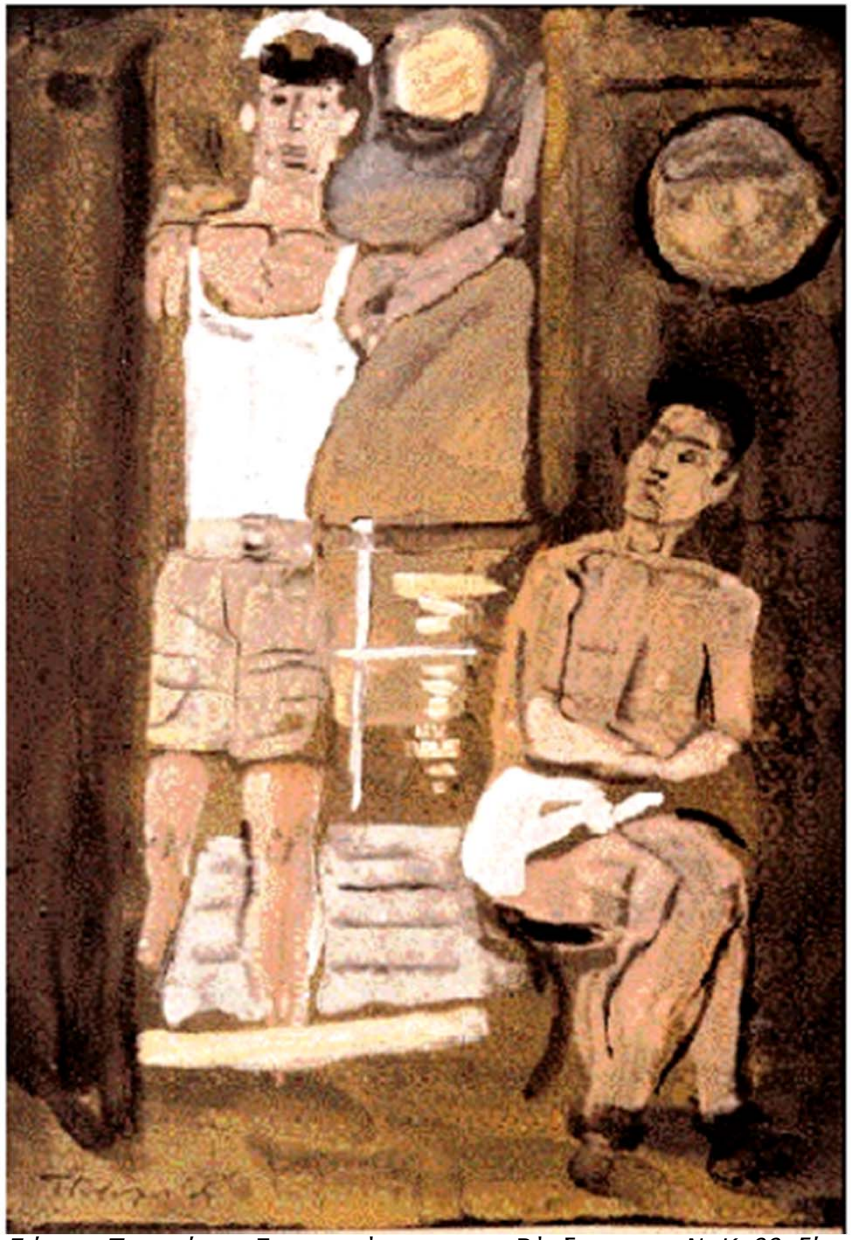


Γιάννης Τσαρούχης, Εικονογράφηση της «Βάρδιας» του *Ν. Καββαδία*

Λεϊσμανίαση

ΘΕΡΑΠΕΥΤΗΡΙΟΝ Ο ΕΥΑΓΓΕΛΙΣΜΟΣ
ΑΘΗΝΑΙ

Τότσικας Χαρίσης

...Κούλικο στο στήθος σου τατού
που όσο κι αν το καις δε λέει να σβήσει
είπαν πως την είχες αγαπήσει
σε μια κρίση μαύρου πυρετού...

Ανακάλυψη

Ο **Sir William Boog Leishman** (1865-1926), ανακάλυψε το πρωτόζωο, στο σπλήνα ασθενούς που κατέληξε από kala-azar, στο Λονδίνο το 1903

Ο Charles Donovan (1863-1951) περιέγραψε στο αίμα ασθενούς, το πρωτόζωο *Leishmania donovani χαρακτηρίζοντάς το* ως αίτιο της νόσου kala-azar

έκφυμα της Ανατολής, Νόσος της Χαλέπας, έλκος της Βαγδάτης, ρόδο της Ιεριχούς, γιούτα, εσπούντια, καλα-αζάρ, πυρετός dumdum, μαύρος πυρετός, χανιώτικο, μούρο, λουμπίνι

Επίπτωση νόσου

Disease	Annual Incidence	Mortality (no of deaths / year)	Prevalence (total number of infected people)
HIV / AIDS	5.6 million	2.6 million	34 million
Malaria	300 million	1-2.7 million	NA
Tuberculosis	7.8 million	1.8 million	1.7 billion
Visceral Leishmaniasis	500,000	80,000	12 million
Cutaneous Leishmaniasis	1.5-2 million	NA	NA

World Health Organization/Tropical Disease Research

Γεωγραφική κατανομή

Subgenus	Complex	Species	Main geographic locations	Main clinical manifestation	Other
Old World					
Leishmania	*L. donovani*	*L. donovani*	India, sub-Saharan Africa, China, Pakistan	Visceral leishmaniasis	Post kala-azar dermal leismaniasis
		*L. infantum**	Mediterranean, Middle East, north and sub-Saharan Africa, Balkans, China	Visceral leishmaniasis	
	L. major	*L. major*	Middle East, Africa, India, China	Cutaneous leishmaniasis ("wet ulcer")	
	L. tropica	*L. tropica*	Middle East, India, southern Europe, western Asia	Cutaneous leishmaniasis ("dry ulcer")	Leishmaniasis recidivans and viscerotropic leishmaniasis
	L. aethiopica	*L. aethiopica*	Ethiopia, Kenya, Yemen	Cutaneous leishmaniasis	DCL
New World					
Leishmania	*L. donovani*	*L. chagasi**	Latin America	Visceral leishmaniasis	
	L. mexicana	*L. venezuelensis*	Venezuela	Cutaneous leishmaniasis	
		L. mexicana	Mexico, Central America, Texas, Oklahoma	Cutaneous leishmaniasis	DCL
		L. amazonensis	Amazon basin, Brazil	Cutaneous leishmaniasis	DCL; has also been associated with viceral leishmaniasis
Viannia	*L. braziliensis*	*L. braziliensis*	Latin America	Cutaneous and mucocutaneous leishmaniasis	
		L. peruviana	Peru and Argentina (highlands)	Cutaneous leishmaniasis	
	L. guyanensis	*L. guyanensis*	Northern Amazon basin, Guyanas	Cutaneous leishmaniasis	
		L. panamensis	Panama, Costa Rica, Columbia	Cutaneous leishmaniasis	

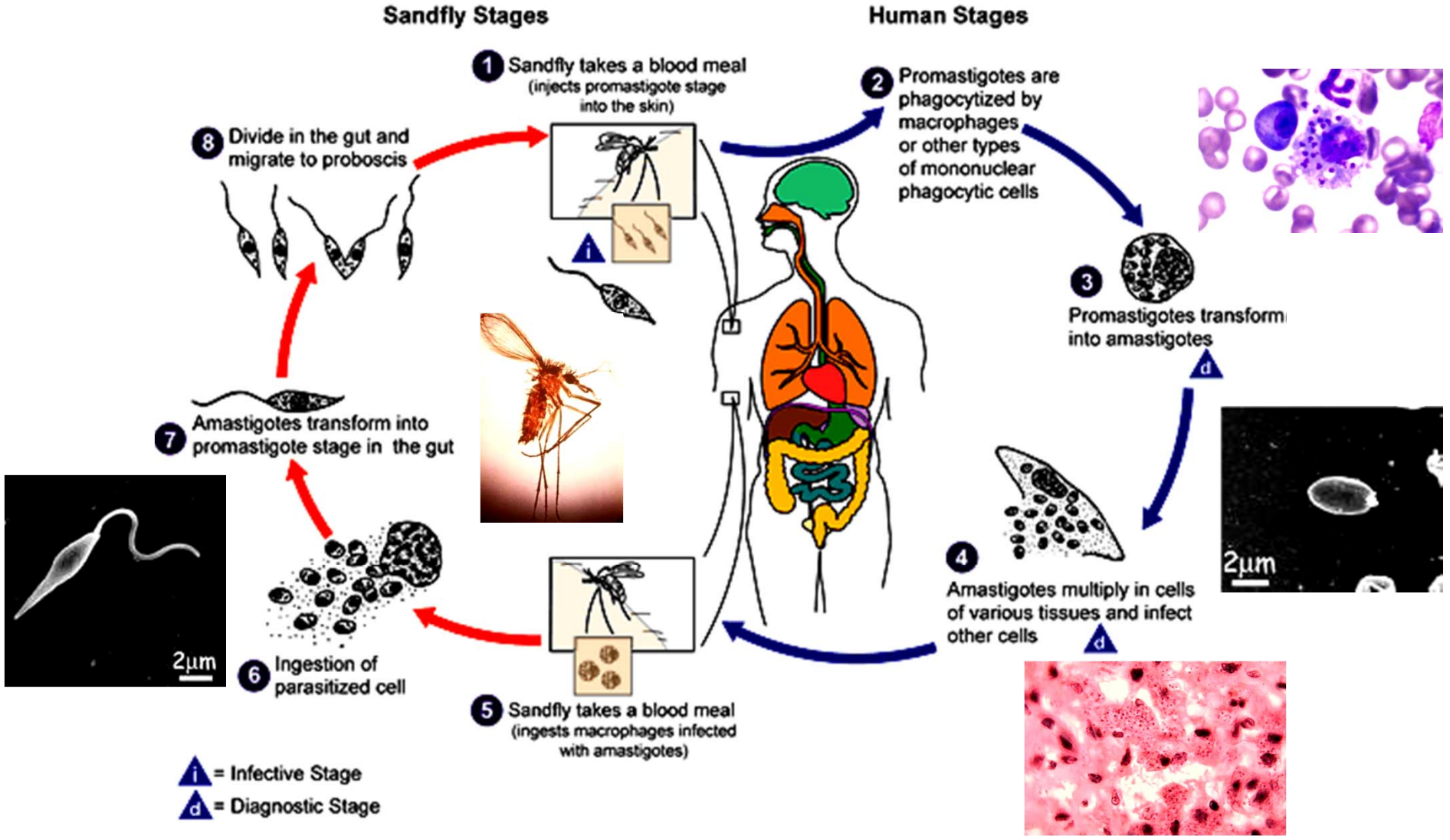
Diffuse cutaneous leishmaniasis: DCL.
Organisms belonging to the subgenus *Leishmania* develop in the sandfly midgut, whereas organisms belonging to the subspecies *Viannia* develop in the hindgut.
* *L. infantum* and *L. chagasi* are now thought to be the same organism.

Μετάδοση

- Φλεβοτόμος (*Phlebotomus* για τον Παλαιό κόσμο/L*utzomyla* για το νέο Κόσμο) από σκυλιά και τρωκτικά
- Κοινή χρήση βελόνας (IvDU)
- Μεταμόσχευση οργάνου
- Μετάγγιση αίματος
- Σεξουαλική επαφή
- Κάθετη μετάδοση

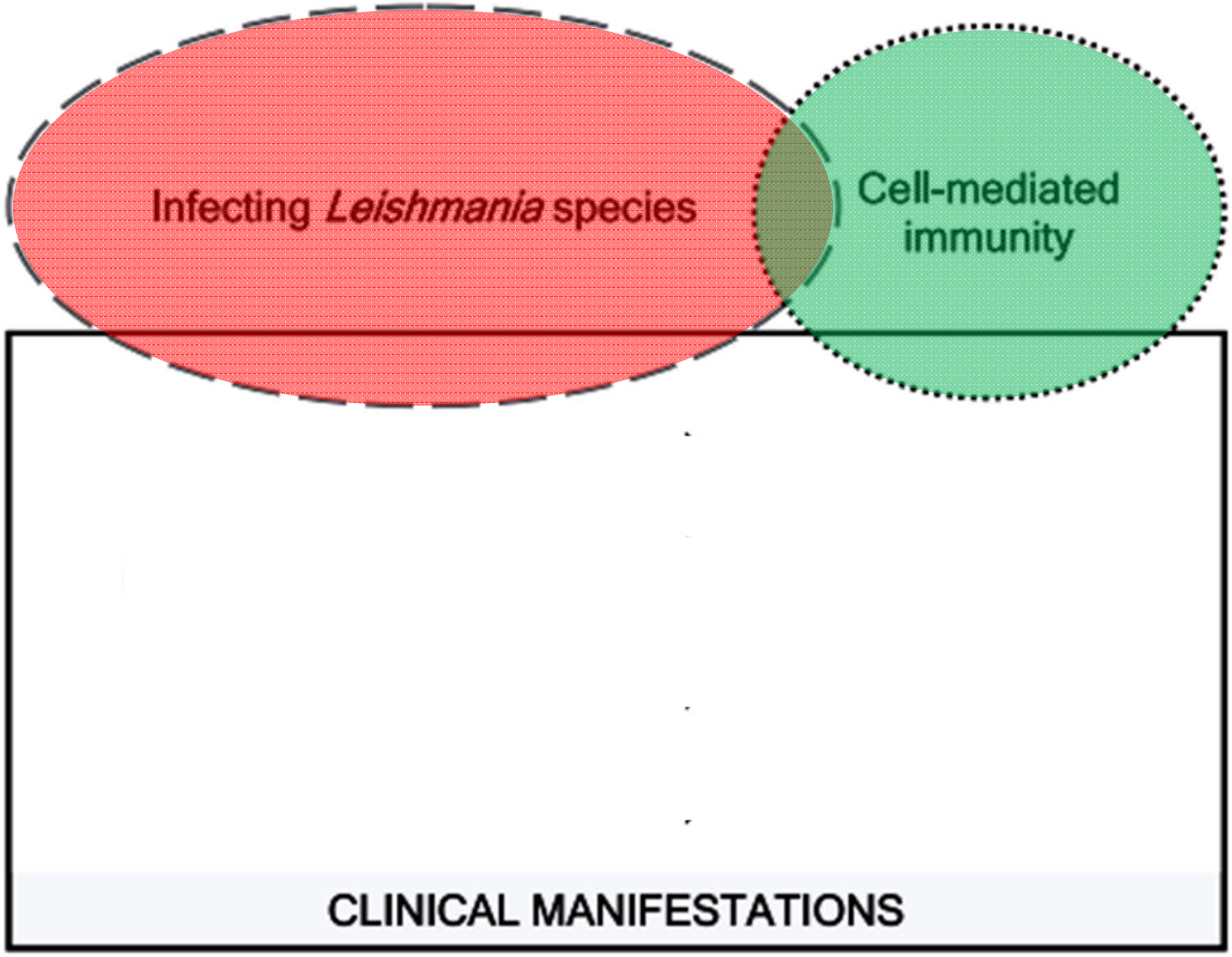
Killick-Kendrjck R.; Ann Parasitol Hum Comp 1990, 65(Suppl 1):37– 42

Κύκλος ζωής



https://www.cdc.gov/parasites/leishmaniasis/biology.html

Μορφές Λεϊσμανίασης



(Degree of effectiveness of cell-mediated immunity represented in black within arrows)

Pace D; Leishmaniasis. J Infect. 2014 Nov;69 Suppl 1:S10-8

Χαρακτηριστικά Λεϊσμανίασης

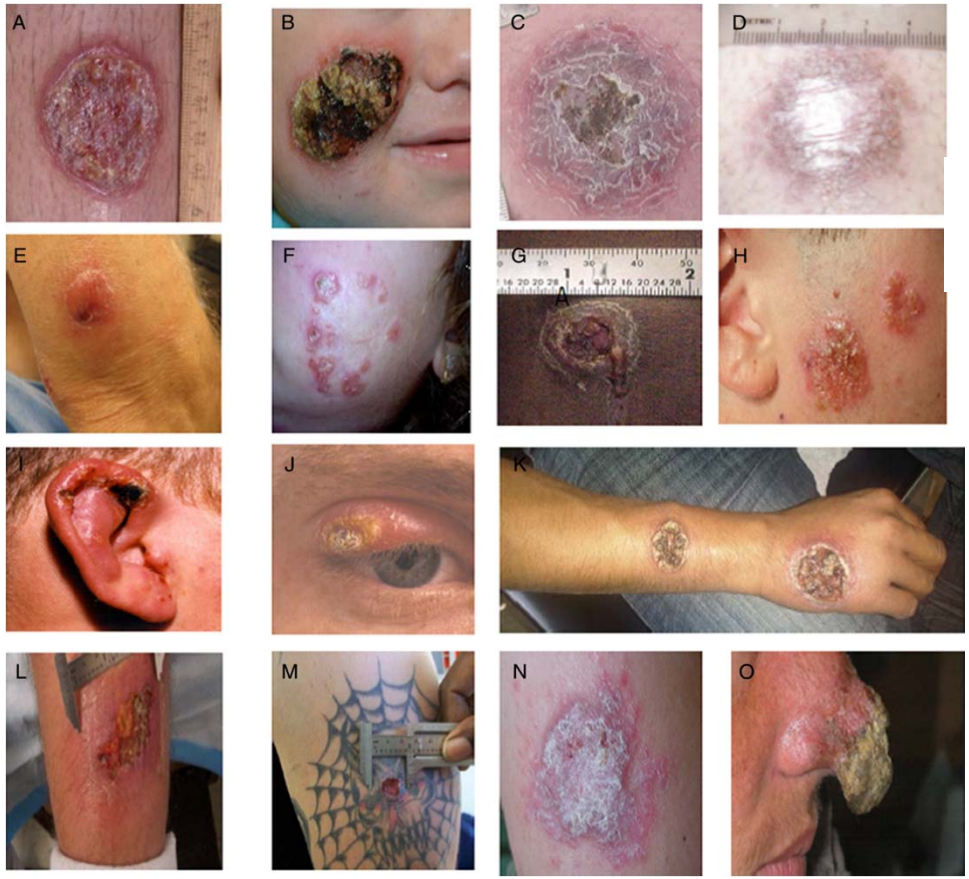
Σε όλες τις μορφές της νόσου τα προτόζωα μοιράζονται κοινούς παθογενετικούς μηχανισμούς:

1.Τα ιστικά μακροφάγα του ξενιστή αποτελούν τον πρωτεύοντα στόχο, ευοδώνοντας τον ενδοκυττάριο πολλαπλασιασμό των παρασίτων.

2.Η ανοσολογική απάντηση του ξενιστή καθορίζει την έκφανση και την έκβαση της νόσου.

3.Η επίμονη ιστική επιμόλυνση είναι χαρακτηριστική

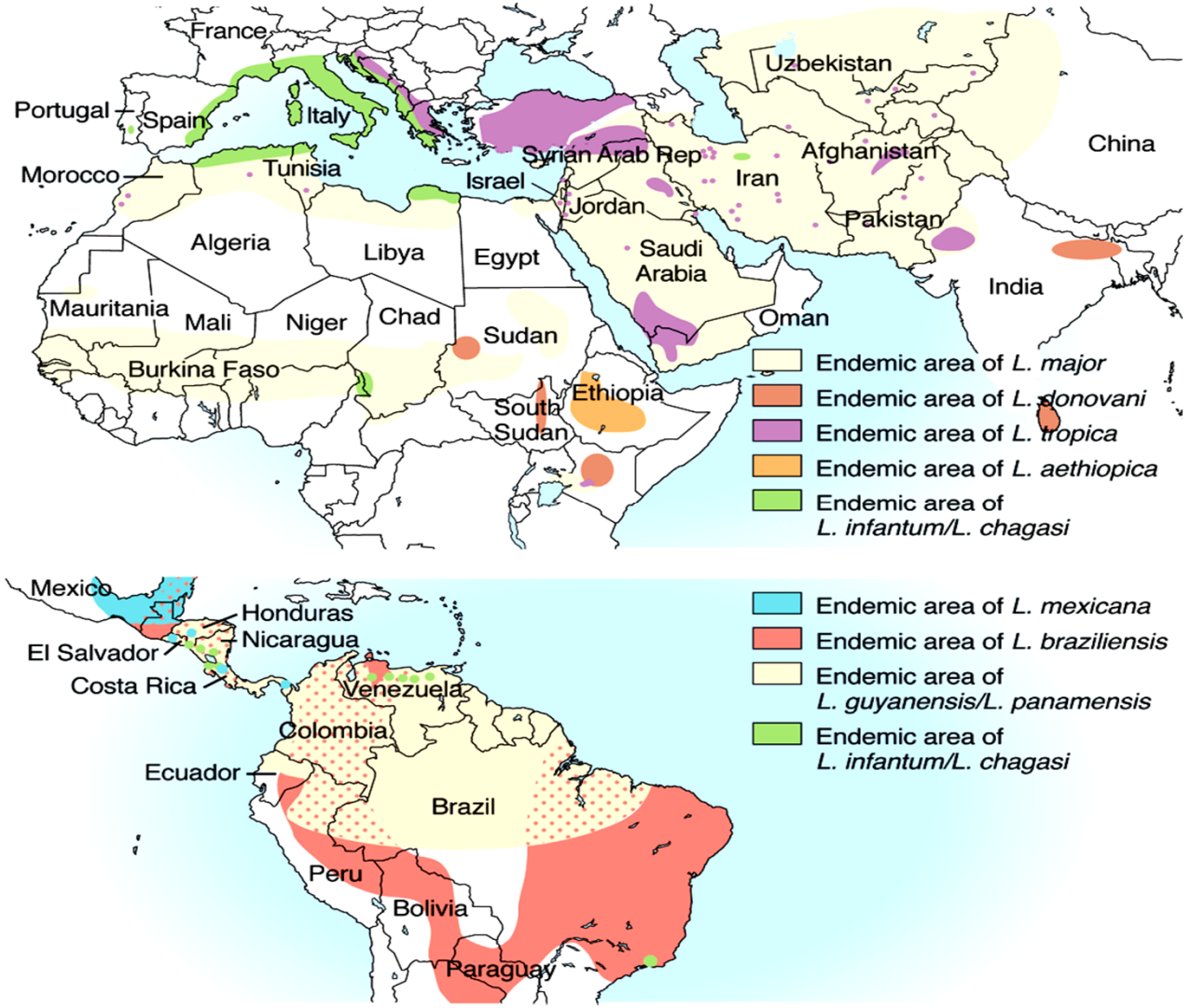
Murray H: et al; Lancet 2005; 366: 1561–77



Δερματική (CL)-Βλεννογονοδερματική Λεϊσμανίαση

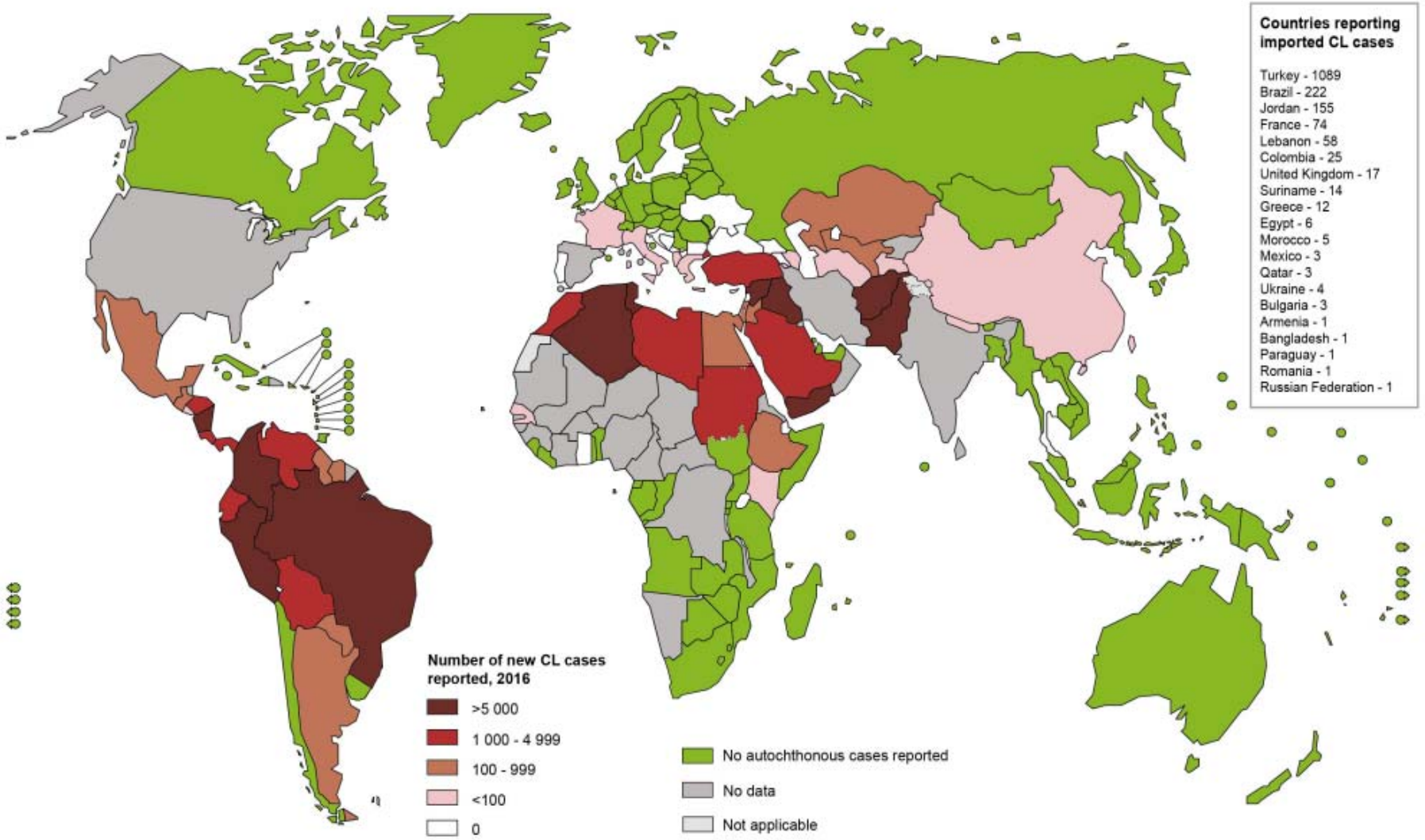
Clinical Infectious Diseases, Volume 63, Issue 12, 15 December 2016, Pages 1539–1557

Γεωγραφική κατανομή CL



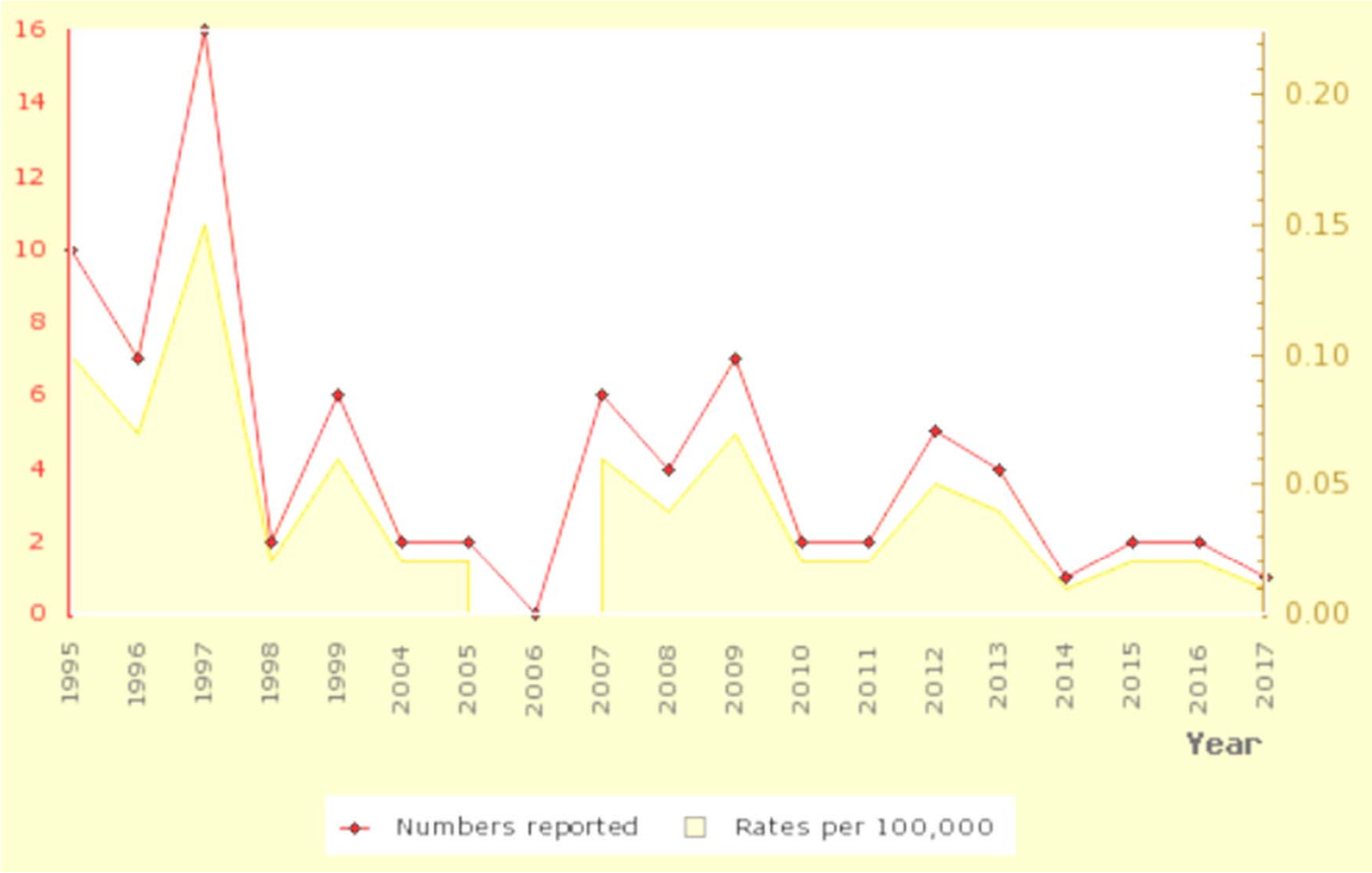
Clinical Infectious Diseases, Volume 63, Pages 1539–1557

Επίπτωση CL, 2016



World Health Organization

Επίπτωση CL στην Ελλάδα



https://web.gideononline.com/web/ebooks/pdf.php?product_code=dcoG170&category=country&file=Infectious-Diseases-of-Greece-by-GIDEON.pdf

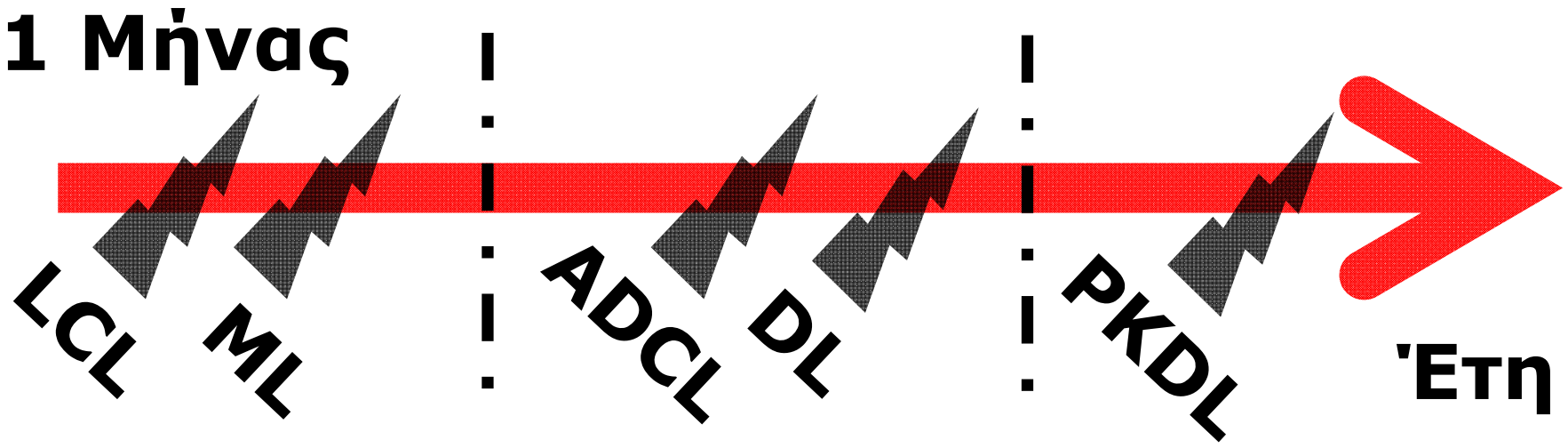
Μορφές CL

Clinical Syndrome	Causative Species [1]	Clinical Manifestation
Localized Cutaneous Leishmaniasis (LCL)	*L. (L.) major* *L. (L.) mexicana* *L. (L.) amazonensis* *L. (V.) braziliensis* *L. (L.) tropica* *L. (L.) aethiopica* *L. (V.) panamanensis* *L. (L.) infantum* *L. (L.) donovani*	Single or limited number of lesions; ulcers formed can be wet or dry with raised crateriform border. Moderate parasite loads in biopsies of the ulcer border; positive DTH [2] response
Mucosal Leishmaniasis	*L. (V.) braziliensis* *L. (V.) panamanensis* *L. (V.) guyanensis* *L. (L.) amazonensis*	Highly inflammatory lesions involving mucosal membranes; can be disfiguring. Rare parasite forms present in biopsies; strong DTH response
Anergic Diffuse Cutaneous Leishmaniasis (ADCL)	*L. (L.) amazonensis* *L. (L.) mexicana* *L. (V.) pifanoi* *L. (L.) aethiopica* *L. (L.) major*	Multiple, disseminated, non-ulcerative nodular lesions; many parasites in lesions; absent DTH response (anergy)
Disseminated Leishmaniasis (DL)	*L. (V.) braziliensis* *L. (V.) panamanensis* *L. (V.) guyanensis* *L. (L.) amazonensis*	Numerous papular/acneiform lesions in ≥2 non-contiguous areas of the body, commonly involving mucosal membranes. Few parasites in lesions; strong DTH response
Post-Kala Azar Dermal Leishmaniasis (PKDL)	*L. (L.) donovani*	Hypopigmented macular, maculopapular, or nodular rash. Interferon γ (IFNγ) response to *Leishmania* antigens. Parasites are present in lesions

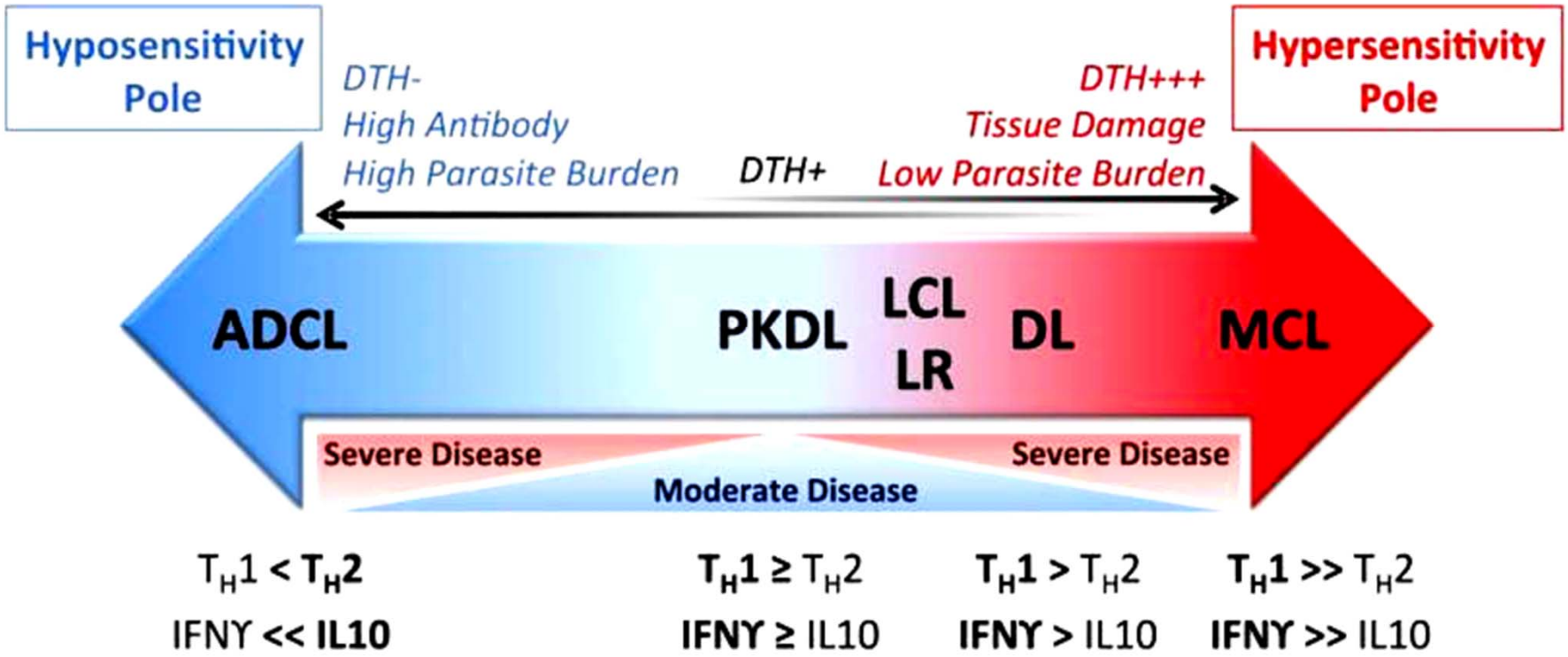
[1] (*L.*) denotes *Leishmania* subgenus. (*V.*) denotes *Viannia* subgenus. [2] DTH refers to a delayed type hypersensitivity response to *Leishmania* antigen, a test that is also called the *Leishmania* skin test (LST) or Montenegro test.

Scorza BM et al; Int J Mol Sci. 2017 Jun 18;18(6)

Χρόνος επώασης CL



Βαρύτητα CL- MCL



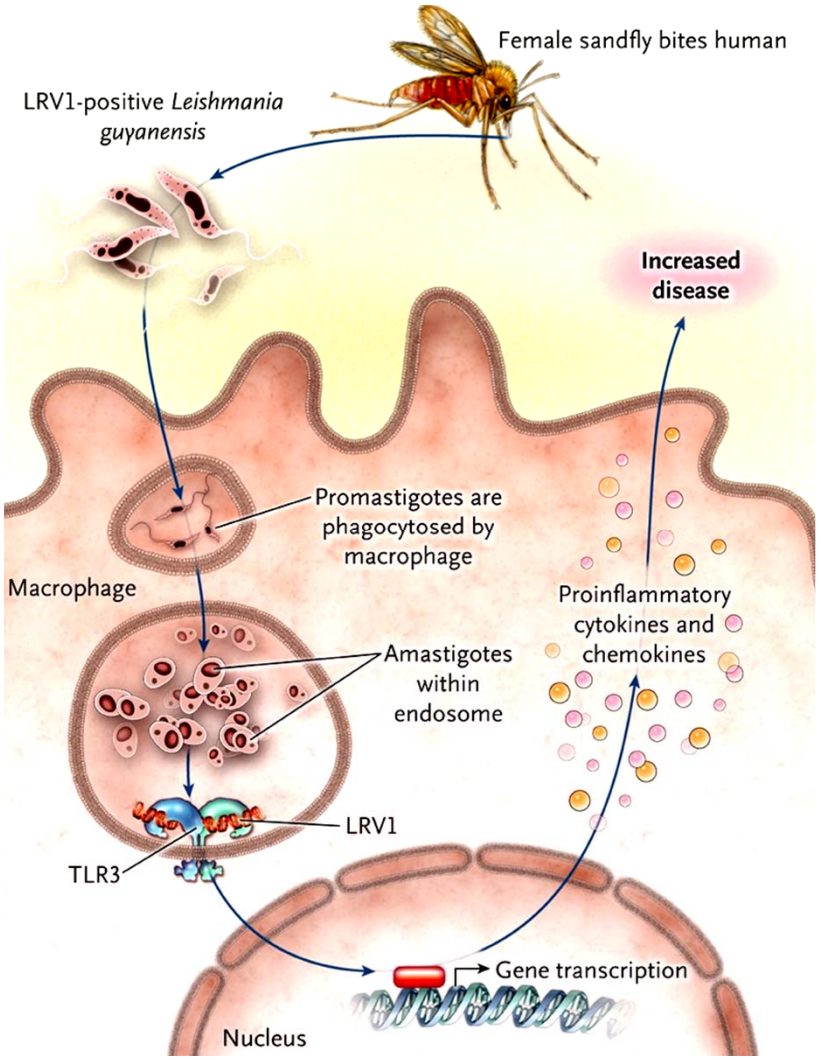
ADCL: Anergic diffuse cutaneous leishmaniasis;
PKDL: Post Kala-Azar dermal leishmaniasis;
LCL: Localized cutaneous leishmaniasis;

LR: *Leishmania* recidivans;
DL: Disseminated leishmaniasis;
MCL: Mucocutaneous leishmaniasis

Scorza BM et al; Int J Mol Sci. 2017 Jun 18;18(6)

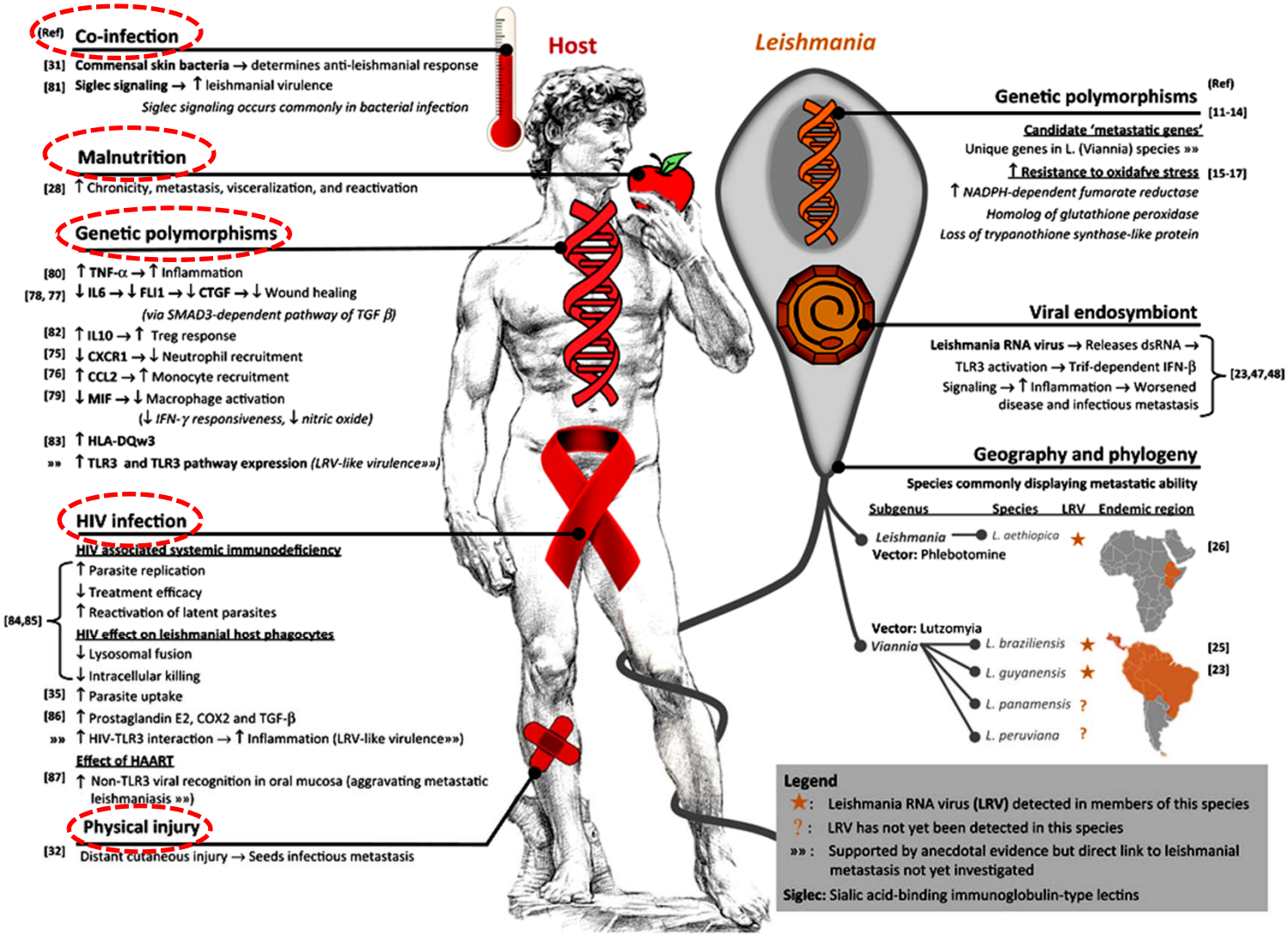
Βαρύτητα CL- MCL

Old world species	Clinical features
L. infantum	Single nodules May ulcerate May resolve spontaneously within 1 year but leave atrophic scars
L. tropica	Multiple painless dry ulcers Heal spontaneously over 1 year but tend to leave disfiguring scars
L. major	Severely inflamed multiple ulcers, may coalesce Heal slowly, leave disfiguring and disabling scars
L. aethopica	Localised nodules; oronasal lesions causing localised anatomical distortion Heal over 2–5 years Causes disseminated cutaneous leishmaniasis more frequently on limbs and face. No ulceration unless immunosuppressed



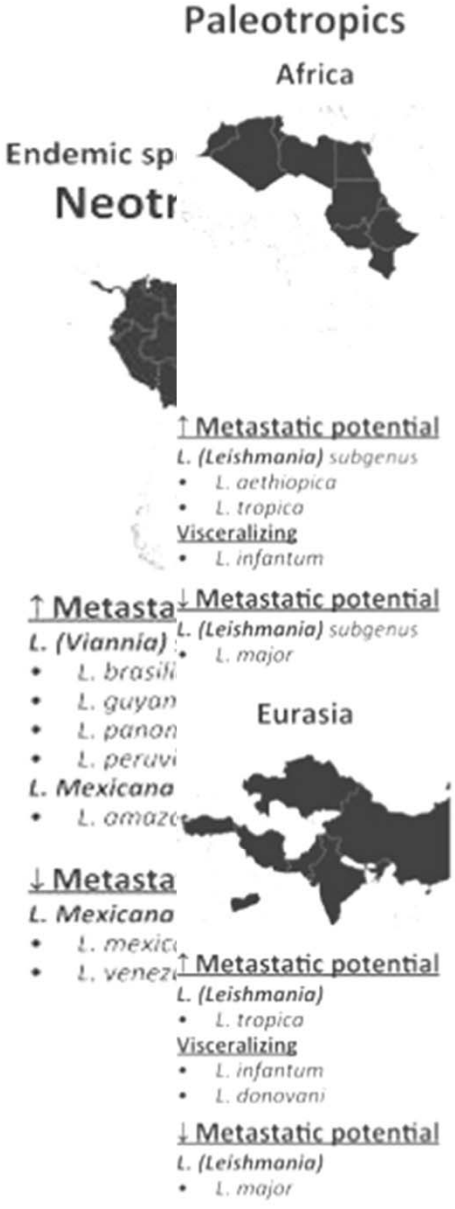
Clinical Infectious Diseases, Volume 63, Issue 12, 15 December 2016, Pages 1539–1557;
Scott P; Leishmania-a parasitized parasite; N Engl J Med. 2011 May 5;364(18):1773-4

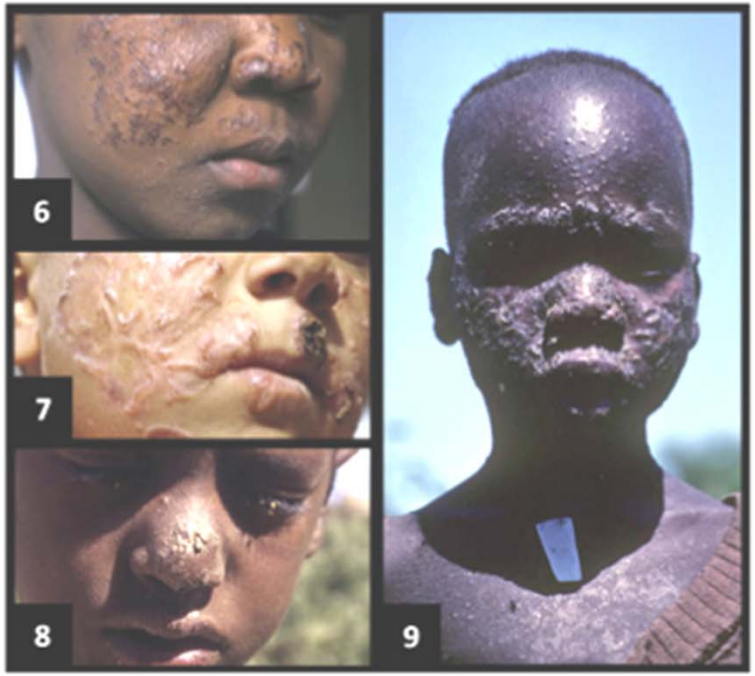
Δερματική (CL)-
Βλεννογονοδερματική Λεϊσμανίαση

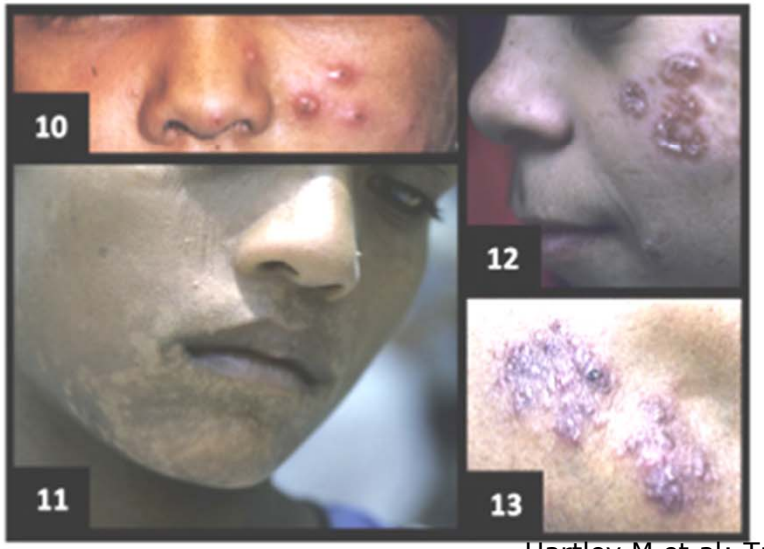


Hartley M et al; Trends Parasitol. 2014 Aug; 30(8): 412–422

Ανοσολογικοί, περιβαλλοντικοί και φυλογενετικοί παράγοντες







6: **DCL** marked by non-ulcerating hyperpigmeted 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

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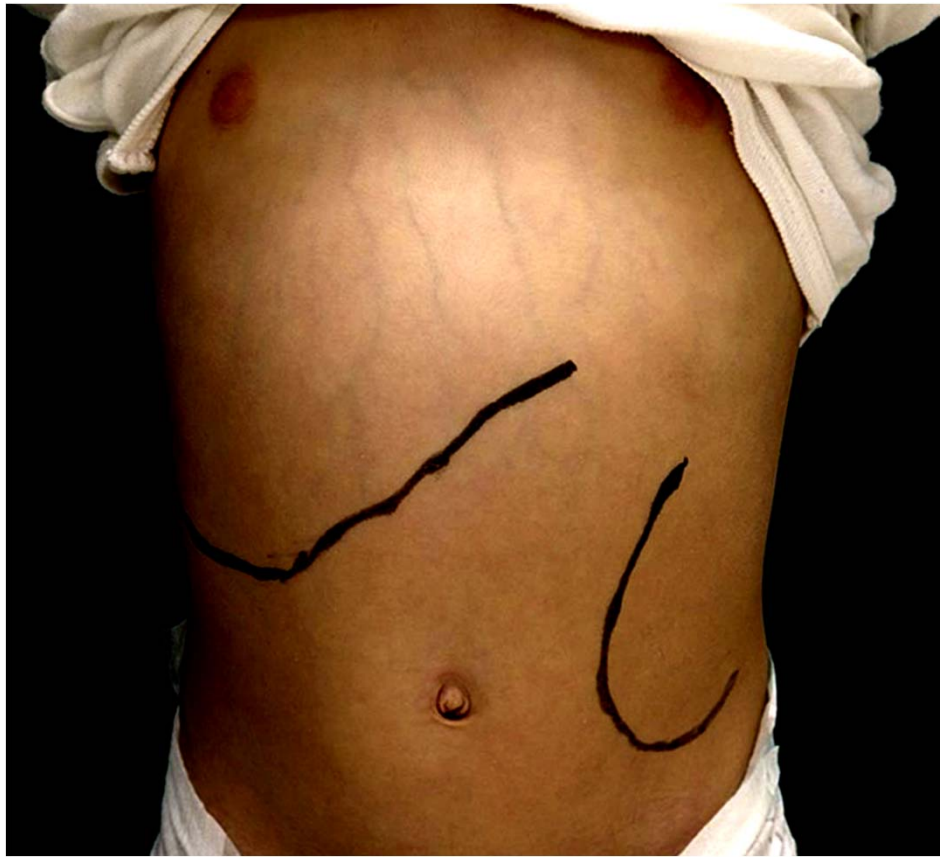
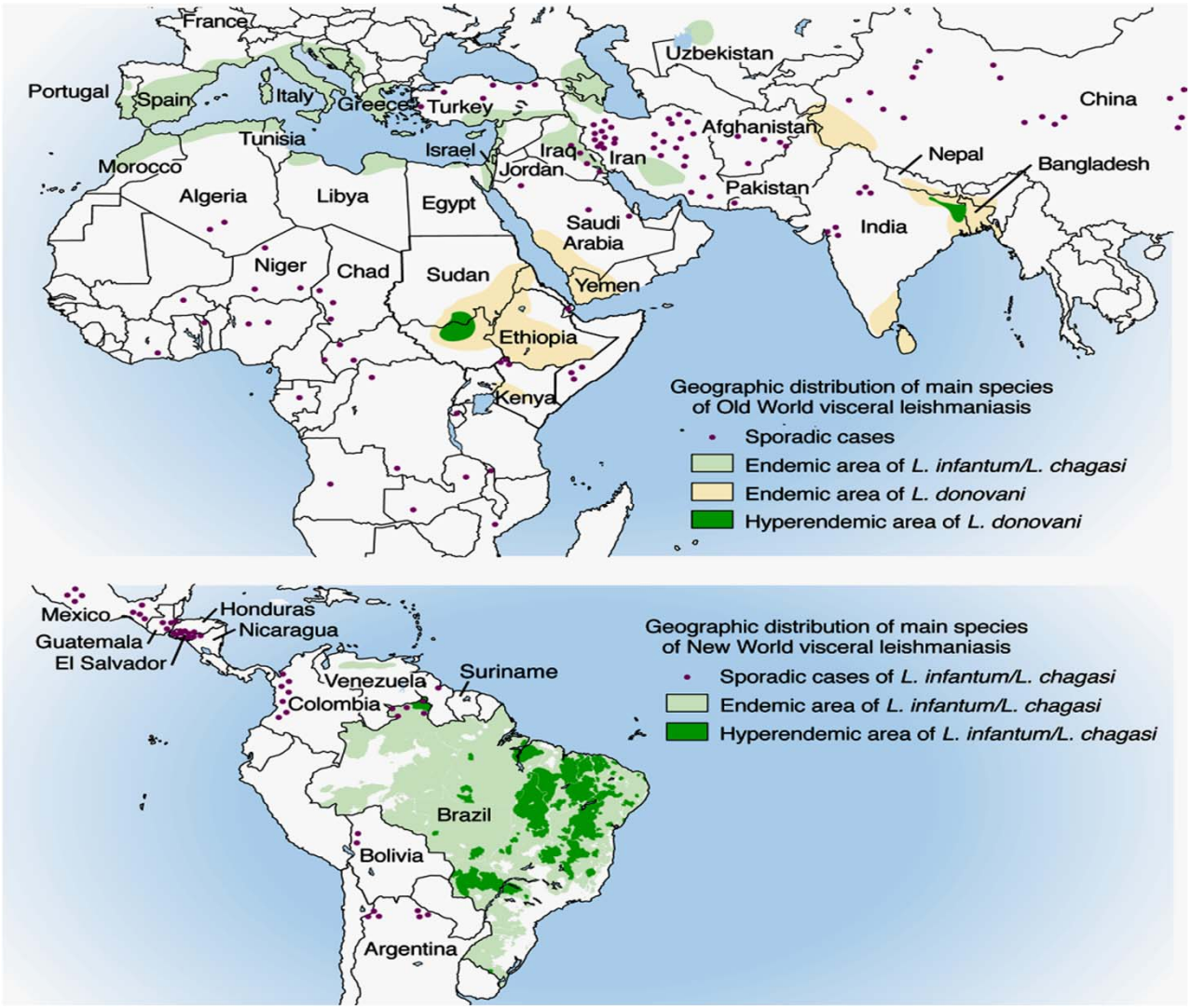
Hartley M et al; Trends Parasitol. 2014 Aug; 30(8): 412–422



Σπλαχνική Λεϊσμανίαση

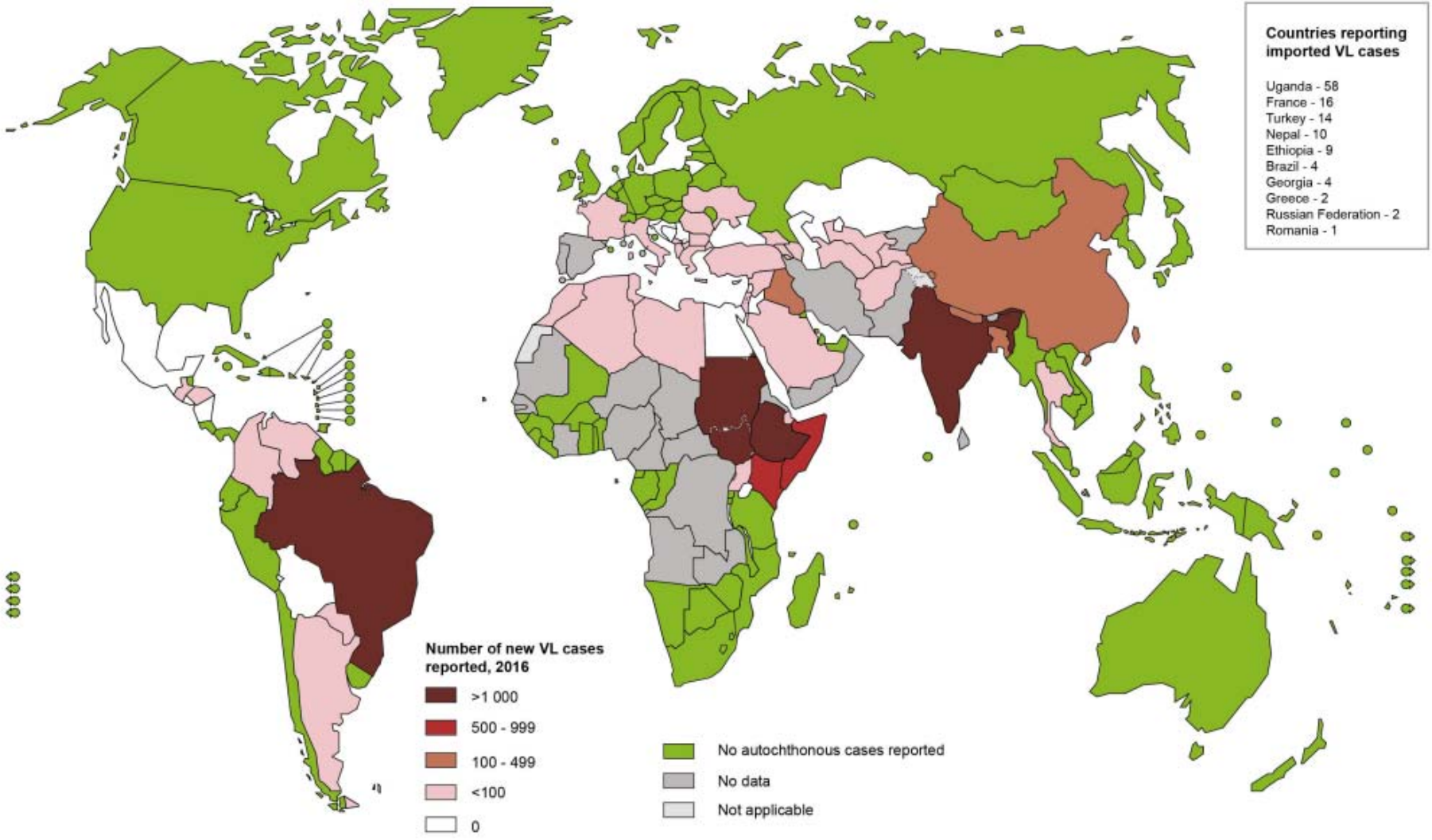
Pace D; Leishmaniasis. J Infect. 2014 Nov;69 Suppl 1:S10-8

Γεωγραφική κατανομή VL



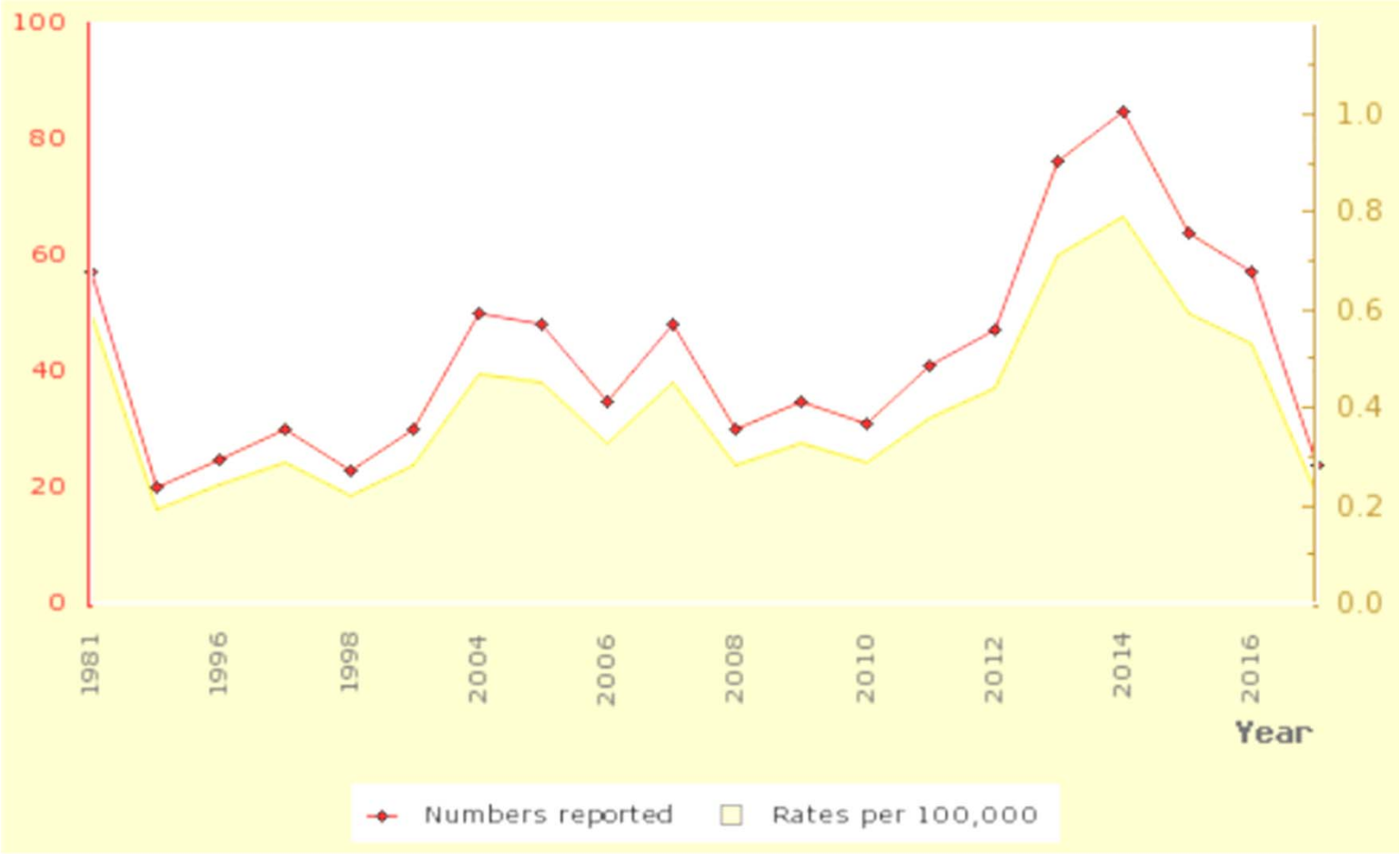
Clinical Infectious Diseases, Volume 63, Issue 12, 15 December 2016, Pages 1539–1557

Επίπτωση VL, 2016



World Health Organization

Επίπτωση VL στην Ελλάδα



https://web.gideononline.com/web/ebooks/pdf.php?product_code=dcoG170&category=country&file=Infectious-Diseases-of-Greece-by-GIDEON.pdf

Χρόνος επώασης VL

2 Εβδομάδες

...έτη

6 μήνες

Murray H: et al; Lancet 2005; 366: 1561–77

Κλινικές εκδηλώσεις VL

Clinical manifestations	Number of patients	%
Hepatomegaly	633	98.0
Splenomegaly	632	97.8
Fever	628	97.7
Pallor	533	82.5
Increased lymph nodes	500	77.5
Increased abdominal volume	463	71.7
Weight loss	462	71.5
Long eyelashes	454	70.3
Dry hair	450	69.7
Asthenia	447	69.2
Anorexia	416	64.4
lower limbs edema	151	23.3
Cough	104	16.2
Diarrhea	102	14.4
Abdominal pain	80	12.4
Bleeding	67	10.4
Jaundice	90	13.9

Εργαστηριακά ευρήματα VL

1. Αναιμία (διήθηση και καταστολή μυελού, αιμόλυση, σπληνική παγίδευση, αιμοφαγοκυτταρική λεμφοιστιοκυττάρωση)
2. Θρομβοπενία (διήθηση και καταστολή μυελού, σπληνική παγίδευση, αιμοφαγοκυτταρική λεμφοιστιοκυττάρωση)
3. Ουδετεροπενία
4. Υπεργαμασφαιριναιμία (διέγερση Β λεμφοκυττάρου)
5. Αυξημένα επίπεδα τρανσαμινασών και χολερυθρίνης
6. Υπολευκωματιναιμία
7. Αντιπυρηνικά αντισώματα- Ρευματοειδής παράγοντας

Kager PA, Rees PH ; Trop Geogr Med. 1986;38(4):371

Διάγνωση Λεϊσμανίασης

Δερματική Λεϊσμανίαση

1. Βιοψία δερματικής βλάβης

Σπλαχνική Λεϊσμανίαση

1. Βιοψία ιστού (μυελός των οστών, ήπαρ, λεμφαδένες) για άμεση μικροσκόπηση, καλλιέργεια, μοριακό έλεγχο
2. Leishmania Abs
3. Καλλιέργεια αίματος, μοριακός έλεγχος

Βλεννογονο-δερματική Λεϊσμανίαση

1. Βιοψία βλάβης

ΚΕΕΛΠΝΟ, Clinical Infectious Diseases, Volume 63, Issue 12, 15 December 2016, Pages 1539–1557

Εργαστηριακή διερεύνηση

V. What Laboratory Tests Should Be Used to Diagnose Leishmaniasis?

Recommendations.

Μέθοδοι και δοκιμές, βι		Ειδικότητα (%)
Μικροσκοπική εξέταση:[10]	14. We recommend using multiple diagnostic approaches to maximize the likelihood of a positive *Leishmania* result, most sensitive assays for the diagnosis of leishmaniasis *(strong, moderate)*.	100

VIII. What Is the Role of Serologic Testing in the Diagnosis of Leishmaniasis?

Recommendations.

20. Serologic testing is recommended for persons with suspected VL in whom definitive diagnostic tests for the parasite (microscopic identification, culture, and molecular tests for parasite DNA) cannot be conducted or have negative results. The sensitivity and specificity of serologic tests depend on the assay and antigens used, as well as host factors. Serologic tests cannot be used to assess the response to treatment. Antileishmanial antibodies can be detected years after clinically successful therapy in some persons *(strong, moderate)*.
21. We suggest that tests for antileishmanial antibodies not be performed as the sole diagnostic assay. Antibodies may be undetectable or present at low levels in persons with VL who are immunocompromised because of concurrent HIV/AIDS or other reasons. The potential for false-negative test results limits the utility of serologic assays in this setting *(weak, low)*.
22. Serologic testing is not recommended as part of the diagnostic evaluation for CL. The currently available serologic assays are neither sensitive nor specific for the diagnosis of CL *(strong, moderate)*.

RECOMMENDATIONS FOR THE TREATMENT OF CUTANEOUS LEISHMANIASIS

IX. In a Person With a Consistent Travel History and Compatible Skin Lesion(s), Is It Necessary to Obtain Parasitologic Confirmation of the Diagnosis of Leishmaniasis Before Starting Treatment?

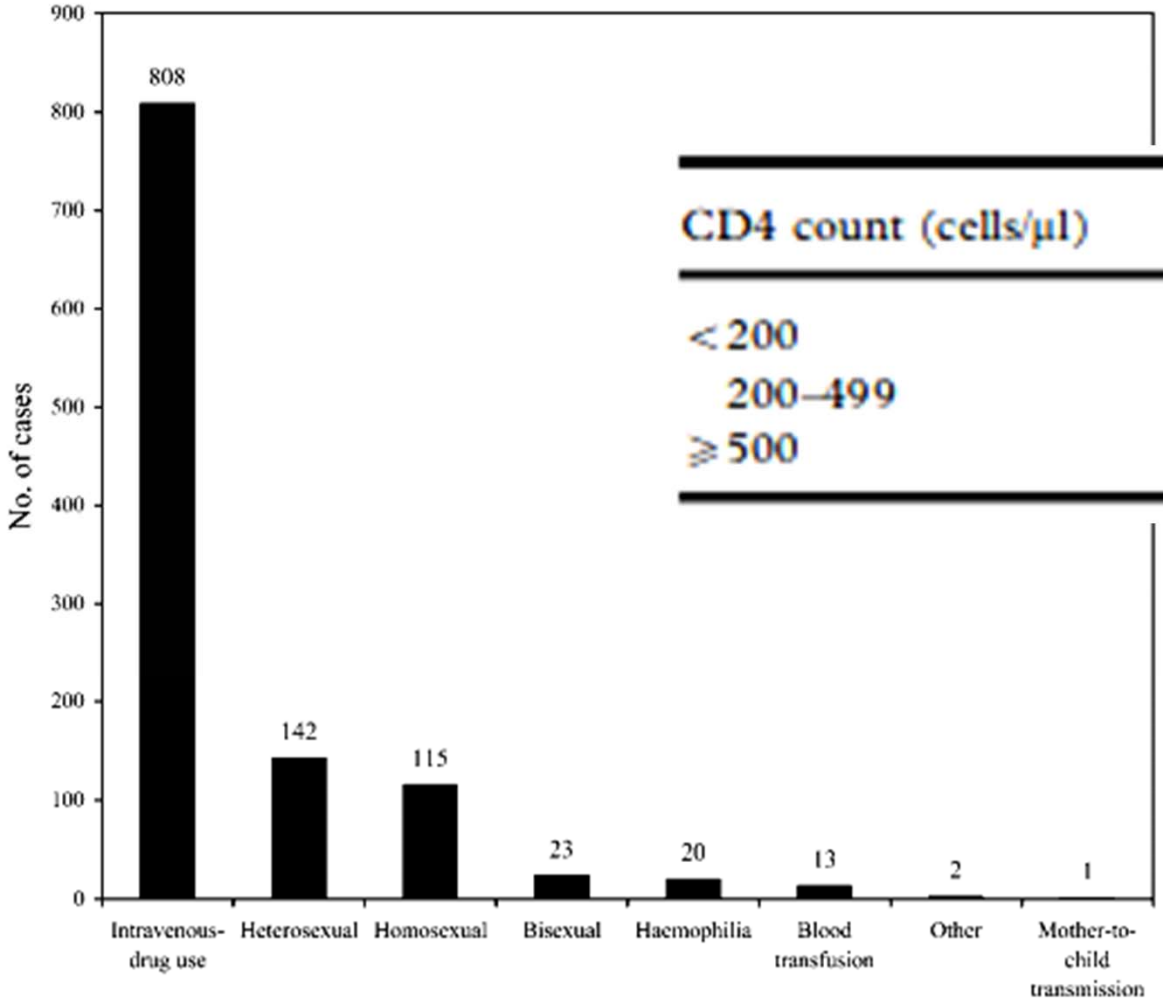
Recommendation

23. After a careful diagnostic evaluation in which neither leishmaniasis nor another diagnosis is confirmed, empiric

Δέρμα	17. *Leishmania* skin testing is not recommended or available in the United States or Canada; there are no standardized, approved, or commercially available skin-test products in North America *(strong, very low)*.	98

ΚΕΕΛΠΝΟ, Clinical Infectious Diseases, Volume 63, Issue 12, 15 December 2016, Pages 1539–1557

HIV/VL
Χαρακτηριστικά ασθενών



CD4 count (cells/μl)	No. and (%) of cases
< 200	789 (92.0)
200–499	59 (6.9)
⩾ 500	10 (1.2)

Pintado V, Martín-Rabadán P, et al.; Medicine (Baltimore) 2001; 80:54

HIV/VL
Μορφή λεϊσμανίασης

Clinical features	No. and (%) of cases
Visceral leishmaniasis (typical)	1126 (87.6)
Visceral leishmaniasis (atypical)	82 (6.4)
Cutaneous leishmaniasis	61 (4.8)
Other	9 (0.7)
Mucocutaneous leishmaniasis	4 (0.3)
Mixed	3 (0.2)

Pintado V, Martín-Rabadán P, et al.; Medicine (Baltimore) 2001; 80:54

HIV/VL
Κλινικά χαρακτηριστικά

Η συλλοίμωξη HIV/VL χαρακτηρίζεται από:

1.Παρόμοιες κλινικές εκδηλώσεις με non-HIV

2.Οι άτυπες εντοπίσεις είναι συχνότερες

Patient[a]	Amastigote location	Year VL was diagnosed	Resides in area where *Leishmania* infection is endemic	CD4 count, cells/mm^3	Fever	Splenomegaly	Hepatomegaly	PMN, cells/mm^3	HB, m*M*/L	PLT, cells/mm^3	Amastigotes on bone marrow smears
1	Stomach	1988	Yes	10	No	No	No	1500	6.9	97,000	Positive
2	Skin	1991	Yes	150	No	Yes	Yes	5000	7.3	493,000	Negative
3	Lung	1991	Yes	18	Yes	Yes	Yes	1500	5.0	71,000	Positive
4	Colon	1993	Yes	102	Yes	No	Yes	2800	5.2	292,000	Positive
5	Duodenum	1993	Yes	6	Yes	Yes	Yes	1200	7.1	68,000	Positive
6	Colon	1993	Yes	60	Yes	No	No	1800	6.8	146,000	Positive
7	Colon	1994	No	3	No	No	No	4000	7.9	145,000	Negative
8	Lung, esophagus	1994	No	10	Yes	No	No	1600	8.8	265000	Positive
9	Stomach	1995	Yes	88	Yes	No	No	1800	5.5	149,000	Positive
10	Duodenum	1995	Yes	1	Yes	Yes	Yes	1300	6.0	90,000	Positive
11	Duodenum	1996	Yes	15	Yes	Yes	No	6500	6.0	52,000	Positive
12	Duodenum	1996	No	19	Yes	Yes	Yes	2500	6.6	48,000	Positive
13	Colon	1996	No	10	No	Yes	Yes	1900	6.2	51,000	Negative
14	Colon	1996	No	6	Yes	Yes	Yes	1900	6.1	119,000	Positive
15	Lung	1997	Yes	15	Yes	No	No	3400	8.3	175,000	Positive

Note. HB, hemoglobin; PLT, platelets; PMN, polymorphonuclear neutrophils.

[a] Patients 3, 6, and 15 were found to have concomitant *Cryptosporidium*, *Histoplasma capsulatum*, and *Pneumocystis carinii* infections, respectively.

n= 91

Rosenthal E, et al; Clin Infect Dis 2000; 31:1093

HIV/VL
Διάγνωση

Source of smeared sample	No. and (%) of samples:		
	Checked	Found positive	Found negative
Bone marrow	1315	1127 (85.8)	188 (14.3)
Blood	244	110 (45.1)	134 (54.9)
Skin	81	71 (87.7)	10 (12.4)
Gastro-intestinal tract	39	37 (94.9)	2 (5.1)
Liver	43	33 (76.7)	10 (23.3)
Lymph node	27	14 (51.8)	13 (48.2)
Spleen	15	13 (86.7)	2 (13.3)
Pleural liquid	11	11 (100.0)	0 (0.0)

Serological tests of VL are less accurate in HIV coinfected individuals

Pintado V, Martín-Rabadán P, et al.; Medicine (Baltimore) 2001; 80:54; van Griensven J et al, PLoS Negl Trop Dis. 2014 Aug; 8(8): e3023

HIV/VL
Πορεία

Η συλλοίμωξη HIV/VL χαρακτηρίζεται από:

1. Σημαντικά χαμηλότερα ποσοστά ίασης
2. Υψηλότερα ποσοστά υποτροπής
3. Υψηλότερη θνητότητα

Alvar J et al; Clin Microbiol Rev. 2008;21(2):334

Θεραπεία

- **Cutaneous: Complex Disease**
  - [Sodium Stibogluconate (Pentostam) or Meglumine antimoniate (Glucantime)] 20 mg/kg/day IV/IM x 20 days
  - Liposomal Amphotericin B 3 mg/kg IV once daily days 1-5 and 10 (J Am Acad Dermatol 68:284, 2013) or daily on days 1-7
- **Cutaneous: *L. braziliensis* of any severity**
  - [Sodium Stibogluconate (Pentostam) or Meglumine antimoniate (Glucantime)] 20 mg/kg/day IV/IM x 20 days
  - Liposomal Amphotericin B 3 mg/kg IV once daily days 1-5 and days 14, 21 or days 1-5 and 10 (J Am Acad Dermatol 68:284, 2013).
- **Mucosal**
  - Liposomal Amphotericin B (regimens vary) with total cumulative dose of 20-60 mg/kg (Trans R Soc Trop Med Hyg 108:176, 2014) or Pentavalent antimony (Sb) [Sodium Stibogluconate (Pentostam) or Meglumine antimoniate (Glucantime)] 20 mg/kg/day IV or IM x 28 days or Amphotericin B 0.5-1 mg/kg IV daily or qod to total dose of 20-45 mg/kg.
- **Visceral**
  - 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:
    - FDA approved regimen for Liposomal Amphotericin B: 4 mg/kg daily on days 1-5, 10, 17, 24, 31 and 38 (total of 40 mg/kg).
    - Reference: Curr Opin Infect Dis 26:1, 2013.

熱病 Antimicrobial Therapy

Εναλλακτικά …

- **Cutaneous: Complex Disease**
  - Fluconazole 200 mg po daily x 6 weeks. Data for *L. major* only.
  - Ketoconazole 600 mg po daily for 30 days. Data for *L. mexicana*, *L. panamensis*, and *L. major*.
  - Miltefosine >45 kg 50 mg po tid; 30-44 kg 50 mg po bid for 28 days. Not FDA approved under 12 years of age or under 30 kg. 2.5 mg/kg/day (up to 150 mg maximum) in other countries. for *L. braziliensis*, *L. guyanensis*, *L. panamensis* only. Limited data or experience available.
  - Amphotericin B 0.5-1 mg/kg IV daily or qod to total dose of 15-30 mg/kg

- **Visceral**
  - Miltefosine >45 kg 50 mg po tid; 30-44 kg 50 mg po bid for 28 days. Not FDA approved under 12 years of age or under 30 kg. 2.5 mg/kg/day (up to 150 mg maximum) in other countries. Resistance to monotherapy in India and parts of Africa
  - Standard Amphotericin B 1 mg/kg IV daily x 15-20 days or qod x 8 weeks (to total of 15-20 mg/kg)
  - Pentavalent antimony (Sb) [Sodium Stibogluconate (Pentostam) OR Meglumine antimoniate (Glucantime)] 20 mg/kg/day IV or IM x 28 days (unless exposure was in Indian subcontinent)
  - Liposomal Amphotericin B 10 mg/kg IV on days 1 and 2) for children with *L. infantum* in Europe

- **Mucosal**
  - Efficacy of oral Miltefosine is variable.
  - Miltefosine >45 kg 50 mg po tid; 30-44 kg 50 mg po bid for 28 days. Not FDA approved under 12 years of age or under 30 kg. 2.5 mg/kg/day (up to 150 mg maximum) in other countries.

熱病 Antimicrobial Therapy

Πορεία νόσου (VL)

XXI. In Persons With Visceral Leishmaniasis, What Parameters Should Be Used to Assess the Clinical Response to Treatment?

Recommendations.

55. Clinical parameters correlate well with parasitologic responses to VL treatment and should be used to monitor the response *(strong, low)*.
56. Parasitologic confirmation of response (such as by repeat bone marrow aspiration for microscopy and culture after treatment) is not recommended in a patient showing a timely clinical response. Antibody levels fall but over many months or longer *(strong, moderate)*.

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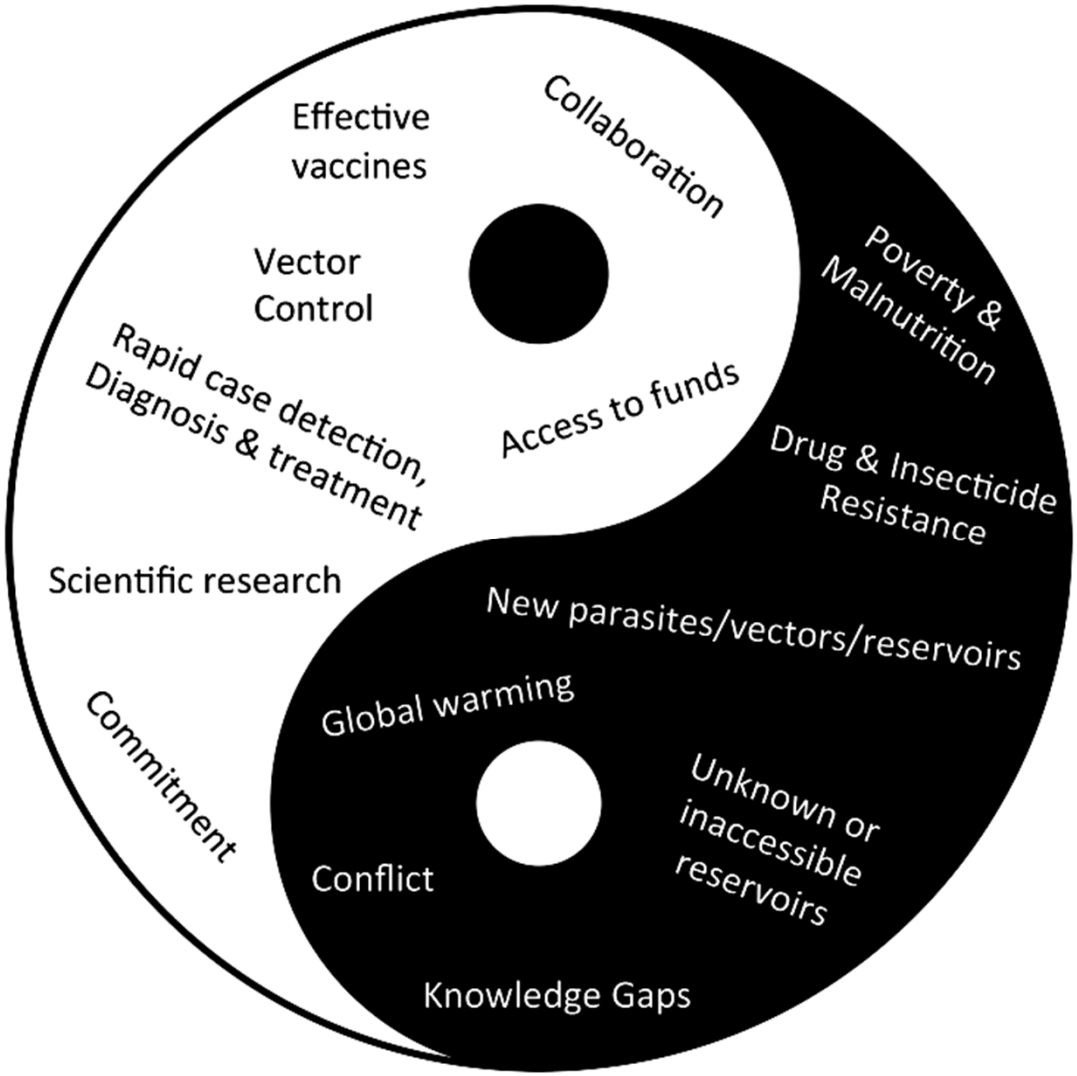
Yin and Yang στον έλεγχο της Λεϊσμανίασης



Shaden Kamhawi; PLoS Negl Trop Dis, 2017 Apr; 11(4): e0005529

Διάγνωση

https://web.gideononline.com/web/diagnosis/index.php

ΕΥΧΑΡΙΣΤΩ ΠΟΛΥ

Otto Dix, *Dr. Mayer-Hermann,*Berlin 1926