a”

^c Includes the two cases that relapsed after antimonial therapy



Case report

Good's syndrome and recurrent leishmaniasis: A case report and review of literature

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We report the case of a 56-year-old Caucasian male affected by thymoma and myasthenia gravis that developed **recurrent visceral leishmaniasis** 11 years after thymectomy. After treatment of each relapse with liposomal amphotericin B the PCR-Leishmania was negative and the patient showed clinical improvement. An immunologic work-up was performed showing lymphopenia with an important decrease in **CD4⁺ T cells (52 cells/ μ)** and CD4/CD8 ratio (0.2). HIV test was negative. On the basis of previous **thymoma and myasthenia gravis** and on the basis of the immunological profile a diagnosis of Good's syndrome was made.



Visceral leishmaniasis in a patient with active HBV/HDV co-infection

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Colomba et al. BMC Infectious Diseases (2019) 19:328
<https://doi.org/10.1186/s12879-019-3947-x>

Antiviral Therapy 10:695–696

BMC Infectious Diseases

Correspondence

Visceral leishmaniasis during pegylated interferon therapy for chronic hepatitis C: first report

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CASE REPORT

Open Access

Direct-acting antivirals and visceral leishmaniasis: a case report

Claudia Colomba⁴, Laura Saporito, Paola Di Carlo, Manlio Tolomeo, Adriana Cervo, Alberto Firenze, Marcello Trizzino and Antonio Cascio

Visceral leishmaniasis causes fever and decompensation in patients with cirrhosis

Infections and fever due to bacterial infections are well-known complications of liver cirrhosis, and often trigger decompensation and death.¹ Visceral leishmaniasis (VL), a protozoan infection endemic in the Mediterranean area, causes a febrile disease, the clinical and laboratory features (splenomegaly, pancytopenia, reduced serum albumin and increased γ -globulin concentrations) of which largely overlap with those of cirrhosis.^{2,3} Although the areas where VL is endemic coincide with areas where the prevalence of cirrhosis is high, no study has described VL in patients with cirrhosis.

During a 12-year period, all patients with cirrhosis admitted for decompensation and fever lasting more than 1 week, unresponsive to broad-spectrum antibiotics, underwent diagnostic procedures for VL. For each case diagnosed as VL, three consecutive cases of bacterial infection observed in the same period were enrolled. Cirrhosis was defined by liver histology or clinical, laboratory, ultrasonographic and endoscopic findings. VL was diagnosed by the immunofluorescent-specific antibody test (IFAT) and confirmed by the identification of *Leishmania* from Giemsa-stained smears of bone marrow or spleen

in three patients.

Apart from a long-lasting fever, there were no clear-cut clues to suspect VL. Some significant differences in the presentation data between VL and bacterial infections were found (table 1), but their clinical use is hampered by a substantial overlap of the laboratory values between VL and bacterial infection cases. Only white blood cell and γ -globulin data are of potential value.

IFAT serology is a sensitive and specific test for the diagnosis of VL in patients with cirrhosis; notably, IFAT was negative in all patients with bacterial infections and in 51 additional patients with cirrhosis without fever (table 1). In a series including 16 patients with

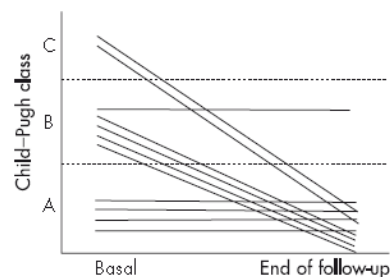


Figure 1 Child-Pugh class before and after treatment for visceral leishmaniasis.

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doi: 10.1136/gut.2007.119495

Case report



***Leishmania infantum* leishmaniasis in corticosteroid – treated patients**

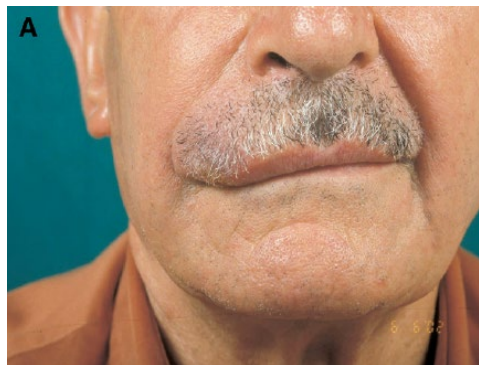
Silvia Pittalis, Emanuele Nicastrì*, Francesco Spinazzola, Piero Ghirga, Michele De Marco, Maria Grazia Paglia and Pasquale Narciso

Case presentation: Three cases of *Leishmania infantum* leishmaniasis in corticosteroid (CS)-treated patients are reported: an isolated lingual leishmaniasis in a farmer treated with CS for asthma, a severe visceral leishmaniasis associated with cutaneous lesions in a woman with *myasthenia gravis*, and a visceral involvement after cutaneous leishmaniasis in a man receiving CS.

Case report: leishmaniasis of the upper lip

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and Luisa Lunardon, MD,^b Milan, Italy

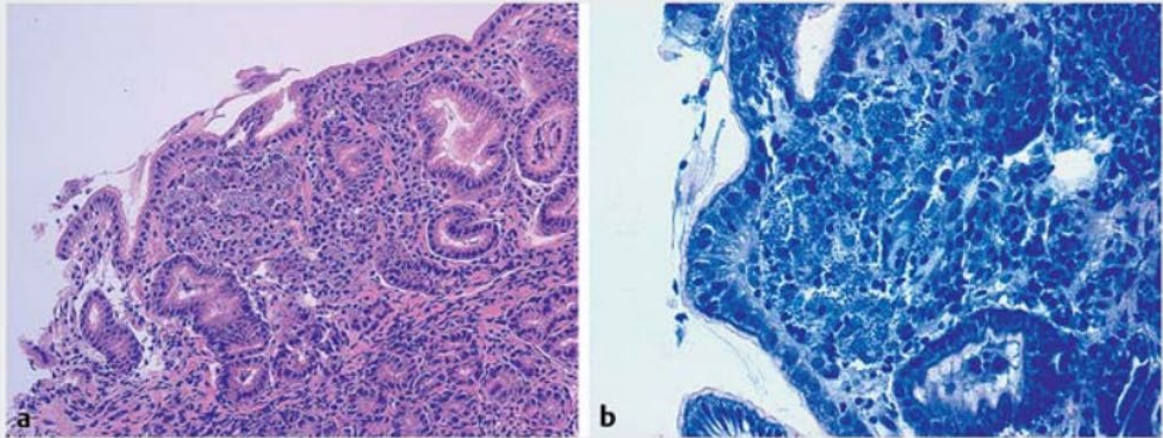
INSTITUTE OF DERMATOLOGICAL SCIENCES, UNIVERSITY OF MILAN, IRCCS FOUNDATION, OSPEDALE
MAGGIORE POLICLINICO, MANGIAGALLI AND REGINA ELENA



Intestinal leishmaniasis: a rare case of enteropathy

We report the case of a 34-year-old immunosuppressed woman who presented with severe malabsorption and weight loss. Her history was remarkable for systemic lupus erythematosus (SLE) complicated by antiphospholipid syndrome, lupus nephritis, and recurrent myocardial pericarditis; she had been treated with combined intensive immunosuppressive regimens. Her antitransglutaminase antibodies were negative and a flare-up of SLE was excluded.

Esophagogastroduodenoscopy revealed remarkable atrophy of the duodenal mucosa, which appeared atypical for both celiac and Whipple disease. A small-bow-



► **Fig. 1** Histology of the duodenal biopsy showing numerous macrophages in the lamina propria of the duodenal mucosa, with abundant intracytoplasmic *Leishmania* amastigote parasites on: **a** hematoxylin and eosin (H&E) staining (magnification $\times 200$); **b** Giemsa staining ($\times 200$).

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Clinical Microbiology and Infection 26 (2020) 1345–1346

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com



Picture of a Microorganism

Intestinal leishmaniasis

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Focal spleen lesions in visceral leishmaniasis, a neglected manifestation of a neglected disease: report of three cases and systematic review of literature

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VL may present with splenomegaly and multiple spleen focal lesions and must be added to the list of possible differential diagnosis of spleen focal lesions. The most common radiological patterns are multiple subcentimetric or centimetric lesions hypoechoic at ultrasonography and hypodense at CT scan. In these cases, PET-CT typically presents with an intense FDG spleen uptake with variable pattern (diffuse, focal or diffuse with superimposed focal uptake).

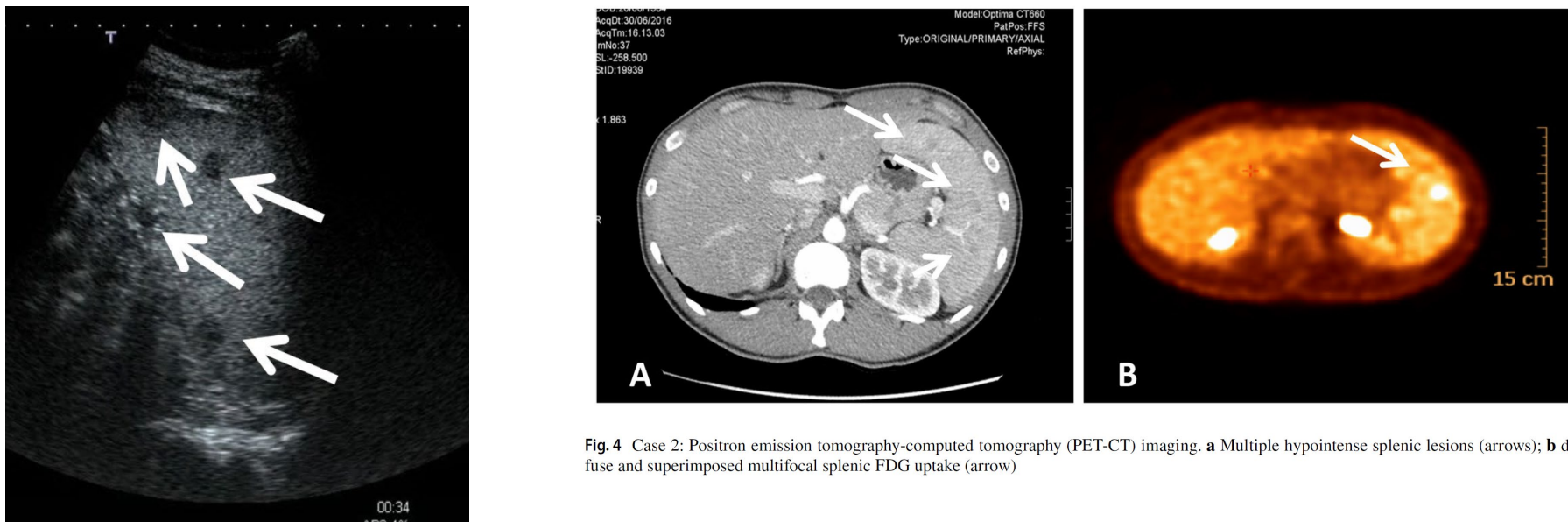


Fig. 4 Case 2: Positron emission tomography-computed tomography (PET-CT) imaging. **a** Multiple hypointense splenic lesions (arrows); **b** diffuse and superimposed multifocal splenic FDG uptake (arrow)



18F-FDG PET/CT in visceral leishmaniasis: uptake patterns in the context of a multiannual outbreak in Northern Italy

Lucia Zaroni¹ · Stefania Varani^{2,3} · Luciano Attard⁴ · Joshua James Morigi^{3,6} · Elisa Vanino^{4,5} · Margherita Ortalli³ · Cristina Fonti¹ · Pierluigi Viale^{4,5} · Maria Carla Re^{2,3} · Stefano Fanti^{1,3} · Valentina Ambrosini^{1,3}

Received: 6 April 2019 / Accepted: 18 June 2019
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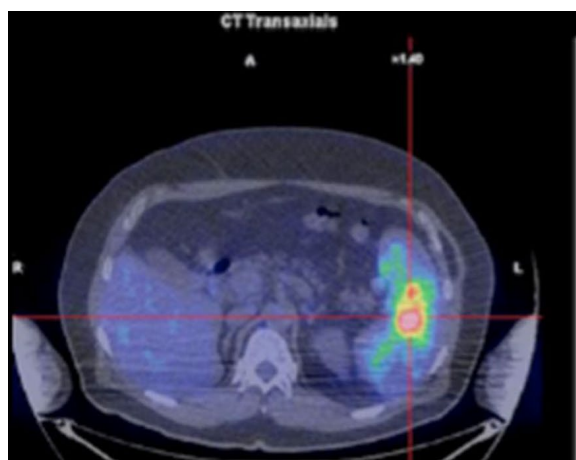


Fig. 2 FDG PET/CT showing multifocal pathological uptake within the spleen. The patient presented with chronic fever. At a diagnostic CT performed 8 days before the PET scan, unclear hypodense nodules

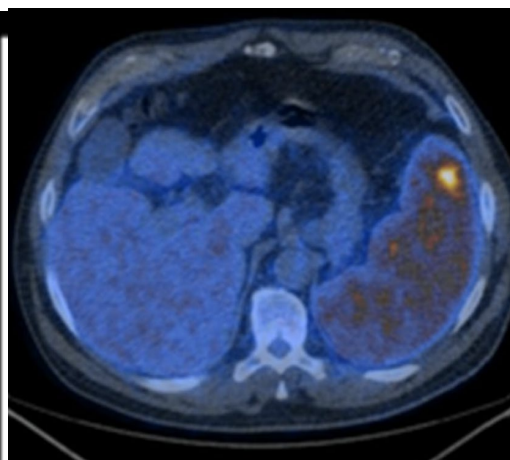


Fig. 3 FDG PET/CT showing multiple focal uptake areas within the spleen (SUVmax = 12.4 at the anterior pole; SLR = 2.9; FDR = 2.2). The images from the low-dose non-diagnostic non-contrast-enhanced CT showed absence

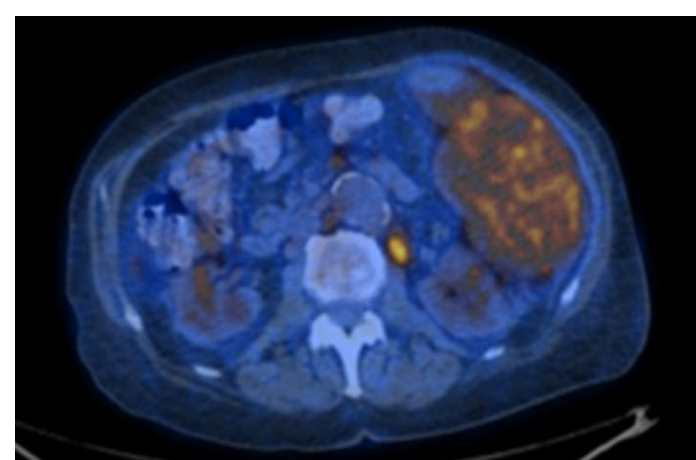


Fig. 4 The image shows diffuse FDG uptake within the enlarged spleen together with extra-splenic hypermetabolic areas in a patient diagnosed with VL after PET/CT. In particular,



Cutaneous and visceral leishmaniasis during anti-TNF α therapy

Claudio Guarneri · Valentina Bevelacqua · James W. Patterson · Georgi Tchernev



Mucocutaneous leishmaniasis in a patient treated with anti-TNF- α therapy

- 49-year-old Caucasian man, a woodsman, born in Albany and living in Tuscany (Italy) since 1999. He had been diagnosed as having AS 20 years ago.
- After the 20th infusion of adalimumab, the patient complained about rhinorrhoea, occasional epistaxis from the left nostril and nose-breathing difficulties

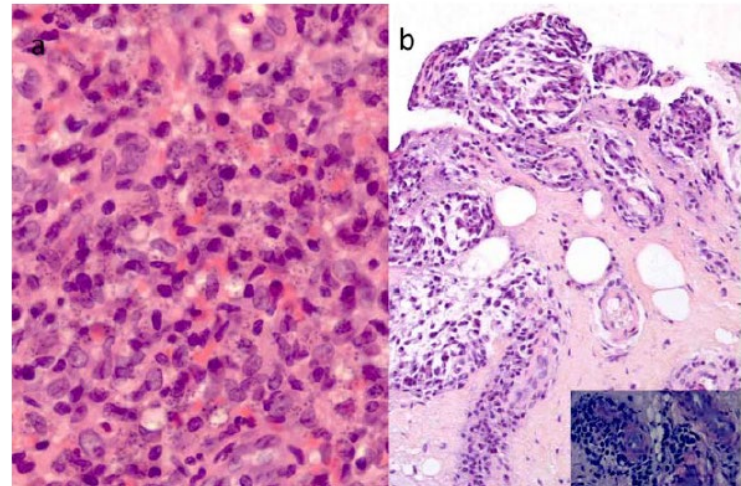


Adalimumab was discontinued, and he was treated successfully with a 5-day course of intravenous (IV) liposomal amphotericin B (total dose 975 mg)

Synovial Leishmaniasis.

Guidelli GM¹, De Stefano R¹, Galeazzi M¹, Selvi E¹.

Clinical Images: Synovial leishmaniasis



- After 3 months and a full ear, nose, and throat examination, adalimumab was reintroduced due to a florid reactivation of AS, leading to good clinical control of the disease within 1 month.
- Two years later, he returned with persistent right knee monoarthritis of 3 weeks' duration

- Adalimumab was stopped, and the patient was re-treated with IV liposomal amphotericin B (3 mg/kg/day for 5 days), with mild improvement of the knee arthritis.
- Two months later, another synovial biopsy was performed, showing complete disappearance of the intracellular parasites

CASE REPORT

Seronegative visceral leishmaniasis with relapsing and fatal course following rituximab treatment

A. Casabianca · M. Marchetti · F. Zallio ·
E. Feyles · E. Concialdi · E. Ferroglia ·
A. Biglino

We describe a case of VL characterized by negative serologic testing, a relapsing course, and a fatal outcome 2 years after the patient had been successfully treated for non-Hodgkin's lymphoma with rituximab. Diagnosis of VL may be further delayed or even missed in patients treated with drugs that interfere with specific antibody production unless specific diagnostic methods, such as bone marrow examination and parasite DNA amplification/detection, are routinely employed.

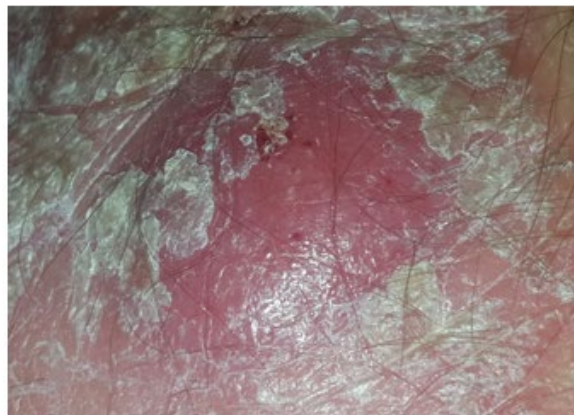
bjh images in haematology

Visceral leishmaniasis after alemtuzumab in a patient with chronic lymphocytic leukaemia

Vincenzo Pitini¹ Antonio Cascio²
Carmela Arrigo¹ Giuseppe Altavilla¹



Figs. 1a and b. Ulcerated lesions by Leishmania onto the oral mucosa (a) and right foot (b) in a 46-year-old patient with psoriasis.



A. Cascio 2018



Leishmania infection in psoriasis.

Colomba C, Saporito L, Bonura S, Campisi G, Di Carlo P, Panzarella V, Caputo V, Cascio A.

J Infect. 2020 May;80(5):578-606. doi: 10.1016/j.jinf.2020.01.019. Epub 2020 Feb 4.

Leishmaniasis and Biologic Therapies for Rheumatologic Diseases

Cascio A, Iaria M, Iaria C.

Semin Arthritis Rheum. 2010 Dec;40(3):e3-5.

Author, yr, country (ref)	Age/sex	Disease	Biological drug (dose) and duration	Immunosuppressive agents associated with biological drug	Previous immunosuppressive agents	LV symptoms	Amastigotes in bone marrow smears	IFAT	PCR	Therapy	Outcome
Romání-Costa et al. 2004 Spain (2)	55/M	Psoriatic arthritis	Infliximab (3 mg/kg) 9 mo	NR	NR for 300 mo	Fever, asthenia, hepatosplenomegaly, pancytopenia	Pos	ND	ND	Meglumine antimoniate (840 mg/d for 28 d)	Cure
Fabre et al. 2005 France (3)	53/F	Rheumatoid arthritis	Infliximab (3 mg/kg) 9 mo	Steroids, azathioprine (100 mg/d)	NR	Fever, splenomegaly, and pancytopenia. Inflammatory markers increased	Neg; Pos a 2nd bone marrow aspirate	1:5120	Pos	Amphotericin B (0.7 mg/kg/d for 15 days, then 0.7 mg/kg every 15 d)	Cure—The patient was then treated for 1 yr with etanercept
Basseti et al. 2006 Italy (5)	69/F	Rheumatoid arthritis	Adalimumab (40 mg every other week) 25 mo	MTX (7.5 mg weekly) and prednisone (5 mg/d) 360 mo	NR	Fluctuant fever with several peaks at 39°C, pancytopenia	Pos	1/160	Pos	L-amB (3 mg/kg/d for 5 d, and 3 mg/kg on d 10).	Cure—MTX was started again after 30 d
Bagalas et al. 2006 Greece (4)	60/F	Rheumatoid arthritis	Etanercept for 18 mo-24 mo before VL; Anakinra, for 2 to 3 weeks 6 mo before VL	NR	Steroids and cyclosporine for 7 yr	Temperature up to 39.5°C every 3 to 4 days, pancytopenia, splenomegaly	Pos	Pos	ND	L-amB (4 mg kg/d, then, due to acute renal failure, 1 mg kg/d, which was gradually increased)	Death due to severe pulmonary infection
Koné-Paut et al. 2007 France (6)	9/F	Systemic juvenile arthritis	Etanercept (to cure an episode of MAS), then anakinra (1 mg/kg/d) 6 mo	NR	Steroids, MTX, cyclosporine.	Fever, scarlet fever-like pruritic rash and hepatosplenomegaly, anemia, thrombocytopenia	Neg	NR	ND	L-amB steroids to cover the risk of MAS	Cure
Tektonidou and Skopouli 2008 Greece (7)	45/M	Psoriatic arthritis	Infliximab (3 and then 5 mg/kg) 3 yr	MTX, prednisolone for 3 yr	NR	High-grade fever, splenomegaly, acute reactive proteins, pancytopenia	Neg	Neg	Pos	L-amB (3 mg/kg/d for 5 d, and 3 mg/kg on d 20)	Cure
Balato et al. 2008 Italy (9)	42/M	Psoriasis	Efalizumab (1 mg/kg/wk) 3 mo	NR	Cyclosporine for 1 mo	Intermittent fever, hepatosplenomegaly, pancytopenia	Pos	1:640	Pos	No anti-leishmania drugs were given	Cure
García-Vidal et al. 2009 Spain (8)	55/M	Rheumatoid arthritis	Infliximab (Tot 40 mg/kg) 11 mo	MTX, steroids	MTX, steroids, azathioprine, cyclosporine for 10 yr	NR	Pos	NR	ND	Meglumine antimoniate	Cure



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Case report

Visceral leishmaniasis and macrophagic activation syndrome in a patient with rheumatoid arthritis under treatment with adalimumab

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Hemophagocytic Syndrome: A Misleading Complication of Visceral Leishmaniasis in Children—A Series of 12 Cases

Marie-Helene Gagnaire, MD^{*}; Claire Galambrun, MD[†]; and Jean Louis Stéphan, MD^{*}

J Int Assoc Physicians AIDS Care (Chic). 2009 Jul-Aug;8(4):217–20. doi: 10.1177/1545109709337902. Epub 2009 Jun 17.

Immune reconstitution visceral leishmaniasis presented as hemophagocytic syndrome in a patient with AIDS from a nonendemic area: a case report.

Patel KK, Patel AK, Sarda P, Shah BA, Ranjan R.

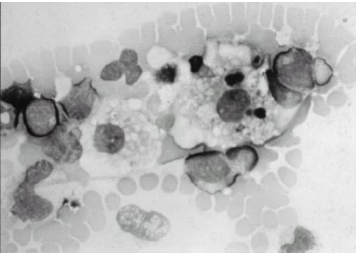
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Abstract

Visceral Leishmaniasis (VL) is endemic in the Ganges and Brahmaputra plains of India. Leishmaniasis/HIV coinfection is on the rise in India and may pose a real diagnostic and therapeutic challenge. HIV-related immunosuppression increases the risk of reactivating leishmaniasis by 100 to 1000 times and it also increases the risk of drug resistant leishmaniasis. Immune reconstitution VL is not very well reported in literature.

Hemophagocytosis is known to occur with various infectious agents like viruses, bacteria, and parasites, but is rare to occur with leishmaniasis. Here the authors describe a case of VL presenting as immune reconstitution disease and hemophagocytosis in an HIV infected patient coming from a nonendemic area.

Hemophagocytic Syndrome: A Misleading Complication of Visceral Leishmaniasis in Children—A Series of 12 Cases



PEDIATRICS Vol. 106 No. 4 October 2000

- Clinico-pathologic entity characterized by **activation and uncontrolled nonmalignant proliferation of T lymphocytes and macrophages, leading to cytokine overproduction.**
- Patients usually present with an acute febrile illness, hepatosplenomegaly, pancytopenia, marked hypofibrinogenemia, and hypertriglyceridemia.
- In children it has been linked to viral, bacterial, fungal and parasitic infection (infection associated HS) and to a broad spectrum of malignancies and genetic disorders, such as Chédiak-Higashi disease, Griscelli disease, XLP syndrome, and familial erythrophagocytic lymphohistiocytosis

Association between Hypertriglyceridemia and Disease Severity in Visceral Leishmaniasis

Mariana Garcez Varela ^{1 2 3}, Mariana de Oliveira Bezerra ¹, Felipe Vieira Santana ¹, Marcos Couto Gomes ¹, Pedro Ribeiro de Jesus Almeida ⁴, Geydson Silveira da Cruz ^{3 5}, Enaldo Vieira de Melo ⁶, Paulo Roberto de Oliveira Costa ⁷, Fabrícia Alvisi de Oliveira ¹, Amélia Ribeiro de Jesus ^{1 3 8}, Roque Pacheco de Almeida ^{1 3 8}

- Severely ill patients had higher mean serum triglyceride levels than non-severely ill patients. There was a significant positive correlation between disease severity score and serum triglyceride levels, very low-density lipoprotein, international normalized ratio for prothrombin time test, total bilirubin, and age.
- An inverse correlation was detected between the disease severity score and mean platelet and neutrophil counts. Hypertriglyceridemia can be a prognostic indicator of severity in patients diagnosed with VL.

Short Report: Quantiferon-*Leishmania* as an Epidemiological Tool for Evaluating the Exposure to *Leishmania* Infection

Nevin Turgay,* I. Cuneyt Balcioglu, Seray Ozensoy Toz, Yusuf Ozbel, and Stephen L. Jones

Department of Parasitology, Ege University Medical School, Izmir, Turkey; Department of Parasitology, Celal Bayar University Medical School, Manisa, Turkey; Cellestis Limited, Carnegie, Australia

Abstract. The aim of the present preliminary study was to investigate the potential of measurement of IFN- γ secretion by T cells into blood plasma using QuantiFERON assay with leishmanial antigens to determine the presence of *Leishmania* infection. Blood samples from cured visceral ($N = 18$), and cutaneous ($N = 20$) leishmaniasis cases, and 20 healthy controls were tested. The IFN- γ responses to *Leishmania major* H2B and *Leishmania infantum* H2B antigens were detected from the majority of treated old visceral leishmaniasis cases, but not from controls. Future studies using larger groups will be required to establish the true potential of the assay for epidemiological screening of leishmaniasis.

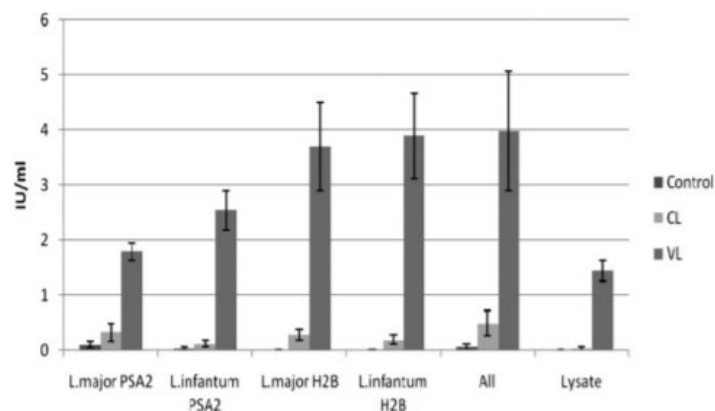


FIGURE 1. IFN- γ responses to leishmanial antigens used in the study (Mean $\pm$ SD). VL, visceral leishmaniasis; CL, cutaneous leishmaniasis; Control, healthy volunteers coming from non-endemic areas.

Immunobiology 219 (2014) 323–328

Contents lists available at ScienceDirect



ELSEVIER

Immunobiology

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

Review

Whole blood assay and visceral leishmaniasis: Challenges and promises

Om Prakash Singh, Shyam Sundar*

Infectious Disease Research Laboratory, Department of Medicine, Institute of Medical Sciences, Banaras Hindu University, India

OPEN ACCESS Freely available online

PLOS NEGLECTED TROPICAL DISEASES

Interferon-Gamma Release Assay (Modified QuantiFERON) as a Potential Marker of Infection for *Leishmania donovani*, a Proof of Concept Study

Kamlesh Gidwani¹, Stephen Jones², Rajiv Kumar¹, Marleen Boelaert³, Shyam Sundar^{1*}

¹ Banaras Hindu University, Varanasi, India, ² Cellestis limited, Chadstone, Victoria, Australia, ³ Institute of Tropical Medicine, Antwerp, Belgium



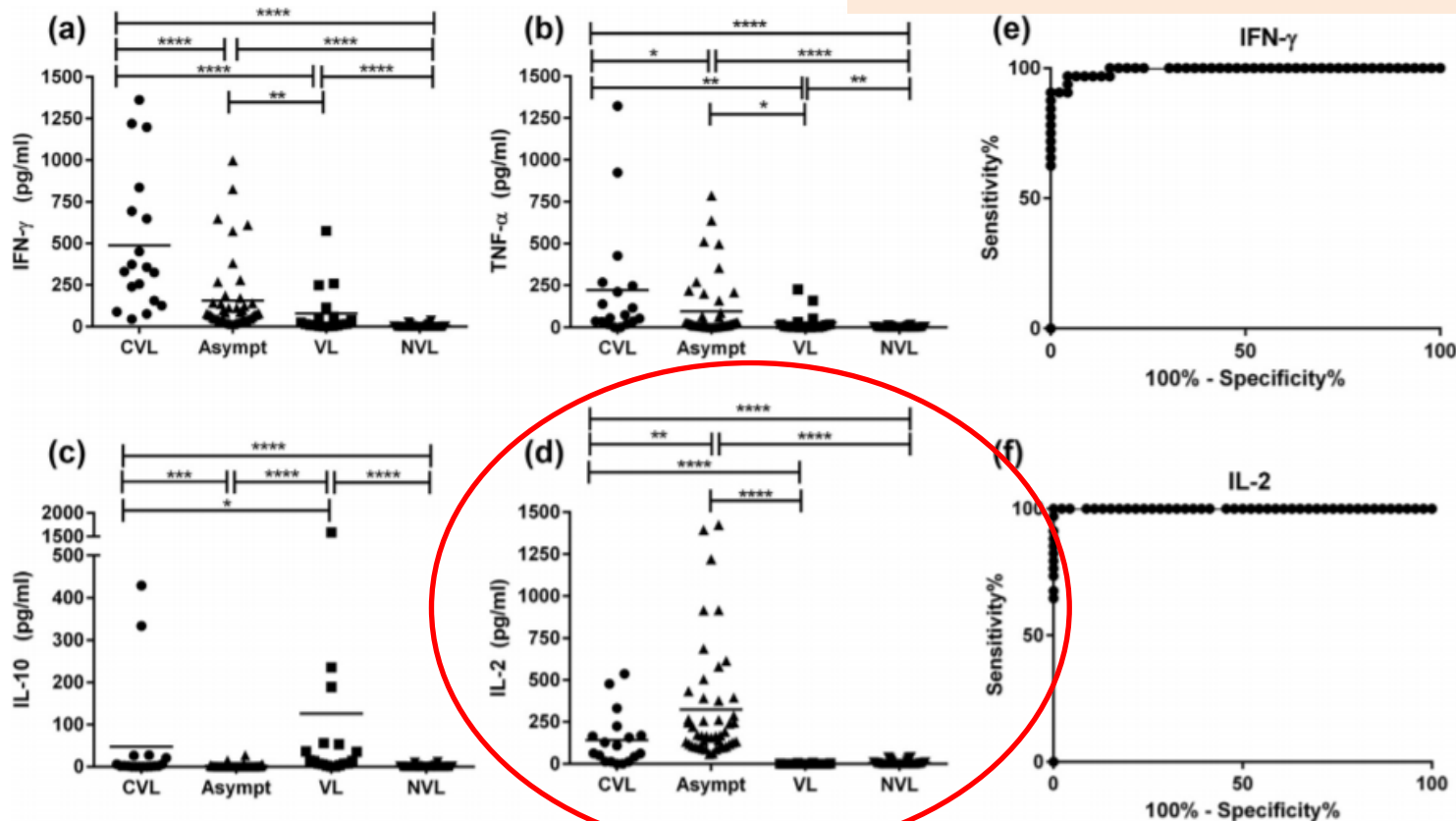
Research note

Interleukin-2 as a marker for detecting asymptomatic individuals in areas where *Leishmania infantum* is endemic

A.V. Ibarra-Meneses¹, E. Carrillo^{1,*}, C. Sánchez¹, J. García-Martínez²,
D. López Lacomba², J.V. San Martín³, F. Alves⁴, J. Alvar⁴, J. Moreno¹

The present work investigates the soluble *Leishmania* antigen stimulation of whole blood from cured persons, those with active disease, and asymptomatic individuals. SLA-stimulated plasma IFN- γ concentrations were recorded, as were those of tumour necrosis factor- α (TNF- α), interleukin-10 (IL-10) and IL-2.

The aim was to establish a simple method for detecting asymptomatic persons in areas where *L. infantum* is endemic





Review

Third Case of Visceral Leishmaniasis in COVID-19: Mini Review Article

Claudia Colomba ^{1,2}, Cristoforo Guccione ¹, Raffaella Rubino ^{3,*}, Michela Scalisi ² , Anna Condemi ^{1,2}, Sara Bagarello ^{1,2}, Salvatore Giordano ² and Antonio Cascio ^{1,3} 

Author/Year	Age	Sex	Immunocompetence	Fever and Pancytopenia	Sample for Diagnosis	Diagnosis	Therapy	Outcome
Miotti 2020	70	M	No	Yes	Blood and bone marrow	Molecular diagnosis	Amphotericin B + dexamethason	Death
Pikoulas 2021	30	F	Yes	Yes	Blood and bone marrow	Molecular diagnosis	Amphotericin B + dexamethason	Full recovery
Present case 2022	4	F	Yes	Yes	Blood	Molecular diagnosis	Amphotericin B	Full recovery



Outbreak of cutaneous leishmaniasis before and during the COVID-19 pandemic in Jahrom, an endemic region in southwest of Iran

Cutaneous leishmaniasis and the COVID-19 pandemic

Samaneh Mazaherifar, Kavous Solhjoo & Amir Abdoli

To cite this article: Samaneh Mazaherifar, Kavous Solhjoo & Amir Abdoli (2022): Outbreak of cutaneous leishmaniasis before and during the COVID-19 pandemic in Jahrom, an endemic region in southwest of Iran, Emerging Microbes & Infections, DOI: [10.1080/22221751.2022.2117099](https://doi.org/10.1080/22221751.2022.2117099)

To link to this article: <https://doi.org/10.1080/22221751.2022.2117099>

- Before the pandemic, the annual occurrence of CL was less than 240 cases per year, while the number of cases was increased to 307 and 771 cases in the first and second years after the pandemic, respectively.
- Molecular detection of some isolates identified *Leishmania major*.
- The **rodent control program was completely interrupted during the first year of COVID-19 outbreak** in Iran (February to December, 2020), then the program restarted again as routine from the summer of 2021 till now. Interrupted rodent control program along with inadequate screening programs of CL patients were probably one of the causes of this outbreak in Jahrom.

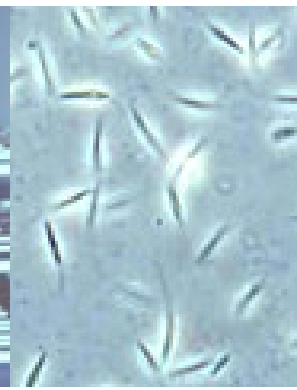
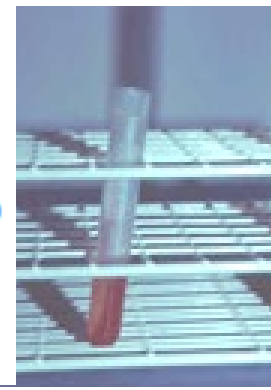
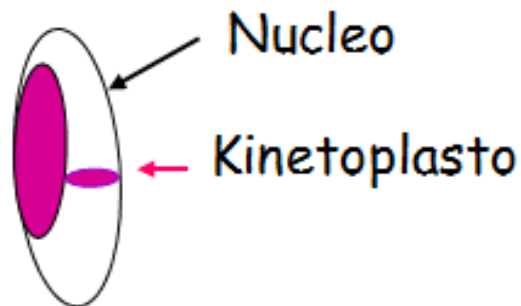
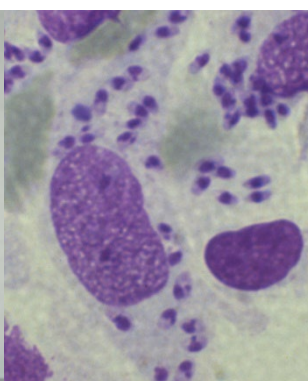
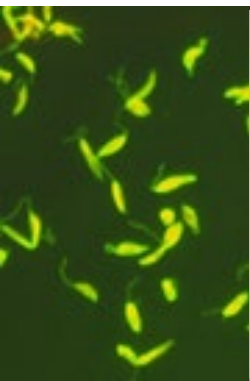
Diagnostic workup

CL/MCL

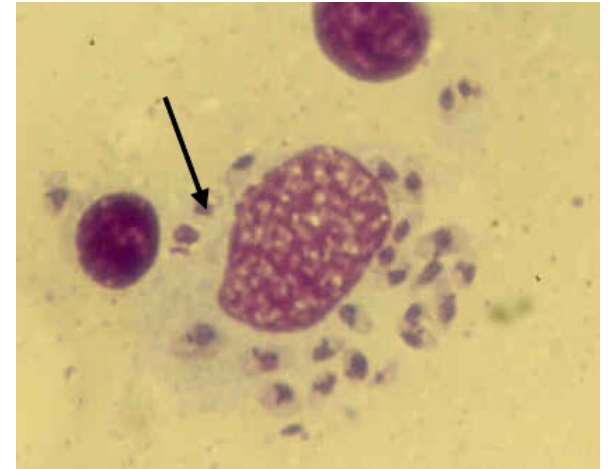
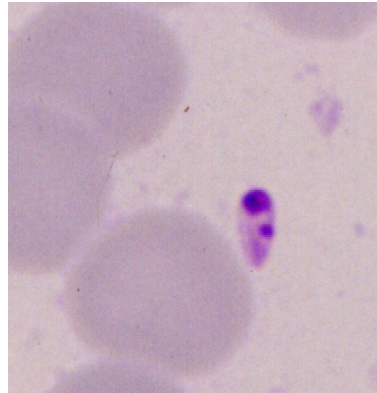
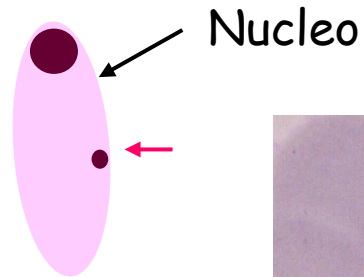
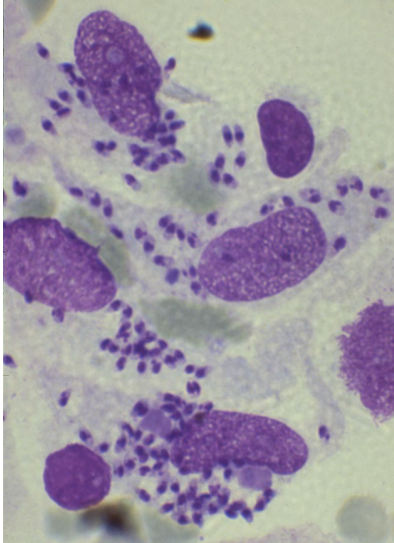
- Biopsy
- Scraping
 - Microscopy
 - Culture
 - PCR
- Serology
- PCR – blood

VL

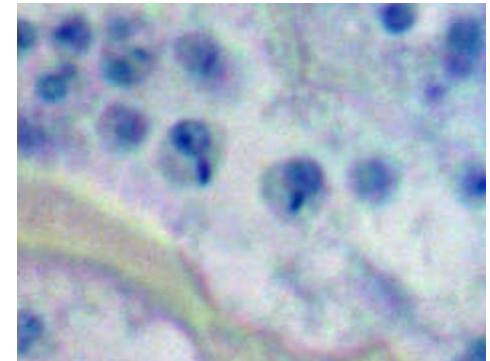
- Serology
- PCR – blood
- Bone marrow aspirate
 - Microscopy
 - Culture
 - PCR



Esame microscopico del midollo osseo



Il sangue midollare viene strisciato su vetrini che fissato in metanolo sono successivamente sottoposto alla colorazione Giemsa e osservati al microscopio (1000 X)



La sensibilità del metodo dipende dall'esperienza dell'osservatore (70-95%)

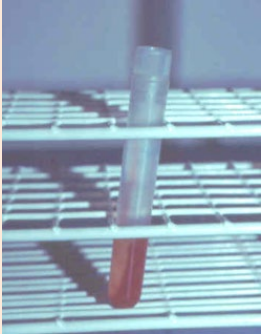
Splenic aspiration



- The procedure is simple, painless and safe if the prothrombin time is normal and the platelet count is above 40000/mm³.
- Palpate the spleen and mark its outline. Using a 1.25inch long ∞ 21-gauge needle attached to a 5ml syringe, penetrate the skin over the spleen. Withdraw the plunger 1ml and plunge the needle into the spleen upwards at an angle of 45° and withdraw immediately, maintaining suction.
- The tiny amount of material obtained is sufficient for culture and smear.

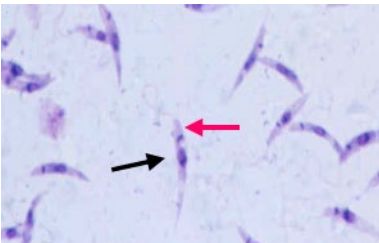
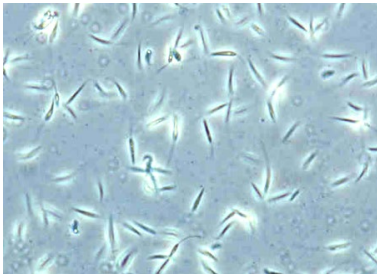
Terreni di coltura

Sono tipicamente dei terreni agar sangue mono o bifasici, non disponibili in commercio:



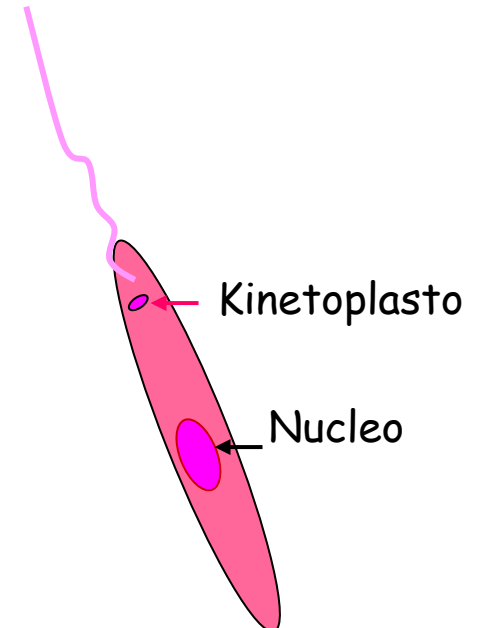
- "EMTM" (Evans modified Tobie medium)
- "Sloppy Evans medium"
- "NNN medium" (Novy, McNeil e Nicolle)

N.B. Terreni liquidi (es. Schneider e RPMI) sono disponibili per *Leishmania* in commercio ma mostrano un'efficienza inferiore ai terreni agar sangue durante l'isolamento in coltura, quindi una minore sensibilità nella diagnosi.



La sensibilità di una coltura dipende da diversi fattori:

- ✓ Tipo di terreno e temperatura d'incubazione (23-24°C)
- ✓ Quantità di materiale seminato



Xenodiagnosi

E' un metodo di diagnosi diretta che permette di rilevare il parassita attraverso l'utilizzo del suo ospite vettore

Il cane viene addormentato ed esemplari da colonia di *Phlebotomus perniciosus* sono lasciati liberi di pungere sulla testa del cane



Flebotomi con pasto di sangue sono raccolti separatamente e dissezionati per la ricerca di promastigoti

INFECTION OF SAND FLIES BY HUMANS COINFECTED WITH *LEISHMANIA INFANTUM* AND HUMAN IMMUNODEFICIENCY VIRUS

RICARDO MOLINA, JEAN M. LOHSE, FEDERICO PULIDO, FERNANDO LAGUNA,
ROGELIO LÓPEZ-VÉLEZ, AND JORGE ALVAR

- To determine the role that *Leishmania infantum*/human immunodeficiency virus (HIV) coinfecting patients could play in the epidemiology of visceral leishmaniasis (VL), we applied direct xenodiagnosis of VL in this study to test the infectivity of six coinfecting patients to colonized *Phlebotomus perniciosus*.
- All patients proved to be infective for the sand flies.
- The infectivity of patients who had still not received specific treatment for VL was inversely proportional to their absolute CD4⁺ T lymphocyte cell count.



Diagnosi molecolare (PCR)

Vantaggi diagnostici:

Elevata sensibilità (teorica ≤ 1 parassita);

Elevata specificità: quasi assoluta

- Assenza di interferenze da parte di altri microorganismi;
- Automatizzazione e riproducibilità

Può essere applicata a qualsiasi tipo di campione:

- Aspirato midollare o linfonodale
- Prelievo splenico
- Sangue periferico (Buffy Coat, PBMC)
- Cute

☐ Fresco, Fissato su vetrino e/o colorato Campione istologico

Pediatrics 2002;109(2).

Polymerase Chain Reaction in the Diagnosis and Prognosis of Mediterranean Visceral Leishmaniasis in Immunocompetent Children

Antonio Cascio, MD*; Sara Calattini, BSc†; Claudia Colomba, MD*; Chiara Scalamogna, MD‡;
Morena Galazzi, BSc†; Massimo Pizzuto, MD‡; Romina Camilli, MD§; Marina Gramiccia, MD§;
Lucina Titone, MD*; Mario Corbellino, MD‡; and Spinello Antinori, MD*

IFAT è il “gold standard” della sierologia per la leishmaniosi

Sensibilità e specificità si avvicinano al 100% nei pazienti immunocompetenti

La specificità non rappresenta un problema nell'area Mediterranea raggiungendo la soglia del 100%

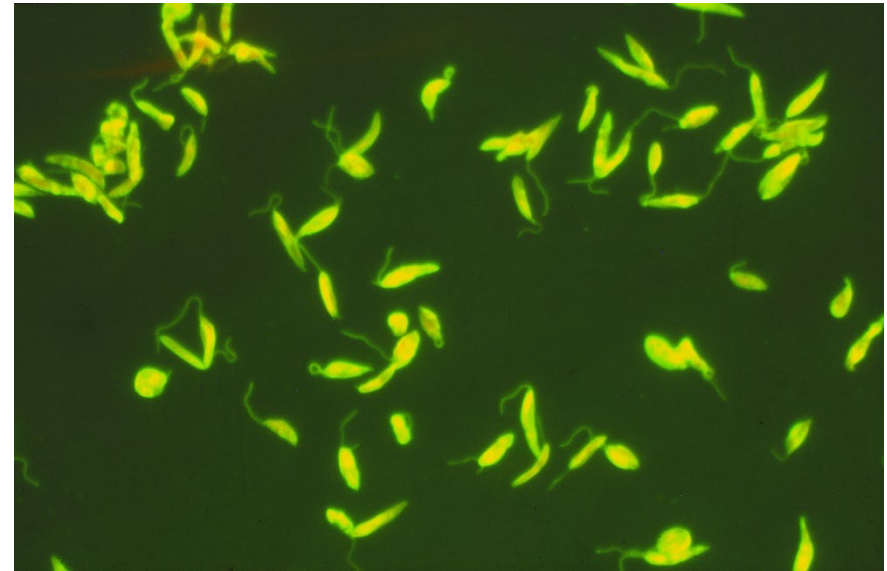
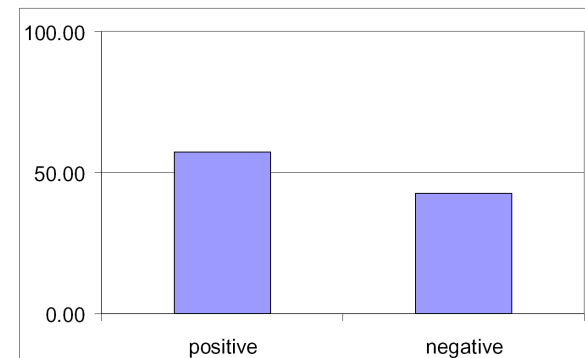
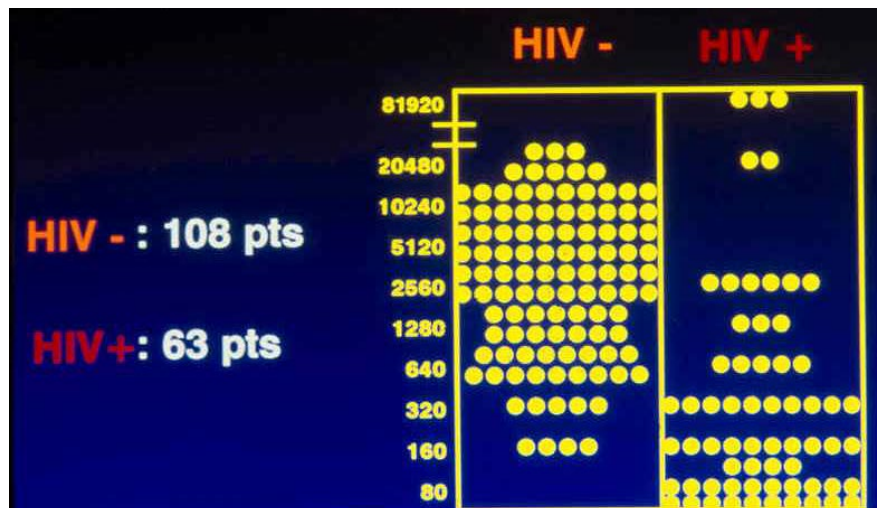
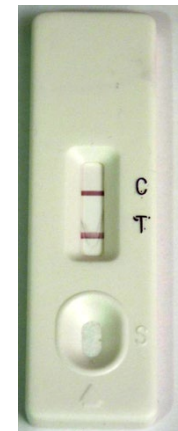
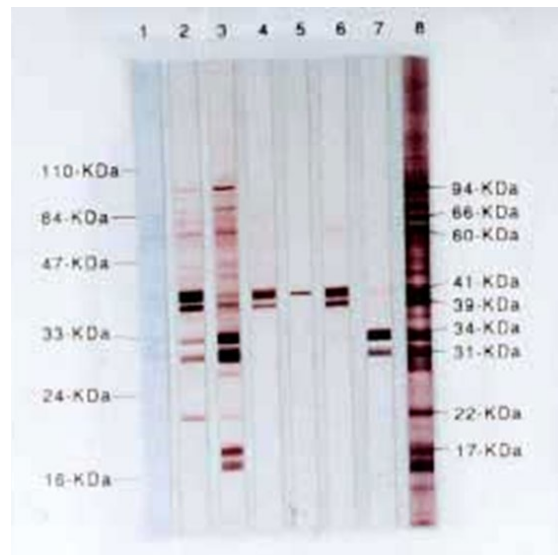
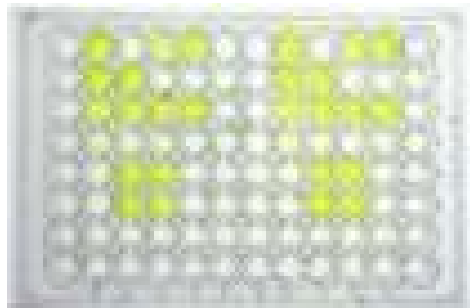
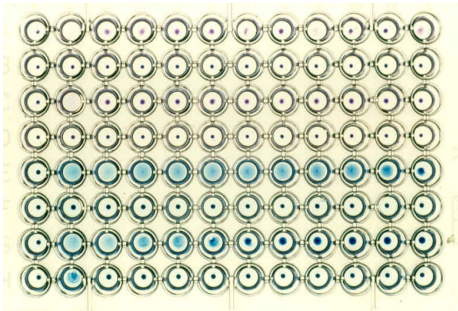


Figure 3: Sensitivity of serology, 941 patients tested, south-western Europe, 1990-1998



Altre tecniche sierologiche....

- ELISA con antigene intero: diminuisce di specificità
- **ELISA con antigene ricombinante: diminuisce di sensibilità**
- Latex test: bassa specificità (58%)
- **DAT: diminuisce di sensibilità**
- Emoagglutinazione indiretta: bassa sensibilità (66%) e specificità (80%)
- **Western Blot: utile come "confirmatory test" (laborioso e poco riproducibile)**



Test rapido
immunocromatografico

Specificità: ~100%

Sensibilità: 77-90%

The role of CD1a expression in the diagnosis of cutaneous leishmaniasis, its relationship with leishmania species and clinicopathological features

Yasemin Yuyucu Karabulut, Funda Kuş Bozkurt, Ümit Türsen✉, Gül Bayram, Gülhan Örekeci Temel, Mehmet Emin Erdal

First published: 15 May 2021

<https://doi-org.bibliosan.idm.oclc.org/10.1111/dth.14977>

Transepidermal elimination in cutaneous leishmaniasis: a multiregional study

Sarah Karram, Asif Loya, Hadi Hamam, Robert H. Habib, Ibrahim Khalifeh✉

First published: 14 February 2012 |

<https://doi-org.bibliosan.idm.oclc.org/10.1111/j.1600-0560.2012.01890.x> | Citations: 33

Langerhans cell marker (CD1a)

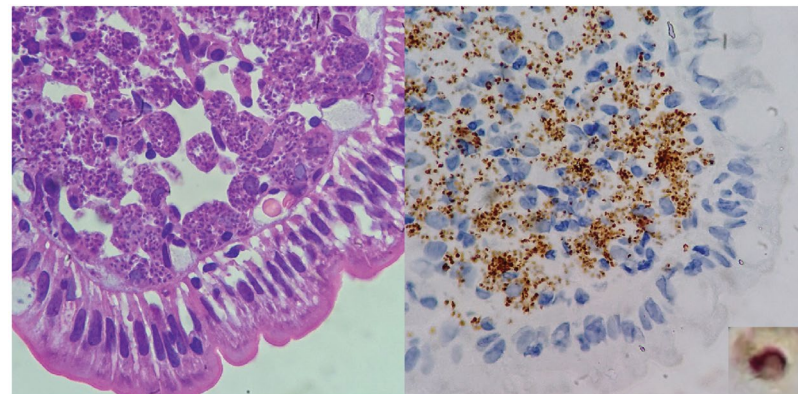
<http://doi.org/10.1590/S1678-9946201961025>

Evaluation of the diagnostic potential of CD1a immunohistochemistry for visceral leishmaniasis

Sami de Andrade Cordeiro Gadelha¹, Maria do Perpétuo Socorro Saldanha da Cunha^{2,3}, Gabriela Maia Coelho¹, Tamises Melo Siqueira Marinho¹, Carlos Gustavo Hirth^{1,2,3}

A possible explanation for this staining overlap could be that the amastigotes acquired the CD1a upon exiting dendritic cells expressing the marker by the process of exocytosis.

Another less likely explanation could be that the CD1a and a leishmania surface antigen have a homologous site, resulting in cross reactivity with the CD1a antibody; however, this will need to be confirmed by further molecular analyses. Explanation aside, the highlighting of amastigotes by CD1a would be helpful especially in cases with a low parasitic index with high clinical suspicion of leishmaniasis.



Therapy

- **CL**
 - Negative serology and negative blood PCR
 - **intralesional meglumine antimoniate**
 - Positive serology and/or positive blood PCR
 - **Liposomal amphotericin B**
- **MCL**
 - **Liposomal amphotericin B** (regimens vary) with total cumulative dose of 20-60 mg/kg
 - **Pentavalent antimony** (Sb) [Sodium Stibogluconate (Pentostam) or Meglumine antimoniate (Glucantime)] 20 mg/kg/day IV or IM x 28 days
- **VL**
 - Liposomal amphotericin B
 - Immunocompetent: Liposomal Amphotericin B 3 mg/kg IV once daily days 1-5 and days 14, 21 (need 21 mg/kg total dose). 40 mg/kg total dose for East African VL.
 - Immunocompromised, HIV/AIDS: Liposomal Amphotericin B: 4 mg/kg daily on days 1-5, 10, 17, 24, 31 and 38 (total of 40 mg/kg). HIV patients may need longer courses as well as maintenance therapy with liposomal amphotericin B (4 mg/kg every 2–4 weeks)

Liposomal amphotericin B for the treatment of visceral leishmaniasis

Caryn Bern ¹, Jill Adler-Moore, Juan Berenguer, Marleen Boelaert, Margriet den Boer, Robert N Davidson, Concepcion Figueras, Luigi Gradoni, Dimitris A Kafetzis, Koert Ritmeijer, Eric Rosenthal, Catherine Royce, Rosario Russo, Shyam Sundar, Jorge Alvar

Table 1. Efficacy and toxicity of various dosing regimens of liposomal amphotericin B (LAmB) in immunocompetent patients with visceral leishmaniasis.

Country	Reference(s)	Study design	No. of subjects		Total AmB dose, mg/kg	LAmB regimen	Percentage of cured subjects	Follow-up duration, months	Reported adverse events ^a
			Total	Per group					
Brazil	[20, 21] ^b	Open-label, dose-finding	32	15	6	2 mg/kg on day 1, 5, and 10	87	6	Fever, 41%; chills, 9%; respiratory distress, 6%; cardiac arrhythmia, 9%; treatment was stopped for 2 subjects
				4	10	2 mg/kg on days 1–4 and 10	100	6	...
				13	14	1–2 mg/kg on days 1–6 and 10	62	6	...
Greece	[22]	Open-label with historical control	123 ^c	41	20	10 mg/kg on days 1–2	98	6	Fever and chills, 7%; no discontinuations of treatment
				30	20	4 mg/kg on days 1–5	90	6	...
Italy	[23]	Open-label, dose-finding	31 ^d	10	30	3 mg/kg on days 1–10	100	12–24	Nonsignificant increase in BUN level; no change in creatinine level; no discontinuations of treatment
				10	21	1–1.4 mg/kg on days 1–21	100	12–24	...
Italy ^e	[24]	Open-label, dose-finding	88 ^f	32	15	3 mg/kg on days 1–4 and 10	91	12	Mild adverse effects; transient increase in BUN and creatinine levels; no discontinuations of treatment
				42	18	3 mg/kg on days 1–5 and 10	98	12	...
				13	24	4 mg/kg on days 1–5 and 10	100	12	...
Italy	[25]	Open-label, dose-finding	106 ^c	16	15	3 mg/kg on days 1–3, 5, and 10	75	12	No adverse events, no change in levels of BUN, creatinine, electrolytes, or liver enzymes
				66	18	3 mg/kg on days 1–5 and 10	98	12	...
				11	21	1 mg/kg on days 1–21	100	12	...
				13	30	3 mg/kg on days 1–10	100	12	...

A 6 day course of liposomal amphotericin B in the treatment of infantile visceral leishmaniasis: the Italian experience

Antonio Cascio^{1,2*}, Lucio di Martino³, Paolo Occorsio³, Raffaella Giacchino⁴,
Salvatore Catania⁵, Anna Rita Gigliotti⁴, Camilla Aiassa⁵, Chiara Iaria^{1,2}, Salvatore Giordano⁶,
Claudia Colomba⁶, Valentina Frasca Polara⁶, Lucina Titone⁶, Luigi Gradoni⁷,
Marina Gramiccia⁷ and Spinello Antinori⁸

Acute Renal Failure Due to Visceral Leishmaniasis by *Leishmania infantum* Successfully Treated With a Single High Dose of Liposomal Amphotericin B

Anna Beltrame, MD,* Alessandra Arzese, MD,*[†] Alessandro Camporese, MD,[‡] Giada Rorato, MD,*
Massimo Crapis, MD,* Giuseppe Tarabini-Castellani, MD,[§] Giuliano Boscutti, MD,[§]
Stefano Pizzolitto, MD,[¶] Giuseppina Caliano, MD,^{||} Alberto Matteelli, MD,[#]
Trentina Di Muccio, MD,** Marina Gramiccia, MD,** and Pierluigi Viale, MD*

*Clinic of Infectious Diseases, Department of Clinical and Morphological Research and [†]Institute of Microbiology, University of Udine, Udine, Italy; [‡]Department of Microbiology, Santa Maria degli Angeli Hospital of Pordenone, Pordenone, Italy; [§]Nephrology and Dialysis Unit and [¶]Division of Anatomic Pathology, General Hospital S. Maria della Misericordia of Udine, Udine, Italy; ^{||}Nephrology Service, Santa Maria degli Angeli Hospital of Pordenone, Pordenone, Italy; [#]Institute of Infectious and Tropical Diseases, University of Brescia, Brescia, Italy; **Unit of Vector-borne Diseases and International Health, MIPI Department, Istituto Superiore di Sanità of Rome, Rome, Italy

DOI: 10.1111/j.1708-8305.2008.00220.x



International Journal of Antimicrobial Agents 25 (2005) 26–30

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Discussion

Treatment of paediatric visceral leishmaniasis: amphotericin B or pentavalent antimony compounds?

D.A. Kafetzis^{a,*}, I.M. Velissariou^a, S. Stabouli^a, M. Mavrikou^b, D. Delis^b, G. Liapi^a

^a Second Department of Pediatrics, University of Athens, P. & A. Kyriakou Children's Hospital, Athens 11527, Greece

Treatment regimes, duration and cost of hospitalization in children with visceral leishmaniasis

Treatment cost regime	Number of patients	Hospitalization days	Medication cost of a 3-year-old (€)	Treatment of a 3-year-old (€)
Antimony a	6	22 [17–28]	10.6	1639
Antimony b	4	12.5 [11–16]	10.6	936
Amphotericin b1	4	6.5 [6–8]	834	1315
Amphotericin b2	6	7 [6–11]	952	1479
Amphotericin b3	6	6.5 [6–8]	834	1315
Amphotericin b4	3	7 [6–8]	834	1351

Antimony a: meglumine antimonate 20 mg/kg/day for 21 days, as an inpatient; Antimony b: meglumine antimonate 20 mg/kg/day for 21 days, as an outpatient; Amphotericin b1: liposomal amphotericin B 4 mg/kg/day for 5 days; Amphotericin b2: liposomal amphotericin B 4 mg/kg/day on days 1–5 and 9; Amphotericin b3: liposomal amphotericin B 5 mg/kg/day for 4 days; Amphotericin b4: liposomal amphotericin B 10 mg/kg/day for 2 days.

... the patients who received liposomal amphotericin B for 2 days, were hospitalized for 6–8 days (median 7 days), due to allergic reactions to the infusion

Glucantim (antimoniato di N-metil-glucamina)

- Soluzione di Sb^5 al 8,5 % (85 mg / ml)
- Venduto in fiale da 5 ml contenenti 1,5 g di farmaco equivalente a 425 mg di Sb^5

Pentostam (stibogluconato di Na)

- soluzione di Sb^5 al 10 % (100 mg/ml)
- Venduto in flaconi multidosaggio da 100 ml



Di Cristina G, Caronia G. Sulla terapia della leishmaniosi interna. Pathologica 1915; 7: 82-83



AmBisome (Liposomal amphotericin B)

- The US Food and Drug Administration licensed AmBisome for treatment of VL and recommended treating
 - immunocompetent patients with 3 mg/Kg daily on days 1-5, 14 and 21 (total 21 mg/Kg)
 - Immunosuppressed patients with 4 mg/Kg daily on days 1-5, 10, 14, 17, 24, 31, and 38 (total 40 mg/Kg)



Miltefosine

- Membrane-active alkyl phospholipid (phosphocholine analogue) that interferes with cell-signaling pathways
- Developed as an antineoplastic agent and now used topically in breast carcinoma skin metastases
- do not have clinical efficacy against tumors when administered orally
- is particularly active in animal models of visceral leishmaniasis



ORAL MILTEFOSINE FOR INDIAN VISCERAL LEISHMANIASIS

SHYAM SUNDAR, M.D., T.K. JHA, M.D., C.P. THAKUR, M.D., JUERGEN ENGEL, PH.D., HERBERT SINDERMAN, PH.D.,
CHRISTINA FISCHER, KLAUS JUNGE, PH.D., ANTHONY BRYCESON, M.D., AND JONATHAN BERMAN, M.D., PH.D.

Methods The study was a randomized, open-label comparison, in which 299 patients 12 years of age or older received orally administered miltefosine (50 or 100 mg [approximately 2.5 mg per kilogram of body weight] daily for 28 days) and 99 patients received intravenously administered amphotericin B (1 mg per kilogram every other day for a total of 15 injections).

NOVEMBER 28, 2002



Conclusions Oral miltefosine is an effective and safe treatment for Indian visceral leishmaniasis. Miltefosine may be particularly advantageous because it can be administered orally. It may also be helpful in regions where parasites are resistant to current agents.

J Antimicrob Chemother 2012; **67**: 2576–2597
doi:10.1093/jac/dks275 Advance Access publication 24 July 2012

**Antimicrobial
Chemotherapy**

Miltefosine: a review of its pharmacology and therapeutic efficacy in the treatment of leishmaniasis

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Natural Resistance of *Leishmania infantum* to Miltefosine Contributes to the Low Efficacy in the Treatment of Visceral Leishmaniasis in Brazil

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Abstract. In India, visceral leishmaniasis (VL) caused by *Leishmania donovani* has been successfully treated with miltefosine with a cure rate of > 90%. To assess the efficacy and safety of oral miltefosine against Brazilian VL, which is caused by *Leishmania infantum*, a phase II, open-label, dose-escalation study of oral miltefosine was conducted in children (aged 2–12 years) and adolescent-adults (aged 13–60 years). Definitive cure was assessed at a 6-month follow-up visit. The cure rate was only 42% (6 of 14 patients) with a recommended treatment of 28 days and 68% (19 of 28 patients) with an extended treatment of 42 days. The in vitro miltefosine susceptibility profile of intracellular amastigote stages of the pretreatment isolates, from cured and relapsed patients, showed a positive correlation with the clinical outcome. The IC₅₀ mean (SEM) of eventual cures was 5.1 (0.4) μ M, whereas that of eventual failures was 12.8 (1.9) μ M ($P = 0.0002$). An IC₅₀ above 8.0 μ M predicts failure with 82% sensitivity and 100% specificity. The finding of *L. infantum* amastigotes resistant to miltefosine in isolates from patients who eventually failed treatment strongly suggests natural resistance to this drug, as miltefosine had never been used in Brazil before this trial was carried out.

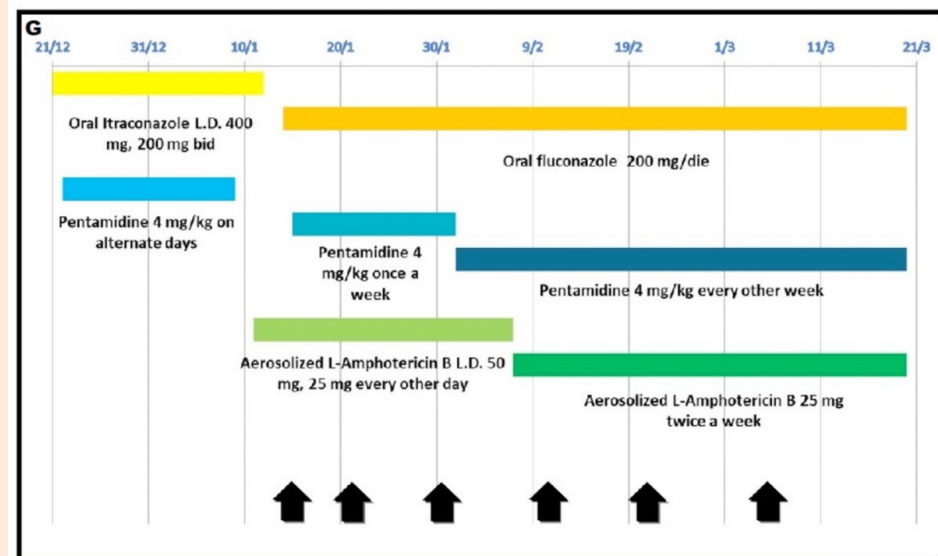
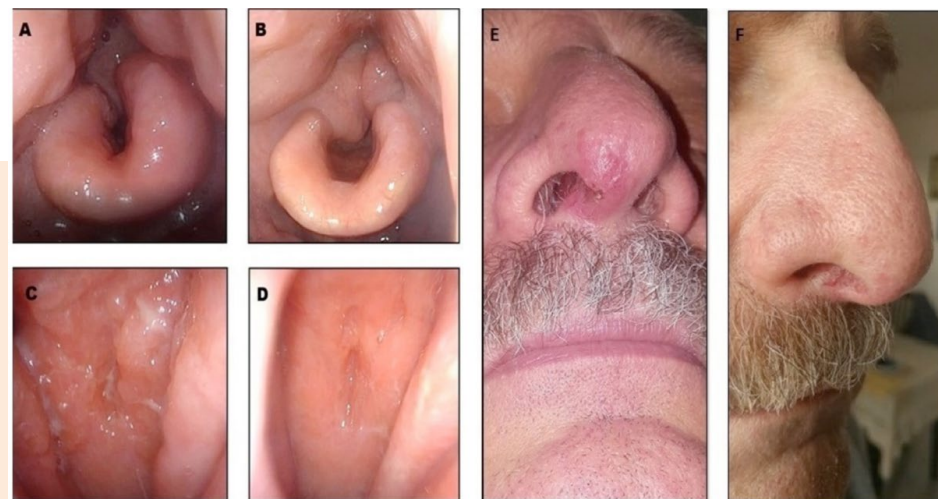


Case Report

Refractory mucocutaneous leishmaniasis resolved with combination treatment based on intravenous pentamidine, oral azole, aerosolized liposomal amphotericin B, and intralesional meglumine antimoniate

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A 65-year-old Italian male patient with chronic kidney disease, arterial hypertension, prostatic hypertrophy, and type-2 diabetes mellitus was referred for severe relapsing MCL acquired in Argentina. ENT examination showed severe diffuse pharyngolaryngeal edema and erythema, partially obstructing the airways. Despite receiving four courses of liposomal amphotericin B (L-AmB) and two courses of miltefosine over a 2-year period, the patient presented recurrence of symptoms a few months after the end of each course. After the patient was referred to us, a combined treatment was started with intravenous pentamidine 4 mg/kg on alternate days for 10 doses, followed by one dose per week for an additional seven doses, intralesional meglumine antimoniate on the nasal lesion once per week for six doses, oral azoles for three months, and aerosolized L-AmB on alternate days for three months. The treatment led to regression of mucosal lesions and respiratory symptoms. Renal function temporarily worsened, and the addition of insulin was required to maintain glycemic compensation after pentamidine discontinuation.



Prot. 35574 del 14/10/2020

0033122-14/10/2020-DGPRES-DGPRES-P



Ministero della Salute

DIREZIONE GENERALE DELLA PREVENZIONE SANITARIA
Ufficio V – Prevenzione delle malattie trasmissibili e profilassi internazionale

DIREZIONE GENERALE DELLA SANITÀ ANIMALE E DEI FARMACI VETERINARI
Ufficio III – Sanità animale e gest. oper. Centro Naz. di lotta ed emergenza contro le malattie animali e unità centrale di crisi

Allegato 5-A

SCHEDA DI NOTIFICA – LEISHMANIOSI VISCERALE

Regione _____ Provincia _____ ASL _____
Comune _____ Distretto _____

Data di compilazione: gg [] mm [] aa [] Data di segnalazione: gg [] mm [] aa []

Dati anagrafici del paziente

Cognome _____ Nome: _____

Sesso: M ☐ F ☐ Data di nascita gg [] mm [] aa []

Luogo di nascita _____
Comune _____ Provincia _____ Stato _____

Codice Fiscale _____

Residenza: _____
Via/piazza e numero civico _____ Comune _____ Provincia _____

Domicilio abituale: _____
Via/piazza e numero civico _____ Comune _____ Provincia _____

ASL di appartenenza _____

Nazionalità _____ Cittadinanza _____

Professione _____ Recapito telefonico _____

Viaggi o soggiorni in regioni diverse dalla residenza/domicilio abituale del paziente o al di fuori dell'Italia

1. _____
2. _____
3. _____
4. _____

Paese visitato _____ data partenza dall'Italia _____ data rientro/arrivo in Italia _____

Motivo del viaggio _____

Informazioni cliniche

Data inizio sintomi gg [] mm [] aa [] Data diagnosi gg [] mm [] aa []

Data ricovero gg [] mm [] aa [] Data dimissione gg [] mm [] aa []

Struttura di Ricovero _____ Reparto _____

Segni e sintomi

Dimagrimento ☐ Linfadenopatia ☐
Epitropione megalia ☐ Anemia ☐
Febbre ☐ Trombocitopenia ☐
Debolezza ☐ Leucopenia ☐
Altro _____
specificare _____

Test di laboratorio

Ricerca anticorpi specifici nel siero

Data prelievo [] [] [] [] [] [] Tipo metodica usata: _____

Titolo _____ Risultato POS ☐ NEG ☐ Dubbio ☐

PCR qualitativa e/o PCR quantitativa

Data prelievo [] [] [] [] [] []

Tessuto aspirato o biopsia di: _____
milza ☐ linfonodo ☐ midollo osseo ☐ fegato ☐
sangue periferico ☐ altro (specificare) _____

Risultato POS ☐ NEG ☐

Esame microscopico

Data prelievo [] [] [] [] [] []

Tessuto aspirato o biopsia di: _____
milza ☐ linfonodo ☐ midollo osseo ☐ fegato ☐
altro (specificare) _____

Colorazione utilizzata: Giemsa ☐ Wright-Giemsa ☐ Altro (specificare) _____

Risultato POS ☐ NEG ☐ Dubbio ☐

Densità

6+ (oltre 100 parassiti per campo) ☐
5+ (10-100 parassiti per campo) ☐
4+ (1-10 parassiti per campo) ☐
3+ (1-10 parassiti per 10 campi) ☐
2+ (1-10 parassiti per 100 campi) ☐
1+ (1-10 parassiti per 1000 campi) ☐
0 (nessun parassita in 1000 campi) ☐

Cultura parassitaria

Data prelievo [] [] [] [] [] []

Tessuto aspirato o biopsia di: _____
milza ☐ linfonodo ☐ midollo osseo ☐ fegato ☐
sangue periferico ☐ altro (specificare) _____

Risultato POS ☐ NEG ☐

Classificazione di caso: ☐ PROBABILE ☐ CONFERMATO ☐
☐ PRIMA INFEZIONE ☐ RECIDIVA/RICADUTA ☐

Tipo caso: _____ IMPORTATO ☐ AUTOCTONO ☐

In caso d'importazione: Paese e località di presunto contagio _____

Note (scrivere in stampatello): _____

Operatore sanitario che ha compilato la scheda: _____ Nome e cognome _____
Ruolo _____ Recapito telefonico _____ email _____

(timbro e firma) _____

ISTRUZIONI E NOTE PER LA COMPILAZIONE

La scheda va compilata per tutti i casi probabili e confermati di Leishmaniosi viscerale
Inviare a: - Ministero della Salute: via mail a malinf@sanita.it;

SCHEDA DI NOTIFICA – LEISHMANIOSI CUTANEA

Allegato 5-B

Regione _____ Provincia _____ ASL _____
Comune _____ Distretto _____

Data di compilazione: gg [] mm [] aa [] Data di segnalazione: gg [] mm [] aa []

Dati anagrafici del paziente

Cognome _____ Nome: _____

Sesso: M ☐ F ☐ Data di nascita gg [] mm [] aa []

Luogo di nascita _____
Comune _____ Provincia _____ Stato _____

Codice Fiscale _____

Residenza: _____
Via/piazza e numero civico _____ Comune _____ Provincia _____

Domicilio abituale: _____
Via/piazza e numero civico _____ Comune _____ Provincia _____

ASL di appartenenza _____

Nazionalità _____ Cittadinanza _____

Professione _____ Recapito telefonico _____

Viaggi o soggiorni in regioni diverse dalla residenza/domicilio abituale del paziente o al di fuori dell'Italia

1. _____
2. _____
3. _____
4. _____

Paese visitato _____ data partenza dall'Italia _____ data rientro/arrivo in Italia _____

Motivo del viaggio _____

Informazioni cliniche

Data inizio sintomi gg [] mm [] aa [] Data diagnosi gg [] mm [] aa []

Ricovero SI ☐ NO ☐
se sì, Data ricovero gg [] mm [] aa [] Data dimissione gg [] mm [] aa []

motivo del ricovero _____

Struttura di Ricovero _____ Reparto _____

Segni e sintomi

Lesioni cutanee ☐ Lesioni alle mucose ☐

Test di laboratorio

PCR qualitativa e/o PCR quantitativa

Data prelievo [] [] [] [] [] []

biopsia cutanea ☐ biopsia mucosa ☐

Risultato POS ☐ NEG ☐

Esame microscopico

Data prelievo [] [] [] [] [] []

biopsia cutanea ☐ biopsia mucosa ☐

Colorazione utilizzata: Giemsa ☐ Wright-Giemsa ☐ Altro (specificare) _____

Risultato POS ☐ NEG ☐ Dubbio ☐

Cultura parassitaria

Data prelievo [] [] [] [] [] []

biopsia cutanea ☐ biopsia mucosa ☐

Risultato POS ☐ NEG ☐

Classificazione di caso: ☐ PROBABILE ☐ CONFERMATO ☐

Tipo caso: _____ IMPORTATO ☐ AUTOCTONO ☐

In caso d'importazione: Paese e località di presunto contagio _____

Note (scrivere in stampatello): _____

Operatore sanitario che ha compilato la scheda: _____ Nome e cognome _____
Ruolo _____ Recapito telefonico _____ email _____

(timbro e firma) _____

ISTRUZIONI E NOTE PER LA COMPILAZIONE

La scheda va compilata per tutti i casi probabili e confermati di Leishmaniosi cutanea
Inviare a: - Ministero della Salute: via mail a malinf@sanita.it;

Thank you



Giovanni Di Cristina
Palermo, 12 settembre 1875 –
Palermo, 27 febbraio 1928

